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Narrow-Band Imaging (NBI) and White Light (WLI) transurethral resection of the bladder in the treatment of non-muscle-invasive bladder cancer

Emanuele Montanari, Jean de la Rosette, Fabrizio Longo,
Alberto Del Nero, Pilar Laguna

Effects of ankle position on pelvic floor muscle electromyographic activity in female stress urinary incontinence: Preliminary results from a pilot study

Maria Angela Cerruto, Ermes Vedovi, William Mantovani,
Carolina D'Elia, Walter Artibani

Urinary apparatus tumours and asbestos: The Ramazzini Institute caseload

Michelina Lauriola, Luciano Bua, Daniela Chiozzotto, Fabiana Manservigi,
Achille Panetta, Giuseppe Martorana, Fiorella Belpoggi

Critical points in understanding the italian version of the IIEF 5 questionnaire

Carolina D'Elia, Maria Angela Cerruto, Francesca Maria Cavicchioli,
Sofia Cardarelli, Alberto Molinari, Walter Artibani

Laparoscopic-endoscopic single-site surgery retroperitoneal ureterolithotomy: Technique and initial experience

Volkan Tugcu, Bircan Mutlu, Volkan Yollu,
Mehmet Yucel, Ali Ihsan Tasci

Solitary lung metastasis after radical prostatectomy in presence of undetectable PSA

Pietro Pepe, Filippo Fraggetta, Francesco Tornabene,
Maurizio Nicolosi, Francesco Aragona

Robotic malfunction during live robotic urologic surgery: Live surprise in a robotic surgery congress

Volkan Tugcu, Bircan Mutlu, Abdullah Erdem Canda,
Erkan Sonmezay, Ali Ihsan Tasci

Spontaneous postmenopausal urethral prolapse: A case report and review of literature

Ugur Yucetas, Muhsin Balaban, Alper Aktas, Bulut Guc

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Contents

Narrow-Band Imaging (NBI) and White Light (WLI) transurethral resection of the bladder in the treatment of non-muscle-invasive bladder cancer	Pag. 179
Emanuele Montanari, Jean de la Rosette, Fabrizio Longo, Alberto Del Nero, Pilar Laguna	
Effects of ankle position on pelvic floor muscle electromyographic activity in female stress urinary incontinence: Preliminary results from a pilot study	Pag. 184
Maria Angela Cerruto, Ermes Vedovi, William Mantovani, Carolina D'Elia, Walter Artibani	
Urinary apparatus tumours and asbestos: The Ramazzini Institute caseload	Pag. 189
Michelina Lauriola, Luciano Bua, Daniela Chiozzotto, Fabiana Manservigi, Achille Panetta, Giuseppe Martorana, Fiorella Belpoggi	
Critical points in understanding the italian version of the IIEF 5 questionnaire	Pag. 197
Carolina D'Elia, Maria Angela Cerruto, Francesca Maria Cavicchioli, Sofia Cardarelli, Alberto Molinari, Walter Artibani	
Laparoscopic-endoscopic single-site surgery retroperitoneal ureterolithotomy: Technique and initial experience	Pag. 202
Volkan Tugcu, Bircan Mutlu, Volkan Yollu, Mehmet Yucel, Ali Ihsan Tasci	
Solitary lung metastasis after radical prostatectomy in presence of undetectable PSA	Pag. 208
Pietro Pepe, Filippo Fraggetta, Francesco Tornabene, Maurizio Nicolosi, Francesco Aragona	
Robotic malfunction during live robotic urologic surgery: Live surprise in a robotic surgery congress	Pag. 211
Volkan Tugcu, Bircan Mutlu, Abdullah Erdem Canda, Erkan Sonmezay, Ali Ihsan Tasci	
Spontaneous postmenopausal urethral prolapse: A case report and review of literature	Pag. 214
Ugur Yucetas, Muhsin Balaban, Alper Aktas, Bulut Guç	
Selected papers from 18th National Congress SIEUN	Pag. 216
17-19 May 2012 - Stresa	

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Via Bassini 41 - 20133 Milano, Italy
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Narrow-Band Imaging (NBI) and White Light (WLI) transurethral resection of the bladder in the treatment of non-muscle-invasive bladder cancer

Emanuele Montanari¹, Jean de la Rosette², Fabrizio Longo¹,
Alberto Del Nero¹, Pilar Laguna²

¹ Urological Department - Medical School of Medicine University of Milan DISS A.O. S. Paolo - Milano, Italy;

² Urological department - Academic Medical Centre Amsterdam - Amsterdam - The Netherlands.

Summary

Objective: Narrow-Band Imaging (NBI) is an optical image enhancement technology that narrows the bandwidth of the light output from the endoscopy system to 415 nm and 540 nm. The aim of the present study is to evaluate the feasibility of NBI transurethral resection of the bladder (TURB NBI) compared to in White Light (TURB WLI) (Feasibility study) and the recurrence rate at the 1-year follow-up in patients treated for non-muscle-invasive bladder cancer (NMIBC) (Recurrence study).

Methods: A total of 92 patients with a suspicion of primary or recurrent bladder cancer were prospectively enrolled in our study. Forty-five were consecutively enrolled to undergo WLI TURB and 47 consecutively to undergo NBI TURB. All patients underwent routine follow-up with flexible WLI cystoscopy every 3 months during the first year and every 6 months during the second year, supplemented by urine examination, urine culture, and bladder washout cytology.

Results: Type I-II complications were reported in 12 patients in the NBI group (25%) and in 10 patients in the WLI group (22%). Patients with High Grade NMIBC who underwent a second look WLI TURB had residual disease in 33% of NBI group and in 43% of WLI group. The recurrence rate at one year follow-up was 35% in NBI group and 50% in WLI group. No statistic significance can be issued for the clinical differences observed.

Conclusions: TURB performed entirely by the NBI technique is feasible and safe. It guarantees a complete and rapid resection of good quality from a pathological point of view. Moreover, the technique is relatively inexpensive with respect to other methods proposed to enhance the detection rate, for which data on operative endoscopy are lacking. In our clinical experience, even if not statistically significant, NBI TURB reduces at one year follow up the recurrence rate of bladder NMI tumours when compared to WLI TURB (35% vs. 50%). Other larger, randomized, prospective trials with longer follow-up periods are required to confirm our outcomes.

KEY WORDS: Non-muscle-invasive bladder cancer; Transurethral resection of the bladder; Narrow-Band Imaging; Complications; Recurrence.

Submitted 3 August 2012; Accepted 31 October 2012

INTRODUCTION

Narrow-Band Imaging (NBI) is an optical image-enhancement technology that narrows the bandwidth of the light output from the endoscopy system to 415 nm and 540 nm. This restriction is obtained by interposing the specific filters after the emission of white light from the xenon lamp. At this range the light is strongly absorbed by haemoglobin enhancing the visibility of

surface capillaries and blood vessels in the submucosa. The blue light (415 nm) enhances the superficial capillary network, the green light (540 nm) the visibility of deeper vessels (1). The NBI filters are switched on and off on the xenon light source or directly on the endoscope. Diagnostic and operative procedures can be then be performed in White Light (WLI) and NBI easily

switching from one to the other when and if necessary. NBI provided excellent results in digestive endoscopy, allowing a more accurate prediction of Barrett esophagus and improving the ability to distinguish neoplastic and non-neoplastic colorectal polyps during screening colonoscopy (2, 3). The introduction of this method to endourology is recent and – for now – NBI promises to be a simple and repeatable method with a low learning curve (4).

The current diagnostic and therapeutic “gold standard” for non-muscle-invasive bladder cancer (NMIBC) is WLI cystoscopy and WLI transurethral resection of the bladder (TURB). Both of these methods have some limits in detection of small papillary tumours, carcinoma in situ (CIS), and residual tumours. NBI can increase the detection rate (DR) of bladder tumours, both as a first diagnosis and during follow-up. Various studies demonstrate the superiority of NBI cystoscopy compared to WLI cystoscopy, in the diagnosis of small papillary tumours and CIS (5-7). The increment of the DR can reduce non-diagnosed lesions, recurrences and progression rates. Moreover from an operative point of view TURB NBI is a safe and accurate technique (8) with a lower residual tumour rate (9).

The aim of the present study is to evaluate the feasibility of TURB NBI compared to TURB WLI (Feasibility study) and the recurrence rate at the 1-year follow-up in patients treated for NMIBC (Recurrence study).

PATIENTS AND METHODS

From January 2010 to July 2011, 92 patients with a suspicion of primary or recurrent bladder cancer were prospectively enrolled in our study. Forty-five were consecutively enrolled to undergo WLI TURB and 47 consecutively to undergo NBI TURB. The study was conducted in accordance with *Good Clinical Practice and the 1964 Declaration of Helsinki*; all patients signed an informed consent before the procedure was performed. The patients underwent preliminary outpatient WLI cystoscopy.

The NBI patient group underwent the endoscopic procedure performed entirely by NBI (from the introduction of the resectoscope to the final cauterization) without switching to the WLI procedure. The WLI patient group was treated entirely by means of the traditional TURB WLI. The same surgeon (F.L.) performed all the TURB procedures; in both cohorts, the Olympus 24 F resectoscope with 12° optics and an endoscopic Olympus Exera II column with a xenon light source and a video processor were adapted for both NBI and WLI visualization. The specimen of each lesion was analysed individually by a pathologist who was blinded to the mode of identification of the single lesion (by WLI or NBI). Histopathologic staging and grading were based on the TNM 2002 and WHO 2004 guidelines.

The necessity of subsequent endovesical chemo/immunotherapy was determined by applying the recurrence risk classification described by the *European Organization for Research and Treatment of Cancer* (EORTC) (10).

All patients underwent routine follow-up with flexible WLI cystoscopy every 3 months during the first year and every 6 months during the second year, supplemented by urine examination, urine culture, and bladder washout cytology. All patients with suspected recurrence on cystoscopic examination or doubtful urine cytology underwent TURB of any visible lesion or TURB mapping (biopsy samples from the trigon, posterior, anterior, and lateral walls, bladder dome, and prostatic urethra).

For the Feasibility study 92 patients were enrolled (Table 1a), TURB NBI technique was compared to the traditional TURB WLI approach by comparing the surgical complication rate according to the *Clavien-Dindo* System (11), mean surgery time and time to catheter removal, rate of absence of muscular tissue in the specimen, false-positive rate.

For the Recurrence study 54 patients were enrolled (Table 1b). 38 patients from the original group were excluded (19 patients NBI and 19 WLI). Of the excluded patients, 12 (64%) in the NBI group and 11 (58%) in the WLI had specimens histologically negative for cancer

Table 1a.

Feasibility study patient baseline characteristics.

	NBI	WLI
Number of patients	47	45
Sex (%)		
Male	36 (76)	40 (88)
Female	11 (24)	5 (12)
Age, mean (range)	73 (40-94)	74.4 (48-95)
Cancer history (%)		
Primitive	16 (34)	27 (60)
Recurrent	31 (66)	18 (40)
Number of lesions (%)		
Single	32 (68)	33 (73)
Multifocal	15 (32)	12 (27)
Lesion size (</> 3 cm)	37/10	24/21

Table 1b.

Recurrence study patient baseline characteristics.

	NBI	WLI
Number of patients	28	26
Sex (%)		
Male	22(78.5)	22 (85)
Female	6 (21.5)	4 (15)
Age, mean (range)	73 (40-82)	74 (48-83)
Mean Follow up	12.2 mos	12.4 mos
Cancer history (%)		
Primitive	10 (36)	16 (62)
Recurrent	18 (64)	10 (38)
Number of lesions (%)		
Single	16 (58)	17 (65)
Multifocal	12 (42)	9 (35)
Lesion size (</> 3 cm)	19/9	16/10

at TURB and have not developed any recurrence during the follow-up. Two patients (10%) in the NBI and 1 (6%) in the WLI group had voluminous HG TCC-NMI tumours (> 3 cm) and underwent elective radical cystectomy. Three patients (16%) in the NBI group and 2 (10%) in the WLI group had a muscle-invasive bladder cancer or CIS refractory to intravesical immunotherapy with bacillus Calmette-Guérin and underwent radical cystectomy as well. Two patients (10%) in the NBI group and 3 (16%) in the WLI have not been part of the complete follow-up regimen. Two (10%) patients in the WLI group died for causes unrelated to bladder cancer during the follow-up period (6 months and 8 months). Out of the 54 patients left 28 underwent TURB NBI and 26 TURB WLI. HG NMI cancer patients (6 NBI 7 WLI) underwent a second look WLI TURB. The overall mean follow-up was 12.3 months (range, 3-18 months). Statistical analyses were performed using the Statistical Package for Social Sciences, version 19.0 (SPSS, PASW 19) and $P < 0.05$ was considered statistically significant.

RESULTS

Feasibility study

Results are reported in Table 2. The groups were homogeneous regarding the size (< 3 or > 3 cm) and the number of lesions ($P > 0.05$), but they were not regarding the history of the tumour (primitive/recurrence; $P < 0.007$). Only 3 patients were treated with endovesical chemo/immunotherapy within 3 months before TURB (2 NBI patients, 1 WLI patient). Type I-II complications were reported in 12 patients in the NBI group (25%) and in 10 patients in the WLI group (22%). Complications included persistent haematuria, resolved with continuous

irrigation catheter, acute retention of urine after removal of the catheter for prostatic hyperplasia, and urinary infection. No patient had endoscopic diathermy or required blood transfusions.

Mean surgical time, mean time of catheterization, the rate of absence of muscular tissue in the specimen and the false positive rate are reported.

Recurrence study

The results are reported in Table 3. The patient baseline characteristics are similar to the feasibility study ones in terms of size, number of the lesions and cancer history. Patients with HG NMI TCC who underwent a second look WLI TURB had residual disease in 33% NBI group (2/6: 1 HGMNI TCC, 1 LGNMI TCC) and in 43% WLI group (3/7 1 HGMNI TCC, 2 LGMNI TCC). The recurrence rate at one year follow-up is 35% in NBI group and 50% in WLI group. No statistic significance can be issued for the clinical differences observed.

DISCUSSION

NBI technique has provided excellent diagnostic results, improving detection rate explained by better visualization of small papillary tumours and CIS; the DR in NBI cystoscopy varies from 55% to 95% and is up to 100% in patients with CIS (5,7).

In 2010, Herr showed that the follow-up for bladder cancer performed with NBI cystoscopy reduces the recurrence of cancer (6) and NBI cystoscopy seems to have a reduced learning curve (4).

These results put NBI on a comparable level to PDD (Photo - Dynamic - Diagnosis) in terms of improved DR in bladder cancer, although currently no comparison studies have been reported.

Table 2.
Feasibility study results.

Characteristics	TURB NBI	TURB WLI	P
False-positive rate	45% (21/47)	29% (13/45)	NS
Complication rate (Clavien-Dindo I-II)	25% (12/47)	22% (10/45)	NS
Mean surgery time, min (range)	26 (10-64)	41 (11-135)	< 0.0005
Mean time to catheter removal, days (range)	2 (1-5)	3 (1-6)	0.001
Rate of absence of muscle tissue in the specimen	6% (3/47)	4.5% (2/45)	NS

NS, not significant.

Table 3.
Recurrence study results.

Characteristics	TURB NBI	TURB WLI	P
HG TCC-NMI	6 (22%)	7 (27%)	NS
LG TCC-NMI	22 (78%)	19 (73%)	NS
Recurrence rate at 1 year	10 (35%)	13 (50%)	NS

NS, not significant.

The next step could be to evaluate whether NBI had a role in operative endosurgical treatment of bladder neoplasm improving technics and results of the traditional WLI treatment: with this purpose we undertook a larger feasibility study and a smaller recurrence study.

We observed that TURB performed entirely with NBI is a feasible, high quality and safe method. No statistically significant differences in complication rates studied with a widely accepted system such as the Clavien-Dindo one has been demonstrated between NBI and WLI TURB.

Moreover the complication types belongs to the group I-II and no re-do surgery or blood transfusion has had to be offered. The quality of the specimen obtained by NBI TURB with a rate of absence of the muscle layer in the TURB specimen is comparable to the WLI TURB.

NBI also had a clear advantage for surgical procedure times compared with the traditional WLI approach. The mean time of the surgical procedure, 26 minutes in the NBI group compared to 41 minutes in the WLI group, suggests that NBI TURB is more rapid than WLI TURB. Even excluding 2 WLI patients and 2 NBI patients with operating times beyond the standard deviation, the NBI resection lasted 14 minutes less than the WLI resection. The size and number of lesions are comparable between the two groups and then the reason for the difference has to be sought in the better technical aspects offered: NBI allows an immediate display of bladder neoplasm or suspicious areas and gives a better view of the lesion edges and bleeding areas, justifying a faster and more precise resection with targeted hemostasis.

The false-positive rate, in our study, 45% for NBI compared to 29% for WLI, is at odds with studies in the literature with false-positive rates ranging from 32% to 36% (7). This false-positive rate is probably linked to inflammatory hypervascularization: in our NBI group 76% of the cases were males with benign prostatic hyperplasia (BPH) and 66% had a previous resection. Unfortunately we cannot state whether NBI diagnostic yield is affected by inflammation secondary to intravesical therapy because only 2 patients in the group underwent instillations within 3 months before TURB. An interesting consideration is that 7 patients in the NBI group with false-positive results (all with a history of previous bladder cancer) have developed cancer recurrence at 3 months. This observation requires more studies to assess whether NBI is able to highlight areas of dysplasia that can rapidly turn into cancer. Our feasibility results may be similar to those reported by Naselli *et al.* (8). To our knowledge at the moment no data are available on NBI cost effectiveness: the technique requires a dedicated optical light filtering technology (Olympus Exera II), which can be, however, shared in the operating theatre with regular endoscopic and laparoscopic procedures. With respect to other enhancement techniques (*Photo Dynamic Diagnosis-PDD*) NBI does not require any drug to be instilled in the bladder before resection. At the moment no data are available on TURB performed completely in PDD. Moving to recurrence study, we chose to consider first cancer recurrence within one year from the TURB, our target event. The effectiveness of the NBI procedure compared to the traditional WLI approach for TURB has recently been assessed in terms of reduction of residual disease in a study by Cauberg *et al.* (9): NBI patients have a residual tumour rate of 15% compared to 30.5% in WLI patients. In our study the resection of the tumour can be considered of good quality considering the presence of muscle in the specimen, we performed a second look TURB in all HGNI TCC, observing residual disease in 33% of NBI and 43% of WLI patients.

