Role of MR Urography in the Evaluation of Obstructive **Uropathies**

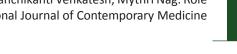
K Padma¹, N V K Sundeep², Srikanth Vankineni³, Manchikanti Venkatesh⁴, Mythri Nag⁵

¹Assistant Professor, Department of Radiodiagnosis, ²Assistant Professor, Department of Radiodiagnosis, ³Associate Professor, Department of Radiodiagnosis, ⁴Associate Professor, Department of Radiodiagnosis, ⁵Junior resident, Department of Radiodiagnosis, Rangaraya Medical College, Kakinada, Andhra Pradesh, India

Corresponding author: Manchikanti Venkatesh, Narayana Medical College, Nellore, Andhra Pradesh, India



How to cite this article: K Padma, N V K Sundeep, Srikanth Vankineni, Manchikanti Venkatesh, Mythri Nag. Role of MR urography in the evaluation of obstructive uropathies. International Journal of Contemporary Medicine Surgery and Radiology. 2022;7(2):B31-B37.



ABSTRACT

Urinary tract obstruction is a common problem encountered by urologists, primary care physicians, and emergency medicine physicians. With recent advances in technology, MR imaging has emerged as single most important modality for evaluation of urogenital tract. MRU combines anatomic imaging as well as quantitative evaluation of the urinary system, without the use of ionizing radiation, in a single test. It has become as an alternative technique to CT scan in view of its multiplanar capability, lack of ionizing radiation and angiographic capabilities. It is the diagnostic modality of choice in pregnancy. Hydronephrosis is the hallmark of obstruction. The test is 98% sensitive for detecting hydronephrosis, but the specificity is 78%. MDCT with its high spatial resolution and multiplanar reconstructions allowed better evaluation of patients with obstructive uropathy including intrinsic and extrinsic causes. In this prospective study of 50 patients selected based on screening who show hydronephrosis, they undergo further evaluation with IVU, CT, MRU were included.

Keywords: MR Urography, Evaluation of Obstructive Uropathies

INTRODUCTION

Obstructive uropathy refers to the structural impedance to the flow of urine anywhere along the urinary tract when urine flow is blocked1. It is one of few reversible causes of renal failure. Early diagnosis and treatment can salvage the kidney2. It can occur at any point in the urinary tract, from the kidneys to the urethral meatus. It can develop secondary to calculi, tumours, strictures, anatomical abnormalities, or functional abnormalities3. Despite remarkable advances in the diagnosis and treatment obstruction still remains a leading cause of damage to the urinary tract. Acute unilateral obstructive uropathy occurs in 1 in 1,000 people.

B/L obstructive uropathy occurs in 1 in 1,0000 people⁴. The condition has a bimodal distribution. In childhood, it is due to mainly to congenital anomalies of the urinary tract. Incidence then declines until after age 60, then incidence rises, particularly in men because of the increased incidence of benign prostatic hyperplasia (BPH) and prostate cancer. In women, obstruction is more likely to occur at a younger age as a result of pregnancy or cervical cancer⁵. In our prospective study, 50 patients selected based on screening who showed hydronephrosis and were further evaluated with IVU, CT and MRU.

MATERIAL AND METHODS

This prospective comparative study was carried out on total 50 adult subjects (both male and females) of age 20-70 yearswere for in this study.

Study Design: Descriptive study.

Sample size: 50 patients.

Sample size calculation: Convenient sampling method was used for the data collection. A total of 50 patients were included in the study.

Subjects & selection method: The study population was drawn from patients who are referred for MRU of the kidney ureter and bladder for evaluation of obstructive pathology detected on ultrasound.

Patients referred to Radiology Department with complaints of flank pain vague abdominal pain, abdominal mass were examined by ultrasonography (USG) and 50 of those with features of dilated pelvicalyceal system were taken up for further evaluation by intravenous urography (IVU), computerised tomography (CT) and magnetic resonance urography (MRU). Images were interpreted and the finding are correlated with surgical findings in forty (40) patients and rest of patients treated by non-surgically conservatively as they were inoperable.

