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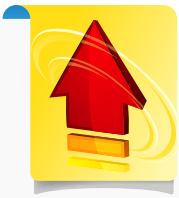
In Patients with LUTS due to BPH,

℞ CONTIFLO ICON™

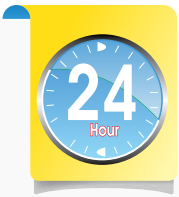
Tamsulosin Hydrochloride 0.4mg **Prolonged Release Tablets**

Tamsulosin with Innovative CONtrolled absorption technology



Delivers consistent drug levels over 24hrs[1,2]

- Better control of bothersome night-time symptoms of LUTS/ BPH, including nocturia
- Better QoS and QoL



Offers 24-hr symptom control[1,2]

- OD dose sufficient

Lower C-max & Drug intake independent of food consumption[1,2]

- Better cardiovascular safety profile
- Patient compliance

LUTS- Lower Urinary Tract Symptoms , BPH-Benign Prostate Hyperplasia, QoL- Quality of Life, QoS- Quality of Sleep, C-max- Maximum concentration of drug in the plasma

Ref: 1.Christopher R. Chapple And Emmanuel Chartier-Kastler. Pharmacokinetic profile of tamsulosin OCAS. Journal Compilation BJU International, 2006;98(2):9-12
2.Phillip K. Introduction and Summary. Journal Compilation BJU International, 2006;98 (2):1-2

Abbreviated Prescribing Information. CONTIFLOTM ICON.

GENERIC NAME: Tamsuosin Hydrochloride Prolonged Release Tablets. COMPOSITION:Each film-coated tablet contains: Tamsulosin HCl IP…0.4 mg (prolonged release.DOSAGE Form: Tablets for oral use. Description: CONTIFLO ICON contains tamsulosin hydrochloride, which is an antagonist of alphaIA adrenoceptors in the prostate. Indications: For the treatment of sign and symptoms of benign prostatic hyperplasia (BPH). DOSE AND METHOD OF ADMINISTRATION: The recommended dose of CONTIFLO ICON (Tamsulosin HCl Prolonged Release Tablet) is 0.4mg once daily. It should be administered approximately one-half hour following the same meal each day. For those patients who fail to respond to the 0.4mg dose after 2 to 4 weeks of dosing, the dose of tamsulosin HCl prolonged release tablet can be increased to 0.8mg once daily. If discontinued or interrupted for several days at either the 0.4mg or 0.8mg dose, therapy should be started again with the 0.4mg once daily doseThe tablet should be swallowed whole and should not be crunched or chewed as this will interfere with the prolonged release of the active ingredient. Pregnancy: Pregnancy category B: Tamsulosin is not indicated for use in women. CONTRAINDICATIONS: Patients with known hypersensitivity to tamsulosin or any other component of this product. Reactions have included skin rash, urticaria, pruritus, angioedema and respiratory symptoms. WARNINGS AND PRECAUTIONS: Possibility of postural hypotension. Patients should be cautioned to avoid situations where injury could result should syncope occur. Tamsulosin should not be used in combination with other alpha adrenergic blocking agents. Caution is advised when alpha adrenergic blocking agents including tamsulosin are co-administered with PDE5 inhibitors. Alpha adrenergic blockers and PDE5 inhibitors are both vasodilators that can lower blood pressure. Concomitant use of these two drug classes can potentially cause symptomatic hypotension. Caution should be exercised with concomitant administration of warfarin and tamsulosin. Patients must be advised about the possibility & seriousness of Priapism. Intraoperative floppy iris syndromehas been observed during cataract surgery in some patients treated with alpha1 blockers, including tamsulosin. Advice patients considering cataract surgery to tell their ophthalmologist about use of contiflo Icon. DRUG INTERACTIONS: Tamsulosin 0.4mg should not be used in combination with strong inhibitors of CYP3A4 (e.g., ketoconazole). Tamsulosin should be used with caution in combination with moderate inhibitors of CYP3A4 (e.g., erythromycin), in combination with strong (e.g., paroxetine) or moderate (e.g., terbinafine) inhibitors of CYP2D6, in patients known to be CYP2D6 poor metabolizers particularly at a dose higher than 0.4mg (e.g., 0.8mg).. SHELF-LIFE: Please see Mfg. Date. Expiry date printed on pack. Do not use product after expiry date which is stated on packaging. Expiry date refers to last day of that month. STORAGE AND HANDLING INSTRUCTIONS: Store below 25□C, protected from light and moisture. Keep all medicines out of reach of children. For more information kindle write to : SUN HOUSE, 201 B/1,WESTERN EXPRESS HIGHWAY, GOREGAON EAST, MUMBAI-400063

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Contents

A Novel Combined Transurethral and Suprapubic Approach for Excision of Mesh at the Bladder Neck

Gabriel N. Schaer[1], Tilmann Moeltgen[2], Gloria Ryu[1], Heimo Magg[1], Zaraq Khan[3], Dimitri Sarlos[1]

Abstract

Introduction and hypothesis: Unrecognized bladder perforation of a tension-free sling is a rare situation. Removal of the intravesical sling has been done by laparotomy or transurethrally. With technique presented here we want to show a minimally invasive approach that allows complete removal of the intraluminal sling material, located at the bladder neck.

Methods: This video shows a novel combined transurethral and suprapubic approach for radical removal of the mesh. Two 3.5-mm trocars were placed suprapubically into a filled bladder. One site was used for an optic with camera and the other for a 3.5-mm grasping forceps to apply tension on the mesh to pull it out of the bladder wall while it was being excised transurethrally with a cystoscope and transurethral scissors.

Results: The patient's postoperative course was uneventful. At 1-month follow-up, the patient was free of dysuria and cystoscopy revealed complete healing of the mesh site. Because of recurrent stress urinary incontinence, another continence sling surgery has been performed (TVT exact). After a follow-up of 2 years, she is continent and free of dysuria.

Conclusions: This novel technique provides an effective means of removing mesh perforated into the bladder, located at the bladder neck, using a combined transurethral and suprapubic approach. The technique is minimally invasive and the applied traction allows complete removal of the intraluminal part of the mesh.

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Keywords: Tension-free vaginal tape, Complication, Bladder perforation, Mesh removal, Minimally invasive

Aim of the Video/Introduction

The widespread use of mesh for stress urinary incontinence (SUI) is generally considered safe; however, it involves the possibility of facing complications such as mesh perforation into the bladder [1]. We present here a 68-year-old woman who was referred to our unit with a 6-month history of severe dysuria and recurrent urinary tract infections in spite of repeated treatments with antibiotics. The patient had suffered from stress urinary incontinence in the past and had undergone a transobturator tension-free vaginal tape placement 2 years ago. Eighteen months after the surgery, she presented with the symptoms described above. Cystoscopy at an outside institution revealed mesh perforation into the bladder along with a bladder stone close to the bladder neck. This complication is classified according to the IUGA/ICS-Prosthesis/Graft Complication Classification System as 4BeT4S3 [2]. A transurethral resection of the bladder stone and mesh was performed. Owing to continued symptoms a repeat cystoscopy was performed 2 months after the procedure, which showed recurrent stone formation with mesh perforation. A second transurethral resection was performed. The patient continued to have recurrent urinary tract infections and was at this time referred to our institution. Cystoscopy revealed recurrent stone formation and mesh perforation.

Methods

Traditionally, perforated mesh into the bladder has been removed with a laparotomy, involving cystotomy, mesh removal, and bladder reconstruction [3, 4]. Transurethral removal, though less invasive, may leave residual mesh in the bladder wall, causing recurrent symptoms, as is seen in our case. Other minimally invasive techniques such as laparoscopic removal and the use of Holmium laser, have also been described in the literature [5, 6]. We describe a novel combined transurethral and suprapubic approach using mini-laparoscopy instruments that provides a radical excision of intraluminal mesh. By using 3.5-mm trocars, it is minimally invasive. The trocars can be placed safely under direct cystoscopic vision. Because of the double camera set up and the availability of different angled scopes, visualization of the entire bladder and therefore mesh excision in any anatomical location in the bladder is possible.

The patient consented to and was admitted for this procedure. Following general anesthesia the patient was prepped and draped in the dorsal lithotomy position. A cystoscope was inserted transurethrally and the bladder was filled with normal saline. Two suprapubic punctures were carried out and 3.5-mm trocars were inserted into the bladder under direct cystoscopic vision (Fig. 1). One surgeon used a 3.5-mm camera optics and a 3.5-mm grasper from the suprapubic side to pull on the stone and the perforated mesh while the other surgeon used scissors transurethrally to resect the mesh and stone. This maneuver allowed for adequate tension on the perforated mesh so that it could be removed adequately. Additionally, the use of two cameras and two

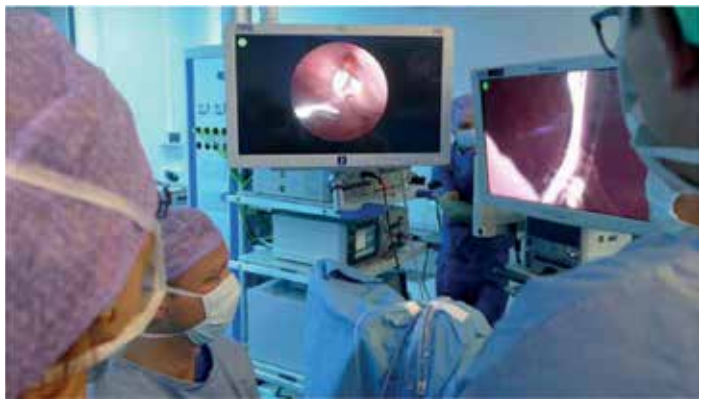

Fig. 1: Set-up of surgeons and video screens: each surgeon needs a separate video screen. Surgeon 1 sits between the patient's legs for the transurethral approach (*left*); surgeon 2 stands on the patient's left side for a suprapubic approach (*right*).

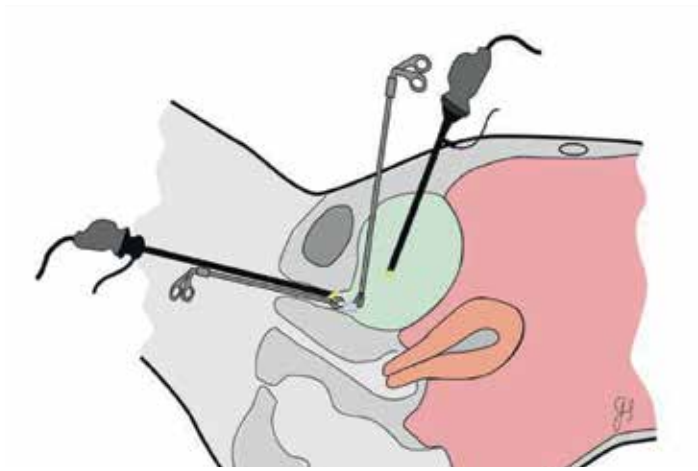

Fig. 2: Schematic view of the instrument setup: a cystoscope and scissors are inserted transurethrally, two suprapubic 3.5-mm trocars are inserted into the bladder and laparoscope and grasper are introduced.

video screens allowed for better visualization in locating the perforation and adequately removing it (Fig. 2). The location of the mesh around the bladder neck would have been difficult to remove with cystoscopic vision only. This can be appreciated in the video, where the suprapubic camera adds additional spatial orientation and ease that leads to removal of the perforated mesh in its entirety. At the end of the procedure, we did not need to leave a Foley or suprapubic catheter. After removal of the small suprapubic trocars, the bladder incision was not closed. The patient's postoperative course was uneventful. At 1-month follow-up, the patient was free of dysuria and cystoscopy revealed complete healing of the mesh site. Because of recurrent stress urinary incontinence, another continence sling surgery has been performed (TVT exact). After a follow-up of 2 years she is continent and free of dysuria.

Conclusion

This novel combined transurethral and suprapubic minimally invasive technique provides an effective means of radically removing the intraluminal parts of a mesh perforated into the bladder

by cutting the mesh under traction. The double access to the bladder can be used to excise mesh in any anatomical location in the bladder; also, locations at the bladder neck that are difficult to reach are accessible.

Compliance with ethical standards

Conflicts of interest None.

Consent Written informed consent was obtained from the patient for publication of this video article and any accompanying images.

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Source: Schaer, G.N., Moeltgen, T., Ryu, G. *et al*. *Int Urogynecol J* (2019). https://doi.org/10.1007/s00192-019-04110-9.

Green-laser Assisted Laparoscopic Partial Cystectomy for Selective Muscle-invasive Bladder Cancer: Technique and Initial Outcome

Jinhai Fan[1], Kaijie Wu[1], Pu Zhang[1], Dalin He[1]

Abstract

Purpose: To describe a green-laser marking technique to assist partial cystectomy, which allows accurate identification of tumour margins, and provide our initial experience with ten patients.
Methods: Between January 2014 and February 2018, ten patients suspected with muscle-invasive bladder cancer and request of bladder-preserving treatment were selected. In each case, bilateral pelvic lymphadenectomy was performed before green-laser assisted laparoscopic partial cystectomy. Under the direct view of cystoscope, the front-firing green-laser incision was performed 0.5–1 cm away from the exterior margin of lesion with adequate depth into the fat tissue. Tumours were then en bloc removed via laparoscope under the tracing of laser beam.
Results: The location of 12 tumours in 10 patients was superior wall in 7 cases, lateral wall in 3 cases, anterior wall in 1 case, and posterior wall in 1 case. All procedures were completed without serious complications. The median operating time was 270 (210–360) min with a median haemoglobin decrease of 11 (3–38) g/L. Nine patients were high-grade transitional cell carcinoma and one patient was urachal carcinoma, and the clinical stage was pT1 in 1 case, pT2 in 4 cases, and pT3 in 5 cases. The pathological evaluation of tumour margins was negative in 10 patients. During the follow-up, no recurrence or metastasis were detected in 8 patients, but 2 patients presented regional recurrence.

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Conclusion: The use of green-laser marking technique during laparoscopic partial cystectomy is a feasible manoeuvre in assisting the accurate incision and minimizing injury to the remaining bladder.

Keywords: Muscle-invasive bladder cancer, Partial cystectomy, Green-laser, New technique

Introduction

Radical cystectomy plus neoadjuvant chemotherapy is the current standard treatment for muscle-invasive bladder cancer. However, the values of radical cystectomy are reduced due to its high surgical risks [1], high complication rates [2, 3], and poor quality of life [4]. Recently, interest in patient quality of life has promoted a trend towards bladder-preserving treatment modalities, including transurethral resection of the bladder tumor (TURBT), modern external-beam radiation therapy (EBRT), chemotherapy, multimodality treatment (MMT), and partial cystectomy (PC).

Partial cystectomy (PC) is superior to the other modalities due to the en bloc removal of tumor masses, adequate incision margins, absence of residual tumors, and accurate tumor staging. In selected patients with bladder carcinoma, an open PC can be performed with similar results and lower morbidity than a series of radical cystectomies [5]. However, making a precise initial incision distant from the tumor can be challenging when no assistance technique is applied for the PC [5]. To achieve a precise incision and minimize injury to the remaining bladder, we introduce a novel green-laser marking technique, and provide our initial experience and early outcomes using this new technique for treatment of muscle-invasive bladder cancer.