TURB was performed entirely with the NBI method, without switching to WLI and vice versa during the pro-

cedures, and the control group received the procedure entirely with WLI approach. However we should underline that the surgeon can choose to switch from NBI to WLI whenever required. Our choice to perform all the procedure with NBI without switching to WLI eliminates the bias "*regression toward the mean*" present in studies on enhancement diagnostic techniques. In a recent paper on 72 and 76 patients who underwent to NBI TURV and standard TURV respectively, Naselli *et al.* demonstrated that NBI TURB reduced the 1-yr and 3-mo relapse probability of almost 40% and 75% respectively (12).

In our study at 1-year follow-up, the rate of recurrence in NBI patients was 35% compared to 50% of those treated with a standard WLI approach. The clinical data are interesting because they suggest new scenarios for NBI TURB. In fact if we consider the risk factors for recurrence based on the EORTC tables the main risk factors are the number and the diameter of the lesions, and the history of previous malignancy (13, 14). The number and the diameter of the lesions in the two groups were comparable, whereas the history of previous malignancy was more prominent in the NBI group (64% vs. 38%). For this reason we should expect a higher recurrence rate in the NBI group, but we observed the opposite. A possible explanation should be sought in the more radical treatment obtained by NBI TURB. The lack of statistical significance could be explained partly by the number of patients enrolled, the short follow-up period, lack of randomization, and the inhomogeneity of the two groups in terms of primary lesions and recurrences.

CONCLUSION

TURB performed entirely by the NBI technique is feasible and safe. It guarantees a complete and rapid resection of good quality from a pathological point of view. Moreover, the technique is relatively inexpensive with respect to other methods proposed to enhance the detection rate, for which data on operative endoscopy are lacking. In our clinical experience, even if not statistically significant, NBI TURB reduces at one year follow up the recurrence rate of bladder NMI tumours when compared to WLI TURB (35% vs. 50%). Other larger, randomized, prospective trials with longer follow-up periods are required to confirm our outcomes.

CONFLICT OF INTERES

The Authors declare that they have no conflict of interest.

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Correspondence

Emanuele Montanari, MD
Urological Department
Medical School of Medicine University of Milan DISS A.O. S. Paolo
Via Antonio di Rudini 8 - 20142 Milano, Italy
emanuele.montanari@unimi.it

Jean de la Rosette, MD
Pilar Laguna, MD
Urological Department - Academic Medical Center
Amsterdam, The Netherlands

Fabrizio Longo, MD
Alberto Del Nero, MD
Urological Department
Medical School of Medicine University of Milan-DMCO S. Paolo
Via Antonio di Rudini 8 - 20142 Milano, Italy

Effects of ankle position on pelvic floor muscle electromyographic activity in female stress urinary incontinence: Preliminary results from a pilot study

Maria Angela Cerruto¹, Ermes Vedovi², William Mantovani³, Carolina D'Elia¹, Walter Artibani¹

¹ Department of Surgery Urology Clinic, University of Verona, Italy;

² Rehabilitation Unit, Policlinic Hospital, Verona, Italy;

³ Department of Medicine and Public Health, University of Verona, Italy.

Summary

Objectives: A standing posture including various ankle positions might effectively facilitate pelvic floor muscle activity (PFMa) in incontinent women, and an ankle dorsiflexion (DS) at 15° was identified as the best position able to increase PFMa. Nevertheless, this ankle inclination is very uncomfortable. We carried out this study aiming at identifying smaller ankle inclinations able to significantly affect PFMa in incontinent women reducing patient discomfort.

Methods: Twenty women, not yet entered menopause and with mild-moderate uncomplicated stress urinary incontinence, were enrolled. An electromyographic (EMG) biofeedback instrument using surface electrodes was employed to measure changes in PFMa while each patient assumed the following different ankle inclinations in upright position: horizontal standing (HS); DS at 5° (5DS), 10° (10DS) and 15° (15DS); and ankle plantar flexion (PS) at 5° (5PS), 10° (10PS) and 15° (15PS).

Results: No EMG differences were found between HS and PS. PFM tension in DS, at whatever angle, was significantly greater than in both HS ($P < 0.020$) and PS ($P < 0.040$). No differences were found between 10DS and 15DS in terms of resting PFMa. Concerning maximal PFMa, it was higher in 10DS than in 15DS ($P = 0.010$), and in 5PS than in both 5DS ($P = 0.006$) and 15DS ($P = 0.010$); no EMG differences were found between 5PS and 10DS.

Conclusions: These preliminary results showed that 10DS in upright standing had comparable effects on resting PFMa than 15DS with same effectiveness and less patient's discomfort, facilitating a better maximal contraction. Moreover a slight PS might effectively facilitate maximal PFMa.

KEY WORDS: Ankle inclination; Biofeedback; EMG; Incontinence; Pelvic floor; Posture.

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INTRODUCTION

Female stress urinary incontinence (SUI) is a quite common problem affecting up to 44% of women in Europe (1). A number of effective treatments are available for this condition, and most authors agree to consider pelvic floor muscle (PFM) training as the first treatment choice among conservative management (2, 3). Aiming at improving PFM activity (PFMa) during PFM training, Chen *et al.* proposed to include various ankle positions as an adjunctive option combined with

this conservative therapeutic approach (4). These authors identified the ankles dorsiflexion at 15° as the best position in upright standing in order to increase PFMa. Nevertheless, this ankles position is very uncomfortable for the patients and some of them are not able to reach this angle. We carried out this study aiming at identifying smaller ankles slants able to significantly affect PFMa in women with SUI reducing patient discomfort.

METHODS

Study population and design

A total of 20 women with mild-moderate SUI (according to SEAPI-QMM) incontinence classification system) (5) were selected on the basis of detailed history taking clinical examination, PFM testing and bladder diary. Patients are excluded who exhibited musculoskeletal problems, such as knee osteoarthritis, ankle joint deformities, lower back pain in the previous 6 months, had undergone major abdominal or pelvic surgery, had severe diseases, diabetes mellitus with insulin treatment, were obese (body mass index $> 30 \text{ kg/m}^2$), had undergone intrauterine device implantation, had pelvic organ prolapse, had severe incontinence (5, 6), or entered menopause. All the selected subjects agreed to participate in this study.

PFM activity measured in 7 different postures

We measured changes in PFMa with an electromyographic (EMG) biofeedback instrument (U-Gym, WellTech s.r.l., Italy) which measures the electronic signals of PFMa using skin surface EMG electrodes positioned at ischiatic tuberosity level, bilaterally. None of the patients had never been instructed to perform PFM exercises before the enrolment. For this reason, before each measurement, the therapist instructed the subjects regarding how to perform PFM testing. Each subject was then asked to stand on an adjustable basculant platform (Baskula-Pegaso 2000), and to assume the following different positions during which EMG recordings of the PFM were made: horizontal standing (HS), with ankles

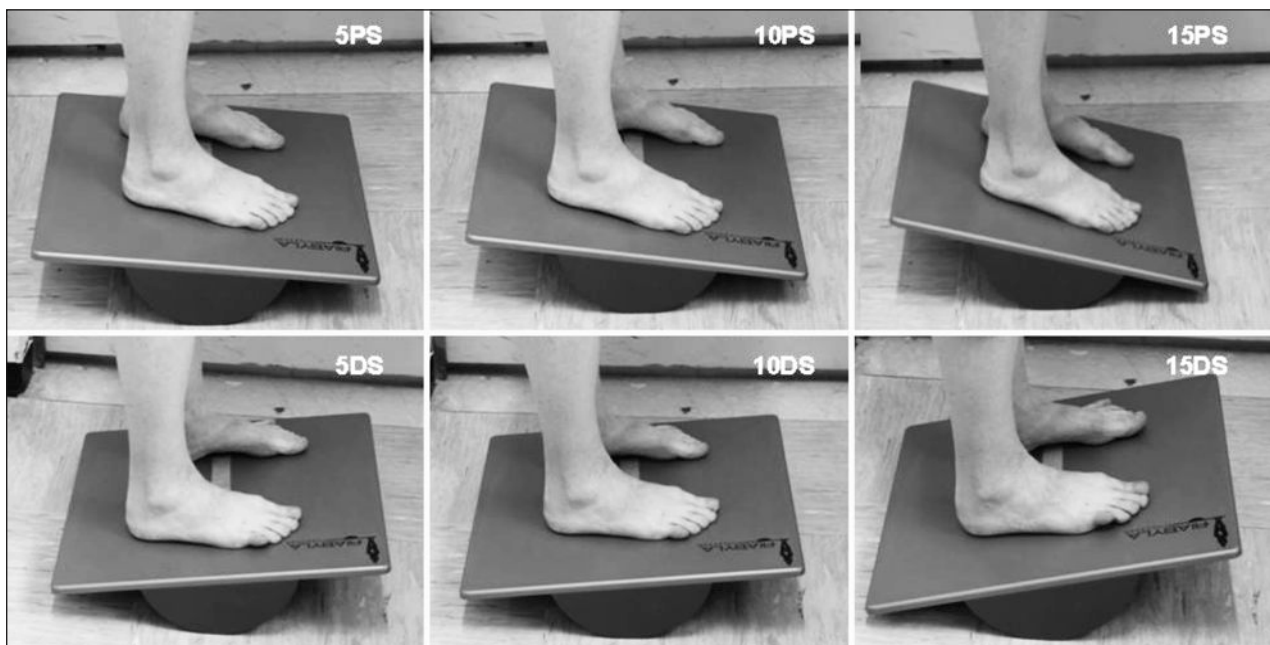
dorsiflexed at 5° (5DS), 10° (10DS) and 15° (15DS), and ankles plantar flexed at 5° (5PS), 10° (10PS) and 15° (15PS) (Figure 1). When the correct procedures were carried out, the subjects could see by way of the visual feedback from the EMG signal on the monitor that the PFMs were contracted as hard as possible. For each position, six 5-second-maximal contractions with a 5-second rest between each contraction were made, and the resting and median maximal contraction EMG activity values were recorded. A rest period of 2 minutes in the HS occurred between a position and the subsequent. For each position, before starting the EMG testing, the subject was asked to stand for 2 minutes on the platform assuming each different ankle inclination for the purpose of postural habituation to eliminate any carryover effect. All subjects were asked to maintain an upright posture without a forward or backward tilt. The various ankle inclinations were created passively using a basculant platform. Overall 7 positions were investigated.

Statistical analysis

Statistical analysis was performed with the Statistical Package for Social Sciences analytical software (version 12.0). PFMa (unit of measure μV) at rest and during maximal contraction were recorded as median values and interquartile range (25th percentile; 75th percentile) (IQR). The Wilcoxon signed-ranks test was used to perform pair-wise comparison of the different procedures conducted on each subject. The level of statistical significance was set at $p \leq 0.05$.

Figure 1.

Adjustable basculant platform to facilitate the various ankles inclinations in plantar flexion at 5° (5PS), 10° (10PS), 15° (15PS), and in dorsiflexion at 5° (5DS), 10° (10DS) and 15° (15DS).



RESULTS

The patient characteristics are shown in Table 1. Table 2 shows median values and IQR of PFMa of resting and during maximal contraction in the different analysed positions. PFM tension in the resting posture while standing with the ankles dorsiflexed at 15° showed the greatest value (51.5 μ V). The median maximal PFMa in any posture was greater than that during the rest periods ($P = 0.001$). Table III shows the P values of differences in PFMa among the various postures of resting and median maximal contractions.

No significant PFMa differences were found between the horizontal standing and ankle plantar flexion postures in terms of both resting and maximal PFMa. PFM tension in upright position with the ankles dorsiflexed at whatever angle was significantly greater than with both HS ($P < 0.020$) and PS ($P < 0.040$) (Table 3). Subjects produced more median maximal PFMa while standing with the ankles plantar flexed at 5° and 15° than while standing with the ankles dorsiflexed at 5° and 15° (5PS-5DS $P = 0.006$; 5PS-15DS $P = 0.010$; 15PS-5DS $P = 0.050$; 15PS-15DS $P = 0.004$). Moreover, median maximal PFMa was higher in 10DS than in 15DS ($P = 0.010$), whilst no differences were found between 10DS and 15DS in terms of PFMa at rest. Also, no EMG differences were found between 15 PS, 5PS and 10DS in terms of median maximal PFMa.

Table 1.

Patient characteristics (n = 20); none of them had entered menopause.

Characteristic	
Age (yr) mean (range)	40 (28-49)
Parity mean (range)	2 (0-3)
Incomplete bladder emptying number (%)	0 (0.0%)
Nocturia number (%)	4 (20%)
Body mass index (kg/m ²) mean (range)	24 (19-30)
Duration of symptoms (yr) mean (range)	10 (3-19)

DISCUSSION

As stated by *Chen et al.* (4) an upright position including different ankle inclinations effectively facilitates PFMa through enhanced pelvic tilt. These positions may be recommended as an adjunctive option combined with PFM training for SUI (4). Unfortunately an ankle inclination in dorsiflexion at 15°, considered by these authors as the best inclination able to enhance both resting and maximal PFMa, is very uncomfortable. We identified the dorsiflexion at 10° as the smallest ankle inclination in dorsiflexion able to effectively facilitate PFMa both at rest and during maximal contraction with less patient's discomfort. The various ankle inclinations were created passively using a basculant platform.

We excluded obese and menopause subjects to avoid further factors able to affect pelvic statics and dynamics. As already stress by *Chen* and showed in Table 2, PFM maximal contraction was greater than that of the resting contraction but the gained value was different. This mechanism implies that maximal pelvic contraction activity was greater than resting activity in any pelvic posture, but the values differed in the specific pelvic postures corresponding to the specific ankle positions. The pelvic tilt range and direction can be easily and passively triggered using various ankle positions (7), and *Chen* was the first who explored the role of specific ankle postures in creating various pelvic tilt angles and their effect on the PFMa in women with SUI (4). The results from *Chen's* study showed that greater resting PFMa occurred in horizontal standing or when standing with the ankles dorsiflexed than when standing with the ankles plantar flexed. In our study a greater resting PFMa occurred only when standing with the ankles in dorsiflexion. We did not find any EMG differences between HS and ankles plantar flexion in terms of PFM tone. To explain the significant differences in resting PFMa from dorsiflexion and plantar flexion postures, we may adopted the same theory proposed by *Chen* and other authors who stated that when subjects stand with the ankles plantar flexed, the pelvis tilts posteriorly, the promontory moves superiorly and posteriorly, and the tip of the coccyx moves anteriorly (4, 8).

Table 2.

Median values and interquartile range (IQR) of PFM activity of resting and during maximal contraction in the different analysed positions.

Position	Median Resting contraction (IQR) (μ V)	Median Maximal contraction (IQR) (μ V)	P value
HS	32.5 (27.8-39.3)	277.8 (148.8-441.0)	< 0.001*
5PS	34.0 (28.0-39.5)	315.0 (163.0-454.5)	< 0.001*
10PS	34.0 (25.8-38.3)	300.8 (174.3-421.8)	< 0.001*
15PS	35.0 (31.5-45.3)	315.0 (184.1-387.3)	< 0.001*
5DS	41.5 (34.0-54.8)	273.3 (154.0-331.3)	< 0.001*
10DS	45.5 (35.3-58.3)	261.0 (191.6-351.9)	< 0.001*
15DS	51.5 (37.0-66.5)	232.3 (155.1-305.0)	< 0.001*

*Statistical significance

HS = horizontal standing; 5DS = ankle joint dorsiflexion in standing at 5°; 10DS = ankle joint dorsiflexion in standing at 10°;

15DS = ankle joint dorsiflexion in standing at 15°; 5PS = ankle joint plantar flexion in standing at 5°; 10PS = ankle joint plantar flexion in standing at 10°;

15PS = ankle joint plantar flexion in standing at 15°; PFM = pelvic floor muscle.

Table 3.

P values of differences in PFM activity among the various postures of resting contraction and median maximal contraction.

	Median Resting contraction	Median maximal contraction
HS-5PS	0.80	0.60
HS-10PS	0.80	0.50
HS-15PS	0.40	0.80
HS-5DS	0.020*	0.050*
HS-10DS	0.020*	0.30
HS-15DS	0.006*	0.060
5PS-10PS	0.70	0.80
5PS-15PS	0.40	0.50
10PS-15PS	0.10	0.10
5DS-10DS	0.50	0.060
5DS-15DS	0.030*	0.70
10DS-15DS	0.10	0.010*
5PS-10DS	0.004*	0.40
5PS-5DS	0.007*	0.006*
5PS-15DS	0.001*	0.010*
10PS-5DS	0.040*	0.070
10PS-10DS	0.002*	0.40
10PS-15DS	0.001*	0.060
15PS-5DS	0.080	0.050*
15PS-10DS	0.050*	0.20
15PS-15DS	0.006*	0.004*

*Statistical significance

Therefore, the lateral attachments of the vaginal wall can also weaken when iliac bones move apart (9). It seemed that a posterior pelvic tilt was easily produced with ankle plantar flexion, but a resting decreased PFMa may be noted in this posture.

Chen found that when his subjects' ankles were kept in a plantar flexion position, it reduced foot flexibility and the PFMa reached its lowest point. In our patients a plantar flexion position allowed them to reach the same resting PFMa than HS with a better median maximal PFMa compared to all the other positions (Table 3). In contrast, with the ankles dorsiflexed, the pelvis tilts anteriorly, and this movement results in the pelvic outlet increasing and the ischiatic tuberosities moving apart (8). Also, the coccyx moves in a backward and upward direction, resulting in the closure of the urethra, bladder neck, and suburethral vaginal wall, and urethral support is also elevated (10).

Contrarily to previously Chen's published work, in our study the pelvic anterior rotation provided certainly an increased resting PFMa during ankle dorsiflexion, but determined a decreased median maximal contraction. Interestingly, an ankle dorsiflexion at 10° showed the same facilitation on resting PFMa than 15° dorsiflexion with a better effect on maximal PFMa. Moreover, while ankles plantar flexed at 5° better improved maximal PFMa than ankles dorsiflexed at 5° and 15°, no EMG dif-

ferences were found between 5PS and 10DS during PFM maximal contractions.