Inclusion criteria

- Patients who are referred for MRU of the kidney, ureter and bladder for evaluation of obstructive pathology detected on ultrasound.
- Age group: 20-70 years.

Exclusion criteria

- Patients with a cardiac pacemaker.
- MRI non-compatible stents and implants.
- Severely obese patients.
- Claustrophobic patients.

Age group: <20years.

Procedure methodology

After written informed consent was obtained, a well-designed proforma was used to collect the data of the recruited patients. The proforma included patients with the signs and symptoms of retroperitoneal masses were included in the study. The patients in whom, masses like complex renal cysts were found during imaging for other pathologies were also included.

USG of the KUB region was done with a 3.5mhz curved array probe of ESOATE MY LAB 40 and SONOLINE ADARA in longitudinal and transverse directions covering all the areas of interest. Both low frequency curvilinear (4 – 6Hz) and high frequency linear (7 – 12 Hz) probes were used.

Plain KUB radiograph was taken in an adequately prepared patient, non-ionic contrast medium (Iopamidol 370mg) was injected intravenously for IVU only when renal parameters were normal. Serial radiographs of the abdomen were obtained at 5, 15 and 30minutes after intravenous injection of contrast in supine position. If no obstruction was defected, the examination was concluded with a full and post void radiograph of the bladder. Additional delayed radiographs were obtained up to 24 hours when indicated.

MDCT was performed on dual slice helical system SIEMENS SONATOM SPIRAL DUAL SLICE CT-scanner. Both plain and contrast study was done. Images were taken with a collimation of 1- 3mm. Non contrast CT (NCCT) was done to start with which was followed by contrast enhanced CT (CECT) if indicated. Diagnosis of calculus was made when high density lesion (200-600HU) was detected along the course of the urinary tract. The level of obstruction was established after studying the serial scans and reconstructed 3D images. Patients with elevated serum creatinine, ionic contrast medium was not used. contrast medium was given only when Blood Urea, Serum Creatinine

were normal and no history of allergic reaction to contrast medium.

MRI studies were performed using 1.5T Bravo.In order to demonstrate the water content of the urinary tract, heavily T₂W pulse sequences were used. TSE sequences were used as options, for obtaining images in short data acquisition time. Combination of a single shot TSE and a half Fourier data (HASTE sequence) improved the contrast between urinary tract and retroperitoneum. Contrast was given in neoplastic pathologies, but excretory MRU was not done. Post processing was performed using maximal intensity projection (MIP) algorithm, calculus was seen as signal void area surrounded by hyperintense urine within the urinary tract, not specific for calculus but may represent blood clot, gas, fungus ball and sloughed papilla.

IVU, CT, USG and MRU results were assessed to determine the comparative efficacy of each diagnostic modality.

The records of 50 patients under the study were maintained. All the data from patient's name, age, sex, hospital number, USG, Xray, MDCT and MRI findings were collected and data was entered in Microsoft excel sheet and SPSS V24.

STATISTICAL ANALYSIS

Data was entered in Microsoft excel sheet and SPSS V24 software. The variables that were encountered like age, sex, organ of origin, size, appearance, echotexture and vascularity are categorical and were presented as percentages. Diagnostic validity of both USG and CT for diagnosing the retroperitoneal masses was assessed using sensitivity, specificity, positive and negative values against HPE findings wherever necessary.

RESULTS

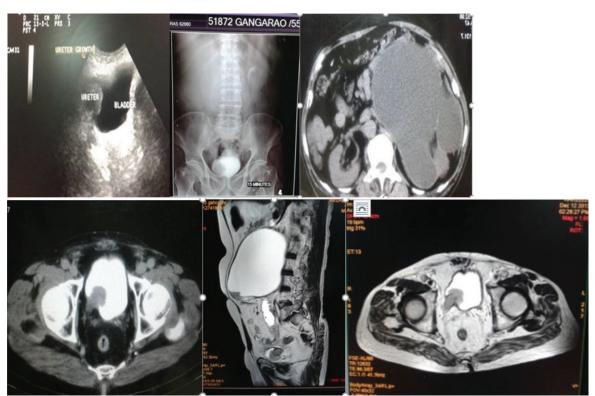
 Age distribution of patient (n = 50):A total number of 50 participants were included in the analysis. 25 female patients and 25 male patients. The age of the study was