Materials and Methods

Institutional review board approval was obtained to perform green-laser assisted laparoscopic PC in 10 patients between January 2014 and February 2018. Prior to the surgery, all patients were diagnosed by pelvic CT scans and cystoscopy accompanied with biopsy to confirm the diagnosis of bladder cancer. In addition, CT scans of the chest and abdomen were also performed for any metastases. The selection criteria were as follows: patients with no more than two solitary tumors outside the trigone of the bladder, patients with no metastases, patients with stage T2 or T3 disease, and patients with a strong desire to preserve the bladder. All procedures were performed by a single surgical team. Perioperative data, including the operation time, intraoperative blood transfusion, decrease in hemoglobin level, intraoperative complications, surgical margins, and postoperative length of hospital stay were recorded and descriptive analyses were used to determine the medians of the collected data. Tumor recurrence or metastases were reassessed through cystoscopy and pelvic CT scans at follow-up.

The surgical procedure was conducted as follows: with the patient under general anesthesia and in the lithotomy position, the transperitoneal approach was applied with five ports, similar to the technique described for laparoscopic radical prostatectomy [6]. Standard pelvic lymph-node

dissection was performed before green-laser assisted laparoscopic PC (Fig. 1a). The bladder was then mobilized to expose the tumor-bearing area.

A cystoscope was inserted into the bladder to identify the tumor, and under this direct view, the green-light laser incision was performed by surrounding the tumor at a 0.5–1 cm distance from the tumor edge (Fig. 1b). The incision was deepened until the fat tissue was reached (Fig. 1c). Occasionally, the operating plane was further extended to the satellite lesions, and the transurethral operation was performed under surveillance with a laparoscope to better determine the tumor location.

Along the prelabeled border, the tumor and its satellite lesions could be easily distinguished by the tracing of the laser beam (Fig. 1d) and could be removed en bloc via a transperitoneal laparoscopy (Fig. 1e). All specimens were collected with an extraction pouch and subsequently removed. Closure was performed with continuous sutures using 2–0 V-Loc (Covidien) suture line (Fig. 1f). No urine leakage or bleeding was detected in the operative field. A tubular drain was placed in the vesical bed. A representative surgical procedure is shown in Online Resource-1.

Results

The green-laser marking laparoscopic PC was completed successfully in all 10 patients without open conversions. The median age of the patients was 61.5 (range 46–74) years with nine males and one female. The median score according to the POSSUM scoring system [7] was 15.5 (12–24).

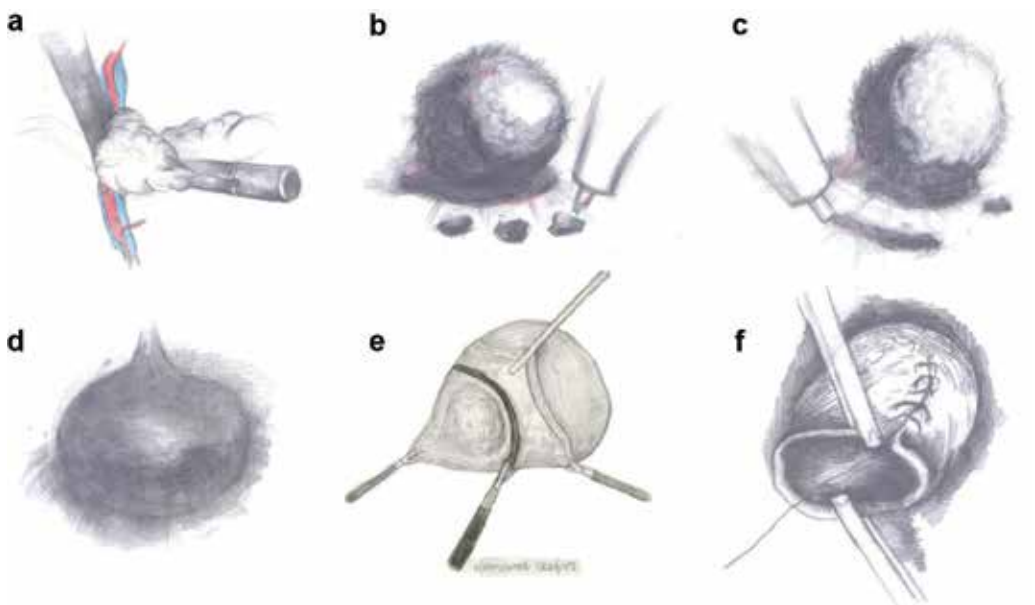

Fig. 1: Schematic diagram of surgical procedure. **a** Pelvic lymphadenectomy. **b, c** A laser-marked incision deepened into the fat tissue of bladder wall surrounding the tumour. **d** The tumour area could be distinguished under surveillance with a laparoscope. **e** The tumour was *en bloc* removed along the prelabeled border. **f** The bladder was sutured.

Table 1: The characteristics of tumours.

Patient	Tumour size/mm	Tumour location	Tumour stage	Tumour grade	Pathology
1	28×28.7×29/19×8×14	Right lateral/ apex	T2N0M0	High grade	TCC
2	24×22	Superior	T2N0M0	High grade	TCC
3	8×6×2/–	Superior/basal	T2N0M0	High grade	TCC
4	33×31×27	Superior	T3N0M0	High grade	TCC
5	28×17	Superior	T2N0M0	High grade	TCC
6	24×37	Posterior	T3N0M0	High grade	TCC
7	13×9	Left lateral	T3N0M0	High grade	TCC
8	57×28	Superior	T3N0Mx	–	Urachal carcinoma
9	23×7	Anterior	T1N0M0	High grade	TCC
10	32×20	Right lateral	T3N0MO	High grade	TCC

The American Society of Anesthesiologists physical status (ASA PS) classification was two in six patients, three in three patients, and one in one patient.

The characteristics of the tumors are shown in Table 1. Postoperative complications were all classified as Clavien–Dindo grade 2 for regular antibiotic use [8]. The median operation time was 270 (210–360) min, with a median decrease in the hemoglobin level of 11 (3–38) g/L. Blood transfusion was not required during the operation for ant of the 10 patients. The median postoperative length of hospital stay was 8 (4–12) days.

In total, nine patients were diagnosed with high-grade transitional cell carcinoma without lymph-node metastases, and one patient was diagnosed with urachal carcinoma; the clinical stages were pT1 in 1 case, pT2 in 4 cases, and pT3 in five cases. The pathological evaluation of the tumor margins was negative in ten patients. All patients received the adjuvant radiotherapy. As shown in Fig. 2 (two representative CT and cystoscopy images of patients), during the follow-up period of 22 (2–52.5) months, no recurrence or metastases were detected in eight patients. However, two patients presented with regional recurrence: one patient presented with in situ tumor recurrence and was given chemotherapy, subsequent radiotherapy, and, finally, conservative therapy due to poor tolerance of the former two therapies; the other patient presented with newly developed recurrence originating from a pre-existing tumor lesion and was finally administered salvage cystectomy treatment. Currently, both patients are alive.

Discussion

In the classic PC procedures, making an initial incision distant from the tumor requires either palpation of the mass or previous knowledge of the tumor location. However, palpation is not

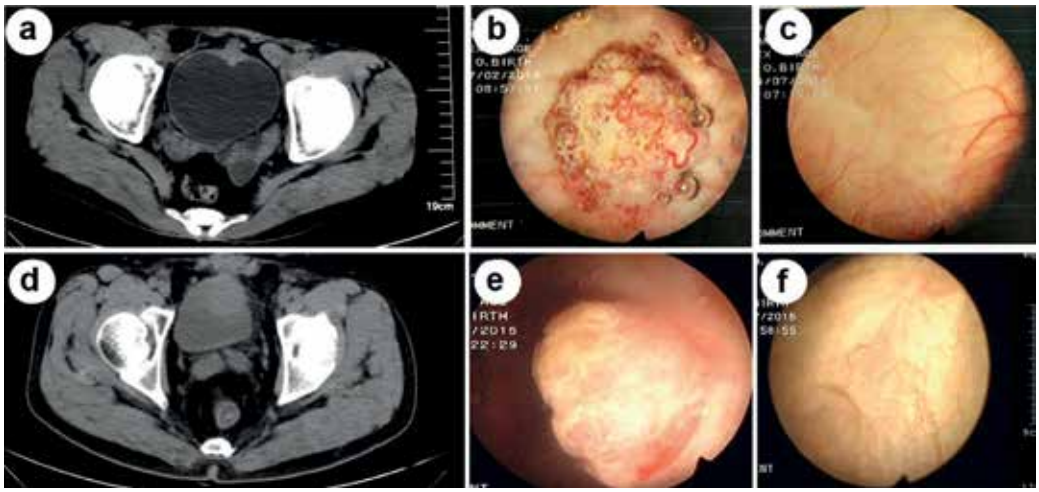

Fig. 2: Representative images of CT scans and cystoscopies. **a–c** Images of pelvic CT scan and cystoscopies before and after the surgery (patient 1, the tumour was located at the superior wall with the size of 24 × 22 cm). **d–f** Images of pelvic CT scan and cystoscopies before and after the surgery (patient 2, the tumour was located at the superior wall with the size of 28 × 17 cm).

efficient for patients who undergo TURBTs. Various techniques have been developed to precisely predict of tumor locations during PCs. The idea of using cystoscopic light to confirm the location of the tumors during surgery has been reported in a case of a patient with endometriosis [9]. Gofrit expanded this idea to the bladder cancer [10], and applied light via a flexible cystoscope pointed toward one edge of the planned elliptical resection area around the tumor, which avoided performing a cystotomy. Kim introduced the India-ink marking technique into the PC procedure [11]. Using India-ink, tattooing was performed 1 cm away from the outer margin of the lesion with adequate depth into the deep muscle layer. The tattooed area could be identified under laparoscopic vision. However, India-ink diffused into and invaded adjacent areas, and thus, a second injection was required [11].

Lasers have been widely used to treat multiple urologic disorders, including bladder cancer [12, 13]. The green-light laser (532 nm) is a recent invention, and deemed a good fit for soft-tissue photovaporization due to its steadily delivered energy, "photoselective vaporization", and hemostatic function. In our previous study, we applied a green-light KTP Laser to en bloc enucleate non-muscle-invasive bladder cancer. In this study, we are the first group to apply this green-light laser to mark the initial incision of PC. Our modified marking technique does not involve contact during the operation and avoids the obturator nerve reflex, and offers a better laparoscopic vision due to the physical nature of the laser. In addition, our technique will not only assist with the accurate incision into and minimize injury to the remaining bladder, but also provide an accurate evaluation of tumor stage and lymph-node metastases.

In this study, two patients with two solitary muscle-invasive tumors experienced disease recurrence after less than 5 years follow-up, which was similar to the results reported by Kassouf

in 37 patients who underwent PCs [14]. However, our experience indicated that green-laser assisted laparoscopic PC was not adaptable for patients with multifocal diseases (defined as tumors in two or more sites), because patients with were at a high risk of disease recurrence [15].

In addition, this technique will not be a preferred option for tumors located at the lateral wall, because the bladder is cushioned from the pelvic sidewall by perivesical fat and loose connective tissue, where the lateral pedicles and branches of the vesical blood supplies are located. To minimize blood loss and adequately expose the resection area, the lateral pedicles should be divided, which would increase the difficulty and risks of the surgery. Therefore, our technique is mainly recommended for lesions located on the superior and posterior walls of the bladder [16].

One critical limitation is that the study had a small sample size and no long-term results. A further study is ongoing, which will include additional cases, and the follow-up period will be prolonged to determine the safety and effectiveness of the procedure.

Conclusion

To achieve precise incisions in PCs, we describe a novel modified technique of green-laser assisted laparoscopic PC. The technique was successful in our small number of cases. The modified technique is a feasible maneuver that assists in planning the incision and minimizes injury to the remaining bladder. The safety and effectiveness of this technique will be further evaluated. Additional cases and longer follow-up times are needed for adequate comparisons among techniques.

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Author contributions Fan: project development and manuscript writing. Wu: data analysis and manuscript writing. PZ: data collection and manuscript writing. DH: project development.

Funding The authors declare that they have no relevant financial interests.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Statement of human rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments.

Informed consent Informed consent was obtained from all individual participants included in the study.

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Source: Fan, J., Wu, K., Zhang, P. *et al. World J Urol* (2019). https://doi.org/10.1007/s00345-019-02712-y.

Vesicoureteric Reflux

Freddy Avni, Marianne Tondeur, Frederica Papadopoulou, Annie Lahoche

Introduction

In case of urinary tract infection (UTI), vesicoureteric reflux (VUR) is considered a significant factor for the recurrence of UTIs and for the development of progressive renal damage. Optimizing its detection is important for the identification of patients at risk. This necessitates a good knowledge of the pathogenesis, the circumstances of occurrence, and the natural history of the disease. In addition, the techniques used for demonstrating VUR must be used at their best and for good purposes (The RIVUR trial investigators 2014; Garin *et al*. 1998; Hellström and Jacobsson 1999; Jakobsson *et al*. 1999; Ismaili *et al*. 2006a, b).

Vesicoureteric reflux results from the lack of a normal valve-like mechanism of the vesicoureteric orifice (Thomson *et al*. 1994). Many factors contribute to the competence of the vesicoureteric orifice, e.g., the location of the orifice, the normal renal function with downhill diuresis, and the hydration of the patient. Refluxing ureters often have a larger diameter, and the ostium is at a more lateral or caudal position. Furthermore, the competence of the vesicoureteric junction is also influenced by the length of the intravesical segment of the ureter: a shorter distance is likely to result in VUR. Primary VUR occurs mainly in neonates and in infants, whereas secondary VUR results from or is associated with various uro-nephropathies. It occurs more often in school-age girls. The exact prevalence of VUR in healthy children is unknown but apparently is between 1 and 2% (Verrier-Jones 1999).

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Diagnosing VUR

Voiding Cystourethrography (VCUG)

To date, voiding cystourethrography (VCUG) is the central method for the initial diagnosis of VUR in children with UTI (or for workup of an antenatal diagnosis of fetal uropathy) (Fernbach *et al.* 2000). The method allows the detection of VUR, its precise grading, and the detection of intrarenal reflux. Grading of VUR is based on the work of the International Reflux Study Group and includes VUR from grade I–V (Table 1) (Figs. 1, 2, 3, 4, 5, and 6) (Lebowitz *et al.* 1985). VURs of higher grades are associated with a greater degree of dysplasia/reflux nephropathy. Also, higher grades of VUR tend to resolve more slowly than milder grades of VUR. A special aspect of VUR, the intrarenal reflux, occurs more often at the upper and lower poles of the kidney and at compound papillae (Fig. 4). It is related to the particular anatomy of the medulla–calyceal complex in these poles that renders intrarenal reflux more prone to occur and scars more likely to develop (Ransley and Risdon 1975; Rolleston *et al.* 1974).

Voiding cystourethrography is also useful as it provides a simultaneous evaluation of the bladder and urethra. The demonstration of voiding dysfunction, bladder wall thickening, or diverticula may help to characterize and understand certain types of VUR (Fotter *et al.* 1986; Koff 1992).

Table 1: VUR grading.