All differences found between our study and Chen's work might be due to the different EMG-assisted biofeedback devices used: Chen employed an instrument with intravaginal probe having surface EMG electrode; in contrast, in order to avoid invasive procedures able to affect the baseline pelvic statics, we decided to use skin surface EMG electrodes positioned at ischiatic tuberosity level, bilaterally. Moreover we considered the results as medians and IQR whilst Chen *et al.* considered means and standard deviation. All these differences make hard a correct comparison between the results from these two studies. Nevertheless, our work seems to confirm the findings from Chen *et al.*, that pelvic tilt might change PFMa and thus be used as an adjunctive technique for PFM training in women with SUI, identifying the role of various ankle inclinations in an upright position.

CONCLUSIONS

These preliminary results showed that 10DS ankles position in upright standing had comparable effects on PFM tone than 15DS, facilitating a better maximal contraction with same effectiveness and less patient's discomfort. Moreover a slight ankles plantar flexion might effectively facilitate PFMa during the maximal contraction. Our

results showed that, contrarily to previous reports, a standing posture with the ankles plantar flexed resulted in a posterior pelvic tilt able to increase the maximal PFMa compared with a standing posture with the ankles dorsiflexed. Moreover we found that an upright standing posture with the ankles dorsiflexed might facilitate anterior pelvic tilt, which in turn increased effective resting PFMa to its greatest point, reducing, on the other hand, maximal PFMa.

CONFLICT OF INTEREST

In this article there is no funding or any disclosure to companies.

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Correspondence

Maria Angela Cerruto, MD
Assistant Professor, Urology Clinic, University of Verona
Piazzale L. Scuro 10 - 37134 Verona, Italy
mariaangela.cerruto@univr.it

Erme Vedovi, MD
Rehabilitation Unit, Policlinic Hospital, Verona, Italy
er.vedovi@virgilio.it

William Mantovani, MD
Department of Medicine and Public Health, University of Verona, Italy
william.mantovani@univr.it

Carolina D'Elia, MD
Department of Surgery Urology Clinic, University of Verona, Italy
karolinedelia@gmail.com

Walter Artibani, MD
Department of Surgery Urology Clinic, University of Verona, Italy
walter.artibani@univr.it

Urinary apparatus tumours and asbestos: The Ramazzini Institute caseload

Michelina Lauriola¹, Luciano Bua¹, Daniela Chiozzotto¹, Fabiana Manservigi¹, Achille Panetta², Giuseppe Martorana³, Fiorella Belpoggi¹

¹ Cesare Maltoni Cancer Research Center, Ramazzini Institute, Bentivoglio, Bologna, Italy;

² Departmental Operative Unit in the Oncology Department, Palliative Care, Bentivoglio Hospital, Bentivoglio, Bologna, Italy.

³ Professor and Chief, Department of Urology, University of Bologna, Italy.

Summary

Many studies have drawn attention to the possible association between occupational exposure to asbestos and tumours of the urinary apparatus. Besides the main etiological agents recognised today – such as smoking, obesity and hypertension – experimental and epidemiological evidence converges on the view that tumours of the kidney and bladder are largely due to occupational exposure to industrial agents: these and their transformation products linger in the body and are eventually eliminated by those organs. That one such agent targeting the urinary system is asbestos has found confirmation in the discovery of asbestos fibres in the urine of populations at risk. We here present 23 cases of work exposure to asbestos in a range of exposure scenarios where the workers developed tumours of the kidney and bladder. The cases came to the attention of the Ramazzini Institute casually.

KEY WORDS: Asbestos; Renal cancer; Occupational exposure.

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TUMOURS OF THE URINARY APPARATUS IN WORKERS EXPOSED TO ASBESTOS

Renal excretion is one of the main elimination pathways for the toxic and carcinogenic chemical agents and metabolites to which man may be exposed. The urinary system is naturally often a target of such agents, the kidney being the filter in which they may be trapped, and the bladder a place where they may linger for a long time before being excreted.

The likelihood that asbestos has a carcinogenic effect on urinary tract tissues is supported by many studies which have shown the presence of asbestos fibre in the urine, caused by the occasional migration of such fibres from the gastro-intestinal wall to the bloodstream then into the urinary pathways (1-4). Asbestos formations have been detected in the kidneys and increased risk of kidney tumours was noted among miners from the Quebec asbestos mine (5). The presence of asbestos fibres in the urine both of occupationally exposed subjects (6-8) and of people who had drunk water contaminated

with amphibolic asbestiform fibres (9, 10) has been documented on various occasions. Evidence of asbestos fibre lodging in the kidneys has come from experimental and epidemiological studies based on autopsy (11-14). It is thought by some researchers that asbestos formations start in the lungs and then migrate to the kidney. Once the asbestos fibres reach they form around asbestos fibres that had migrated to the kidneys in their own right. This is based on the demonstration that, once they reach the lungs by inhalation, they may pass the alveolar barrier, cross the interstitium and reach the lymph vessels and blood circulation; from there the fibres get distributed throughout the organs and tissues in concentrations that vary with local conditions (15). The highest concentration of asbestos fibres, outside the lungs, has been found in the kidney (high pressure and fast flow) and in the liver (high micro-vascular permeability); it is lower in the brain (owing to the blood-brain barrier) (16).

1. Renal tumours

➤ Epidemiology

Renal tumours occupy ninth place in the list of neoplasias commonly found in industrialised countries. They include carcinoma of the renal parenchyma (92%), carcinoma of the transition cells of the renal pelvis and ureter (7%) and Wilms' infancy tumour (1%) (17-19). Although often were considered as renal tumours, renal pelvis and ureter tumours are urothelial neoplasms, therefore they are affected by the same risk factors of bladder cancer, the most frequent urothelial malignancy. Roughly 80% of renal parenchymal tumours are clear-cell (non-papilliferous) adenocarcinomas; the remainder are papilliferous/chromophilic (~ 15%) or chromophobic (~ 5%) tumours and carcinomas of the collector ducts (< 1%) (18).

It is estimated that some 273,500 new cases of renal carcinoma are diagnosed every year in the world, amounting to 2% of all tumours (20). The highest incidence is recorded in North America, the lowest in Asia and Africa. In Europe 86,000 new cases are observed every year, 8,200 of them in Italy which occupies nineteenth place among the European countries, the incidence being considerably higher in men (5,600) than in women (2,600) (17, 21). As well as differences between continents, there are considerable differences within one and the same continent or even the same nation. In Europe, for example, 15.2 cases per 100,000 inhabitants are found in the Czech Republic and 2.9 in Serbia (22). In Italy the incidence of renal tumour observed in the north-east (9.0/100,000 men and 3.9/100,000 women) is three times higher than in a southern province like Salerno (3.6/100,000 men and 1.6/100,000 women) (23).

From 1973 to 2000 the incidence of tumours to the kidney and renal pelvis increased by 47% in men and 65% in women, a rate of about 2% per year (24). In the subsequent decade (1999-2008) this increase rose to 3% (2.8% men and 3.1% women) with 20.4 cases per 100,000 in the age bracket 50-54 years, 43.5 cases per 100,000 in that between 60 and 64 years, and 70.0 per 100,000 for the population between 75 and 79 years of age (25).

➤ Situations, risk factors and exogenous agents

We here list the agents and general factors, as well as occupational situations, which are likely to increase the risk of renal carcinoma in man, going by the epidemiological evidence.

- Smoking: it doubles the risk of carcinoma of the renal parenchyma, triples the risk of tumours of the renal pelvis. An increased risk has been observed to correlate with the number of cigarettes: 1.3-1.6 for a 20-40 packets/year consumption, 9.3 for consumption over 40 packets/year (26, 27).
- Obesity: the risk is thought to grow by 24% in men and 34% in women with each 5 kg/m² increase in the body mass (28).
- Hypertension: an increased dose-response risk has been observed, correlating with high blood pressure values (23).
- Diet: diets rich in fruit and vegetables correlate inversely with increased risk of renal cancer (29).

- Occupational situations: as recognised to date, the risk factors and agents mentioned above seem to be causally involved in the onset of about half the renal tumours observed (18). This lends all the greater importance to epidemiological and experimental evidence connecting occupational exposure to the aetiology of renal cancer. The agents most frequently associated with renal tumours in the literature are: 1,3-butadiene, vinyl chloride, vinylidene chloride, trichloroethylene, tetrachloroethylene, aspartame and asbestos (23, 30-33).

➤ Renal tumours in workers exposed to asbestos

One of the experimentally and epidemiologically identified carcinogens for the kidney is asbestos. More and more experimental and epidemiological studies are now confirming the causal link between cancer of the kidney and occupational exposure to asbestos, as discovered back in the 1970s (34). One experimental study performed in 1976 on Wistar rats orally treated with a suspension of chrysotile showed an increase in the incidence of renal carcinoma (35). Medium-length asbestos fibres (chrysotile) were administered to Fisher F344 rats in their food on its own and with 1,2-dimethylhydrazine dichlorohydrate (DMH), a known carcinogen: among the females treated with asbestos a significant increase ($P < 0.05$) was noted in the incidence of mixed tumours of the kidney (34/175, 19%) as compared to DMH alone (13/125, 10%) (36). In a more recent study Wistar rats were treated with asbestos fibre (amosite) via intratracheal instillation. After six months' treatment no neoplastic lesions were found in the kidneys, but significant glomerulosclerosis and interstitial tubulo-fibrosis were found (37).

Increased incidence of renal carcinoma was observed in a cohort study on 17,800 insulation workers in the United States and Canada over the period from 1967 to 1986 (38, 39). Here 37 deaths by renal neoplasm were recorded, a relative risk (RR) of 1.96 which is statistically significant ($P < 0.001$) against expectation (Table 1). A second epidemiological study on 1,074 American workers employed in various sectors including textiles and asbestos-cement-based products, showed a statistically significant increase in renal tumour deaths: 7 cases observed versus 2.54 expected, with a Standardized Mortality Ratio (SMR) of 2.76 (Confidence Interval (CI) 95%: 1.29-5.18) (40). Another cohort study on 1,500 workers exposed to asbestos brought to light malignancies of the kidney that the authors considered correlated with asbestos exposure (41). Yet another case-control study based on 518 cases spread over 37 hospitals in Massachusetts, as identified between 1981 and 1984, showed increased incidence of renal adenocarcinoma induced by asbestos (42). McCredie and Stewart's case-control study in Australia evinced an RR of 1.62 (CI 95%: 1.04-2.53) for renal neoplasias, versus a sample of the general unexposed population (43). High incidence of kidney tumour was observed in workers with a cumulative exposure to asbestos of 300 mpcf.y (millions of particles per cubic foot per year) (44). In 1994 a high number of cases of renal tumour in Denmark were correlated with occupational exposure to asbestos (45). Another case-control study on workers exposed to asbestos and belonging to various job categories in vari-

Table 1.*Deaths among 17,800 insulation workers in the USA and Canada from 1/1/1967 to 31/12/1986 (1).*

Causes of death	Deaths expected (2)	Deaths observed		Observed/expected difference		SMR (3)	
		Death certificate	Cause ascertained (4)	Death certificate	Cause ascertained	Death certificate	Cause ascertained
Total deaths, all causes	3.453,50	4.951	4.951	1.497,50	1.497,50	143***	143***
Total neoplasias, all locations	761,41	2.127	2.295	1.365,59	1.533,59	279***	301***
Pulmonary neoplasia	268,66	1.008	1.168	739,34	899,34	375***	435***
Pleural mesothelioma (5)	–	89	173	89,00	173,00	–	–
Peritoneal mesothelioma (5)	–	92	285	92,00	285,00	–	–
Neoplasia of the larynx	10,57	17	18	6,43	7,43	161	170*
Neoplasia of the oropharynx	22,02	38	48	15,98	25,98	173**	218***
Gastrointestinal neoplasia (6)	135,69	188	189	52,31	53,31	139***	139***
Digestive system neoplasia (7)	191,66	324	269	132,34	77,34	169***	140***
Renal neoplasia	18,87	32	37	13,13	18,13	170**	196***
Total non-infective lung diseases	144,82	465	507	320,18	362,18	321***	350***
Asbestosis (5)	–	201	427	201,00	427,00	–	–
Other causes	2.547,27	2.359	2.149	-188,27	-398,27	93***	84***

1) From Selikoff & Seidman, 1991 (modified) (39); * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

2) Expected deaths were calculated from age-specific death rates of white males produced by the U.S. National Center for Health Statistics, 1967-1986.

3) Standardised mortality ratio: deaths observed/deaths expected $\times 100$.

4) Number of deaths recorded after acquisition and revision of clinical and/or surgical and/or autopsy documentation. Failing such documentation, we considered death certificates.

5) Mortality rates unavailable since considered rare causes of death.

6) Neoplasias of the oesophagus, stomach and colon-rectum.

7) Neoplasias of the oesophagus, stomach, colon-rectum, liver, gall bladder and bile ducts.

ous countries (Australia, Denmark, Germany, Sweden and the USA) confirmed the significant increase in renal neoplasias (RR = 1.4; CI 95%: 1.1-1.8) (46). In 2000 Gamble and Lewis published the results of two studies on deaths among three cohorts of American refinery and petrochemical industry workers. The studies showed that renal tumour decease increased in all three cohorts. The relative risk (RR = 1.86) in one cohort, especially, was of statistical significance (47, 48).

2. Tumours of the bladder

➤ Epidemiology

Malignant tumours of the bladder (MTB) are the fourth neoplasia in order of frequency, above all in men where the ratio vis-à-vis women is 3.5:1. There are estimated to be around 200,000 new cases per year worldwide (49). The elderly are at greater risk than the young: after the age of 70, the risk is about 30 times higher than in more youthful age brackets (21, 50).

According to recent data, MTB represents 4.8% of all tumours in the two sexes (6.9% in men and 2.5% in women) with a mortality rate of 3.4% and 1.5% in men and women respectively (50). In the United States the incidence tended to rise until 1990 in both sexes, but mortality is now diminishing especially among men (51). Over the period 2002-2006 the incidence among males in the United States was 37.1 per 100,000 inhabitants and 9.3 per 100,000 women. Over the same period mortality was 7.5 and 2.2 per 100,000 among men and women respectively (52). The highest rates were recorded in North America, North Africa, the Middle East and Europe - particularly Italy, Spain and French Switzerland with incidences higher than 30 per 100,000 men. The highest

death rates were recorded in Denmark, Spain, Poland, Malta and Ireland. In Europe mortality increased up to the Eighties, above all in the South and East, and then tapered between 1988 and 2000 (53). In women the highest death rate found is around 2-3 per 100,000 in Denmark and Great Britain (54).

MTBs also reflect racial differences. For example, in the USA the Filipinos' and Afro-Americans' risk of developing a vesical carcinoma is respectively one-fifth and half that of whites. This finding with MTBs runs counter to the trend with other kinds of tumour where the incidence and mortality of Afro-Americans is always higher than among whites (55). In developed countries the incidence is twice as high in urban and industrialised areas as it is in the countryside. The differences are more marked among men than women. In the United States between 80 and 95% of MTBs are transition-cell carcinomas (56). The remaining malignant tumours are basically squamocellular carcinomas and adenocarcinomas. Some authors think the percentage of squamocellular carcinomas is growing steeply among blacks as compared to whites (12% vs 2%) and again, more in women than in men (18.3% vs 7.6%) (57). The latency period of MTBs (the interval between start of exposure and onset of neoplasia pathology) varies according to type and intensity of exposure to factors and agents responsible. The latency period for cancer of the bladder ranges between 6 and 20 years, with a maximum of 45 years. The most commonly reported mean time is 20 years (58).

➤ Situations, risk factors and exogenous agents

Clinical-pathology findings from a hundred years ago (i.e. the historical dawn of bladder carcinogenesis) down to today's epidemiological surveys and experimental research

enable us to identify the exogenous carcinogen risks for the bladder.

We here list the agents and general factors, as well as occupational situations, which entail an adequately proven risk of bladder cancer in man, according to epidemiology (51, 59):

- Smoking: a relation has been found between the number of cigarettes smoked and the risk run.
- *Schistosoma haematobium*: the high incidence of vesical carcinoma among patients with schistosomiasis is a problem for some areas of Africa and the Middle East, especially Egypt.
- Occupational situations: colouring industry (aromatic amines and related agents), aluminium industry, coal distillation, combustion products from engines, shoe, furniture, rubber and textile industries.

➤ *Tumours of the bladder in workers exposed to asbestos*

It is thought that a sizable part of MTBs (5-25%) can be put down to occupational origin (56). There is mounting evidence of a causal link between tumours of the urinary apparatus, including bladder cancer, and occupational exposure to asbestos. This is hardly surprising if one thinks that many carcinogens, and especially their active biotransformation products, are excreted in the urine. The literature shows a heightened risk of MTB in at least 40 different job categories, including paint-sprayers, truck drivers, electricians, mechanics, turners, barmen and waiters. A case-control study carried out in Spain between 1978 and 1982 examined 406 patients of the La Paz Hospital, Madrid, whose diagnosis of bladder cancer was associated with occupational exposure to asbestos (60). An increase in urinary tract tumours was observed in a German case-control study for 1977-1985 focusing on asbestos-exposed workers (Odds Ratio (OR) = 1.3, IC 95% = 0.7-2.5) from various categories, including foundries where the environment was heavily contaminated with asbestos (OR = 1.6, IC 95% = 0.8-2.9) (61). An epidemiological study performed in Finland on 33 patients from a surgical clinic over the period October-December 1988, revealed that out of 28 MTB sufferers, as many as 17 (61%) had been occupationally exposed to asbestos, and in 94% the exposure was certain (OR = 2.4, IC 95% = 0.9-8.4) (62). A cohort study on worker deaths at a shipyard in Genoa demonstrated an increase in MTB in relation to asbestos fibre associated with aromatic polycyclic hydrocarbons, industrial oils and welding fumes. One notes especially that the bladder cancer latency among the workers involved proved to be about 25 years of continuous exposure, an important fact for follow-ups on people exposed (63). Another case-control study in four Canadian provinces evidenced a further confirmation of an association between MTB and exposure to certain chemical agents such as: asbestos (OR = 1.69, IC 95% = 1.07-2.65), mineral lubricant oils (OR = 1.64, IC 95% = 1.06-2.55), benzidine (OR = 2.20, IC 95% = 1.00-4.87) (64). The cohort study on workers at the Porto Torres petrochemical works in Sardinia (5,350 males were included in the follow-up) showed an increased risk of MTB (RR = 1.46; 95% IC 1.09-1.96) in the sub-cohort of workers potentially exposed to asbestos (65).