Cause of Obstruction	MRU			IVU		
	No. of Cases Done	No. of Cases Diagnosed	Success Rate%	No. of cases done	No. of Cases Diagnosed	Success Rate%
Calculus Obstruction	13	11	84.61	11	10	90.9
Malignant	23	23	100	20/23	5	25
Benign(Strictures and extrinsic compression)	7	7	100	7	3	42.86
PUJ Obstruction	6	6	100	4/6	4	100
Congenital	1	1	100	1	1	100
Table-1: MRU Vs IVU for diagnosing cause of obstruction						

Cause of Obstruction	MRU			USG		
	No. of Cases Done	No. of Cases Diagnosed	Success Rate%	No. of cases done	No. of Cases Diagnosed	Success Rate%
Calculus	13	11	84.61	13	8	61.54
Malignant	23	23	100	23	10	43.47
Benign	7	7	100	7	3	42.85
PUJ	6	6	100	6	6	100
Congenital	1	1	100	1	0	-
Table-2: MRU Vs USG for diagnosing cause of obstruction						

21-70 yrs. Most common age group in males was 61-70yrs due to more incidence of bladder and prostatic carcinoma. Most common age group in females was 41-50yrs due to increased incidence of cervical and ovarian malignancies. In this study increased female

- incidence compared to previous studies was due to pelvic pathologies and increased incidence of uterine and ovarian malignancies.
- Distribution according to the symptoms: Pain in the flank was the commonest presenting feature in 46% patients,

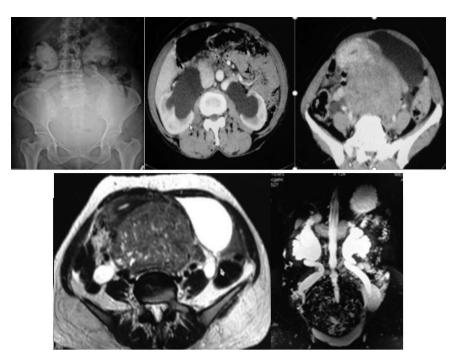


Case-1: Right distal ureteric growth with non-functioning kidney with a filling defect on right side of bladder and left gross HUN with cortical thinning.

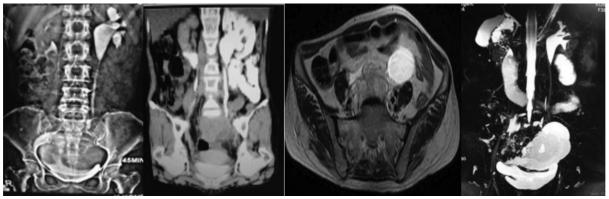
MRU			СТ		
No. of Cases Done	No. of Cases Diagnosed	Success Rate%	No. of cases done	No. of Cases Diagnosed	Success Rate
13	11	84.61	13	13	100
23	23	100	23	20	86.95
7	7	100	7	5	71.4
6	6	100	6	3	50
1	1	100	1	1	100
	Done 13 23 7	No. of Cases No. of Cases Done Diagnosed 13 11 23 23 7 7	No. of Cases Done No. of Cases Diagnosed Success Rate% 13 11 84.61 23 23 100 7 7 100 6 6 100	No. of Cases Done No. of Cases Diagnosed Success Rate% No. of cases done 13 11 84.61 13 23 23 100 23 7 7 100 7 6 6 100 6	No. of Cases Done No. of Cases Diagnosed Success Rate% done No. of Cases Diagnosed 13 11 84.61 13 13 23 23 100 23 20 7 7 100 7 5 6 6 100 6 3