Grade	Findings
Grade I	VUR limited to the ureter
Grade II	VUR up the renal cavities without dilatation
Grade III	VUR into the renal cavities inducing dilatation and eversion of the calyces
Grade IV	Moderate-to-marked dilatation of the ureter and pyelocalyceal system
Grade V	Marked tortuosity and dilatation of the ureter and pyelocalyceal system

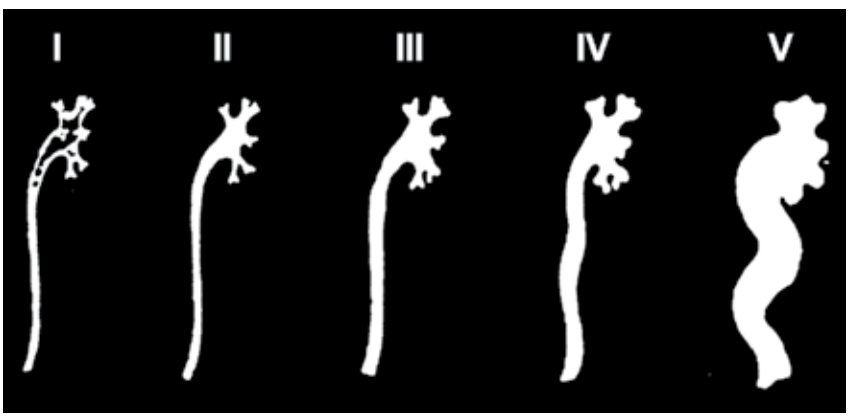

Fig. 1: VUR grading.

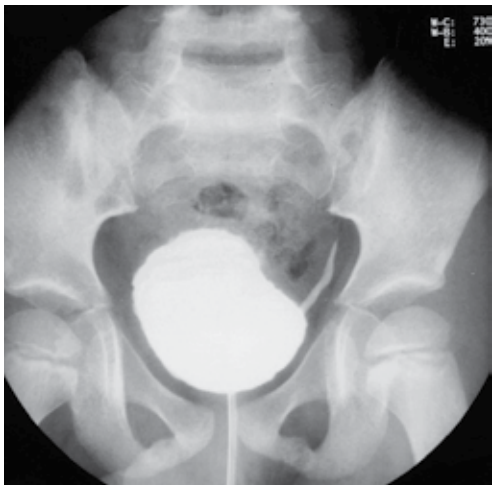

Fig. 2: VCUG: left VUR grade I.

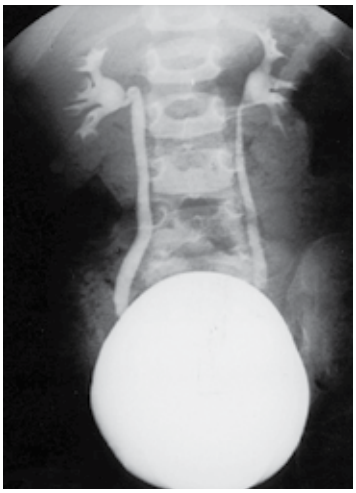

Fig. 3: VCUG: bilateral VUR grade II.

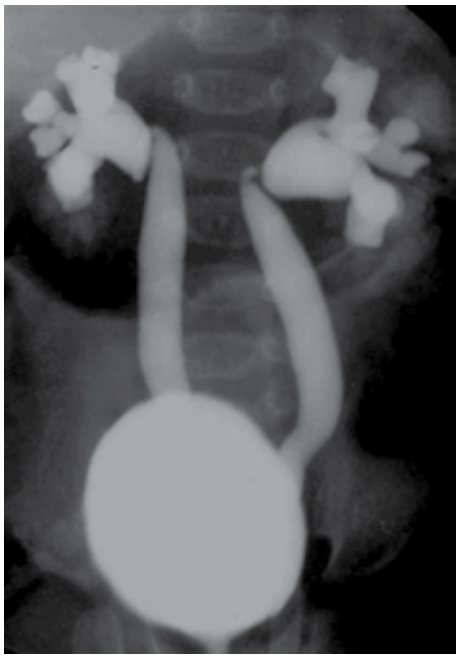

Fig. 4: VCUG: bilateral VUR grade III with left intrarenal reflux.

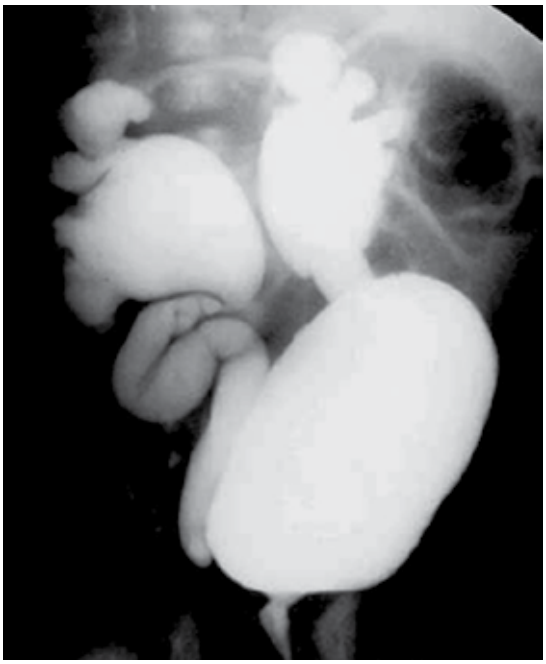

Fig. 5: VCUG: bilateral VUR grade IV.

Urethral obstruction, whatever its origin, may also be associated with secondary VUR (Fig. 7). The drawbacks of the method are that the procedure is invasive, necessitating bladder catheterization or puncture, and that it is an irradiating technique. Fortunately, the newer pulsed fluoroscopy cystographic technique reduces the radiation dose almost as low as radionuclide studies

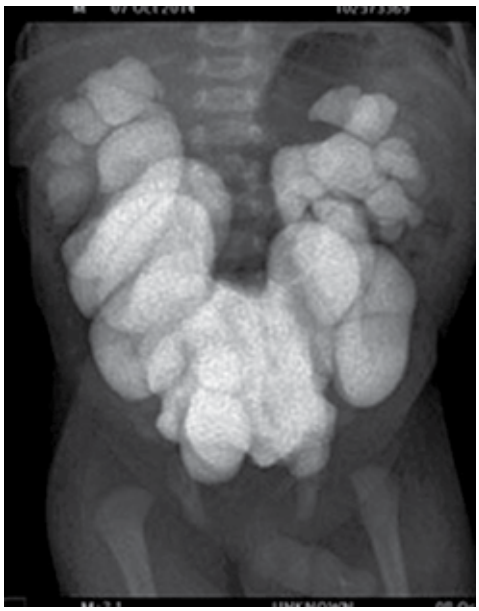

Fig. 6: VCUG: bilateral VUR grade V.

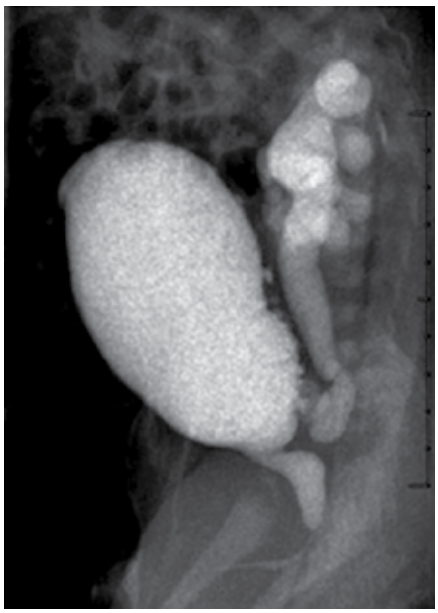

Fig. 7: VUR and PUV. VCUG, micturition phase, showing typical PUV associated with left grade IV VUR.

(ovarian dose 0.017–0.052 mGy, mean dose: 0.029 mGy) (Kleinman *et al*. 1994; Hernandez and Goodsitt 1996).

Another limitation of the technique is that conventional VCUG underestimates the occurrence and degree of VUR. Cyclic filling of the bladder has been shown to improve the detection rate of VUR by 3% in a second and up to 18% in a third filling. This is of particular interest in neonates or in other patients with low vesical capacity (Fig. 8) (Gelfand *et al*. 1999; Papadopoulou *et al*. 2002; Riccabona 2002).

Pitfalls of VCUG include underestimation of the degree of VUR in case of reflux into an already dilated and obstructed ureter (refluxing megaureter) or when VUR and ureteropelvic obstruction coexist (Bomalaski *et al*. 1997); due to the obstruction, the refluxing urine may not reach the pyelocalyceal system (see below). Finally, reflux of contrast into the vagina during the micturition phase of the VCUG is commonly observed and should not be regarded as a sign of ectopic insertion or of fistula (Fig. 9) unless the refluxed contrast fills a distended vagina or unless there is no clear separation between the vagina and urethra. In such cases a variant of urogenital sinus must be suspected (Lebowitz and Avni 1980).

Direct Radionuclide Cystography (DRNC)

Even if DRNC lacks resolution, this approach is attractive since it delivers a lower radiation dose than pulsed fluoroscopy VCUG or continuous fluoroscopy VCUG (Lee *et al*. 2006a, b; Ward *et al*. 2008).

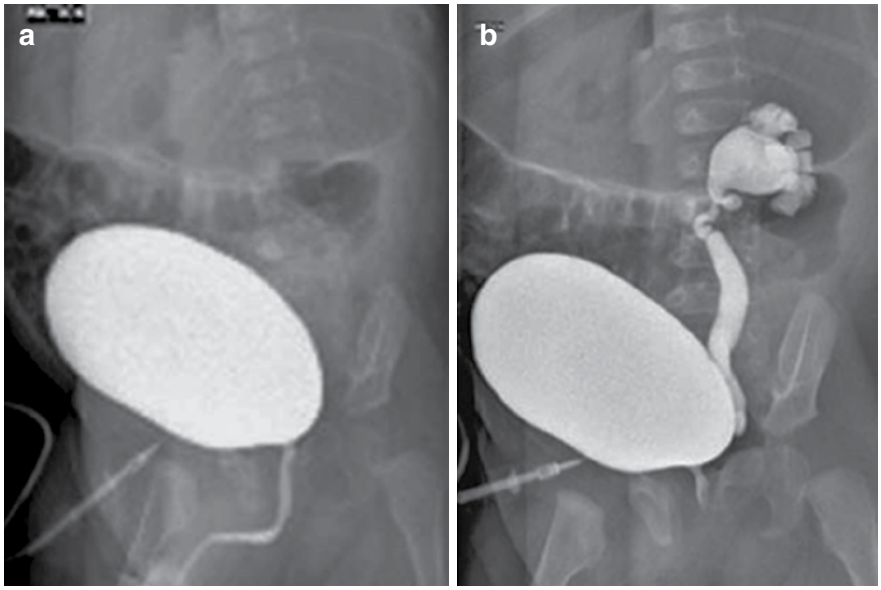

Fig. 8: Cyclic VCUG. (**a**) No VUR is demonstrated at the first filling. (**b**) Left grade III/IV VUR appears during the third filling.

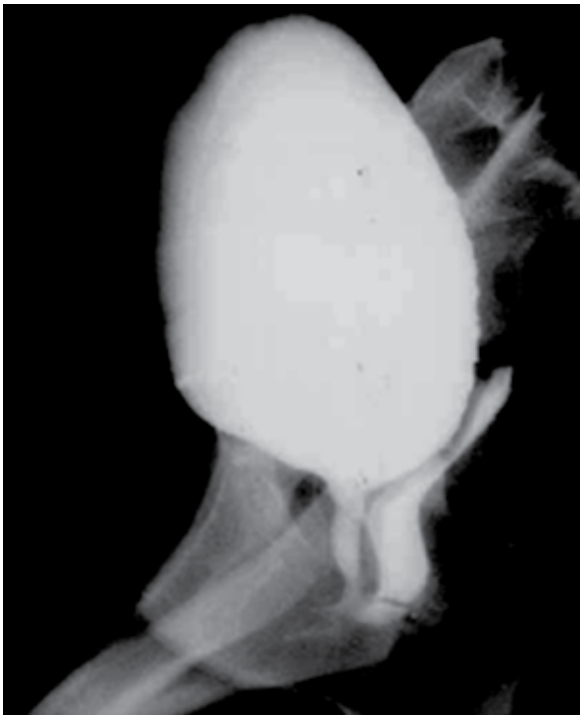

Fig. 9: VCUG (voiding phase): retrograde filling of the vagina.

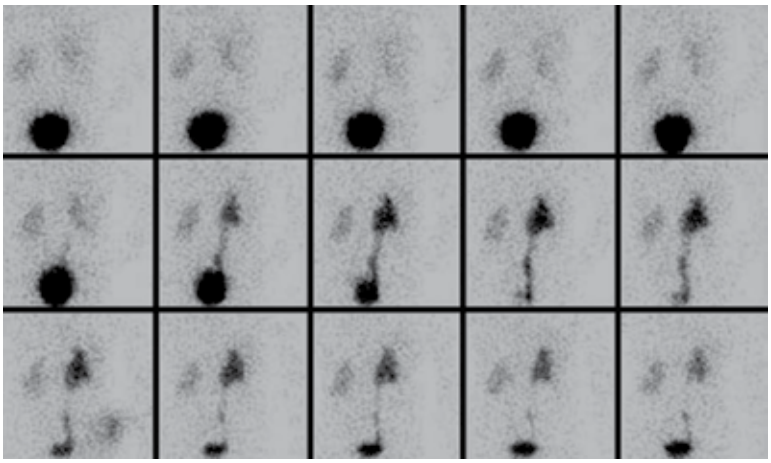

Fig. 10: Indirect cystography performed after the end of the renogram; right VUR during the micturition phase.

Direct radionuclide cystography requires bladder catheterization as well. Still, numerous studies have demonstrated that DRNC is more sensitive than VCUG in detecting VUR (Dalirani *et al*. 2014). This is not surprising: VUR is intermittent, and DRNC, by allowing an uninterrupted image registration during a longer duration, detects a higher number of reflux episodes. DRNC is however less sensitive in detecting intrarenal reflux and grade I VUR (Mozley *et al*. 1994; Unver *et al*. 2006); it does not provide anatomical information about the bladder or urethra (Fig. 10).

The unquestionable indications of DRNC are the follow-up of patients with previously known VUR and the screening of siblings of patients with VUR as VUR may be present in 25% of these siblings (Wan *et al*. 1996; Fettich *et al*. 2003; Piepsz and Ham 2006).

Indirect Radionuclide Cystography (IRC)

In IRC, the isotopic tracer is injected intravenously in the framework of the measurement of the separate kidney functions; the presence of VUR is evaluated on the late micturition phase of the procedure (Fig. 11). This technique presents several advantages over the direct procedures: it is noninvasive and more physiological. However, IRC does not study the bladder-filling phase nor it images the micturition phase; the method misses VUR in a significant number of children: a negative examination can therefore not exclude VUR (De Sadeleer *et al*. 1994); moreover, performing IDRC is possible only in children who are toilet trained, i.e., over 3–4 years of age (Gordon *et al*. 2001).

Ultrasound

Ultrasound (US) has gained popularity for the evaluation of the urinary tract in children. It is easily performed, and, since it is a non-irradiating technique, it is well accepted by the parents.

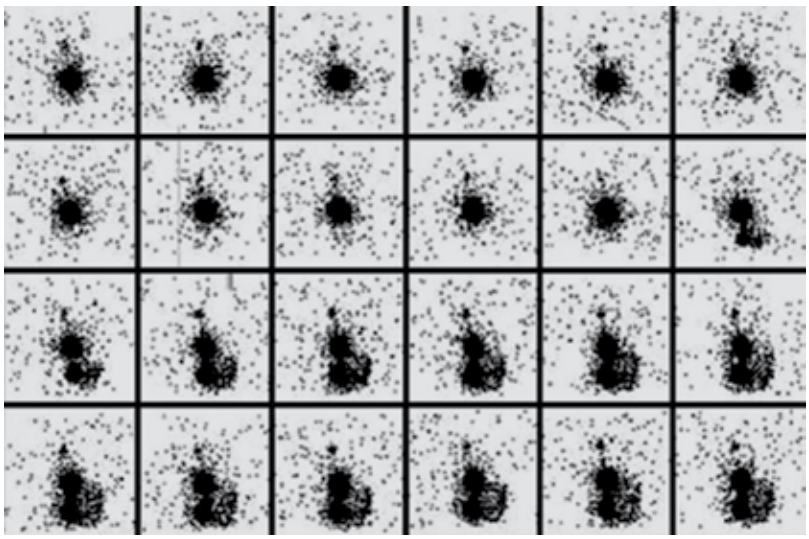

Fig. 11: Direct cystography: left VUR during both the filling and the micturition phases.