To the best of our knowledge, the first study pointing to

increased risk of MTB dates from 1965, a survey on electrical industry workers which is a sector much polluted by asbestos – see the specific exposure scenario that follows – given the almost ubiquitous use of asbestos in electric-cables (66). This observation of electrical workers at increased risk of MTB was subsequently confirmed by many papers (67-69), including one that shows the combined results of 11 case-control studies (OR = 3.99, IC 95% = 1.10-14.51) (70). One Spanish study covering from 1998-2000 on 1,219 bladder cancer patients and 1,271 control patients found a statistically significant affect, all the more marked in exposures of ten years and more: the workers involved were from the medical gas-electricity sector (OR = 3.94, IC 95% = 1.49-10.44) and the electrical sector (OR = 1.31, IC 95% = 0.62-2.77) (71). The risk of MTB appears significantly greater when the exposure is a lasting one (over 10 years): this is confirmed by the study published by Cassidy *et al.* in 2009 (OR = 4.37, IC 95% = 1.62-11.77) and that by Colt *et al.* in 2011 which points to statistically significant increased risks run by car electricians (OR = 1.5, IC 95% = 1.02-2.3) and an increase among other electricians as well (OR = 1.1, IC 95% = 0.6-2.1) (72,73).

Several studies in the literature point to an increased risk of MTB in foundry workers, another category heavily exposed to asbestos, as described in Case 1 below. Claude *et al.* published a case-control study on 531 urinary tract patients from a range of different jobs including foundries (OR = 1.56, IC 95% = 0.84-2.91) as well as thermo-electric power stations and kilns (OR = 2.17, IC 95% = 0.84-5.57) (69).

THE RAMAZZINI INSTITUTE CASELOAD ON URINARY APPARATUS TUMOURS AND ASBESTOS

In 1995 Professor Cesare Maltoni and his group at the Ramazzini Institute first encountered a renal tumour in a worker occupationally exposed to asbestos. In a quite random way since then our attention has been drawn to another 22 cases, all men (the most gender exposed in the past) who had tumours of the urinary apparatus. The 23 cases include 18 kidney cancers, 2 of the ureter, and 3 of the bladder, traceable to asbestos exposure at work in various exposure scenarios recounted at first hand. In what follows we present an account of these cases in the order of presentation. The data are summarised in Table 2.

Appendix with individual case descriptions is available at <http://architurologia.it/index.php/it/supplements>.

DISCUSSION AND CONCLUSIONS

Tumours of the urinary apparatus are on the increase in the most industrialised countries and regions. The many epidemiological and experimental studies show that many agents can cause such tumours, and asbestos is emerging as one of them.

Asbestos is the generic name for a series of natural fibrous silicates which are widespread in nature and were extensively used in the last century in a range of manufacturing sectors: building, railways, shipyards, textile firms, the

Table 2.*Asbestos-related tumours of the urinary system: the Ramazzini Institute caseload.*

Case N.	Patient initials	Place of work	Exposure scenario: exposure to asbestos	Period of exposure (length)	Diagnosis	Year of diagnosis	Age at diagnosis	Latency
1	MZ	BO, MO	Foundry: thermal and electrical insulation of kilns, protective gear	1964-1991 (27)	Renal carcinoma	1990	46	26
2	PN	PD	Officine Stanga (Firema): lining and insulation of railway carriages	1969-1998 (29)	Renal oncocytoma asbestosis	1999 (48)	51	30
3	CT	BO	State railways: lining and insulation of railway carriages	1972-1989 (17)	Renal adenocarcinoma	1989	37	17
4	MM	BO	State railways: lining and insulation of railway carriages	1941-1974 (33)	Renal carcinoma	1994	70	53
5	GS	BO	State railways: lining and insulation of railway carriages	-	Renal carcinoma	1988	72	-
6	GP	BO	Casaralta Componenti (Firema): lining and insulation of railway carriages	1977-1987 (10)	Renal carcinoma	-	-	-
7	SE	NA	Metalworking firm: lining and insulation of railway carriages	-	Renal neoplasia	1985	79	-
8	CN	BO	Sugar refinery (home exposure): lining and insulation	1938-1960 (22)	Renal carcinoma	1995	59	57
9	CV	GE	Shipyard: thermal and electric-cable insulation, lining	1962-1999 (37)	Carcinoma of the ureter	1997	58	35
10	PC	BR, SA, VE, TA, FG, LE	Petrochemical: thermal and electric-cable insulation, insulation and gaskets	1969-1975 1977-1992 (21)	Renal carcinoma	2001	53	32
11	TL	RA	Compagnia Portuale: movement flows, transport and storage bags of asbestos, insulation and lining	1962-1981 (19)	Renal adenocarcinoma	1980	43	18
12	ED	RA	Compagnia Portuale: movement flows, transport and storage bags of asbestos, insulation and lining	1960-1984 (24)	Renal carcinoma	1995	69	35
13	GG	RA	Compagnia Portuale: movement flows, transporting and storing bags of asbestos, insulation and lining	1972-1992 (20)	Renal carcinoma	2004	55	32
14	VM	MO	Car coachworks: electric-cable insulation protective tubing for engines	1963-1991 (28)	Renal carcinoma	2007	66	44
15	IB	RE	Carpentry: insulating railway carriages	1975-1987 (12)	Renal neoplasia	2006	76	31
16	FM	RM	State railways: lining and insulating railway carriages	1954-1992 (38)	Bladder carcinoma	2009	75	55
17	LC	BO	Magneti Marelli: thermal and electric-cable insulation for kilns, protective gear	1974-1990 (16)	Renal carcinoma	1990	53	16
18	BG	BO	Magneti Marelli: thermal and electric-cable insulation for kilns, protective gear	1976-1983 (7)	Renal carcinoma	2004	77	28
19	MM	BO	Magneti Marelli: thermal and electric-cable insulation for kilns, protective gear	1970-2002 (32)	Ureteral carcinoma	2001	52	31
20	EB	MO	Magneti Marelli: thermal and electric-cable insulation for kilns, protective gear	1974-2012 (38)	Renal carcinoma	2001	49	27
21	EM	BO	Sugar refinery-Magneti Marelli: lining, insulation, thermal and electric-cable insulation for kilns, protective gear	1962-1991 (29)	Bladder carcinoma	1993	57	31
22	OS	MO	Car coachworks: electric-cable insulation protective tubing for engines	1974-1998 (24)	Renal carcinoma	2009	62	35
23	DG	FE	Magneti Marelli: lining, insulation, thermal and electric-cable insulation for kilns, protective gear	1980-present (32)	Bladder carcinoma	2008	52	28

ceramics industry, brickworks, foundries and sugar refineries. Its main uses are as: 1) asbestos-cement for building materials (roofing, walls, panels, ceilings, floors, conduits), pipelines (aqueducts, oil lines), basins and tanks; 2) insulating material (heat, electricity, sound) in various types of building (factories, public buildings,

homes) and in pipes, boilers, vehicles, rolling stock, ships, etc.; 3) friction parts (brakes); 4) paper and board; 5) textiles; 6) plastics; 7) gaskets; 8) filters. Apart from these main uses, asbestos has been employed in innumerable ways. One recent estimate is that about 3,000 uses have been listed (4).

In Italy about 75% of asbestos went into asbestos-cement. The remaining 25% was almost entirely used in the textile sector, gaskets, paper and board. Asbestos spread more or less everywhere because of its multiple properties: resistance, non-flammability, insulation, durability, low cost. Such qualities make it non-degradable. It lingers indefinitely in the environment; once it penetrates the organism, it is partly retained by tissues along its route. Its carcinogenic effects on the human organism are irreversible, all the evidence suggests. Again, nowadays asbestos, though ubiquitous, is at its highest and most dangerous concentration in certain work and living conditions. It is difficult to list all the work conditions at risk. Exposure to asbestos occurs to: those who extract it, those who make asbestos-based products, those who handle such materials, repairers and demolishers of asbestos-containing materials, port stevedores, transporters and all whose work environment is polluted by asbestos. One occupational category thought to be most exposed and at the greatest carcinogenic risk from asbestos are the technicians making, checking, cleaning and demolishing rolling stock containing asbestos. In Italy asbestos was extensively used by the railways from the 1930s to the 1970s in the form of panels and lagging strips for various parts of locomotives, infrastructure, and also making asbestos-cement sleepers for rail-track. From the places where it is employed, movement, wear and tear and vibration spread it inside rolling stock, in depots and in outdoor and indoor repair workshops, in and around railway stations, and also in workers' homes, since they carry asbestos fibre on their hair and work clothes. Another work category at high risk of asbestos-related cancer is that of dockers heavily and permanently exposed as large quantities of the material are shifted, loaded, unloaded and stored. At least until the late-Eighties, the lack of collective or individual protection measures, as well as lack of information about the risk of inhaling the fibres, further increased the degree of environmental exposure.

The IARC has classified asbestos as a carcinogen for man (Group 1) and states that it gives rise to mesothelioma, lung, larynx and ovary tumour and – somewhat less proven – tumours of the pharynx, stomach and colon-rectum (74). INAIL sees neoplasias of the lung, pleura, peritoneum, pericardium and the tunica vaginalis testis as highly attributable to asbestos exposure, and (to a lesser degree of probability) neoplasias of the larynx and gastrointestinal tract.

Greater controversy still surrounds the aetiological role of asbestos in tumours of the urinary apparatus, despite the existence of wide scientific documentation of a causal link (not least, the finding of asbestos fibres in exposed workers' urine and kidneys). The 23 cases from the RI caseload here published give grounds for thought on various counts. First, they comprise workers whose asbestos exposure was certain and recognised: many of them worked directly or indirectly on the railways, or were dockers, shipyard workers, foundry workers or from sugar refineries where the massive asbestos pollution is proven. Among them are cases recognised by INAIL as heavily and continuously exposed to asbestos, or suffering from asbestosis which is a specific marker for asbestos exposure. The sec-

ond reason is the length of exposure and time of latency (the period from when exposure starts to when the neoplasia sets in): respectively 26.2 years (range 7-57) and 33.1 years (range 16-57). Such time-frames are most frequently observed in occupational tumours and may be seen as expressing the high environmental oncogenic potential to which the workers were exposed. Again, the early mean age at onset (59.6 years: range 37-79) points to an occupational origin. The 43.5% of these tumours set in below 55 years of age, 10 years earlier than the incidence rates observed in men over the period 2006-2008 (20). Lastly, the RI caseload came to our notice quite randomly and is not the result of a systematic epidemiological survey detailing the exposure scenario of the worker categories involved: if anything, it underestimates the situation. Let us not forget that it took decades before official recognition was given to pleural mesothelioma – nowadays considered the most specific asbestos-related tumour. Bearing in mind the wide range of risk categories and the picture painted by the scientific literature, we urgently need to implement measures to protect workers and their families, as well as the population at large. Nationwide and internationally, it is to be hoped that new epidemiological efforts will be made to quantify the global cancer risk from asbestos – especially in view of all the “unexpected” malignancies that have occurred – and improve prevention strategies as well as obtaining legislative recognition of the occupational origin behind these neoplasias. Greater light might be shed on this if the categories exposed to asbestos were regularly monitored by oncologists – a project the Ramazzini Institute has in mind to undertake, responding to pressure from workers and as a way of standing by them in this difficult phase.

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Correspondence

Fiorella Belpoggi, PhD
Centro di Ricerca sul Cancro Cesare Maltoni,
Istituto Ramazzini, Castello di Bentivoglio,
Via Saliceto 3 - 40010 Bentivoglio (BO), Italy
belpoggif@ramazzini.it

Critical points in understanding the Italian version of the IIEF 5 questionnaire

Carolina D'Elia, Maria Angela Cerruto, Francesca Maria Cavicchioli,
Sofia Cardarelli, Alberto Molinari, Walter Artibani

Dept. of Urology, Urology Clinic, A.O.U.I. Verona, Italy.

Summary

Purpose: The aim of these study is to assess the understanding of the Italian version of the IIEF-5 questionnaire (International Index of Erectile Function) and the impact of patient's demographic and clinical characteristics on it.

Materials and Methods: Each patient was asked to self complete the Italian version of the IIEF-5 questionnaire and to self report demographic information and any difficulties to complete the questionnaire and which question was considered more difficult to understand.

Results: A total of 89 patients were included in this study. Patients mean age was 61.2 ± 15.4 (standard deviation = SD) years. The mean IIEF score at the time of the visit was 13.5 ± 8.5 (SD). The questions considered more difficult to understand were number 5 (26%), number 4 (20%) and number 1 (20%). Statistically significant differences between patients with and without problems in completing the questionnaire were found in terms of education level ($p = 0.0026$).

Conclusions: Patients with a lower educational level have more difficulties in understanding the questionnaire and the most difficult questions are items number 5, 4 and 1.

KEY WORDS: Erectile function; Questionnaire; Scale; Psychometric evaluation.

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INTRODUCTION

The National Institutes of Health (NIH) Consensus Panel has defined erectile dysfunction (ED) as the consistent inability to attain or maintain a sufficient penile erection for an adequate sexual performance (1).

The prevalence of male erectile dysfunction (MED) has been estimated at 13% to 28% of men aged 40 to 80 years worldwide and at 52% of men aged 40 to 70 years in the *Massachusetts Male Aging Study* (2). Moreover MED has a great impact on health-related quality of life.

The evaluation of erectile function is mainly based on a self-assessment using questionnaires such as the *International Index of Erectile Function* (IIEF) (3).

The IIEF is a validated patient-reported 15 items questionnaire that has been shown to be a cross-culturally and psychometrically valid scale of male erectile dysfunction. This instrument is psychometrically easy to administer in research and clinical settings. The IIEF demonstrates adequate sensitivity and specificity for detecting treatment-related changes in erectile function and has been

used in several studies, performed in a variety of clinical settings and geographic locations.

IIEF investigates the domains of Erectile Function, Orgasmic Function, Sexual Desire, Intercourse Satisfaction and Overall Satisfaction.

In 1999, the IIEF was recommended by the *1st International Consultation on Erectile Dysfunction* and sponsored by the *World Health Organization* (4).

Rosen *et al.* developed in 1999 an abridged five item version of the 15-item IIEF, the IIEF-5, also known as the *Sexual Health Inventory for Men* (SHIM), in order to diagnose the presence and severity of MED (5). Like the IIEF itself, the SHIM has been translated into 32 languages and has been adopted as a standard diagnostic aid for office screening of MED.

The IIEF-5 consists of five questions in two domains, including four questions on erectile function and one question on intercourse satisfaction. It has been developed and validated to discriminate most highly between

men with and without MED. Each IIEF-5 item is scored on a five-point ordinal scale, with lower values representing poorer sexual function.

This questionnaire seems to be a reliable and simple tool, useful in the screening of MED patients.

To the best of our knowledge, there is a lack of studies evaluating the comprehension of the Italian version of IIEF 5.

The purpose of this study was to evaluate the factors which might influence the understanding of the IIEF questionnaire in the Italian population.

MATERIALS AND METHODS

This study is performed like a cross sectional study, in line with the definition by *Abramsson et al.* (6), in order to examine the comprehension of the IIEF 5 in a population of patients attending our outpatient clinic.

We collected data from > 18-year old patients, presenting with several urological complaints, attending our outpatient clinic from 1st February 2011 to 31st March 2011.

Each patient was encouraged to self complete the Italian version of the International Index of Erectile Function (IIEF-5) questionnaire and the International Prostate Symptom Score (IPSS) questionnaire and to self report personal information about age, body mass index (BMI), marital status, education, job. The physician reported information about comorbidities, Eastern Cooperative Oncology Group (ECOG) performance status (7), Charlson comorbidity index (8), New York Heart Association (NYHA) evaluation.

All patients were invited to report, in a specific section of the questionnaire, if they found any difficulties to complete the questionnaire and which question was considered more difficult to understand (see Appendix A).

Moreover, the physician reported whether each patients needed help to complete the questionnaire or not.

The answers to the questions that were replied properly were defined as "appropriate", and the questions left unanswered or replied with more than 1 answer were defined as "inappropriate".

Data were reported as mean and standard deviations (SD). To analyze differences between two independent groups we used the following nonparametric tests: the Mann Whitney U test, the chi-square test, with correction or Fisher's method as appropriate.

In all tests, statistical significance was set at 0.05. All statistical tests were performed using InStat for MAC.

RESULTS

We collected and analyzed data from 89 male patients. Patient mean age was 61.2 ± 15.4 (SD) years. The mean IIEF-5 score at the time of the visit was 13.5 ± 8.5 (SD); mean BMI was 26.8 ± 3.7 .

Sixty-three out of 89 patients (70.7%) were married, and 38 (42.6%) had a high education level (high school diploma or university degree).

With regards to comorbidities, 44 patients (49.4%) had a Charlson score of 0,84 (94.3%) showed an ECOG performance status of 0,81 (91%) presented a NYHA of 1.

Table 1.
Characteristics of the patients.

	n	%
Age (yrs + DS)	61,2 ± 15,4	
BMI	26,8 ± 3,7	
Marital status		
Married	63	70,7
Not Married	26	29,3
Education level		
Primary school	51	57,3
Secondary + high	38	42,7
Charlson score		
0	44	49,4
1	14	15,7
2	22	24,7
3	6	6,8
4	3	3,4
ECOG performance status		
0	84	94,3
not 0	5	5,7
NYHA		
1	81	91
2	7	7,8
3	1	1,2
Diabetes	12	13,4
Hypertension	41	46
Smokers	9	10,1

Twelve patients (13.4%) were affected by diabetes, 41 (46%) had hypertension and 9 (10.1%) were smokers (Table 1).

The most frequent reason of the evaluation was the presence of lower urinary tract symptoms (LUTS): 26 out of 89 (29%). Fourteen patients (15.7%) reported difficulty in completing the questionnaire, and needed help from an attendant or a physician during the visit; 95% (n = 85) of patients completed the questionnaire accurately. The questions considered more difficult to understand were the following: number 5 (Appendix A) (25,9%), number 4 (20,5%) and number 1 (20,5%).

No statistically significant differences between patients without and with problems in completing the questionnaire were found in terms of mean age (60.1 ± 16.1 years vs 67 ± 13.3 , respectively; $p = 0.51$), BMI (26.6 ± 3.3 vs 27.5 ± 5.5 ; $p = 0.67$), marital status, Charlson score, ECOG performance status, NYHA score, diabetes, hypertension, and smoke ($p > 0.05$).

We did not documented statistically significant differences between IIEF scores of low educational (13.1 ± 8.6) and high educational level patients (14.0 ± 8.5) $p = 0.58$.