Level of Obstruction	No. of Patients	Total No. of Patients	Percentage		
PUJ and Proximal 1/3 rd ureter	13	50	26		
Mild 1/3 rd Ureter	13	50	26		
Distal 1/3 rd Ureter VUJ	24	50	48		
Table-4: Table shows the percentage of patients with obstructions at different levels					

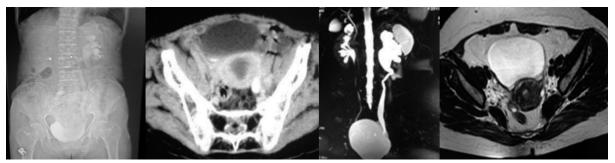
Diagnostic Modality	No. of Cases done	No. of Cases Diagnosed Level of Obstruction Localised	Percentage		
IVU	43	37	86.45		
USG	50	27	54		
СТ	50	45	90		
MRU	50	50	100		
Table-5: Diagnostic accuracy of different modalities with reference to localization of the level of urinary obstruction					



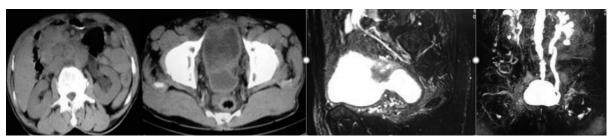
Case-2: Large posterior wall uterine fibroid with compression effect and displacement of bladder and uterus anteriorly



Case-3: Left extra renal pelvis with mild HUN, bladder showing filling defect on left side.



Case-4: Cervical malignancy with endometrial collection and left ureter infiltration.



Case-5: Prostatic growth infiltration of bladder on left side and left terminal ureter

due to hydronephrosis. Abdominal distension was the second commonest symptom in 18% patients, most common compliant in pelvic masses, bowel malignancies. Next haematuria in carcinoma bladder patients, bleeding per vagina in case of cervical malignancies, decreased urine output indicates nephropathy with elevated renal parameters.

- Distribution according to the organ of origin: Most common cause of obstruction was urinary calculi in 26% followed by PUJ strictures in 12%. Compared to previous studies malignancies predominant due to increased incidence and more treatment options.
- IVU was not performed in 7 patients due to elevated renal parameters in 6 patients, one patient was allergic to contrast. IVU was not a useful modality for diagnosing the cause of obstruction in case of malignancies, it did not provide information outside ureters.

DISCUSSION

MR urography is now a viable alternative to Ultrasound and CECT in selected patients such as those allergic to iodinated contrast agents, pregnant woman (or) patients for whom radiation exposure is of great concern⁶. Recent technical improvements show that this technique is able to offer a highly accurate morphological and comprehensive functional diagnostic evaluation of the urinary tract in most conditions. It has the potential to become the preferred imaging modality for the diagnosis of suspected Ureteral disease, significantly decreasing the need for Ultrasound and Retrograde pyelography⁷.

50 cases of obstructive uropathy were evaluated by four different modalities to use the grades of hydronephrosis, cause of obstruction and level of obstruction. While evaluating a patient with obstructive uropathy, the main aim of the radiological investigations is to confirm the presence of obstruction in the renal colleting system and accurately define its site and cause. Such information is crucial to plan the appropriate treatment option.

Results of the present study were compared to similar studies conducted previously in patients with obstructive uropathy. In the present study the highest incidence of patients was in the age group of 41-50 years in female 61-70 in males. It is different from previous studies because in this study malignancies are more compared to other causes. In females 41-50yrs age group more common due to increased incidence of cervical malignancy and ovarian malignancies and recurrence after surgery or radiotherapy.

In the present study the most common complaint was flank pain which was reported in 48% of patients. The second most common presenting complaint was abdominal distension which was reported in 18% of the patients.

In the present study the most common cause of obstructive uropathy was calculus disease. The occurrence of calculus obstruction was in 26% of the patients.

PUJ obstructions / strictures were the second most common cause of obstruction in 12% of patients.

The grading of HDN detected accurately in all cases by MRU. The level of obstruction was detected in all cases accurately by MRU compared to others. MR urography

failed to show smaller ureteric calculi that were seen in IVU, CT in 2 patients. The cause of obstruction was missed in 2 patients. These are small calculi, sensitivity and specificity of MRU for the demonstration of calculi increased with contrast enhanced T₁weighted urography.