Because the patients are small, high-resolution transducers can be used and the urinary tract is nicely displayed.

The role of the technique for screening patients at risk of having VUR has been very controversial. Many authors suggest that conventional US in no way replaces VCUG in patients at risk; for these authors, US detects only 25–45% of patients with VUR (Di Pietro *et al.* 1997; Zerin *et al.* 1993). Unfortunately most of these studies underestimate the value of US because they rely on the presence of urinary tract dilatation as the only sign of VUR. Many other US signs have been described in association with VUR (Table 2) and should be looked for (Avni *et al.* 1997; Hiraoka *et al.* 1994; Hiraoka *et al.* 1997; Tsai *et al.* 1998). Renal pelvis dilatation is certainly an important sign of VUR, but the problem is also to determine the degree of dilatation that should be considered abnormal: 7 mm in the newborn and 10 mm in older children seem to be a good cutoff for diagnosing dilatation (Stocks *et al.* 1996; Marra *et al.* 1994; Walsh and Dubbins 1996). The detection of calyceal or ureteral dilatation is an important supplementary finding, and both have been shown to be associated with VUR (Newell *et al.* 1990; Leroy *et al.* 2010). A varying dilatation of the pelvis is suggestive of VUR (Fig. 11). The lack of corticomedullary differentiation is also commonly associated with VUR (Figs. 12 and 13). These signs, as well as an overall increased cortical hyperechogenicity, could result from high intravesical pressure and ischemic damage, which lead to glomerular ischemic damage and renal dysplasia (Hulbert *et al.* 1992). Small kidneys or renal cortical thinning, features of renal dysplasia, may also be associated with VUR and with high pressure damage already in utero (Gobet *et al.* 1999). Another interesting US sign that can be associated with VUR is pelvic and ureteral wall thickening (Fig. 13). The sign is not specific as it can be encountered in cases of UTI, renal transplant rejection, as well as postoperatively. Yet once the other etiologies such as postoperative status are excluded, a VCUG seems justified

Table 2: US signs that can be associated with VUR.

Renal pelvic dilatation
Variable dilatation
Ureteral dilatation
Calyceal dilatation
Loss of corticomedullary differentiation
Signs of dysplasia
Pelvic and ureteral wall thickening
Hyperechoic medulla
Color Doppler turbulence in dilated ureters
Enlarged bladder

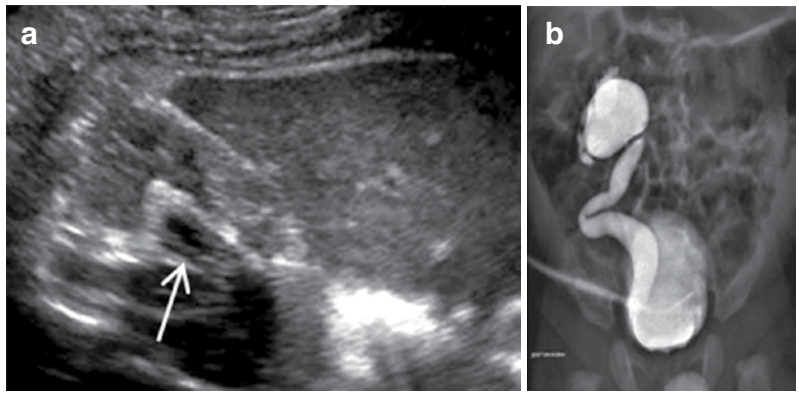

Fig. 12: US anomalies in case of VUR. (**a**) Transverse scan of the right kidney: small kidney and thickening of the renal pelvis wall (*arrow*). (**b**) VCUG demonstrating a right grade IV VUR.

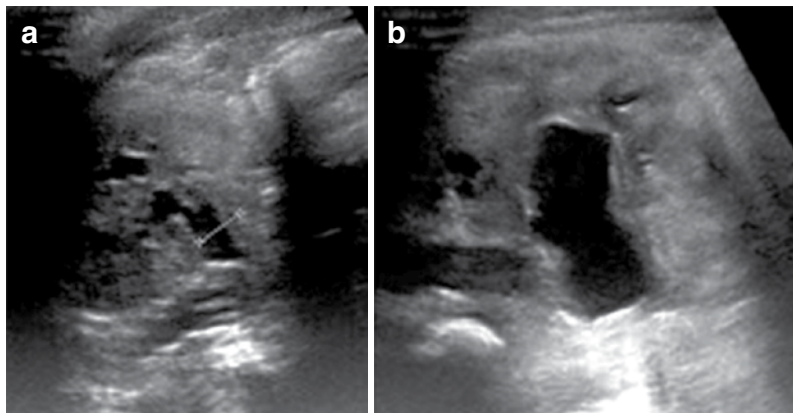

Fig. 13: US anomalies in case and VUR: varying renal pelvic dilatation. Transverse scans of the right renal pelvis. (**a**) With a full bladder, the renal pelvis measures 7 mm. (**b**) After micturition, the dilatation increased to 13 mm.

(Robben *et al*. 1999). Finally, ureteral dilatation has been shown to be the most accurate sign predicting VUR (Leroy *et al*. 2010). Using all these US data, one should be able to detect 65–85% of patients with VUR and particularly the high-grade cases (III–V) (Avni *et al*. 1997; Tsai *et al*. 1998; Hiraoka *et al*. 1997).

Color Doppler sonography (CDS) has been proposed as an adjunct to conventional US for the detection of VUR. First, the visualization of the ureteric jet by means of color Doppler US was thought to mean there was no VUR (Salih *et al*. 1994). Although it might be interesting to localize the ureteric orifices (Strehlau *et al*. 1997), other studies did not confirm this hypothesis. The use of CDS for the demonstration of VUR in dilated ureters has also been reported with VUR; the refluxing urine displays different colors related to the variable direction of flow. Unfortunately this can only be obtained when the ureters are dilated (Matsumo *et al*. 1996).

Contrast-enhanced Voiding Urosonography (ce-VUS)

During the last two decades, contrast-enhanced voiding urosonography (ce-VUS) has emerged as a sensitive and radiation-free imaging modality for the detection and follow-up of VUR in children (see also Sect. VUR and UVJ Obstruction). The examination is performed with US and introduction of microbubble-containing US contrast agents in the bladder through a catheter (Fig. 13). During filling and voiding, the bladder, ureters, and kidneys are continuously monitored for possible VUR detection. During voiding the urethra is imaged through a perineal or lower abdominal approach for any structural abnormalities such as posterior urethral valves or stenosis. The diagnosis of VUR is made when echogenic microbubbles are seen entering into the ureters and renal collecting systems (Fig. 14) (Darge *et al*. 1998). On ce-VUS, VUR can be graded in five grades in a similar manner as on VCUG (Darge and Troeger 2002). Intrarenal reflux can also be clearly seen with contrast-specific imaging mode (Figs. 15 and 16). The diagnostic accuracy of ce-VUS with first- or second-generation ultrasound contrast agents has been assessed in many comparative studies with VCUG or RNC and found high in almost all (Darge *et al*. 1999; Berrocal *et al*. 2005; Mentzel *et al*. 1999; Vassiou *et al*. 2004; Ascenti *et al*. 2004; Darge *et al*. 2005; Kis *et al*. 2010; Papadopoulou *et al*. 2012).

The increasing awareness of the radiation risks in the pediatric population has resulted in the worldwide acceptance of the ce-VUS as an alternative option in VUR imaging and has been incorporated in imaging recommendations by the Uroradiology Task Force members of the European Pediatric Radiology Society (Riccabona *et al*. 2008; 2012). Moreover, the availability of more stable second-generation US contrast agents and the advances in US technology with the development of contrast-specific imaging modes resulted in progressive improvement of ce-VUS's diagnostic accuracy both in VUR as well as in urethral morphology imaging (Figs. 16 and 17) (Papadopoulou *et al*. 2006; Duran *et al*. 2009). Due to its complete lack of radiation, the examination can be performed in more than two or three cycles resulting thus in a higher depiction rate of intermittent VUR compared to conventional imaging methods, especially in young infants (Papadopoulou *et al*. 2006). On top of that, ce-VUS with ultrasound contrast agents has a favorable safety profile reported in several studies (Riccabona *et al*. 2012;

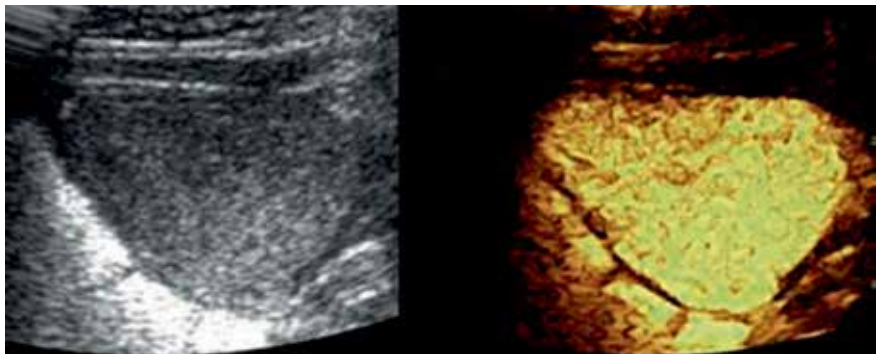

Fig. 14: Simultaneous dual imaging of the bladder during filling, saggital baldder view. Echogenic contrast filling the bladder is better seen on contrast-specific mode (on the *right*) than on conventional gray-scale imaging (on the *left*).

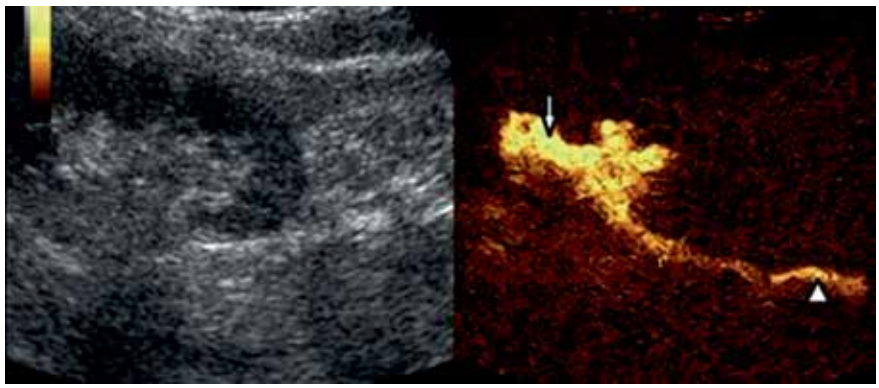

Fig. 15: VUR grades II–III on the left kidney on sagittal view of a 5-year-old girl. Refluxing contrast microbubbles slightly dilate the left ureter (*arrowhead*) and the major calyces (*arrow*), better seen on contrast-specific imaging (on the *right*).

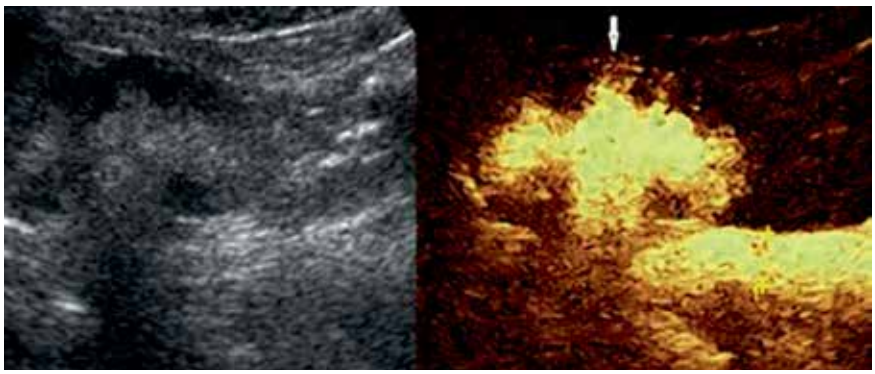

Fig. 16: Grade IV reflux on sagittal view of the left kidney in a 4-month-old girl. The significantly dilated ureter (measured 9 mm between the crosses) and pelvicalyceal system are better seen on contrast-specific imaging (on the *right*). Intrarenal reflux is also clearly seen in the parenchyma (*arrow*) on the middle part of the left kidney during the second cycle of ce-VUS.

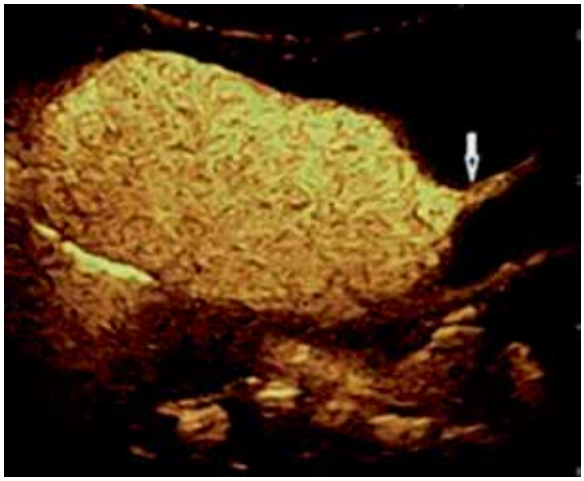

Fig. 17: Urethral imaging during voiding on ce-VUS. Normal female urethra (*arrow*) of a 4-month-old girl is imaged through abdominal approach.

Duran *et al*. 2012; Papadopoulou *et al*. 2014). Disadvantages of the method are that catheterization is still required and that US contrast agents are not yet available or approved for pediatric use in all countries.

Magnetic Resonance (MR) Urography

Intravenous urography (IVU) should no longer be performed for the anatomical (or functional) assessment of the urinary tract damaged by VUR. Instead, MR urography (MRU) should be performed whenever necessary and available (Koyicigit *et al*. 2014).

On MRU, several features may suggest VUR in patients examined for other urological reasons: the discovery of a small irregular kidney, thinned parenchyma, dilated and clubbed pyelocalyceal system, and dilatation of the ureters without obstruction (Fig. 18). Conversely, whenever such findings are encountered, a VCUG should be performed in order to confirm the presence of VUR. It is worth noting that massive VUR occurring during an MR urography may fill the renal cavities. Therefore, a catheter might be introduced into the bladder prior to an MRU performed in a patient with known high-grade VUR (Lebowitz and Avni 1980).

Take Away

Voiding cystourethrography, using the newest pulsed fluoroscopy technique, is the most suitable technique for characterizing VUR with all important anatomical features additionally allowing for a panoramic overview. US, with all its potential applications, should be utilized as a screening method in patients at risk. Ce-VUS and isotopic cystographies should be used as follow-up techniques but may be considered as a first-line investigation in females potentially complemented by VCUG.