Statistically significant differences between patients without and with problems in completing the questionnaire were found in terms level of education ($p < 0.05$). Moreover, no significant difference was detected between patients who completed the questionnaire in a not appropriate manner and those who did not ($p = 0.4$).

DISCUSSION

Erectile dysfunction, as demonstrated in the Cologne study and in the MMAS (2), is a high prevalence disease, with a age-related increase from 2.3% to 53.4% (8).

The IIEF 5 questionnaire is the diagnostic tool that can provide the highest age specific and overall ED prevalence (9) and it is the more used self reported questionnaire evaluating erectile dysfunction.

Several papers evaluated the comprehension of the IIEF questionnaire among outpatients clinic.

In 2008 *Serefoglu et al.* (11) analyzed the influence of patient age, education level, and household income on the understanding of the IIEF, in order to evaluate the patients characteristics that can influence the questionnaire comprehension in a cohort of 430 patients.

At the first visit, only 67.2% of the patients responded properly to all of the questions and the most improperly answered question of the IIEF was the item 14 (overall satisfaction). Also in our study the most difficult item was the item 5 (corresponding to the item 7 of the IIEF), a question regarding the intercourse satisfaction of the patient. Older age, lower educational level and/or lower income status may influence the understanding of the questionnaire and the accuracy of the answers: the colleagues demonstrated that the percentage of improper answered questions increased as age increased, whereas it decreased parallel to the increase in educational level and household income ($p = .027$, $p < .001$, $p = .008$, respectively) (11).

Moreover, in 2011 *Ozturk et al.* (12) evaluated also the impact of patient age and educational level on the understanding of the Turkish version of Index of Erectile Function (IIEF), showing that older patients (≥ 60 years) of age and patients with lower education (primary school graduates) could benefit from the assistance of a physician while completing this questionnaire, founding a statistically significant difference between the "self administered" IIEF and the "physician assisted" IIEF (12). Recently, *Bayraktar et al.* (13), evaluating a cohort of 374 patients, remarked that the assistance of a physician can increase the comprehensibility of the IIEF questionnaire in elderly patients and in those with low education levels. About 28% of the patients requested assistance in completing the questionnaire; the number of patients requiring assistance increased with age (about 32% among over 60 year-old patients) and decreased as the level of education increased (34.4% vs 12.% among primary and university graduates, respectively; $p < 0.05$) (13).

Moreover, the results from the physician-assisted IIEF showed an high degree of internal consistency in all patients' groups. Physician assistance increased the comprehensibility of the IIEF and increased the rate of questionnaire completion, suggesting that in some patient groups (elderly, low education) the physician-assisted IIEF may be helpful.

In our experience on 89 consecutive patients in an outpatient clinic, lower educational level can statistically significantly increase difficulties in completing the IIEF 5 questionnaire ($p = 0.0026$) and our patients present more difficulties in understanding the questions 5, 4 and 1 of the IIEF questionnaire. We did not find statistically significant difference between patients without and with

problems in completing the questionnaire in terms of median age, BMI, marital, Charlson score, ECOG performance status, NYHA score, comorbidities or lifestyle.

As regards European studies, *Wiltink et al.* (14) in 2003 validated the German version of the IIEF in patients with ED, Peyronie's disease and controls, showing that about 73% of the patients rated the comprehension as good or very good, 26% as moderate and 1% as very bad. Moreover, 70% of the respondents used the definition of sexual intercourse, sexual activity, ejaculation and sexual stimulation presented on each page of the questionnaire and for 65% of them these definitions were helpful while answering the questionnaire (14).

According to our data, only 15.7% of the patients reported difficulties in understanding the questionnaire and the need for assistance during the filling out, even in absence of definitions of the terms used in the test.

To the best of our knowledge, no other study evaluated the comprehension of the Italian version of the IIEF 5 questionnaire.

Italy is a country with a high average age (about 77 years), and with the majority of the population with a low degree of schooling, achieving the highest level of education as only the middle school license (about 30%) (15).

The data of our population lead us to believe that the patient referring to our clinic have difficulties in understanding the questionnaire and could benefit from the presence, within the text, of the definitions of some terms used and, maybe, from the simplification of any items, as well.

Filling out a questionnaire dealing with the sexual activity can create anxiety, especially in the elderly, which are less accustomed to discuss about their sex live. Looking at the media, we might believe there are no sexual taboos. Conversely, sex diseases remains difficult to discuss, mainly in view of ancient cultural heritage.

People hardly discuss their own sexual experiences and behaviour, and need information and counselling (16), especially if they are elderly with a low schooling grade. Moreover, we did not find an Italian validation of the IIEF 5, and several different version of this questionnaire are used by the physicians.

We believe that it would be more appropriate to facilitate the understanding of the questionnaire, rather than implementing the assistance given by the physician, to allow a self-compilation of questionnaire and avoid possible bias.

Catania et al. (17) suggest that males patients tend to be influenced by variations in item wording, interviewer gender, and respondent control, and this could be a possible bias.

Limitations of this study are certainly represented by the low number of sample, which does not allow a proper assessment of the demographic and clinic characteristics that may influence the understanding of the questionnaire, and the lack of an assessment of inter observer reliability of the questionnaire, difficult to perform taking into account a national health system like the Italian one. A further development of these observations, in addition to the identification of a subgroup of patients who might benefit from medical assistance during filling out

the questionnaire, could be represented by a modification of the items considered most difficult to understand and by a validation of the definition of a group of terms such as “ejaculation” “sexual activity”, “erection” and “sexual satisfaction” present in each page of the questionnaire.

This modification could be tested on a larger cohort of patients, properly as part of a multi centric Italian study.

CONCLUSION

In our experience, patients with lower educational level have more problems in completing IIEF 5 questionnaire and the most difficult questions are number 5, 4 and 1. Several modification are needed, in order to create a more easy form of IIEF 5 questionnaire, with clearer and easier definitions, aiming at developing a reliable screening instrument, suitable for all subgroups of patients.

APPENDIX A: Italian version of IIEF-5 used in the study

- 1) La Sua capacità di raggiungere e mantenere l'erezione è stata:
 - Molto bassa
 - Bassa
 - Moderata
 - Alta
 - Molto alta
- 2) Dopo la stimolazione sessuale ha raggiunto un'erezione sufficiente per la penetrazione:
 - Non ho avuto alcuna attività sessuale
 - Quasi mai/mai
 - Poche volte
 - Qualche volta
 - La maggioranza delle volte
 - Quasi sempre/sempre
- 3) Durante il rapporto sessuale, è riuscito a mantenere l'erezione dopo la penetrazione:
 - Non ho avuto alcuna attività sessuale
 - Quasi mai/mai
 - Poche volte
 - Qualche volta
 - La maggioranza delle volte
 - Quasi sempre/sempre
- 4) Durante il rapporto sessuale, mantenere l'erezione fino alla fine del rapporto è stato:
 - Non ho avuto alcuna attività sessuale
 - Estremamente difficile
 - Molto difficile
 - Difficile
 - Abbastanza difficile
 - Facile
- 5) Quando ha avuto un rapporto sessuale, ha provato piacere:
 - Non ho tentato di avere rapporti sessuali
 - Quasi mai/mai
 - Poche volte
 - Qualche volta
 - La maggioranza delle volte
 - Quasi sempre/sempre

Ha avuto difficoltà nella compilazione del questionario?

- no
- sì

Se sì, quale domanda del questionario le ha creato più difficoltà? _____

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Correspondence

Carolina D'Elia, MD
Dept. of Urology, Urology Clinic, A.O.U.I. Verona,
P.le L.A. Scuro 10 - 37134 Verona, Italy
karolinedelia@gmail.com

Maria Angela Cerruto, MD
mariaangela.cerruto@univr.it

Francesca Maria Cavicchioli, MD
francesca.cavicchioli@gmail.com

Sofia Cardarelli, MD
sofiacarda@yahoo.it

Alberto Molinari, MD
yefet83@yahoo.it

Walter Artibani, MD
walter.artibani@univr.it

Dept. of Urology, Urology Clinic, A.O.U.I. Verona,
P.le L.A. Scuro 10 - 37134 Verona, Italy

Laparoscopic-endoscopic single-site surgery retroperitoneal ureterolithotomy: Technique and initial experience

Volkan Tugcu ¹, Bircan Mutlu ², Volkan Yollu ², Mehmet Yucel ³, Ali Ihsan Tasci ⁴

¹ Associate Professor, Bakırkoy Dr. Sadi Konuk Training and Research Hospital, Department of Urology, Istanbul, Turkey;

² Assistant Dr., Bakırkoy Dr. Sadi Konuk Training and Research Hospital, Department of Urology, Istanbul, Turkey;

³ Assistant Professor, Dumlupınar University Faculty of Medicine, Department of Urology, Kutahya, Turkey;

⁴ Professor, Bakırkoy Dr. Sadi Konuk Training and Research Hospital, Department of Urology, Istanbul, Turkey.

Summary

Objective: Laparoscopic-endoscopic single-site surgery (LESS) is a nearly scarless surgical technique. The aim was to assess the results of our initial LESS retroperitoneal ureterolithotomy (LESS-RU) experience and our technique.

Material and methods: Primary indication for LESS-RU procedure in this study was obstructive or impacted ureteral stone(s) larger than 15 mm and located in the middle or upper part of the ureter in those patients in whom prior interventions have failed. Eighteen patients underwent LESS-RU for upper or middle ureteric stone by one experienced laparoscopist, between December 2008 and December 2009. Patient characteristics, operative details, complications, use of analgesic medication and time to return to work were recorded. **Results:** Eighteen cases were successfully accomplished. The mean patient age was 40.1 yr (19-60 yr), and median BMI was 27.7 kg/m² (21-32). The mean operative time was 69.9 min (50-150 min), and the mean blood loss was 31.9 ml (20-70 ml). Mean stone size was 18.1 mm (range: 16-22). No patient required morphine for pain relief and the main use of oral analgesics was for two days. In postoperative follow-up there was a minimally scar and good cosmetic results were detected.

Conclusions: LESS-RU proved to be safe and feasible. We think that LESS-RU will take place of laparoscopic ureterolithotomy in the near future with better cosmetic results. Further clinical investigation in comparison to the established techniques should take place to evaluate the outcome of LESS-RU.

KEY WORDS: Laparoscopy; Laparo-endoscopic single site surgery; LESS; LESS-ureterolithotomy.

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INTRODUCTION

Minimal invasive surgical techniques has evolved in treatment of urinary stone diseases the last three decades with introduction and common use of extracorporeal shock wave lithotripsy (SWL), percutaneous nephrolithotomy (PNL), and ureteroscopy (URS) (1, 2).

With improved instrumentation availability and increase in surgical education and practice, these techniques have decreased the need for open surgical techniques.

However, these minimally invasive techniques may not be suitable for the treatment of some patients with large, hard, long standing or impacted ureteral calculi (1).

Less postoperative pain, shorter hospital stay and better cosmesis are the advantages of the laparoscopy compared with conventional open surgery. Laparoscopic operations in urologic surgery have significantly increased in last year's (2-6). According to the type of procedure, standard

laparoscopic surgery usually needs three to six ports and each port increases the potential morbidity associated with internal organ damage, bleeding, port-site hernia, and decreasing the cosmetic outcome (7, 8). Laparoendoscopic single site surgery (LESS), which is performed with the open Hasson technique used for primary port access, has arisen with intent of decreasing associated risks. Recently, developed bent and articulating instruments and specialized multilumen ports made LESS applicable. Early clinical series with LESS technique have advocated the feasibility of the technique with safety and high success rates in urologic procedures (9-15). Previously we have reported that the safety and effectivity of LESS-Simple Nephrectomy (LESS-SN) was comparable with Conventional Transperitoneal Laparoscopic-Simple Nephrectomy (CTL-SN). LESS-SN was performed with a surgical incision within the umbilicus to hide surgical scar (16).

In the present study, the feasibility, and efficacy of LESS Retroperitoneal Ureterolithotomy (LESS-RU) was evaluated with our initial experience with 18 cases. To the best of our knowledge, this study is one the first large series with LESS-RU that has been reported.

MATERIALS AND METHODS

A retrospective chart review was performed to evaluate the clinical and demographical features of the patients who underwent LESS-RU for obstructive or impacted ureteral stone(s) in to Bakirkoy Dr. Sadi Konuk Education and Research Hospital between December 2008 and December 2009. All patients have signed informed consent for LESS-RU and currently there is no limitation for the insurance system in our country. The informed consent has included the indications, contraindications and other aspects of the LESS-RU.

Patient selection for LESS-RU

Primary indication for LESS-RU procedure in this study was obstructive or impacted ureteral stone(s) larger than 15 mm and located in the middle or upper part of the ureter in those patients in whom prior interventions have failed. None of the patients had previous abdominal or retroperitoneal surgery. Eighteen patients were available and all were included in the study. In 12 of 18 patients, three sessions of ESWL were unsuccessful and in other six patients, ESWL was relatively contraindicated due to ureteral obstruction. The stones were located in the middle ureter in three patients and in the upper ureter in 15 patients. The calculi were on the right side in nine patients and on the left side in the other nine patients.

Preoperative evaluations

All patients were evaluated with biochemical renal function tests, urine analysis, plain kidney ureter bladder (KUB) films, ultrasonography (USG), and intravenous urography (IVU). All patients had normal total renal-function values (normal serum creatinine). The ipsilateral kidney was found to excrete normally in IVU in all patients.

Operative technique, instrumentation and procedures; The patients received perioperative antibiotics and were

Figure 1.

Retroperitoneal incision (2.5 cm) was performed just below the tip of the 12th rib (midway between the costal margin and the iliac crest in the posterior-axillary line).

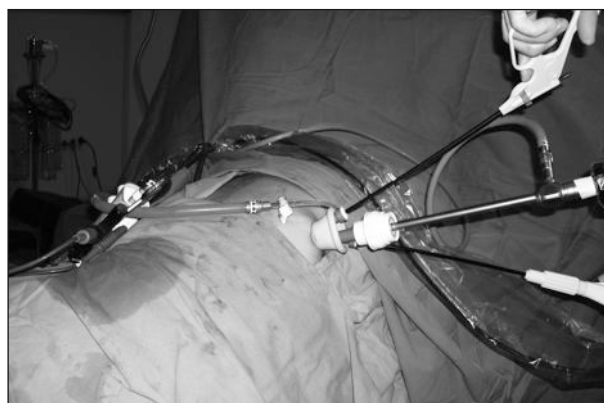


operated on under general anesthesia and orotracheal intubation. Prophylactic antibiotics were administered as needed. Operating room setup was the same as for standard laparoscopic cases. The patient was placed in the full flank position with the side ipsilateral to the stone up and 2.5 cm incision was performed just below the tip of the 12th rib (midway between the costal margin and the iliac crest in the posterior-axillary line). After fascial incision, the posterior pararenal space was exposed bluntly with index finger as far as the peritoneum and a sufficient space for the introduction of a balloon dilator was achieved (Figure 1).

The retroperitoneal operative cavity was established by the method of air balloon dilation. SILS-port (Covidien, Norwalk, USA) was inserted through the incision (Figure 2). The elastic device slightly hourglass shaped can be deployed through a 2.5-cm fascial incision. It has

Figure 2.

SILS-port was introduced into the retroperitoneal operative space and the instruments were inserted through channel of the SILS Port.



four openings: one for insufflation and three that can accommodate trocars 5 to 12 mm sized (17).

The SILS-port was introduced into the retroperitoneal operative space with the help of a clamp and pneumoretroperitoneum was created with carbon dioxide insufflations. Pneumoretroperitoneum pressure was kept at 10-15 mmHg. The instruments were inserted through one of the 5-mm channels and the 12-mm channel of the SILS Port.

A 5-mm 300 high definition rigid laparoscope (*Karl Storz Endoskope, Tuttlingen Germany*) with an integrated camera (*Karl Storz, Tuttlingen, Germany*) was used along with two working instruments. All operative procedures were performed with a combination of instrumentations including flexible forceps and needle drivers (*Cambridge Endoscopic Devices, Cambridge, MA* and *Tyco Healthcare Group, LP*) and conventional laparoscopic (straight) instruments including scissors, ultrasound scissors, and bipolar forceps. The roticulating forceps have 7 degrees of freedom that include pitch and yaw wrist action, which allow for triangulation despite a near-parallel location of the instrument shafts (18). The roticulating forceps (*Cambridge Endoscopic Devices, Cambridge, MA*), held in the right hand, is used to expose the tissue. The straight instrument in the left hand is used to dissect the tissue and to cut.

The dissection in all cases was completed using a combination of roticulating forceps and a straight instrument (e.g., scissors, bipolar forceps) inserted through one of the 5-mm channels and the 12-mm channel of the SILS-Port.

After introduction of laparoscope in to the operative field, ureter was identified anterior to the psoas muscle and the calculus was traced. The ureteral stone was identified as a ureteral bulge and was confirmed by perception of a gritty sensation with an atraumatic Endograsper. A longitudinal ureterotomy was performed over the stone by a cold knife. The stone was extracted and placed on the psoas for later removal in a bag. The distal obstruction was ruled out by inserting a number

eight feeding tube into the ureter and injecting saline through one of the laparoscopic ports. The ureterotomy was closed with interrupted 4-0 absorbable sutures with intracorporeal suturing technique (Figure 3A). Two or three sutures were used according to the ureterotomy size. A drain was leaved in the retroperitoneal operative space in all patients. Operative time and blood loss were recorded in all patients. Blood loss was measured from aspiration materials.

Post-operative period

All patients were let to oral feedings and mobilized on the same evening of operations. Routine physical activities were not limited. The drainage tube was removed when the drainage volume was less than 50 mL per day. Patients with prolonged or increased drainage were evaluated by creatinine levels of the drainage material to exclude urinary leakage. Drainage volumes, presence of urinary leakage and complications were recorded in all patients.