In PUJ obstruction the ureter below the level of obstruction was demonstrated, which was not clearly seen in IVU, CECT. Existence of any aberrant vessel can be picked up with the case by MR angiography it combined with the MRU. Another advantage of MRU over other modality that it could demonstrate the pathology even in non-functioning kidney. Transitional cell carcinoma of PCS, ureter which is multifocal and causing non-functioning of kidney the sites are clearly demonstrated in our case, where IVU completely failed due to non-excretion of kidney, CT to some extent useful, but failed to show all sites.

MRU especially valuable tool for the excellent characterization of pelvic masses that cause urinary tract obstruction⁸. It accurately determined the cause of obstruction that is ureteral infiltration, adhesions in cervical, bladder, prostatic, ovarian, bowel malignancies with in short time, no radiation, no contrast administration so useful in patients with elevated renal parameters compared to IVU and CT⁹. Without contrast CT may not clearly demonstrate the obstruction. MRU also performed well in the delineation of obstructed retrocaval ureter for detecting the course¹⁰.

Calculus was detected by NCCT in 13 out of the 50 patients which was the most common cause of hydronephrosis in this study group. USG had been the initial investigation for evaluation of acute flank pain. Calculi were missed during ultrasonography in 5 patients as they were lodged in midureter and lower ureter with mild HDN. This was due to the small size and bowel gas, which made visualization difficult. USG had helped to diagnose the grades of hydronephrosis very precisely in all fifty cases. All six cases of PUJ obstruction were evaluated by USG and level of obstruction was detected correctly. However, it was unable to provide information on functional aspect and whether the obstruction was complete (or) incomplete. USG detected ureteral adhesions/infiltration in 10 out of 23 various malignancies (ca cervix, ovarian, bladder, ureter, colorectal, prostatic malignancies) failed in 13 cases, but the level of obstruction was not accurately delineated. Benign conditions the cause of obstruction was detected in 3 out of 7. Although the lesion identified, it was not clearly detected that condition lead to hydronephrosis. Retrocaval ureter was not detected by USG.

The site and size of the calculus were clearly defined during IVU, however it failed in one case due to non-excretion of contrast and bowel gas shadows. Functioning of kidney can be determined by IVU. IVU had an advantage over the other modalities in determining whether the PUJ obstruction is partial or complete. Disadvantage of IVU was it provides limited information on mural pathology and none on extramural pathology like pelvic malignancies (ovarian carcinoma, fibroid uterus, cervical malignancies). Sometimes the cause of obstruction was suggested by presence of abnormal soft tissue opacity or loss of normal soft tissue outlines.

All calculi were detected by NCCT associated finding

like hydronephrosis, hydroureteronephrosis, perinephric stranding and ureteric edema were also demonstrated. However, it provides limited information about the ureteric wall and intraluminal pathology like TCC, ureteric strictures. PUJ obstruction also detected but not useful in kidneys with delayed excretion, non-excretion as ureters are not clearly delineated. In pelvic malignancies sensitivity more if contrast CT was done, but not useful in elevated renal parameters. Another limitation was high radiation dose.

MRU can be used to thoroughly evaluate the renal parenchyma, the PCS, and the rest of urinary tract in a single imaging study as in CT urography but without radiation exposure and IV contrast administration. Excellent contrast resolution and lack of ionizing radiation make MRU as a useful technique for non-invasively evaluating the entire urinary tract.MRU better contrast resolution than CT urography.

Niall and Russel et al., compared NECT with IVU in the assessment of urinary obstruction¹¹. IVU showed 64% sensitivity and 92% specificity in diagnosing calculus obstruction. In the present study IVU was 91% success rate in diagnosing calculus obstruction.

In studies conducted by Sudah et al., and Riva et al., MRU could diagnose the level of obstruction with a sensitivity of 93.8% and specificity of 100%¹².