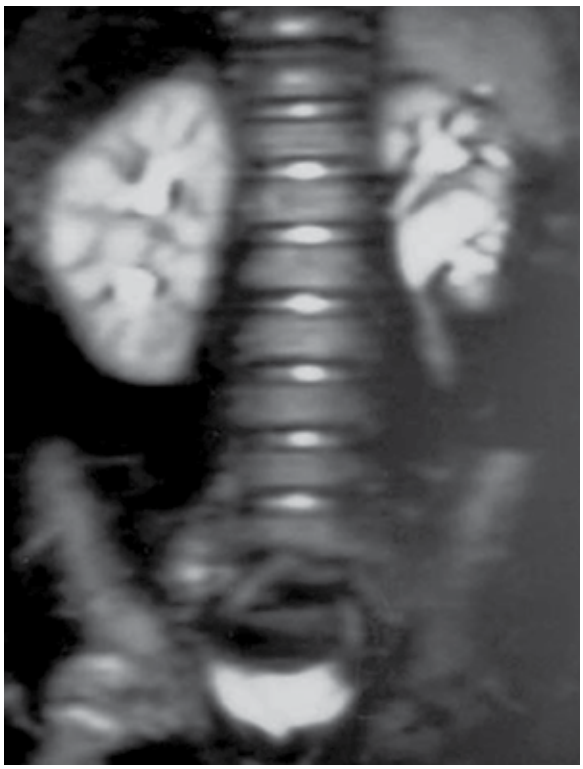

Fig. 18: Fetal reflux nephropathy. MR urography shows a small left kidney in a 2-month-old baby boy with VUR (SPIR T2 sequence).

Detection of VUR: Circumstances

Postnatal Workup of Antenatally Diagnosed Fetal Uropathies

Antenatal diagnosis of fetal anomalies by obstetrical US has led to the detection of an increasing number of fetal uro-nephropathies. The attitude toward antenatally diagnosed uropathy has now been standardized, leading to increased detection of VUR (Avni *et al.* 1998; Zerin *et al.* 1993; Van Eerde *et al.* 2007; Lee *et al.* 2006a, b; Ismaili *et al.* 2006a, b; Riccabona *et al.* 2008). Furthermore, VCUG is performed selectively in the neonatal period based on obstetric US findings if confirmed on neonatal US.

Primary VUR is demonstrated more and more frequently and has become one of the leading causes of neonatal urinary tract dilatation (Zerin *et al.* 1993). Noteworthy, making a precise diagnosis of VUR in utero is more difficult, unless variability of the pelvic dilatation is observed during the obstetrical US examination (Hiraoka *et al.* 1994; Walsh and Dubbins 1996); another circumstance under which VUR is directly diagnosed in utero is the so-called megacystis–megaureter association (see below).

Perinatal VUR differs notably from VUR detected in older children, which occurs mainly in girls. Among patients with perinatal VUR, two groups are encountered: a group with mild VUR

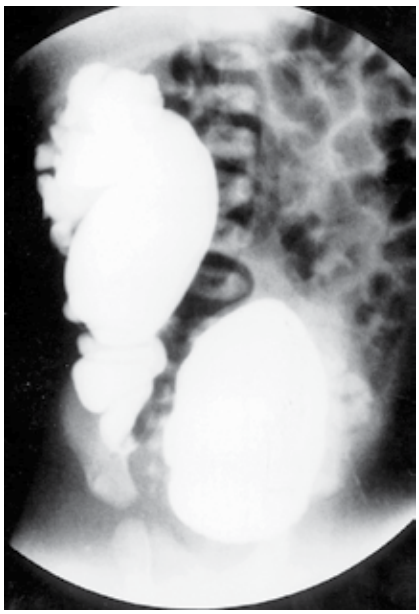

Fig. 19: Massive right grade V VUR in a baby boy. The renal function was impaired.

and usually normally functioning kidneys and a second group with severe VUR into massively dilated ureters, which is associated with renal damage at birth (the so-called fetal or congenital reflux nephropathy) (Fig. 19). This has led to the CAKUT concept (congenital anomalies of the kidneys and urinary tract) describing the association between renal dysplasia and hypoplasia with urinary tract malformation (Najmaldin *et al*. 1990; Anderson and Rickwood 1991; Yeung *et al*. 1997; Ismaili *et al*. 2006a, b). The first type of VUR is often an incidental finding during neonatal VCUG; it is encountered equally in girls and boys. The second most severe type is almost exclusively detected in baby boys already during fetal life, and this particularity has led to a theory associating this frequent occurrence of severe VUR in baby boys with a transient fetal bladder outlet obstruction (Avni and Schulman 1996; Sillen 1999a,1999b). Whatever its grade, VUR in children tends to resolve more often than VUR detected in older patients.

Nonneurogenic Bladder–Sphincter Dysfunction

Voiding dysfunctions are another condition in which VUR is often detected. Nonneurogenic voiding dysfunction is a frequent disorder mostly occurring in school-age girls. Most theories hypothesize that in such patients, VUR is not primary but secondary to the bladder–sphincter dysfunction. Treatment of this type of VUR is unsuccessful unless the dysfunction is treated as well (Snodgrass 1998; Sillen 1999a).

Urodynamic studies coupled to a VCUG are mandatory for the proper management of severely affected patients (Fotter *et al*. 1986; Sillen 1999a; Pfister *et al*. 1999). On VCUG, the bladder wall

appears trabeculated and thickened, diverticula may be present, the urethra is wide (so-called spinning top urethra), and the bladder neck appears tightened (Baunin *et al.* 1993).

Urinary Tract Infection

The relation between VUR and UTI has been largely debated (Gordon 1995). It seems that UTI does not cause VUR and that VUR does not cause UTI (Shanon and Feldman 1990), but the prevalence of VUR among children with UTI varies between 18 and 35% (Finnell *et al.* 2011); so, if VUR is present, the risk for recurrence of UTI is increased with renal scarring and late renal failure as consequences. As VCUG is an invasive procedure, important work has been performed aiming to define groups of children at risk to develop renal scars in which performing VCUG would be mandatory to choose the appropriate strategy. The respective roles of US and Tc^{99m}-DMSA scan were studied, but there was an important heterogeneity between studies: the age of the children and the timing performing either Tc^{99m}-DMSA or US or both were different. It is therefore not surprising that conflicting results were obtained: while Hansson suggested performing VCUG only in patients with Tc^{99m}-DMSA renal lesions (Hansson *et al.* 2004), Hoberman *et al.* concluded that Tc^{99m}-DMSA scan was not useful (Hoberman *et al.* 2003). Lee observed an important probability of high-grade VUR when both Tc^{99m}-DMSA scan and US were altered (Lee *et al.* 2009), and Bayram *et al.* showed that, in the absence of other risk factors for UTI, the association of mild Tc^{99m}-DMSA scarring and normal US excludes high-grade reflux (Fig. 20) (Bayram *et al.* 2014). Taking into account that patients with low-grade VUR have a very low risk for renal scarring, several authors suggested that antimicrobial prophylaxis would be unnecessary in these children (Pennesi *et al.* 2008; Roussey-Kesler *et al.* 2008; Montini and Hewitt 2009). Different guidelines were published (Awas *et al.* 2015; Roberts 2011; Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management 2011; Tekgul *et al.* 2012). Some of these recommendations are discussed by De Palma *et al.* (De Palma and

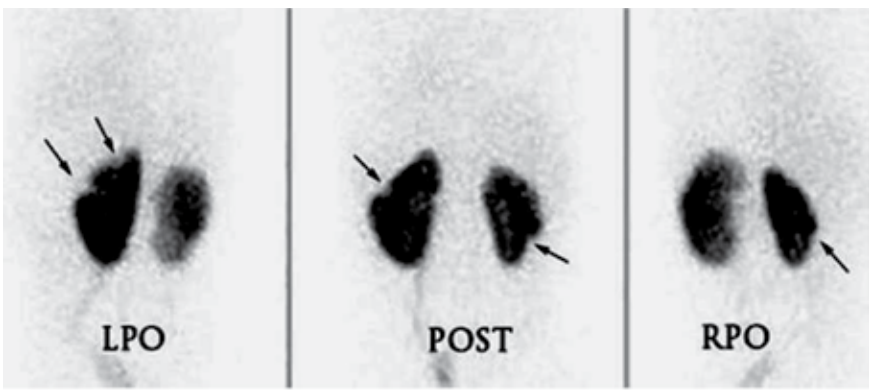

Fig. 20: DMSA scan–static mode. Three incidences are usually obtained: left posterior oblique (*LPO*); posterior (*POST*); right posterior oblique (*RPO*). Scars at the left external edge of the left kidney and at the lower part of the right kidney (*arrows*).

Manzoni 2013); Springer *et al*. underline that these guidelines, most of which are based upon nonstandardized diagnostic procedures, do not take into account several parameters such as cost-effectiveness and quality of life (Springer and Subramanian 2014). Recently a large prospective double-blind study including more than 600 children with VUR who received either antimicrobial prophylaxis or placebo showed a significantly lower risk for recurrent UTI in the treatment group (The RIVUR trial investigators 2014; Couthard *et al*. 2008); the authors concluded that the "watchful waiting" approach without performing VCUG should be questioned. Still, the need for performing VCUG in the workup of febrile or of recurrent urinary tract infection remains controversial.

Familial VUR

The familial occurrence of VUR may justify the use of a screening procedure in order to detect affected siblings. For this purpose, US and direct radionuclide cystogram or ce-VUS appear to be the most appropriate techniques (Heale 1997; Fettich *et al*. 2003).

Secondary VUR

As mentioned above, VUR may be associated with voiding dysfunction; furthermore, VUR is frequently associated with bladder outlet obstruction whatever its origin or with neurogenic bladder disorders (Figs. 21 and 22). Therefore, a VCUG is the best adapted examination for evaluating these patients; furthermore, analysis of the micturition phase and evaluation of the urethra must be part of every VCUG (Van Gool 1995).

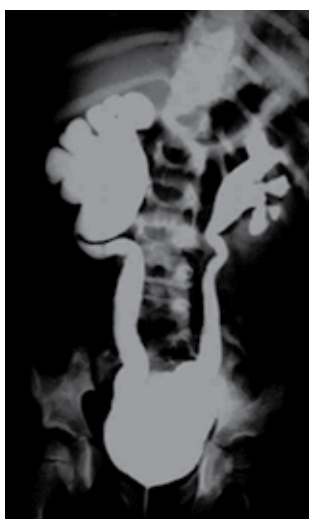

Fig. 21: Bilateral grade III VUR in a 12-year-old boy with neurogenic bladder.

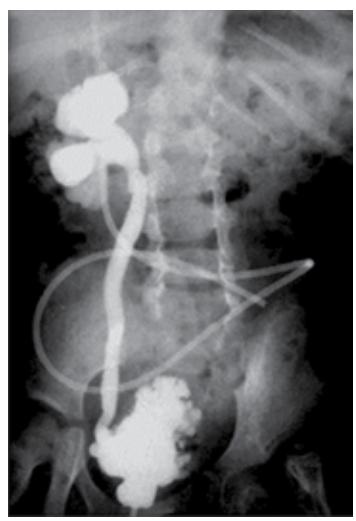

Fig. 22: Right grade III–IV VUR in an 8-year-old patient with neurogenic bladder and ventriculoperitoneal shunt.

Take Away

Vesicoureteric reflux is mainly detected during the workup of congenital uropathies, UTI, and bladder dysfunction.

Particular Presentations of VUR

Vesicoureteric Reflux and Pelvi-ureteric Junction Obstruction

The coexistence of VUR and pelvi-ureteric junction (PUJ) obstruction (PUJO) occurs in 10–14% of patients undergoing surgery for PUJO and in 1% of patients in whom VUR is detected (Fig. 23). In these patients, proper medical management will depend upon the accuracy of the evaluation. Imaging has to differentiate between a true PUJO associated with VUR (in which case, pyeloplasty should be performed first) and a pseudo-PUJO secondary to severe VUR, in which case ureteral reimplantation should be performed first (Bomalaski *et al.* 1997). On the VCUG, the VUR may sometimes hardly reach the dilated pelvicalyceal system. In case of complete obstruction, no urine will opacify the collecting system, whereas in pseudo-obstruction, some contrast will reach the dilated pelvicalyceal system (Fig. 24). In such patients, MRU shows at best the obstructed PUJ.

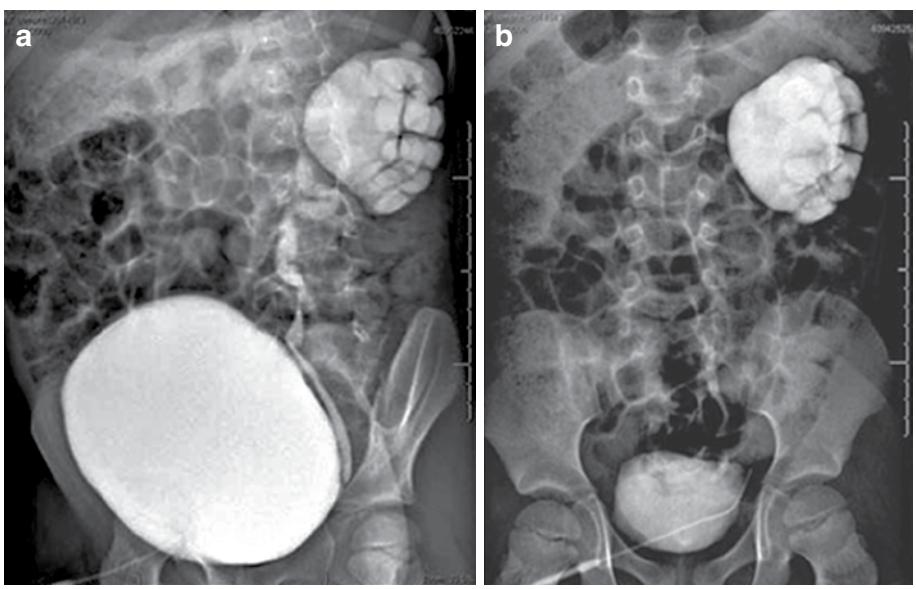

Fig. 23: VUR and PUJO on VCUG. (**a**) During the filling phase, the renal pelvicalyceal system appears markedly dilated compared with the mildly dilated ureter. (**b**) After micturition, the pelvicalyceal system remains dilated above the PUJ.

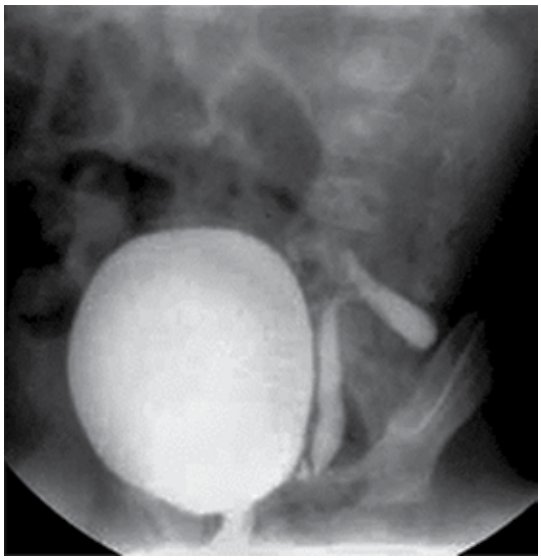

Fig. 24: VUR and PUJO. Neonatal left PUJO and VUR (antenatal diagnosis of UPJ obstruction). The refluxed urine merely reaches the dilated pelvicalyceal system due to the severe UPJ obstruction. This could be misdiagnosed as grade I.