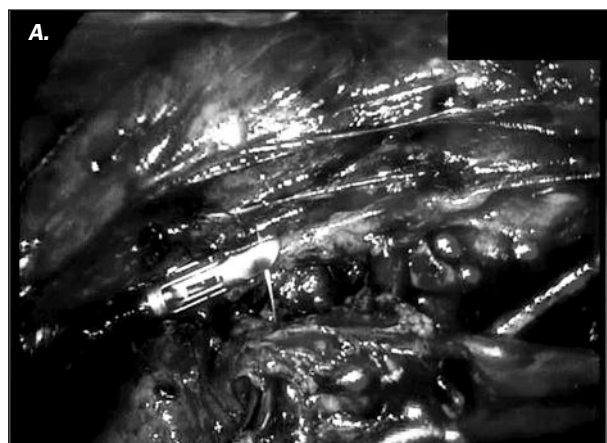
Analgesia management

Analgesic were not routinely administered but sodium diclofenac (75 mg intramuscularly) and/or paracetamol (500 mg oral) were given to achieve analgesia control whenever needed by each patient. Analgesic usage and visual analog pain scores were measured on the day of operation, postoperative day one, and day two. The evaluation of perceived pain was achieved by using VAS score. Visual analogue scale (VAS) score was clearly explained to each patient before examination. VAS score, in which 0 for minimum (no pain) and 10 for maximum (the worst possible pain), was used to evaluate pain scores as a questionnaire form.

Post-operative routine assessments for all patients included serum creatinine assay, urinalysis, and USG one month after the operation. In addition, IVU examinations were performed in all patients three months after the operation. Post-operative incision scar is shown in Figure 3B.

Figure 3.

A) Intraoperative view. B) Postoperative scar.



RESULTS

Patient characteristics were given in Table 1. Eighteen patients were available and all were included in the study. Male/Female ratio was 10/8. The average age was 40.1 years (range: 19-60). The average body mass index was 27.7 kg/m² (range: 21-32).

LESS-RU was successfully completed through the single incision in 18 patients. No conversion to standard laparoscopy or an open procedure was noted. All stones were removed in one session and with no residual stones in none of the patients. The mean blood loss was 31.9 ml (range: 20-70); no transfusion was required. Mean operative time was 69.9 min (range: 50-150).

The mean hospital stay was 2.7 days (range: 1-15) and the mean time to resume work was 6.4 days (range: 4-20). Mean postoperative drain removal time was 2.7 (range: 1-15) days. In two patients prolonged drainage was observed. In one of these two patients drainage was managed conservatively (drain was removed on the postoperative day five). In the other case (our first case) a prolonged drainage (more than 10 days) was observed and treated with a ureteral JJ stent (drainage ceased on day five following placement of ureteral JJ stent). Surgical site infection was not observed in any patient. One patient had a temperature of 38°C on postoperative day two, which responded to antipyretics and antibiotics.

The mean analgesic dose used on the day of operation was 75 mg (range: 0-150) sodium diclofenac. None of the patients required morphine or other opioid derivatives. Mean VAS scores on the day of operation, postoperative day one and postoperative day two were 1.83 (1-4), 0.66 (0-2) and 0.11 (0-1), respectively.

Port site scar was followed with clinical and photographic documentation in all the patients. A clinical impression was obtained that LESS-RU technique has resulted with fewer scar formation. Postoperative incision scar after three months is shown in figure 3B.

All patients were clinically evaluated three months after LESS-RU. All were symptom-free and ultrasonography, urinalysis and serum creatinine assay results were within normal ranges. All patients had normal findings on follow-up IVU with no urinary tract obstruction and ureteral stricture.

Table 1.
Patient characteristics.

Patient number (n)	18
Gender (m/f)	10/8
Age (years)	40.1 (19-60)
BMI (kg/m²)	27.7 (21-32)
Stone size (mm)	18.11(16-22)
Operation time (min)	69.9 (50-150)
Blood loss (ml)	31.9 (20-70)
Drain removal (day)	2.7 (1-15)
Complications (n)	
Prolonged urinary leakage	2
Fever	1
Return to work (day)	6.4 (4-20)

m: male; f: female; BMI: body mass index

DISCUSSION

Standard techniques in laparoscopic urological procedures require the insertion of three to six laparoscopic ports directed to the surgical site. Ports may be introduced with a transabdominal or retroperitoneal approach. Sometimes, during laparoscopic surgery additional port insertion can be needed. All additional port insertions may be considered as an increased risk of morbidity from pain, bleeding, hernia and/or internal organ damage, and even undesirable cosmesis. All these risk factors may be observed independently of the size of the trocar site incisions (7, 8).

Continuous refinements of the surgical technique and of laparoscopic instrumentation allow a limited surgical incision (such as in LESS). Also the use of natural orifice transluminal endoscopic surgery (NOTES) eliminated the need for several skin incisions (9-15). Optimization of these procedures aims to make easy the handling of the instruments, to optimize visceral retraction, and to decrease the clashing of the instruments (19, 20). Their feasibility as well as their safety should be tested in urologic procedures (9-15).

The first transperitoneal laparoscopic ureterolithotomy was performed by *Raboy et al.* in 1992 (21). In 1992, Gaur described retroperitoneal laparoscopic surgery by hydraulic balloon dilatation system with straightforward access to the retroperitoneum (22). Due to smaller working space and difficulty in identifying the anatomic structures most laparoscopic surgeons have not preferred the retroperitoneal approach, particularly for the LESS.

Further advancements in technical equipment and several technical modifications such as ability of parallel port insertion and handling, roticulation, and intracorporeal suturing entailed the feasibility of LESS-RU with the elimination of the multiple triangulated ports used in traditional laparoscopic surgery and (19, 20, 23).

Both the transperitoneal and retroperitoneal approaches are available in laparoscopy and LESS. The advantages of the retroperitoneal approach, compared with the transperitoneal approach, include more direct access to the retroperitoneal organs, less need for visceral retraction, elimination of the risk of intraperitoneal contamination with tumor or infection, and absence of peritoneal irritation by insufflated CO₂. The disadvantages of the retroperitoneal approach, compared with the transperitoneal approach, include a smaller working space, difficulty in identification of anatomic structures, and clashing of instruments during dissection.

The results of our first experiences with LESS-RU have suggested that LESS-RU is feasible and safe for use in surgical treatment of upper and mid ureteral stones. LESS-RU was observed to be acceptable for the patients with better cosmesis.

All our patients were stone-free after LESS-RU. This was similar with the results of previous series of laparoscopic ureterolithotomy (21, 24). In our study, all upper ureteral stones were successfully managed and all patients were rendered stone free without conversion to open or conventional laparoscopic surgery.

In our series, two of the eighteen patients had prolonged postoperative urinary drainage. One of them became dry at fifth day, and the other had prolonged postoperative

urinary drainage that necessitated placement of a JJ stent. For this case, that was our first patient, we did not use the roticulating needle holder. Therefore, we believe that the use of the roticulating needle holder in LESS-RU makes suturing more feasible. In the literature, Faroog Qadri *et al.* reported a 2.38% rate of urinary leakage (3 out of 820 patients) in their series of retroperitoneal laparoscopic ureterolithotomy (RLU) and Kijvikai *et al.* reported leakage only in one out of 30 cases (25, 26). LESS-RU required longer operative time in the first cases. As we got used to the technique and to the instruments, the operation time became shorter. The duration of the procedure ranged between 50-150 minutes in our series while it was between 45-120 minutes and 75-270 minutes in the series of RLU reported by Faroog Qadri *et al.* and Kijvikai *et al.*, respectively (25, 26). In our study the mean analgesic dose used on the day of operation was 70 mg diclofenac sodium, whereas mean dosage of 30 mg of Ketoprofen® was used postoperatively by Jeong *et al.* in their series of RLU (1).

One of the major complications of LUL is stenosis. Too tight sutures may lead to ureteral-wall ischemia and further stenosis. During ureteral suturing aim should be approximation of the ureteral edges in order to facilitate healing and not to be watertight. Moreover electrical burn to the ureter may be another predisposing factor for stricture formation and we think that using cold knife for this purpose is a wiser choice. Bellman and Smith suggest that the ureterotomy has to be made in a longitudinal manner, because disrupting of the ureteral blood supply is limited with a longitudinal than a transverse incision (27). We did not observe any ureteral strictures in any of the 18 patients at 3-month follow-up by IVU in our series. These results were similar with those previously reported in other RLU series (25, 26).

Recent studies show that LESS and LESS-RU can be used for ureteral stones (28-30). Although the current study assessed the safety and feasibility of LESS-RU, the number of cases is too low for drawing any solid conclusions. In general, further clinical evaluation is deemed necessary in order to establish LESS-RU as an alternative to LUL. Moreover, the evolution of conventional laparoscopic surgery to LESS may not have the same impact that laparoscopy had over open surgery. Accumulation of experience with the flexible instruments will improve operative times. The current cases were performed by a laparoscopic surgeon with experience in performing hundreds of laparoscopic procedures. Although it is feasible for LESS-RU to be performed by less-experienced laparoscopic surgeons, the learning curve is expected to be steep.

The introduction of pre-bent instruments would provide new options for LESS instrumentation.

CONCLUSION

The results of this study have suggested that LESS-RU is a feasible and safe option (with better cosmetic results) for patients with obstructive or impacted ureteral stones when SWL has failed or is not feasible. Thus further clinical studies are needed to evaluate all aspects of this procedure.

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Correspondence

Volkan Tugcu, MD

Associate Professor, Bakırkoy Dr.Sadi Konuk Training and Research Hospital, Department of Urology, Istanbul, Turkey
volkantugcu@yahoo.com

Bircan Mutlu, MD

Volkan Yollu, MD

Assistant Dr., Bakırkoy Dr.Sadi Konuk Training and Research Hospital, Department of Urology, Istanbul, Turkey

Mehmet Yuçel, MD

Assistant Professor, Dumlupınar University Faculty of Medicine, Department of Urology, Kutahya, Turkey
myucel75@gmail.com

Ali Ihsan Tasci, MD

Professor, Bakırkoy Dr. Sadi Konuk Training and Research Hospital, Department of Urology, Istanbul, Turkey

Solitary lung metastasis after radical prostatectomy in presence of undetectable PSA

Pietro Pepe¹, Filippo Fraggetta², Francesco Tornabene³, Maurizio Nicolosi³,
Francesco Aragona¹

¹ Urology Unit - Cannizzaro Hospital, Catania, Italy;

² Pathology Unit - Cannizzaro Hospital, Catania, Italy;

³ Thoracic Unit - Cannizzaro Hospital, Catania, Italy.

Summary

Clinical recurrence in the absence of biochemical PSA failure is uncommon and accounts for less than 1%; we report a rare case of solitary lung metastasis in a patient with undetectable PSA level (<0.1 ng/mL) after radical prostatectomy (RP) for prostate cancer (PCa). An asymptomatic 75-year-old man nine years after RP showed a solitary lung mass (about 2 cm) at chest radiography; the 18-FDG-PET/CT confirmed the presence of an isolated mass suspicious for primitive pulmonary cancer. The initial histological specimen after RP showed a mixed acinar and ductal PCa (Gleason score 7, pT3aN0 stage, negative surgical margins). A segmental pulmonary resection was performed and definitive specimen demonstrated a single ductal PCa metastasis; after six months from surgery the patient was free from recurrence. In conclusion, in patients with atypical PCa variants imaging studies may be considered in the follow up even in presence of undetectable PSA because they could benefit from early salvage therapy.

KEY WORDS: Solitary lung metastasis; PSA; Prostate cancer; Recurrence; PSA failure.

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INTRODUCTION

The prostate specific antigen (PSA) has become an invaluable tool in the diagnosis and follow up of patients with prostate cancer (PCa); a PSA value below 0.2 ng/mL reflects absence of recurrence after radical prostatectomy (RP), on the contrary biochemical failure (PSA kinetics, PSA velocity, PSA doubling time) is the first evidence of disease progression preceding clinical manifestation of metastatic disease by 5 years to 7 years (1). Because of the very high negative predictive value of undetectable PSA level (< 0.1 ng/mL) after RP, such patients usually are considered disease free and do not require any additional imaging test or even digital rectal examination (DRE).

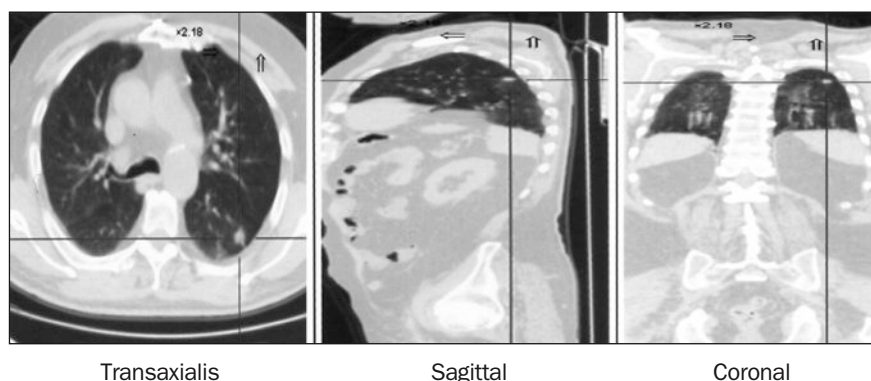
Clinical recurrence in the absence of biochemical PSA failure is uncommon and has been previously presented in few selected case reports (2-8). A case of isolated lung recurrence in a patient with undetectable PSA level after RP is herein reported.

CASE REPORT

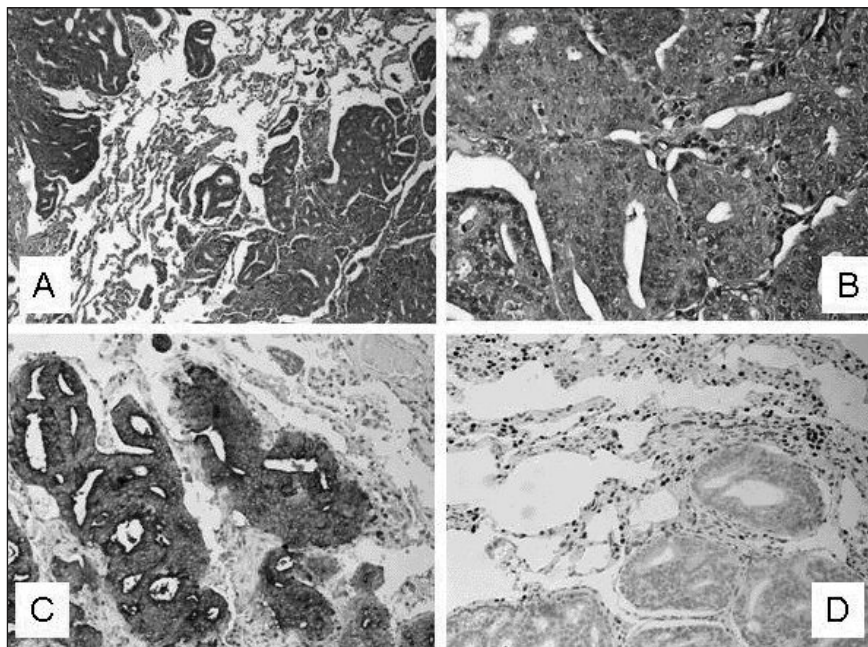
A 75-year-old man nine years after RP showed at chest radiography a solitary lung mass (about 2 cm) of the upper left lobe. At the time of PCa diagnosis the patient had a serum PSA equal to 8.3 ng/mL with positive DRE, negative lung and abdomen computerized tomography (CT) and negative bone scintigraphy. Initial definitive histology showed a mixed acinar and ductal PCa characterized by Gleason score of 7 (4 + 3), pT3aN0 stage and negative surgical margins; the patient did not performed any adjuvant treatment and underwent PSA evaluation every six months. When the lung mass was diagnosed the patient was asymptomatic, PSA value was undetectable, chest CT and 18-FDG-PET/CT showed a solitary lung mass suspicious for primitive cancer (Figure 1). A segmental pulmonary resection was performed and definitive specimen demonstrated a ductal PCa metastasis with a diameter equal to 2 cm (Figure 2). The surgery was successful and the patient was discharged after 10

Figure 1.

18-FDG-PET/CT: solitary lung mass (about 2 cm) of the upper left lobe.

**Figure 2.**

Lung metastasis showed a prevalent cribriform growth pattern (A) with neoplastic cells presenting evident nucleoli (B). Tumour was strongly immunoreactive for PSA (C) and negative for TTF1 (D) thus supporting the prostatic origin of the lesion.



days from metastasectomy; six months after surgery the patient performed a 18-FDG-PET/CT resulting free from recurrence.

DISCUSSION

The characteristic features of patients with PCa who experienced disease progression with low or undetectable PSA levels included Gleason scores > 7 and atypical histologic variants (small cell, ductal and neuroendocrine cancers) (2, 4, 9); disease progression despite undetectable PSA levels virtually never

of all prostate cancer cases (4).

Our patient underwent pulmonary surgery for the suspicious of primitive lung cancer and we were surprised when definitive histology showed a ductal PCa metastasis.

In conclusion, clinical progression to metastatic disease after RP can occur despite undetectable PSA levels; although this is an uncommon clinical scenario, in patients with undifferentiated tumors or atypical cancer variants imaging studies may be considered for follow up even when the PSA level remains undetectable because they could benefit from early salvage therapy.

occurred in the ordinary low-risk patient (ie, clinical T1c with Gleason scores of 6). Lung metastases in advanced PCa stage are not isolated and the clinical incidence is significantly lower than autopsy rates; in a series of terminal patients, pulmonary metastases were clinically and autopsy detectable in 5.7% and 25%, respectively (2). Solitary pulmonary recurrence from PCa without concurrent bone or lymph metastases is unusual and difficult to detect; the data showed in literature mainly refer to patients in whom PSA failure come before clinical metastases (3-6). *Fabozzi et al.* (7) in a series of 1290 patients found radiologic evidence of solitary pulmonary metastases in only 11 (0.86%) cases; recently, *Wallis et al* (3) in a literature review found only 18 patients with solitary lung metastasis combined with PSA recurrence who underwent different salvage treatment (surgery, hormone therapy or chemotherapy). *Chao et al.* (5) and *Smith et al.* (8) in two patients with isolated lung metastasis reported a clinical benefit from metastasectomy: in the first case PSA become undetectable and in the second the patient resulted free from recurrence for 12 years, respectively. Recently, *Leibovici et al.* (2) on 4145 patients with PCa reported only 2 (0.2%) men with isolated lung recurrence in presence of undetectable PSA level.