Our study of 50 patients of obstructive uropathy, successfully combines the protocols and recommendation of the studies by PC Khanna et al., MRU versus IVU in obstructive uropathy A prospective study of 30 cases.

Present study also able to produce the results of Colkk Sen et al., who have compared MRU, IVU, U/S and CT to detect the cause and demonstrate the site of obstruction in a group of 25 patients². The sensitivity for detection of level of obstruction was 88% for USG, 68% for IVU, 92% for CT and 100% for MRU. For detecting the cause of obstruction MRU was 100% sensitive in detecting PUJ obstruction, malignant, other conditions, but 82% in detecting calculi. CT was 100% sensitive in detecting calculi, 66% for PUJ obstruction, malignant disease, 33% in other conditions. IVU was 88% sensitive in detecting calculi, 66% for PUJ obstruction, 33% in malignant disease, 0% in other conditions. USG was 82% sensitive in detecting calculi, 100% for PUJ obstruction, 66% in malignant disease, 50% in other conditions.

CONCLUSION

To conclude static fluid MRU utilising low magnetic field had excellent diagnostic utility in patients of obstructive uropathy¹³. It scored well compared to other modalities especially for non-calcareous obstruction, like carcinoma of bladder, carcinoma cervix, ovarian malignancies, metastatic deposits, colorectal malignancies infiltrating ureter. Due to its superior soft tissue resolution scored well compared to others. In carcinoma cervix patients compared to others MRU very useful as it clearly depicts ureteral infiltration, useful for planning treatment¹⁴. We can also do follow up studies as there is no radiation, also useful in patients with elevated renal parameters where CECT is not useful. It outlines dilated PCS even in the presence of poor renal function, detected urinary calculi and depicted PUJ and

extrinsic and intramural obstructions especially the ureter course distal to obstruction well delineated in case of partial obstruction.USG is a very good initial screening modality for evaluation of obstructive uropathy, but requires confirmation by other modalities¹⁵. IVU is safe, inexpensive, easily available for evaluation of functional aspect of obstruction. Not useful in non-excreting kidneys for patients with elevated renal parameters¹⁶. IVU doesn't provide information about ureteric wall and extrinsic pathologies.NCCT is the ideal modality to investigate patients of suspected calculi, NCCT and CECT may not demonstrate mural pathologies of ureter, however it demonstrates the level of obstruction¹⁷.

REFERENCES

- Ahmad I, Ilyas M, Khan I, Robbani I, Wazir BS. Magnetic resonance urography in the evaluation of obstructive uropathy. Adv Hum Biol 2018;8:91-101.
- Magnetic Resonance Urography in Obstructive Uropathy, Col KK Sen, Brig C Mohan, SM+, Brig BS Verma#.
- Silverman SG, Leyendecker JK, Amis ES. What is the current role of CT Urography and MR Urography in the evaluation of the Urinary Tract? Radiology 2009; 250:309-323.
- Jonathan S Chávez-Iñiguez, Goretty J Navarro-Gallardo, Ramón Medina-González, Luz Alcantar-Vallin, Guillermo García-García. Acute Kidney Injury Caused by Obstructive Nephropathy. International Journal of Nephrology, vol. 2020.
- Ahmad I, Ilyas M, Khan I, Robbani I, Wazir BS. Magnetic resonance urography in the evaluation of obstructive uropathy. Adv Hum Biol2018;8:91-101.
- Xie D, Nehrenz GM, Bianco F, Klopukh B, Gheiler E. Magnetic Resonance Urography as an Imaging Modality for Urinary Stone Diseases. J Clin Nephrol Ren Care 2017;3:022.
- Leyendecker JR, Barnes CE, Zagoria RJ. MR urography: techniques and clinical applications. Radiographics 2008;28(1):23-46.
- Shokeir AA, El-Diasty T, Eassa W, Mosbah A, Mohsen T, Mansour O et al. Diagnosis of noncalcareoushydronephrosis: role of magnetic resonance urography and noncontrast computed tomography. Urology. 2004; 63(2):225-9.
- C. C. A. Nolte-Ernsting, et al.. MR Urography Today. Abdominal Imaging 2003;28(2):191-209.
- 10. Prakash Muthusami, Ananthakrishnan Ramesh. Appearances of the circumcaval ureter on excretory urography and MR urography: A single-center case series.Indian J Radiol Imaging. 2013; 23(1): 81–85.
- Niall O,Russel J, McGregor R et al.A comparison of non-contrast computed tomography with excretory urography in the assessment of acute flank pain. J Urol. 1999; 161: 534-537.
- Sudah M, Vanninen R, Partanen K, et al; MR Urography in Evaluation of Acute Flank Pain: T2-Weighted Sequences and Gadolinium- Enhanced ThreeDimensional FLASH Compared with Urography. Am. J. Roentgenol. 2001; 176: 105 – 112 P.
- P C Khanna 1, N D Karnik, B G Jankharia, S A Merchant, Anagha R Joshi, K U Kukreja Magnetic