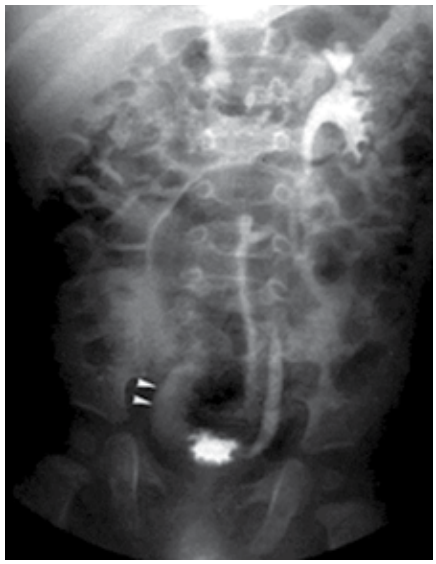

Fig. 25: VUR and UVJ obstruction; at VCUG: left grade II VUR; the right VUR is very subtle (*arrowheads*) because of the dilatation and obstruction of the ureter.

Vesicoureteric Reflux and Ureterovesical Junction (UVJ) Obstruction

Vesicoureteric reflux and obstruction at the ureterovesical junction (UVJ) may coexist; therefore, a VCU should be part of the workup of every dilated ureter. Also, the presence of an obstruction at the UVJ may lead to an underestimation of the degree of VUR; the refluxing contrast may show fluid levels and will dilute within the urine already present in the dilated ureter, and it may not be detected at all (Fig. 25). Furthermore, the VUR may not reach the pelvicalyceal system due to the marked ureteral dilatation. The proper surgical management of this association, if indicated, should include ureteral modeling along with reimplantation using an antireflux procedure.

Reflux and Lithiasis

The incidence of urolithiasis among patients with VUR is approximately 0.5%, whereas the incidence of VUR among patients with lithiasis is about 8%. Any functional or anatomical abnormality of the urinary tract that favors stasis of the urine facilitates the development of lithiasis (Fig. 26). Removal of the stone alone or removal together with a ureteral reimplantation must be discussed case by case (Kraus *et al*. 1999).

Vesicoureteric Reflux into an Unused Ureter

The normal downhill flow of urine from the kidney toward the bladder is one of the mechanisms preventing VUR. In case of diversion, renal transplant, or partial nephron-ureterectomy, urine may reflux from the bladder into the ureteral stump (Cain *et al*. 1998). It is best visualized on VCUG, but the condition may sometimes be identified on US (Fig. 27). In most cases, no further complication occurs. Rarely, suprainfection may occur, and in such cases, the stump may have to be removed or occluded by cystoscopic injection of bulking agents.

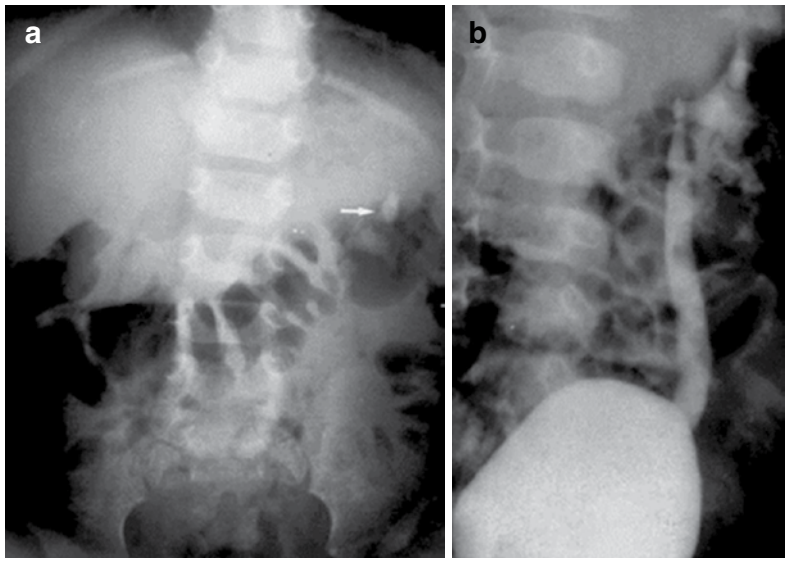

Fig. 26: VUR and lithiasis. (**a**) Plain film of the abdomen showing the lithiasis. (**b**) VCUG: left grade II.

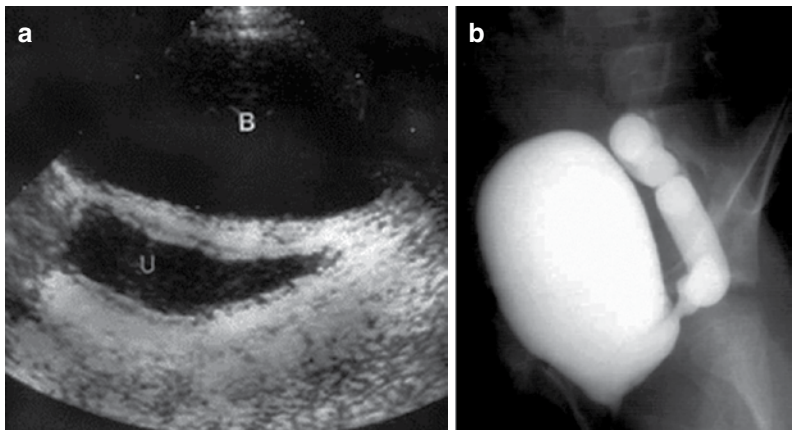

Fig. 27: VUR in unused ureter after upper pole heminephrectomy and partial ureterectomy. (**a**) On US, a dilated blind-ending ureter (*u*) is visualized behind the bladder (*B*); (**b**) On VCUG, reflux into the unused ureter.

Yo-yo Reflux

Yo-yo VUR refers to uretero-ureteric or pyelo-pelvic reflux occurring into incomplete duplex kidneys. The urine refluxes from one collecting system to the other, and surgery, if necessary, must be aimed at preventing this passage (Gonzales 1992).

The (So-called) Megacystis–megaureter Association

In the megacystis–megaureter association, massive bilateral grade IV or V VUR is present. During micturition, the bladder empties normally through the urethra but also through reflux into the ureters (Fig. 28a–d). At the end of micturition, the bladder is completely empty, but only for a very short time. It refills immediately with the refluxed urine; as such, the bladder is never really empty, and the volume of urine within the bladder increases continuously. A vicious circle begins, and the bladder wall thickens progressively because of increasing voiding difficulties (Willi and Lebowitz 1979; Lebowitz and Avni 1980). This diagnosis can be made already in the fetus: a large bladder and bilateral fetal uretero-hydronephrosis are present. In the megacystis–megaureter association, the amount of amniotic fluid is normal, and this helps to differentiate this entity from urinary dilatation secondary to posterior urethral valves in which oligohydramnios is more often present (Mandell *et al*. 1992).

Vesicoureteric Reflux and Duplex Kidneys

Vesicoureteric reflux may occur in both moieties of a duplex kidney, but it is much more frequent into the lower pole (Fig. 29). VUR in duplex systems is associated with the more lateral opening of the corresponding ureteral orifice. This type of VUR may be associated with renal damage at the corresponding lower moiety (reflux nephropathy; see below). Severe VUR into the lower pole system may be associated with significant urinary tract dilatation, which may obscure the presence of a duplex system. VUR into a lower moiety has a potential of spontaneous resolution just as VUR can spontaneously resolve into a single collecting system (Claudon *et al*. 1999).

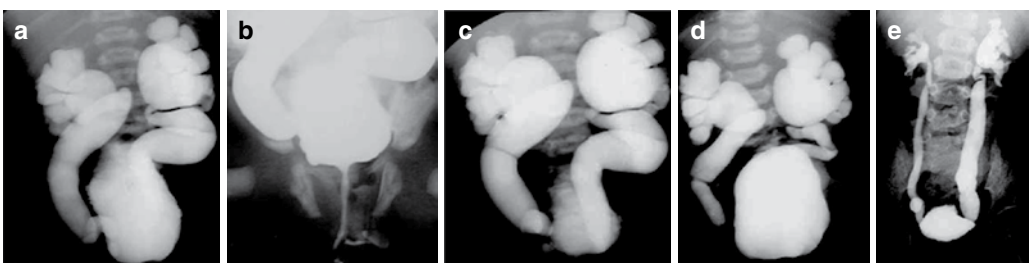

Fig. 28: VCUG, megacystis–megaureter association in a newborn girl. (**a**) Prevoiding: bilateral grade IV–V VUR. (**b**) Voiding: normal urethra. (**c**) Postvoiding: the bladder is almost empty, but the VUR has increased. (**d**) A few seconds later, the bladder has refilled with the refluxed urine. (**e**) At age 2, VUR is still present but has improved.

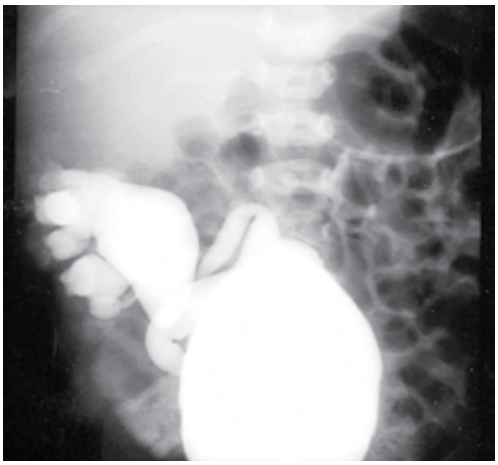

Fig. 29: Grade IV VUR into the lower pole of a right duplex system.

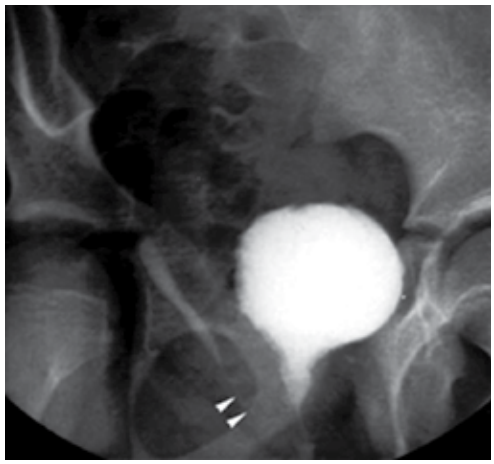

Fig. 30: VUR into a ureter that inserts at the level of the bladder neck.

Vesicoureteric Reflux into Ectopic Ureter

Vesicoureteric reflux into an ectopic ureter that opens into the urethra or near the bladder neck may be difficult to visualize during a conventional VCUG (Fig. 30). Cyclic filling of the bladder helps to demonstrate this condition, which is usually, but not always, associated with a duplex collecting system. A single-system ectopic ureter is usually associated with a markedly dysplastic kidney.

Iatrogenic VUR

Inadvertent catheterization of a ureterocele (Ucele) during a VCU may lead to VUR into an upper pole of a duplex kidney. Reflux into an upper pole also occurs after endoscopic unroofing of an ectopic Ucele (Fig. 31) (Blyth *et al.* 1993).

Vesicoureteric Reflux and Bladder Diverticulum

Bladder diverticulum reflects a weakness of the bladder wall. Its presence next to a ureteral orifice may lead to secondary VUR; the ureter is progressively included within the diverticulum (Figs. 32 and 33). In such a case, VUR will not resolve spontaneously and will require surgical correction (Blane *et al.* 1994).

Vesicoureteric Reflux in Case of Other Uropathies

Contralateral VUR may be present in about 10–20% of patients with multicystic dysplastic kidney (Fig. 34). VUR is also present in a significant number of other uropathies, i.e., horseshoe kidney,

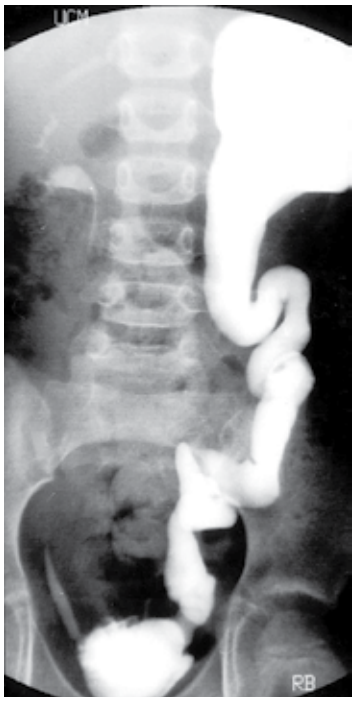

Fig. 31: Iatrogenic VUR. VUR into the left upper pole has occurred after endoscopic incision of an ectopic ureterocele.

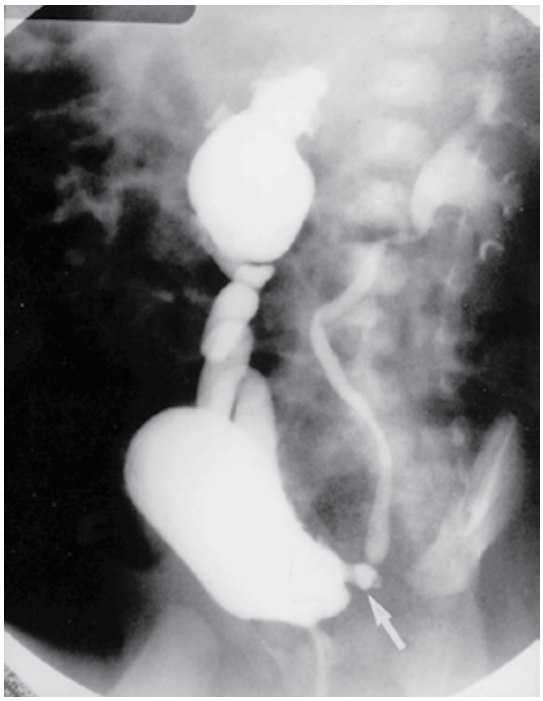

Fig. 32: VUR and bladder diverticulum. Bilateral VUR. Left grade II; a small diverticulum is also present (*arrow*).

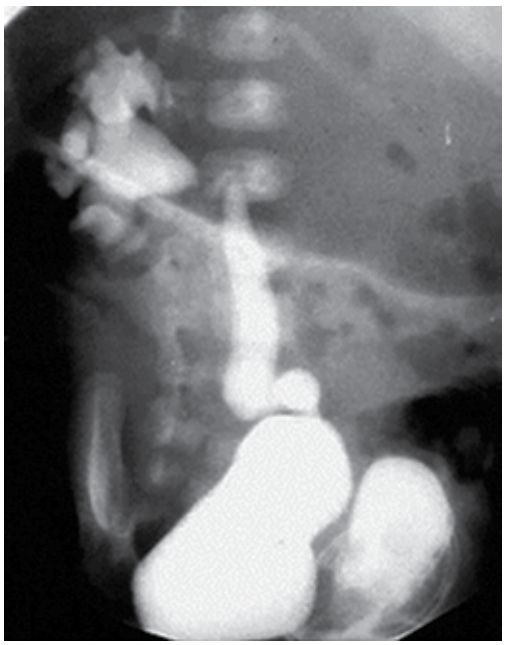

Fig. 33: VUR and large diverticulum; postvoiding film of a VCUG; a large diverticulum is filled along with the right grade III VUR.