In our clinical case, to our knowledge the first with isolated recurrence after RP without PSA failure, the solitary lung metastasis was secondary to ductal PCa that is a rare histological subtype of PCa, accounting for 0.4% to 0.8%

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Correspondence

Pietro Pepe, MD
Urology Unit - Cannizzaro Hospital
Via Messina 829 - Catania, Italy
piepepe@hotmail.com

Filippo Fraggetta, MD
Pathology Unit - Cannizzaro Hospital
Catania, Italy

Francesco Tornabene, MD
Maurizio Nicolosi, MD
Thoracic Unit - Cannizzaro Hospital
Catania, Italy

Francesco Aragona, MD
Urology Unit - Cannizzaro Hospital
Via Messina 829 - Catania, Italy

Robotic malfunction during live robotic urologic surgery: Live surprise in a robotic surgery congress

Volkan Tugcu¹, Bircan Mutlu¹, Abdullah Erdem Canda²,
Erkan Sonmezay¹, Ali Ihsan Tasci¹

¹ Bakirkoy Dr. Sadi Konuk Training and Research Hospital, Urology Clinic, Istanbul, Turkey;

² Ankara Atatürk Training and Research Hospital, 1st Urology Clinic, Ankara, Turkey.

Summary

Background: Robotic-assisted laparoscopic radical prostatectomy (RARP) has increasingly become a preferred treatment of choice. Since it is a device dependant surgery, robotic surgery may be a challenging procedure due to failure.

Methods: We report how we managed to complete successfully a case of RARP with laparoscopic approach in spite of right robotic arm failure during live surgery.

Results: A 56-year-old male patient diagnosed with localized prostate cancer (PCa) (Gleason score 3 + 3 = 6) with a serum prostate specific antigen (PSA) level of 7.6 ng/mL was elected for a live RARP case during the 1st Turkish National Robotic Surgery Congress in 2011. Following 120 minutes from starting the RARP procedure, the right robotic arm failed surprisingly with a “recoverable fault” message appeared on the screen. Pressing “recover fault” button did not work and the right arm operated for few seconds more but the fault repeated again. We replaced the robotic instruments, shut down and restarted the system again that were all useless. Finally, all of the arms were out of order and we were not able to use the robot anymore. Therefore, we laparoscopically completed the procedure successfully without converting to open surgery.

Conclusions: Although da Vinci surgical system failure rarely occurs, surgical team should be prepared to convert to open or complete the procedure laparoscopically. Having previous laparoscopic experience seems to be an advantage in order to complete the procedure without converting to open. Patients should be informed about the possibility of robotic failure and about its consequences before the surgery.

KEY WORDS: Da Vinci robot; Robotic malfunction; Robotic failure; Radical prostatectomy.

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INTRODUCTION

Radical prostatectomy (RP) provides long-term cancer control in patients with localized prostate cancer (PCa) (1). Robot-assisted radical prostatectomy (RARP) has increasingly become a preferred treatment of choice both by patients and urologists since its introduction in 2001 (2). Although robotic surgery is a major technological advancement, instrumentation failure during robotic surgical procedures is a challenging problem for the operating team.

Herein, we report how we managed to complete successfully a case of RARP with laparoscopic approach following right robotic arm failure (*da Vinci-S surgical robot, Intuitive Surgical, Sunnyvale, CA*) that occurred during

live surgery at the 1st Turkish National Robotic Surgery Congress that was held in Istanbul, Turkey in 2011. To the best of our knowledge, this is the first case report related with da Vinci-S surgical robot failure that occurred during live surgery in a robotic surgery congress.

CASE REPORT

A 56-year-old male was referred to our outpatient clinic with lower urinary tract symptoms. His serum prostate specific antigen (PSA) level was 7.6 ng/mL. Digital rectal examination was normal without any nodules. Trans Rectal Ultrasound (TRUS) demonstrated a 26 cc prostate

and TRUS guided 14-core prostate biopsy revealed prostatic adenocarcinoma with a Gleason score of 6 (3+3) that was detected in 1 core.

This patient was elected as a candidate for a RARP procedure to be operated as a live surgery during the 1st Turkish National Robotic Surgery Congress. His body mass index (BMI) and American Association of Anesthesiologists (ASA) Score were 27 kg/m² and 2, respectively. After patient positioning, insertion of trocars and docking of the surgical robot, we started the live RARP case with audience in the congress hall watching the procedure with great interest. Almost 120 minutes following the start of the RARP procedure, just after insertion of the prostate into the endobag and before starting the urethro-vesical anastomosis, surprisingly right robotic arm failed and a message of "recoverable fault" appeared on the screen.

We pressed the "recover fault" button and the right arm operated for a few seconds. However, the fault repeated again. We removed the robotic instruments and undocked the robot, shut down and restarted the robotic system however, this time none of the arms were working and we were not able to use the surgical robot anymore. Therefore, we decided to complete the case with laparoscopic approach and performed the urethro-vesical anastomosis laparoscopically. Console time was 120 minutes and laparoscopic surgery time was 40 minutes. Therefore, overall surgery lasted 160 minutes with an estimated blood loss of 60 mL.

Postoperative patient follow up was uneventful. Patient was discharged following drain removal on the postoperative day 3. Urethral catheter was removed on postoperative day 10. Patient was fully continent on 1st-month follow-up and serum PSA value was 0.01 ng/mL. Pathology of the surgical specimen revealed prostatic adenocarcinoma with a Gleason score of 6 without any extracapsular extension. Surgical margins were negative and there was no seminal vesicle or vas deferens invasion for which a pT2a stage was assigned.

We immediately informed the manufacturer's company and the problem related with the robotic system was solved by the manufacturer's technician on the same night.

DISCUSSION

Robotic assisted urological procedures are increasingly being performed and currently, RARP is the most commonly used approach in the surgical treatment of localized PCa in the United States (3).

We have been using the da Vinci-S 4-arm surgical system since March 2009 at our institution and until now we have performed 200 RARP cases. Apart from the malfunction described above, we experienced another failure (a non-recoverable fault) that occurred in the system prior to anesthesia induction of a patient, before performing our 20th RARP. We shut down and restarted the system but it did not operate. Therefore, we postponed the case. We informed the manufacturer's company and the problem was solved by the manufacturer's technician on the same night again.

Cost and probable robotic malfunction during robotic

surgery seem to be the major concerns of this high technological surgery (4, 5).

The fault that we faced during live surgery was initially a recoverable fault that turned out to be an unrecoverable fault that prevented us using the surgical robot in order to complete the case. Because our team is experienced in laparoscopic urology, we were able to complete the case with laparoscopy.

Therefore, surgeon's previous laparoscopic experience seems to be essential to be able to complete the robotic procedures laparoscopically, thus the patient may still benefit from the advantages of minimally invasive approach including shorter hospital stay and less post-operative pain. Without any previous laparoscopy experience, one has to convert the case to open surgery. Surprisingly, this robotic fault repeated in the following 5 more cases. During these cases, almost in the middle of each case, the fault occurred with a message of "recoverable fault" that appeared on the screen, 6 or 7 times each time. We pressed "recover fault" button each time and thereafter the second robotic arm kept on working without any problems and we were able to complete the following cases. We informed the robot company after each time we faced this problem, they checked the surgical system but the fault was not recognized. In the literature, others also reported similar system errors but none of them occurred during live surgery as happened to us (8, 9). Therefore, it might be wise to have somebody who is experienced in laparoscopy or is able to complete the robotic surgical procedure that is being performed as a live robotic surgical case in a congress or symposium with conventional laparoscopy. Otherwise, the case has to be converted to open if robotic malfunction occurs during live surgery and could not be fixed at that moment. The occurrence of this malfunction during a live robotic surgery session in a robotic urology congress definitely made the session very interesting with many comments and discussion from the audience and participants.

The rate of non-recoverable fault was reported to be 0.4% in the literature (6). Recently, Akbulut *et al.* have reviewed the published literature related with robotic malfunction during robotic surgery (7). According to their review, most of the reported robotic malfunctions are related with setup joint, robotic arms, power, monitor, camera, optical, hand piece, console, software and the system itself (7).

Due to their review, robotic malfunction rate is between 0.5% and 4.6% (7).

CONCLUSIONS

Although malfunction of the robotic surgical system is reported to be very low, when it happens, conversion to either laparoscopic or open surgery is always possible. Therefore, patients should be informed about this possibility before the robotic surgery. Previous adequate laparoscopic experience of the console surgeon or one of the surgical team members might be important that could enable the team to complete the procedure laparoscopically that might also benefit the patient particularly in a live surgery session.

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Correspondence

Volkan Tugcu, MD
Associate Professor of Urology
Bakirkoy Dr. Sadi Konuk Training and Research Hospital
Urology Clinic, Istanbul 34147 Turkey
volkantugcu@yahoo.com

Abdullah Erdem Canda, MD
Ankara Atatürk Training and Research Hospital, 1st Urology Clinic
Ankara, Turkey.

Bircan Mutlu, MD
Erkan Sonmezay, MD
Ali Ihsan Tasci, MD
Bakirkoy Dr. Sadi Konuk Training and Research Hospital
Urology Clinic, Istanbul 34147 Turkey

Spontaneous postmenopausal urethral prolapse: A case report and review of literature

Ugur Yucetas¹, Muhsin Balaban², Alper Aktas², Bulut Guc³

¹ Istanbul Training and Research Hospital, Urology Clinic, Istanbul, Turkey;

² Kartal Training and Research Hospital, Urology Clinic, Istanbul, Turkey;

³ Marmara University School of Medicine, Istanbul, Turkey.

Summary

Urethral prolapse is a circular protrusion of the distal urethra through the external meatus. It is very rare condition seen mostly in black premenarcheal black girl and occasionally in postmenopausal white women. We present a case of spontaneous urethral prolapse in 63-year-old postmenopausal white women with successful management with estrogen treatment.

KEY WORDS: Menopause; Urethra; Prolapse.

Submitted 18 September 2012; Accepted 31 October 2012

INTRODUCTION

The eversion of urethral mucosa via meatus is defined as the urethral prolapse and it is described firstly by Solingen in 1732. This condition is very rare in female and mostly seen in premenarcheal black girls and occasionally in postmenopausal white women (1). Because urethral prolapse is so rare, the rate of misdiagnosis is high. The differential diagnosis of urethral mass are broad, ranging from a simple urethral caruncle to rhabdomyosarcoma. Conservative treatment is the first choice in the young women but surgical excision can be necessary in the strangulated cases (2). In this case report, we present a postmenopausal spontaneous urethral prolapse to increase the knowledge of this rare condition and review of the literature.

CASE REPORT

A sixty three-year old female patient was admitted our institution with history of severe dysuria, frequency and gross hematuria for five days. In her past medical history, she had three vaginal delivery. Physical examination was revealed a rounded, reddish purple, hemorrhagic doughnut-shaped mass protruding from the anterior vaginal wall (Figure 1a). Urinary system radiologic evaluation was completely normal and urine analysis showed microscopic hematuria. To exclude malignancy and clarify the hematuria, cystoscopy was performed and there was no abnormality in the bladder. Then 18 F Foley catheter was

indwelled and patient discharged the same day. Topical estrogen cream applied to prolapsed urethra 3 times daily for 3 weeks, in combination with sitz bath. After the therapy, the urethral prolapse resolved and voiding symptoms of patient improved (Figure 1b).

DISCUSSION

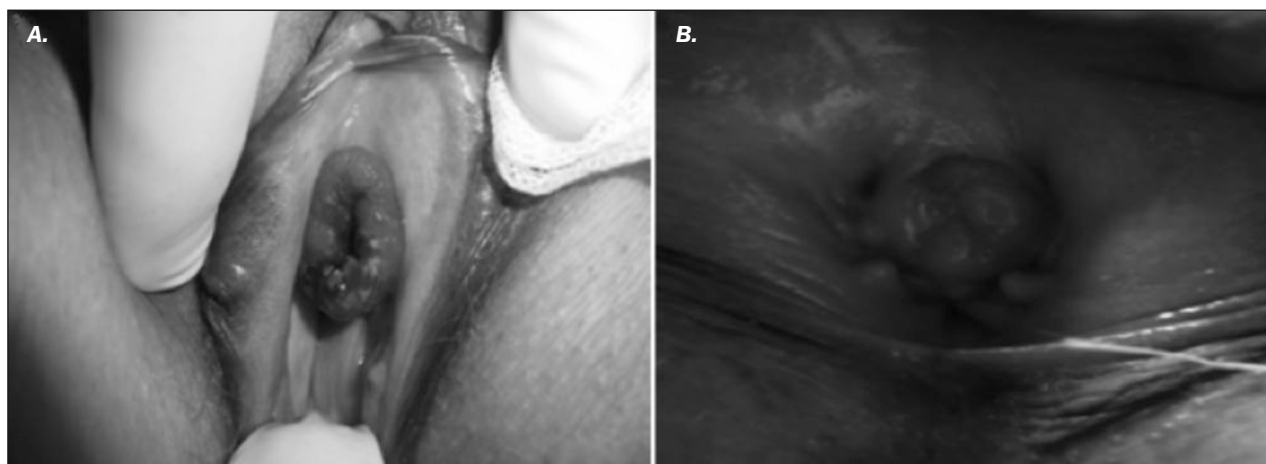
Urethral prolapse is a pathological situation which occurs when the mucosa evaginates beyond urethral meatus, resulting in vascular congestion and edema of the prolapsed tissue. The exact cause of urethral prolapse is unknown but it has been linked to the hypoestrogenic state, perineal trauma (childbirth), neuromuscular disorders, and poor nutrition and hygiene (3). Risk factors for urethral prolapse in children include increased intraabdominal pressure as a result of chronic coughing or constipation. In our patient, there was no evidence of increased intraabdominal pressure and any other etiologic factor that lead to urethral prolapse. Postmenopausal low estrogen may have been the etiology for spontaneous urethral prolapse in our case.

Urethral prolapse is relatively uncommon and has bimodal age groups. It occurs almost exclusively in black girls younger than 10 years, and rarely in postmenopausal white women.

The most common symptom for the pediatric patient is vaginal spotting. Sexual abuse should be considered in all

Figure 1.

*A: reddish purple, hemorrhagic doughnut-shaped mass protruding from the anterior vaginal wall.
B: urethral view after the estrogen therapy.*



children with genital complaints (4). In postmenopausal women vaginal bleeding is fairly common and microscopic or macroscopic hematuria can be seen. Other symptoms include dysuria, frequency, urgency and difficulty voiding. Our patient presented with dysuria, frequency and macroscopic hematuria.

The diagnosis of the urethral prolapse depends on the physical examination. The presence of urethral canal in the centre of the swelling tissue is pathognomonic. The differential diagnosis of urethral prolapse include prolapse of the bladder, prolapse of a urethral polyp, ureterocele, ectopic ureter, urethral cyst, hydrometrocolpos, condyloma acumulate, periurethral abscess, and sarcoma botryoides (4). If the diagnosis is not completely certain after a detailed history and careful physical examination, the patient should be examined under general anesthesia to rule out more serious lesions. Surgical excision and pathologic examination confirm the diagnosis. Conservative treatment for urethral prolapse include local hygiene with sitz baths and topical antibiotic, steroid and antibiotic use. Although conservative treatment is mostly efficient for younger patient, sometimes fails in postmenopausal women and surgery is mandatory. The effectiveness of medical therapy is debated in the literature. Some authors report local application of antibacterial ointment allows symptoms of the prolapsed mucosa to resolve. In one series, the prolapsed urethra persisted at a 3-year follow-up, even though the symptoms disappeared (5). In another series, treatment of urethral prolapse with topical estrogen cream resulted in complete involution in 3-6 weeks, without recurrence (6). Failure of medical therapy or presence of strangulated urethral prolapse mandates surgical excision. We applied three weeks topical estrogen with sitz bath to our case, and urethral prolapse improved without need any further intervention. In conclusion, urethral prolapse is uncommon condition which occurs only in women. Initial approach to this rare entity should be conservative and surgery is indicated only if strangulation of urethral prolapse occurred or medical therapy failed.

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Correspondence

Ugur Yucetas, MD
Istanbul Training and Research Hospital, Urology Clinic
Istanbul, Turkey

Muhsin Balaban, MD
Yeni mh. Pegaz sok. Soyak Evreka: A5-44
Soganlik, Kartal - 34880 Istanbul, Turkey
muhsinbalaban1980@yahoo.com

Alper Aktas, MD
Kartal Training and Research Hospital, Urology Clinic
Istanbul, Turkey

Bulut Guc, MD
Marmara University School of Medicine
Istanbul, Turkey

**SELECTED PAPERS FROM
18th NATIONAL CONGRESS
SOCIETÀ ITALIANA DI ECOGRAFIA UROLOGICA
ANDROLOGICA NEFROLOGICA**

Stresa, 17-19th May 2012

Guest Editor

Pasquale Martino



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Discorso del Presidente della SIEUN al 18° Congresso Nazionale di Stresa del 17 maggio 2012



Pasquale Martino

Gentili Autorità, autorevoli Colleghi, carissimi Amici, graditissimi Ospiti, desidero porgervi il più cordiale saluto ed il mio sincero ringraziamento, per essere oggi presenti così numerosi a questa cerimonia inaugurale del 18° congresso della società italiana di ecografia urologica andrologica e nefrologica, organizzato in questa splendida cornice di Stresa dall'amico e vicepresidente della SIEUN Paolo Consonni.

Organizzare oggi un congresso non è assolutamente facile: la situazione economica in cui versa il nostro paese è nota a tutti e ben si comprende la grande difficoltà che si incontra nel riuscire a reperire i fondi.

Ringrazio quindi particolarmente Paolo e la segreteria organizzativa the office, nelle Sig. Paola e Cristiana per l'impegno profuso e chiaramente tutte le ditte farmaceutiche e di strumentazione che con il loro contributo hanno permesso la realizzazione di questa manifestazione.

Il programma scientifico di questo congresso, ritengo sia molto stimolante e nello specifico accanto a tematiche sicuramente innovative approfondirà argomenti di consolidata tradizione ecografica nel campo urologico, andrologico e nefrologico, che necessitano di una puntuale disamina alla luce delle novità tecnologiche attualmente presenti; tecnologie che, specialmente in campo urologico, nei tempi hanno fatto passi da gigante.

Questo prorompente cammino testimonia dell' incisivo apporto che l'Ultrasonografia ha fornito in questi ultimi anni allo sviluppo delle scienze mediche e al miglioramento dei livelli di salute e di benessere della popolazione.

Sono particolarmente orgoglioso del numero e della qualità dei lavori scientifici, alcuni stranieri, pervenuti.

Questa mattina abbiamo avuto un corso pratico, molto seguito di ecografia interventistica, in diretta dalla sala operatoria di Castellanza, dove vari colleghi si sono alternati e ci hanno mostrato come l'ecografia ha indubbiamente un ruolo fondamentale nel soltanto nella diagnosi, ma anche come guida privilegiata nelle tecniche chirurgiche mini invasive, che oramai rappresentano il futuro della chirurgia urologica.