- resonance urography (MRU) versus intravenous urography (IVU) in obstructive uropathy: a prospective study of 30 cases J Assoc Physicians India. 2005;53:527-34.
- 14. G. A. Verswijvel, et al. Magnetic Resonance Imaging in the Assessment of Urological Disease: An All in One Approach," European Radiology. 2000;10,(10):1614-1619.
- 15. G. Sigmund, et al. RARE MR Urography in the Diagnosis of Upper Urinary Tract Abnormalities in Children. Pediatric Radiology 1991:21(6);416-420.
- A. Karabacakoglu, et al. Diagnostic Value of Diuretic Enhanced Excretory MR Urography in Patients with Obstructive Uropathy. European Journal of Radiology 2004;52(3):320-327.
- 17. C. C. A. Nolte-Ernsting, et al., "MR Urography: Examination Technique and Clinical Applications," European Radiology 2001;11(3):355-372.
- 18. P. Aerts, et al. Breath Holding MR Urography Using the Haste Technique. American Journal of Roentgenology, 1996;166:543-546.
- 19. F. Regan, et al. MR Urography Using HASTE Imaging in the Assessment of Ureteric Obstruction. American Journal of Roentgenology 1996;167:1115-1120.
- 20. Rothpearl, et al. MR Urography: Technique and Application. Radiology 1995;194:125-130.
- M. E. O'Malley, et al. MR Urography: Evaluation of the Three Dimensional Fast Spin Echo Technique in Patients with Hydronephrosis. American Journal of Roentgenology 1997;168(2):387-392.
- 22. M. Tsubota, et al. Utility of Cine MR Urography of Urinary Tract and Comparison with Static MR Urography. Radiation Medicine 2004;22:212-217.
- K. Szopinsky, et al. Magnetic Resonance Urography: Initial Experience Low Dose GD DTPA Enhanced Technique. European Radiology 2000(10): 1058-1064.
- J. Hughes, et al. MR Urography: Evaluation of Different Techniques in Non Dilated Tracts. Clinical Radiology 2002;57(11):989-994.
- T. El Diasty, et al. Diuretic Contrast Enhanced Magnetic Resonance Urography versus Intravenous Urography for Dipiction of Non Dilated Urinary Tracts. Abdominal Imaging 2003:28(1):135-145.
- F. B. Ergen, et al. 3D Excretory MR Urography: Improved Image Quality with Intravenous Saline and Diuretic Administration. Journal of Magnetic Resonance Imaging 2007;25(4):783-789.
- C. C. A. Nolte-Ernsting, et al. Gadolinium Enhanced Excretory Urography after Low Dose Diuretic Injection: Comparison with Conventional Excretory Urography. Radiology 1998:209;147-157.
- J. Zielonko, et al. MR Urography of Obstructive Uropathy: Diagnostic Value of the Method in Selected Clinical Groups. European Journal of Radiology 2003;13(4);802-809.

Source of Support: Nil; Conflict of Interest: None

Submitted: 10-03-2022; Accepted: 15-04-2022; Published online: 17-05-2022