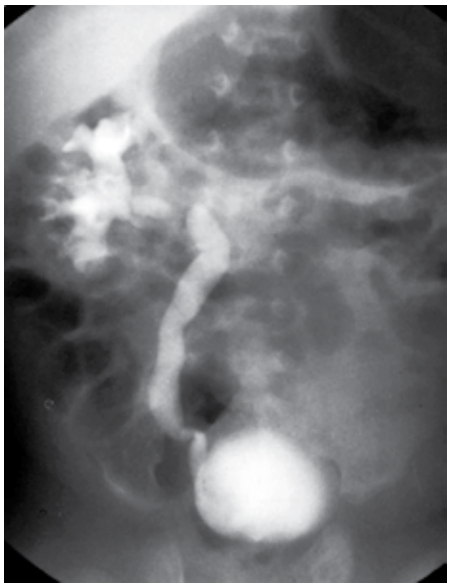

Fig. 34: Right grade II VUR in a case of a left multicystic dysplastic kidney.

crossed fused kidney, PUJ, and UVJ obstruction. Therefore, a VCU should be advised for a complete workup in complicated cases (Atiyeh *et al.* 1992; Ring *et al.* 1993; Song *et al.* 1995; Avni *et al.* 1997; Cascio *et al.* 1999).

Fetal Reflux

Primary fetal reflux is one of the most common causes of fetal renal dilatation. As mentioned above, gross dilatation resulting from high-grade reflux occurs essentially in baby boys. In utero VUR may also be secondary and associated with bladder outlet obstruction and especially with posterior urethral valves (Kaefer *et al.* 1995; Sillen *et al.* 1992).

Take Away

Vesicoureteric reflux may be an isolated finding, but it may also be encountered in many other circumstances. Its management must be adapted to each individual presentation.

Natural History, Treatment, and Follow-up of VUR

Conservative Treatment

For years, the proper treatment of VUR has been controversial, and attitudes have varied (Weiss *et al.* 1992; Smellie *et al.* 1992). Antenatal diagnosis of VUR in asymptomatic patients has brought dramatic modifications in the management of VUR. In infants, several retrospective and

prospective studies have shown the potential for spontaneous resolution of a large number of primary VURs (Assael *et al.* 1998; Yu *et al.* 1997; Ismaili *et al.* 2006a, b). Among infants, VUR tends to resolve or at least to improve markedly in 75% of the patients within 2–3 years; higher grades of VUR (grades IV–V) resolve to a lesser extent than VUR of low or moderate grades (I–III) (Fig. 28e) (Herndon *et al.* 1999).

Following all the data that has been accumulated, the presently accepted attitude tends much more toward medical than surgical management of VUR. Patients with high-grade VUR (III–V in boys, IV–V in girls) are placed under prophylactic antibiotherapy and followed, clinically and with imaging, up to the moment they are toilet trained. Renal growth can be monitored by US every 6–12 months; if needed renal function is controlled by Tc^{99m}-ECD or Tc^{99m}-MAG3 used simultaneously with Cr-EDTA.

The same scheme can be applied to VUR into both moieties of the duplex collecting system or into the lower pole of a duplex system.

After that the patients are toilet trained and if no complication has occurred, no further follow-up is needed (Robinson *et al.* 2014; Springer and Subramanian 2014; Arlen *et al.* 2015; Hari *et al.* 2015).

In older children, the attitude must be adapted to the previous history of the patient and to the clinical data. Medical treatment should be favored as much as possible. However, recurrent UTI, poor renal growth, and poor social environment would be arguments toward proposing an alternative treatment. Whenever a voiding dysfunction is also present, resolution of the VUR will be achieved only if the voiding anomaly is managed at the same time (Sillen 1999a).

Surgical Treatment

As mentioned above, surgical treatment of VUR should be considered whenever conservative treatment has not been successful or cannot be conducted satisfactorily. This includes patients in whom decreasing renal function is observed, patients presenting recurrent UTI under correct antibiotic therapy, and patients whose family members are unable to follow the conservative treatment. The presence of bladder diverticula would also require surgical treatment of VUR. In all patients with secondary VUR, proper management of the anomaly that has resulted in VUR should be considered before treating the VUR (Jodal *et al.* 1999; Jodal and Lindberg 1999).

Ultrasound is usually sufficient for the postsurgical follow-up and demonstrates well the ureteral reimplantation; immediate postoperative dilatation is almost always present but usually transient. In any abnormal clinical course or if the dilatation increases, MRU may be necessary for the proper management of the patients in order to exclude hematoma or urinary leakage (Rypens *et al.* 1992).

Endoscopic Treatment

The injection under the ureteral orifice bulking agents has been proposed as an alternative to surgery. The results in terms of short-term VUR resolution are similar to the success rate of surgery.

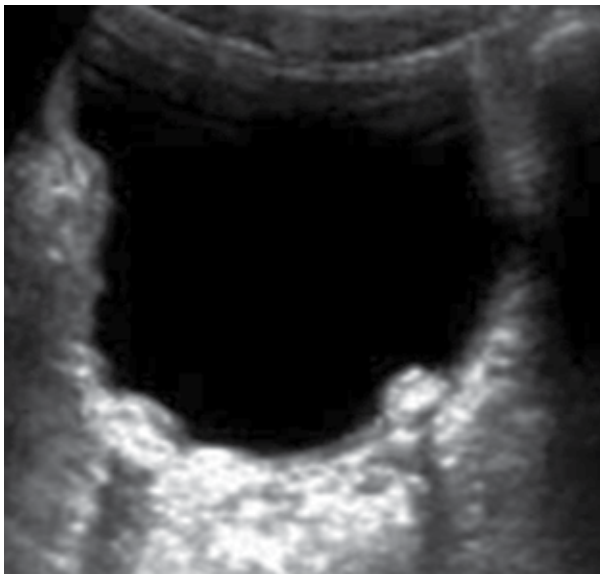

Fig. 35: Injection of antireflux bulking material on US – transverse scan of the bladder. Echoic nodules are visible at both UVJ with acoustic shadowing.

Injections should be proposed to non-resolving low-grade VUR associated with recurrent UTI.

The paste injected under the ureteral orifice is well demonstrated on US studies (Fig. 35). US studies are also helpful in order to demonstrate the rare cases of complications (persisting obstruction). In long-term studies, granuloma-like masses can be found on US studies; they appear as highly dense nodules on CT (Rypens *et al.* 1992; Läckgren *et al.* 1999; Schulman *et al.* 1990).

Complications of VUR

The aim in detecting VUR and initiating rapidly a prophylactic treatment is to prevent long-term complications (Arant 1991; Olbing *et al.* 1992; Bailey *et al.* 1992; Goldraich and Goldraich 1992; Merrick *et al.* 1995). This topic has been and remains controversial. The main concern remains understanding the factors that lead to the development of renal scars, the so-called reflux nephropathy (RN), and preventing complications such as renal hypertension, complicated pregnancies, renal failure, and finally end-stage renal disease (Jungers *et al.* 1996). The role of imaging is first to detect all patients at risk (having VUR or congenital dilating uropathies) and then those that have already developed RN (Jakobsson *et al.* 1999; Gordon 1995; Caione *et al.* 2004).

Take Away

Vesicoureteric reflux tends to resolve spontaneously in a large number of patients; therefore, a conservative treatment of VUR is preferable. Follow-up is achieved by US, isotopes, and optimized VCUG.

Fetal Reflux Nephropathy

It was long thought that renal scars occur only following a UTI. The antenatal diagnosis of fetal uropathies has revealed that renal damage/dysplasia already exists at birth with no relation to UTI. In utero, VUR has deleterious effects on renal parenchyma, probably due to backward high pressure. This leads to reduced renal growth (Najmaldin *et al*. 1990). Many of the kidneys with fetal RN already show reduced function on isotopic studies in the neonatal period (Assael *et al*. 1998). On imaging, the kidney appears small and irregular with a cortical thinning (Fig. 18). The pyelocalyceal system may be dilated and clubbed. The presence of fetal RN may explain why patients with congenital uropathies that are protected by prophylactic antibiotic therapy nevertheless progress toward renal failure (Mana *et al*. 2004; Caione *et al*. 2004; Gobet *et al*. 1999; Stock *et al*. 1998).

Imaging RN and the Progression of Renal Disease

Dimercaptosuccinic acid scanning is considered as the gold standard technique for the demonstration of RN lesions. DMSA has the advantage of being a low-irradiating technique with a high rate of detection of late sequelae (Fig. 20). However, it brings no information on the pelvicalyceal system. It is less accurate in case of poor renal function. US can demonstrate the typical lesions of RN: cortical thinning and irregularities (Fig. 37). However, compared to DMSA, US is not accurate enough for assessing the number and extent of renal scars (Stokland *et al.* 1999). Another difficulty for US is to differentiate scars from fetal lobulation and interrenicular fat deposition. The role of US is mainly to monitor renal growth. MR urography can also display the parenchymal lesions (Koyicigit *et al*. 2014) (Fig. 18).

Magnetic resonance urography has been shown to demonstrate RN. The technique appears accurate for demonstrating both the scars and the pelvicalyceal system (Figs. 35, 36, and 37a). The technique could develop as the gold standard once it becomes more accessible (Chan *et al*. 1999). Some patients with RN may progress toward renal failure, as progressive glomerulosclerosis and fibrosis develop in the damaged kidney (Matsuoka *et al*. 1994; Bernstein and Arant 1992). Compensatory hyperfiltration may occur in less damaged areas, detectable on US studies as diffuse or localized cortical hyperechogenicity (Figs. 37b and 38) (Damry *et al*. 2005). These areas should not be misinterpreted as renal tumors.

Take Away

The role of imaging is to detect not only VUR but also its complications: reflux nephropathy. Presently, DMSA scanning and MRU are the best techniques available for this purpose.

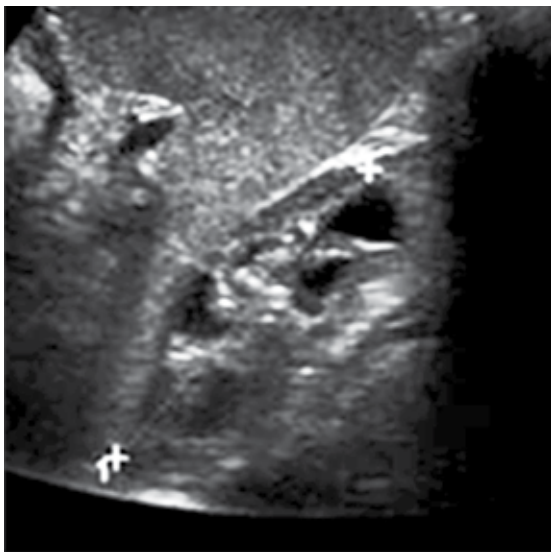

Fig. 36: Reflux and UTI nephropathy. An 8-year-old boy with long history of VUR and recurring UTI. Sagittal scan of the left kidney with irregular thinning of the parenchyma.

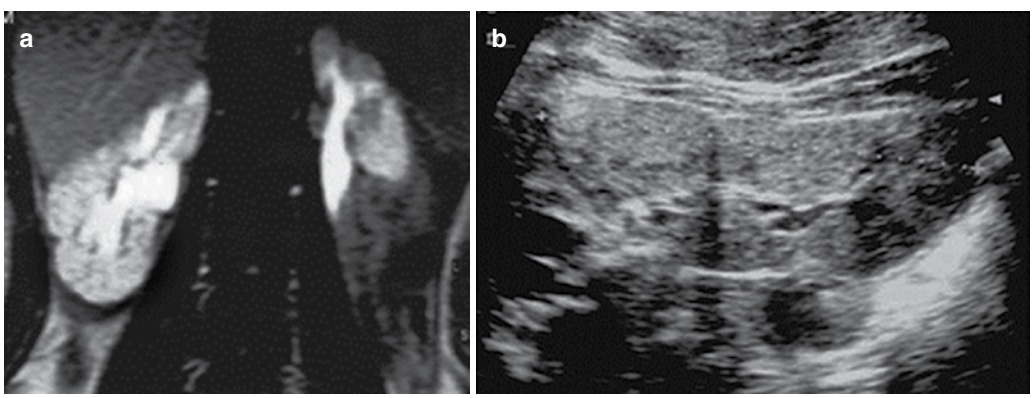

Fig. 37: Reflux nephropathy in a 9-year-old girl with known VUR and hypertension. (**a**) MRU: typical scarred kidney and clubbed pelvicalyceal system (TFE T1 sequence with gadolinium). (**b**) US: sagittal scan of the right kidney; diffuse hyperechogenicity of the renal cortex in association with glomerular hyperfiltration.

Conclusion

Voiding cystourethrography is the main investigation that can be used in order to detect VUR. US is used for monitoring renal growth and postoperative settings; however, ce-VUS is an alternative for detecting and documenting as well as grading VUR. DMSA scan, at present, and MRU, probably more in the future, are used as complementary examinations in order to detect the patients at risk for further complications.

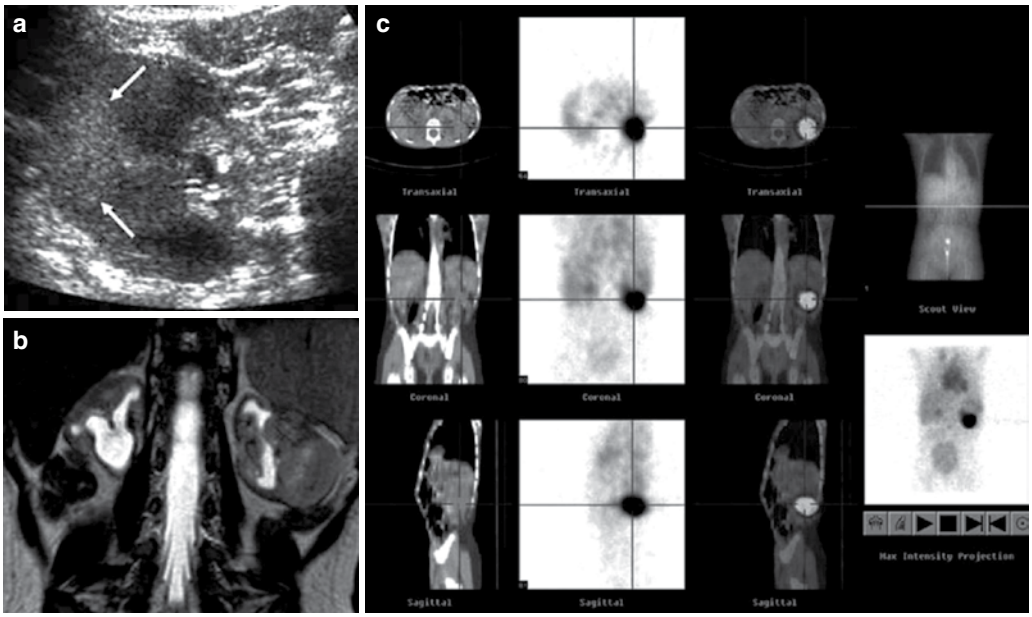

Fig. 38: Localized pseudotumoral pattern of glomerular hyperfiltration in a case of reflux nephropathy. (**a**) US: transverse scan of the left kidney; hyperechoic ill-defined area in the external part of the kidney (marked by *arrows*). (**b**) MRU: T2-weighted sequence displays bilateral small irregular kidneys with distorted pelvicalyceal systems and a "tumoral" appearance of the left kidney. (**c**) Tc^{99m}-DMSA–SPECT-CT: the outer part of the left kidney highlights suggesting hyperfunction.

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Endovascular Treatment of Ureteroarterial Fistula Using A Covered Stent, Evaluated by Intravascular Ultrasound: A Case Report

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Abstract

Background: Ureteroarterial fistula is a rare life-threatening complication of indwelling ureteral stents. The mechanism has not yet been fully evaluated using intravascular imaging.

Case presentation: An 84-year-old female was referred to our unit because of large volume pulsatile bleeding from the left ureter during routine stent exchange in the urology department. The hematuria was initially managed by rapidly exchanging for a new stent; however, the patient went into hypovolemic shock due to acute blood loss. The patient underwent implantation of the bilateral ureteral stents due to urinary retention caused by retroperitoneal fibrosis 2 years ago. To prevent ureteral infection, occlusion of the stents and stone formation, the stents were exchanged every 6 months. Computed tomography revealed contact between the left ureter and the common iliac artery. Therefore, ureteroarterial fistula was suspected and endovascular therapy was performed. Although angiography did not show definite blood flow into the ureter, a soft guidewire was advanced from the subintima of the external iliac artery to the left ureter. The diagnosis of ureteroarterial fistula was confirmed. Intravascular ultrasound identified the stent in the ureter and its connection to the subintima of the external iliac artery. The ureter did not contact directly to the inner lumen of the iliac arteries according to the ultrasound findings; therefore, we considered that the risk of stent-graft infection might not be high. After coil embolization of the ipsilateral internal iliac artery, a covered stent was implanted in the external iliac artery to seal the

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subintimal entry. The patient had no further episodes of any gross hematuria on dual anti-platelet therapy, when the ureteral stent was exchanged three time during 1 year after the endovascular therapy.
Conclusions: We demonstrated a case of ureteroarterial fistula, in which intravascular ultrasound allowed to visualize the communication between the ureter and the subintimal lumen in the external iliac artery.

Keywords: Ureteroarterial fistula, Endovascular therapy, Covered stent-graft, Coil embolization, Intravascular ultrasound

Background

Ureteroarterial fistula (UAF) is an uncommon condition first described in 1908 by Moschcowitz (Moschcowitz 1908). It occurs as a result of a fistulous communication between a ureter and an aorta or iliac artery. UAF is classified into primary (15%) and secondary (85%) types based the cause (Pillai *et al*. 2015). Secondary causes result from pelvic cancer (70.3%) and prior interventions including surgery (69.5%) combined with radiation (48.3%), and the most common risk factor was presence of a chronic indwelling ureteral stent (73.7%) (Das *et al*. 2016). The mechanical fixation of the ureter appears to lead to inflammation and fibrosis in the adjacent artery during pulsation; however, the mechanism has not yet been fully evaluated using intravascular imaging. We report a case of UAF caused by a ureteral stent placement in which intravascular ultrasound (IVUS) was used to evaluate the communication through the subintimal lumen of the external iliac artery (EIA).

Case Presentation

An 84-year-old female was referred to our unit after the urologist encountered large volume pulsatile bleeding from the left ureter during routine stent exchange. The hematuria was initially managed by rapidly exchanging for a new stent; however, the patient went into hypovolemic shock due to acute blood loss. The patient had a history of urinary retention due to retroperitoneal fibrosis caused by immunoglobulin G4-related disease 2 years ago. Ureteral stents were placed in the patient's bilateral ureters. To prevent ureteral infection, occlusion of the stents and stone formation, the stents were exchanged every 6 months. After the hematuria, computed tomography (CT) scan did not show the injury of the left kidney and ureter; however, revealed contact between the ureter and common iliac artery (CIA) (Fig. 1a-b, axial imaging in Additional file 1: Movie S1 and sagittal in Additional file 2: Movie S2). Therefore, UAF was suspected. In order to facilitate the need for ongoing exchanges of the ureteral stent in the future, endovascular therapy (EVT) was performed. A 6.0-Fr sheath was placed via the left common femoral artery and a 4.5-Fr guiding sheath with a length of 120 cm was inserted via the left radial artery. Baseline angiography did not show blood flow into the ureter from iliac arteries (Fig. 2a and Additional file 3: Movie S3) (Das *et al*. 2016). The CIA and EIA were too large for OPTICROSS IVUS™ compatible with 0.014-

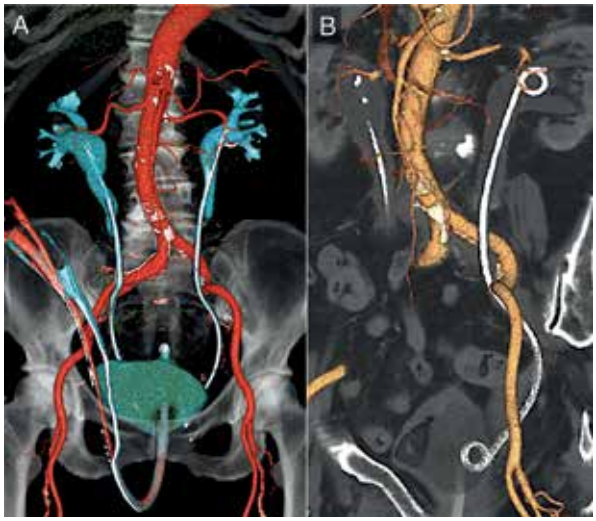

Fig. 1: Computed tomography after the hemostasis of hematuria. **a** Computed tomography (CT) showed the crossing of the left ureter with a stent over the distal common iliac and internal iliac arteries. **b** CT imaging in the angulated 30-degree left anterior oblique position.

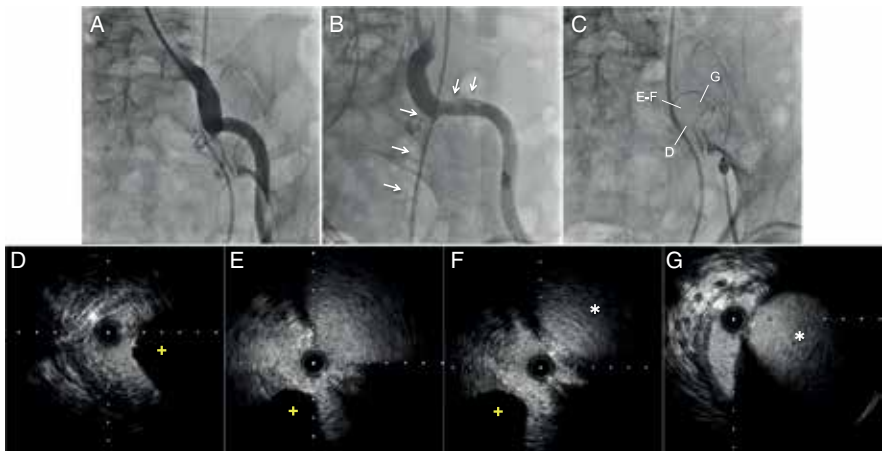

Fig. 2: The endovascular procedure and the findings of intravascular ultrasound. **a**. Baseline angiography did not show the blood flow into the left ureter from the left iliac arteries. **b** and **c** A 0.014-in. guidewire was advanced into the left ureter along the stent from the subintimal lumen of the external iliac artery (*white arrows*). The anatomical findings were evaluated by intravascular ultrasound (IVUS). **d** IVUS detected the stent with an acoustic shadow (*yellow plus signs*) in the left ureter. **e**–**g** IVUS detected the communication between the ureter and subintimal lumen of the EIA (*white asterisks denote true lumen of the left external iliac artery*).

wires (Boston Scientific, MA, US) to identify the connection of the UAF. Next, we considered that angiography via a micro-catheter could evaluate the connection between the internal iliac artery (IIA) and the left ureter. We attempted to advance a 0.014-in. Gladius guidewire™ (Asahi Intecc, Aichi, Japan) to the IIA; however, the wire proceeded from the EIA to the left ureter unintentionally (Fig. 2b and c). The diagnosis of UAF was confirmed. IVUS allowed to visualize the stent in the ureter and the subintimal lumen of the EIA without evidences of a definite tract and aneurysm in the connection (Fig. 2d-g and Additional file 4: Movie S4). As mechanical stimulation of the

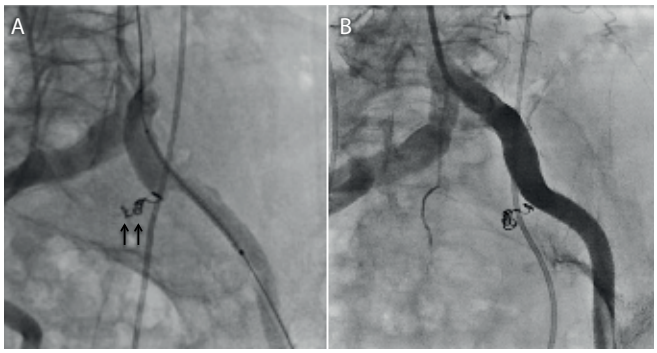

Fig. 3: Implantation of the covered stent and coil embolization. **a** A Viabahn stent graft of 9.0 × 50 mm was implanted to cover from the crossing of the left ureter and iliac artery to the distal entry of the subintimal lumen (*black arrows denote coils in the left internal iliac artery*). **b** The final angiography revealed complete closure of the subintimal lumen and the internal iliac artery.

ureteral stent could enlarge the subintimal space of the iliac arteries and cause a new UAF to the ipsilateral IIA in the future, coil embolization of the IIA was performed using three Interlocking Detachable Coils™ (two 2.0 mm × 4.0 cm and one 3.0 mm × 6.0 cm; Boston Scientific, MA, US) via the 4.5-Fr guiding sheath. The ureter did not contact directly to the inner lumen of the iliac arteries according to the IVUS findings; therefore, we considered that the risk of stent-graft infection might not be high. Then, after replacing the 6.0-Fr with a 9.0-Fr sheath, a Viabahn covered stent™ of 9.0 × 50 mm (W.L. Gore & Associates, Flagstaff AZ, US) was implanted from the common iliac artery (CIA) to the entry of the subintima in the EIA (Fig. 3a). Because angiography revealed type I endoleak into the EIA, an Assurant balloon-expandable stent™ of 10 × 30 mm (Medtronic, Frauenfeld, Switzerland) was implanted in the proximal portion of the CIA to press the covered stent to the arterial wall. Final angiography showed closure of the IIA, subintimal lumen, and endoleak (Fig. 3b). The left ureteral stent was exchanged immediately after the EVT, and hematuria did not occur. The patient had no major post-operative complications and was discharged from the hospital. The ureteral stents were exchanged three time during 1 year after the EVT, and the patient had no further episodes of any gross hematuria on dual anti-platelet therapy. The left ankle brachial index was within normal limit at 1 year after the EVT.

Discussion

Ureteroarterial fistula is a rare complex problem involving multiple organ systems, usually occurring in patients with significant comorbid conditions due to malignancy, irradiation, previous surgical interventions and indwelling ureteral stents (Das *et al.* 2016; Turo *et al.* 2018). A previous report demonstrated that a pseudoaneurysm was detected in up to 38% of cases with UAF, and CT could show an enhancing mass near the crossing of the ureter (Van den Bergh *et al.* 2009). However, the reported diagnostic rates with CT are only 42–50% in cases without aneurysms, because it is often difficult to detect a direct fistulous communication between the artery and ureter via cross-sectional imaging (Van den Bergh *et al.* 2009). The current review demonstrated that the angiography was the best modality for the diagnosis of UAF; however, the angiography could detect the bleeding in still only 72.4% (Das *et al.* 2016). Contrast extravasation into the ureter might not occur when a ureteral stent or clots are at the site and tamponade the leak. Although the baseline angiography did not reveal the definite blood flow into the ureter and EIA

in our case, the soft wire proceeded into the ureter from the EIA through the subintimal lumen which was visualized by the IVUS. The subintimal lumen of EIA might be made by the stimulation of the ureteral stent, and this was one of the mechanisms of UAF after ureteral stent implantation. To the best of our knowledge, our case report is the first to demonstrate the morphological findings of UAF using intravascular imaging. Although the diagnosis was made by unintentional wire crossing of UAF in the present case, it would be preferable that imaging examinations confirmed the evidence of UAF before the interventions. Vision PV-.035 IVUS™ compatible with 0.035-in. wires (Philips/Volcano, Amsterdam, the Netherlands) might be effective to observe the whole walls of iliac arteries because the penetration depth is superior to that with 0.014-in. wires.

Treatment of UAF includes excision of the involved arterial segment with extra-anatomic bypass or primary repair. However, open surgical repair is often difficult, because the patients have a history of pelvic intervention and hemodynamic instability due to hemorrhage (Fox *et al.* 2011). Therefore, an endovascular approach using covered stents and coil embolization has become the treatment of choice for UAF (Van den Bergh *et al.* 2009). Previous studies have reported that the immediate success rate of EVT using stent-graft or metallic stents was 85%–100% (Fox *et al.* 2011; Okada *et al.* 2013). However, the hematuria recurrence-free rates at 1 and 2 years were 76.2% and 40.6%, respectively (Okada *et al.* 2013). The mechanism of this high recurrence rate appears to be the ongoing process of inflammation and advancement of malignancy. The stent grafts are more preferable to prevent re-bleeding than metallic stents; however, have inherent risk of recurrent infection (Fox *et al.* 2011). In this case, IVUS revealed that the ureter had the communication to the retrograde subintimal space of the let EIA; therefore, the stent graft did not touch the ureter and the ureteral stent directly. We considered that the stent graft might not be affected by the post-operative urinary infection. Moreover, the present case report suggests that the re-bleeding could be owing to the late enlargement of the subintimal space of iliac arteries caused by the friction injury of the ureteral stent. Because angiography and IVUS detected the entry of the subintimal space in the EIA 25.0 mm distal from the crossing of the ureter, a covered stent with a length of 50.0 mm was implanted to seal both the crossing and the distal subintimal entry. In addition, because the subintimal lumen could advance into the ipsilateral IIA in the future, coil embolization of the IIA was performed before stent-graft implantation.

Another issue of the EVT is re-occlusion of iliac arteries; however, the previous report demonstrated that limb ischemia was more common with surgical repair (67%) than the EVT (50%) in cases with UAF (Fox *et al.* 2011). Moreover, the primary patency after stent-graft implantation was superior to that after metallic stents in iliac arteries (Bracale *et al.* 2019). Because the dual-antiplatelet therapy at least 6 months could provide the high primary patency rate of stent grafts in iliac arteries (Bracale *et al.* 2019), we considered that the EVT using Viabahn covered stent™ might be the appropriate treatment in the present case.

Conclusions

We demonstrated a case of UAF, in which IVUS allowed to visualize the communication between the ureter and the subintimal lumen in the EIA. The fistula could be treated using a covered stent

and coil embolization; however, careful follow-up is necessary because the subintimal lumen may be enlarged by the stress of ureteral stents.

Abbreviations
CIA: Common iliac artery; CT: Computed tomography; EIA: External iliac artery; EVT: Endovascular therapy; IIA: Internal iliac artery; IVUS: Intravascular ultrasound; UAF: Ureteroarterial fistula

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Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions
KH, TF and MM analyzed and interpreted the patient data regarding the endovascular therapy and the clinical course. KH wrote the article. KS analyzed and interpreted the patient data regarding the urological management. NI is expected to have drafted the work and substantively revised the work. All authors read and approved the final manuscript.

Ethics approval and consent to participate
The case report was approved by the institutional review board of our hospital, and the approval number is 27–33.

Consent for publication
Written informed consent for publication was obtained from the patient.

Competing interests
The authors declare that they have no competing interests.

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*Konstantinos Dimitropoulos and Stavros Gravas , Fixed-dose combination therapy with dutasteride and tamsulosin in the management of benign prostatic hyperplasia Ther Adv Urol. 2016 Feb; 8(1): 19–28.
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