Sono certo quindi che il congresso offrirà validi spunti di discussione e sono sicuro che ciascuno dei partecipanti potrà tornare a casa arricchito.

Passiamo ora alla Società.

Quest'anno l'attuale Comitato Direttivo della SIEUN termina il suo mandato e durante questo congresso ci saranno le nuove elezioni.

Ruberò solo pochi minuti per fare il punto su quello che la Società ha fatto in questi ultimi quasi quattro anni, che hanno caratterizzato il suo mandato e la mia Presidenza.

Le linee programmatiche che l'attuale Comitato Direttivo della SIEUN dal suo insediamento, avvenuto nel settembre del 2008, in occasione del centenario della SIU, si era proposto sono state quasi tutte realizzate:

Abbiamo oramai consolidato i rapporti con le più importanti società scientifiche, abbiamo intensificato gli stessi con le Università e con le Asl.

Molti dei soci della SIEUN fanno parte come docenti del corso di perfezionamento universitario di ecografia urologica ed andrologica, presente oramai da molti anni, più di sedici, presso l'università di Bari ed in passato di Perugia.

Alcuni componenti dell'attuale direttivo della SIEUN fanno parte del gruppo di lavoro sull'imaging, della Società Italiana di Urologia. Gruppo che organizza, tra l'altro, corsi pratici durante i congressi nazionali della SIU; quest'anno è anche impegnato nella realizzazione delle linee guida sulla ecografia urologica e andrologica.

Sono stati individuati dei delegati regionali della società che coprono tutto il territorio nazionale, questo al fine di avere una pluralità culturale di più soggetti per concorrere alla diffusione della ecografia in campo uro-nefro-andrologico che sia correttamente eseguita per il bene del paziente, è già alcuni, supportati dalla società, hanno organizzato corsi ed eventi scientifici e gli altri li stanno imitando.

Nel 2011 è stato organizzato, ad opera del delegato regionale della Sicilia, il dott. Barbera, il primo corso regionale SIEUN che ha avuto un buon successo.

Oramai il sito web della SIEUN, dopo diversi anni di buio è una realtà, questo anche grazie all'apporto logistico ed economico della ditta Bruel e Kjaer, che ringrazio pubblicamente.

Per questo congresso è stato possibile inviare gli abstracts dei lavori via web, e, a brevissimo, sarà lo stesso per quanto riguarda il pagamento delle quote associative. Il sito si propone di diventare il punto di incontro dei vari soci che potranno, attraverso una news letter, scambiarsi informazioni.

Anche quest'anno la società curerà la pubblicazione degli Atti in lingua Inglese sulla rivista indicizzata dell'archivio italiano di Urologia ed Andrologia, da sempre la rivista ufficiale della SIEUN, e questo mi riempie di orgoglio.

Abbiamo inoltre buttato le basi per la realizzazione di un atlante con dvd di ecografia a cui parteciperanno i più illustri cultori italiani e stranieri in campo urologico ed andrologico e riteniamo diventerà un testo base per i cultori della materia: sono sicuro che il Comitato Direttivo eletto porterà a compimento tale opera.

Il buon livello scientifico che la società negli ultimi anni ha raggiunto è dimostrato da fatto che la stessa è stata, e continua ad essere, presente con corsi relazioni e letture, nei congressi delle più prestigiose società specialistiche di Urologia ed ultrasuoni, le cito la SIU (Società Italiana di Urologia), l'AURO.it (Associazione Urologi Italiani), la SIA (Società Italiana di Andrologia), la SIN (Società Italiana di Nefrologia); la SIUrO (Società Italiana di Urologia Oncologica), la SIUD (Società Italiana di Urodinamica), la SUICMI (Società Urologica Centromeridionale e delle Isole), l'ESUI (Section of Urological Imaging della Società Europea di Urologia, la SIUMB (Società Italiana di Ultrasonologia in Medicina e Biologia).

E nel 2012 saremo ancora presenti in congressi nazionali ed internazionali.

Come abbiamo già visto in questo congresso sono presenti molti Presidenti di queste Società che danno lustro e arricchiscono con le loro letture magistrali questa manifestazione.

Gli incontri scientifici che la società organizza sono patrocinati dalle più importanti società scientifiche italiane e alla stessa società è stato richiesto il patrocinio per numerosi congressi nazionali, questo a dimostrazione della considerazione che la SIEUN si è costruita in questi anni

La SIEUN insieme alla SIUrO ed ad altre società è stata tra quelle fondatrici del Gruppo Italiano Biopsia prostatica, che ha elaborato le linee guida, che quest'anno vedranno una versione aggiornata durante la consensus conference che si terrà a Bologna, a giugno durante il congresso nazionale della Società Italiana di Urologia Oncologica, presieduto dal Prof. Martorana.

Il Comitato Scientifico e Direttivo della Società durante i Congressi Nazionali individua i migliori contributi scientifici proposti che vengono premiati. Durante questo congresso consegneremo il premio in memoria di un collega "Giuseppe Pace" che verrà consegnato insieme ad altri premi, a giovani colleghi che si sono distinti con i loro contributi scientifici. Ci sarà inoltre un premio speciale in memoria del Dott. Mario Sarteschi, recentemente scomparso, che sarà consegnato al migliore contributo in tema di ecografia andrologica.

Nel 2010 durante il 17° congresso Nazionale della nostra società, che ho avuto l'onore di organizzare a Bari, l'assemblea dei soci ha ratificato alla unanimità il nuovo statuto dalla società, che finalmente è al passo con i tempi.

Come si può quindi intuire, Il Consiglio Direttivo, in questi ultimi anni ha lavorato alacremente, sia sul piano organizzativo che scientifico, come testimoniato dalle numerose riunioni effettuate e questo ha fatto sì che la società potesse essere conosciuta ed apprezzata.

Attualmente il numero degli iscritti in regola negli ultimi quattro anni, è aumentato del 40% e il bilancio economico della società, nonostante le ristrettezze del momento, risulta consolidato e di questo sicuramente ne sarà contento il tesoriere.

Tanta strada è stata fatta, ma tanta ne rimane ancora da percorrere, con la soddisfazione e la gioia delle mete raggiunte e con lo sguardo attento a nuovi obiettivi che potranno essere realizzati con l'impegno costante e la partecipazione attiva di tutti.

Desidero ringraziare i Soci, i Delegati Regionali, il Comitato Scientifico e soprattutto i componenti del Comitato Direttivo, per i successi raggiunti.

Li cito personalmente il past president Guido Virgili, i vice presidenti Paolo Consonni e Paolo Rosi, i consiglieri: Marco Bitelli, Giuseppe Deramo, Roberta Gunelli, Giovanni Liguori, Luigi Mearini, Francesco Petrarulo, Vincenzo Scattoni, il tesoriere, Andrea Galosi ed il segretario e amico Silvano Palazzo, che ha diviso con me ansie e successi. Un grazie ad ognuno di voi per il sostegno e il contributo che mi avete voluto dare in questi quattro anni, sicuramente stimolanti e densi di soddisfazioni.

Sono certo che il nuovo Comitato Direttivo eletto consoliderà i risultati ottenuti in modo che la SIEUN possa raggiungere vette sempre più alte nel panorama uro-andrologico italiano.

Ringrazio tutti voi per la pazienza e dichiaro aperto il 18° Congresso della Società Italiana di Ecografia Urologica, Andrologica Nefrologica.



ORIGINAL PAPER

TURP and PVP treatments are really similar? From subjective feeling to objective data. Pilot study (proof of concept) prospective randomized trial

Giuseppe Albino, Ettore Cirillo Marucco

U.O. di Urologia, Ospedale "L. Bonomo", Andria, ASL BAT, Italy

Summary

Transurethral resection of the prostate (TURP) is the gold standard of surgical treatment of the BPH. Alternative surgical techniques have been developed for patients with blood coagulation disorders secondary to anticoagulants or antiplatelet intake. The photoselective vaporization of the prostate (PVP) by Green Laser is a technique used with the aim of obtaining tissue ablation with instantaneous hemostasis. In our experience we sensed the feeling of some differences between the two technologies. For each patient, we calculated the difference (Δ) between Q_{max} , Q_{med} , PMR to 6 months after surgery compared with preoperative measurements (ΔQ_{max} , ΔQ_{med} , ΔPMR). In the comparison between PVP and TURP the differences between the results, in terms of ΔQ_{max} (11.04 vs. 8.9 ml/sec), ΔQ_{med} (5.87 vs. 3.64 ml/sec), ΔPMR , are not statistically significant, therefore it is clear that if we consider the average of the results, significant differences do not come out between the two techniques. Instead, the real differences emerge from consideration of standard deviations: the higher standard deviations of Q_{max} and Q_{med} of PVP compared to TURP (8.29 vs 5.01; 5.51 vs 1.64) indicate that the final result of an intervention being performed by TURP is nearest to the expected preoperatively result; on the contrary the final result of an operation being performed by PVP shows a significantly higher variability. As regards for our clinical decision it follows that the proposal of a surgical procedure which shows the "risk" of a higher variability of the final result is justified only in cases of high cardiovascular or blood coagulation "risk".

KEY WORDS: PVP; TURP; Vaporization; BPH.

INTRODUCTION

The treatment of benign prostatic hyperplasia (BPH) with lower urinary tract symptoms (LUTS) can be pharmacological or surgical. Transurethral resection of the prostate (TURP) is the gold standard of surgical treatment (1-3). The use of bipolar resectors has further improved the efficacy and safety of TURP. Unfortunately, the men with LUTS due to BPH, because of the age, have a high incidence of cardiovascular risk and blood coagulation disorders due to the intake of anticoagulants or antiplatelet agents. For this reason, alternative surgical techniques have been developed, including those that use laser technology. The photoselective vaporization of the prostate (PVP) by Green Laser is a technique used with the aim of obtaining tissue ablation with instantane-

ous hemostasis (4). The efficacy and safety of the PVP are shown in 152 indexed articles, 23 of which are reviews. In our experience we felt some differences between the two technologies. This study has helped us to pick them up objectively.

MATERIALS AND METHODS

The patients who were included in the study, had the following characteristics: they had LUTS and prostate gland < 60 g in weight, measured by ultrasonography, they had absence of bladder stones, and no history of episodes of acute urine retention and no clinical finding for prostate cancer. The mere suspicion of prostate can-

cer by PSA or DRE was considered an exclusion criteria. One hundred and five consecutive patients were enrolled and randomized in two groups, according to a proportion of 2:1. Patients in group I underwent a cervico-urethral disobstruction intervention by TURP with Gyrus bipolar resector; patients in group II underwent PVP with 80W KTP (70 TURP vs 35 PVP).

TURP with bipolar gyrus resector

The Gyrus Plasmakinetic Superpulse System has already been reported several times (5, 6). It consists of a 17 mm-long, gold-plated, crescent-shaped cutting tool, with no major differences from the standard monopolar instruments. The positive and negative poles are on the same axis and are isolated from each other by a ceramic connecting piece (7).

The Plasmakinetic Generator (Gyrus Medical) generates strong, pulsatile, bipolar energy, which generates the working temperature on the cutting tool, permitting maximum tissue dissection with minimum collateral damage. In addition to allowing effective cutting, it has been constructed to achieve optimum hemostasis and prevent adherence to the tissue. Only a small proportion of the energy applied leads to tissue vaporization, which means that the tissue remains for histological analysis, as with monopolar TURP. One main advantage of the bipolar instrument is that it is possible to use normal saline solution (NaCl 0.9%) as irrigating fluid. The absence of reverse current is intended to decrease the risk of burns and subsequent stricture formation (8, 9). Studies already published have described advantages of bipolar resection with regard to the frequency of the TUR syndrome (10, 11).

PVP by KTP "Green light" laser

By a laser generator with a potassium titanyl phosphate (KTP) crystal, we obtain a light with 532 nm wavelength. Because the KTP laser is strongly absorbed by hemoglobin and minimally absorbed in water, the KTP laser effectively enables vaporization rather than coagulation of prostatic tissue and has excellent hemostasis ability (12).

In 1998, Malek *et al.* reported the first clinical trial with a 60 W KTP laser (13). Later, the GreenLight company improved the power of the 520 nm laser up to 80 W KTP and 120 W high-performance system (HPS) with lithium triborate (LBO), which have led several urologists to use these new instruments for BPH treatment (14). PVP is considered to be an easier technique for the urologist to master, and the operator can create a similar postoperative prostatic fossa resembling that of TURP (15). The indication for PVP is almost the same as with TURP. With the use of the 80 W KTP laser instrument, prostates larger than 80 ml can be effectively treated (16). As the 120 W HPS laser entered the urologic stage, treatment of large prostates became easier than before. PVP can be used in patients with a high risk of treatment-related complications, in elderly aged 80 years or older, and even in anticoagulant users (17). Usually PVP can be performed in a smaller diameter cystoscopic sheath. The camera unit has to be protected from the laser light by a specific filter.

The GreenLight laser has a green color as the name

implies. Without the filter, the video monitor will be filled with green color whenever the laser firing is on. Normal saline is recommended as the irrigating fluid and can be drained continuously through the drainage system. After the cystoscopic instrument is inserted, the operator should check the intravesical environment and the position of the ureteral orifices. Laser firing should be under the guidance of the red guiding light. Vaporization can be started at the 6 o'clock position of the bladder neck or at one of the two lateral lobes of the prostate. Effective lasing makes many air bubbles in the cystoscopic field of vision. During vaporization, the position of the trigone, bladder neck, and ureteral orifices should be imprinted in the surgeon's mind for protection from unwanted damage. After making sufficient space in the prostatic fossa mimicking TURP, a Foley catheter needs to be placed for several to 24 hours before a voiding trial (18).

Each patient performed a uroflowmetry, with evaluation of the maximum flow (Qmax), average flow (Qmed) and ultrasonography for the measurement of post-micturitional residual (PMR) before surgery and 6 months after surgery (19, 20).

The results of the two groups were compared and evaluated by statistical analysis (t-test and standard deviation).

RESULTS

For each patient, we calculated the difference (Δ) between Qmax, Qmed, PMR to 6 months after surgery compared with preoperative measurements (Δ Qmax, Δ Qmed, Δ PMR).

In the Tables 1, 2 we report for each group the arithmetic means of Δ Qmax, Δ Qmed, Δ RPM, statistical significance (p) confidence intervals (CI) and standard deviations (dev. stand.).

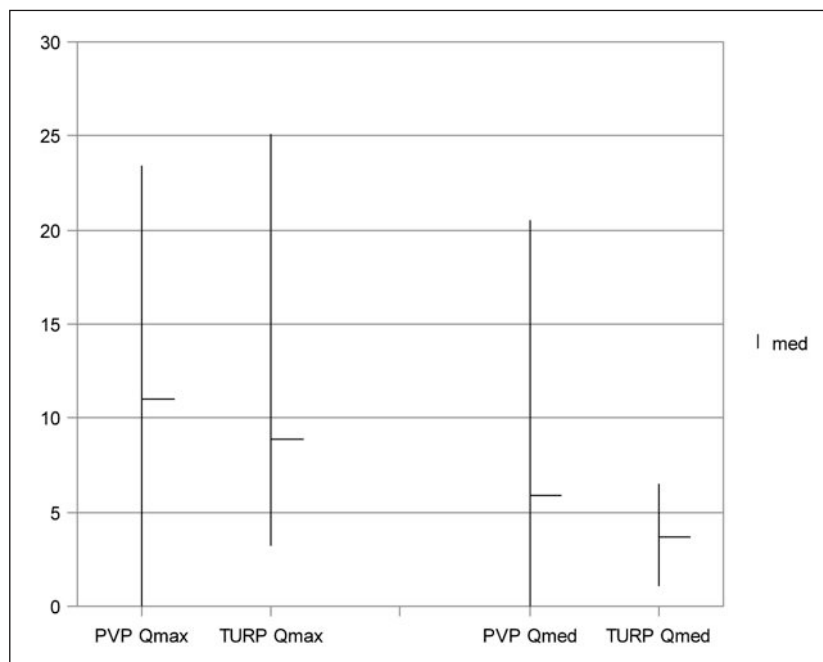
Table 1.
Results.

	PVP	TURP	p
Patients	35	70	
Δ Qmax ml/sec	+11.04	+8.9	n.s.
CI	0-23.4	3.2-25.1	
Dev. Stan	8.29	5.01	
Δ Qmed ml/sec	+5.87	+3.64	n.s.
CI	0-20.5	1.1-6.5	
Dev. Stan	5.51	1.64	
Δ RPM ml	-43	-86.15	n.s.
CI	-10-60	-20-200	
Dev. Stan	28.87	52.05	
	One patient has undergone TURP	One patient received blood transfusion	

DISCUSSION

Since the comparison between PVP and TURP differences between the results, in terms of Δ Qmax, Δ Qmed, Δ RPM, are not statistically significant. It means that "on average" flowmetry improvement between the two techniques is comparable. This evidence confirms what has already occurred in the indexed literature (21, 22).

Table 2.
Confidence intervals.



Therefore it is clear that, considering the average of the results, significant differences do not emerge between the two techniques. If one looks at the literature concerning the comparison between TURP and PVP with Green Light 80W laser, one realizes that in all cases only the average values of ΔQ_{\max} , ΔQ_{med} , ΔRPM were always taken into account. We noticed that the confidence intervals and standard deviations have never been taken into account. Instead, the real differences emerge from consideration of standard deviations: the higher standard deviations of Q_{\max} and Q_{med} of PVP compared to TURP (8.29 vs 5.01; 5.51 vs 1.64) indicate that the final result of an intervention being performed by TURP is nearest to the preoperatively expected result; on the contrary the final result of an operation performed by PVP shows a significantly higher variability. A different picture emerges from the comparison between TURP and Light Green 120-W Laser: the most recent case series show comparable results for both average outcomes and the confidence intervals (23).

This means that the final outcome of an intervention with Green Light 120-W should have a degree of variability similar to that of an operation performed by TURP. So if the data of literature are confirmed, the PVP is close to the gold standard represented by TURP, not with the Green Light 80-W but with the Green Light 120-W.

CONCLUSIONS

"On average" the final results of a cervico-urethral dissection by PVP or TURP are comparable but, when we consider the individual patient, it is possible that more patients of those undergoing PVP than TURP, may be disappointed in their expectations. For our clinical decision

it follows that the proposal of surgical procedure which shows the "risk" of a higher variability of the final result is justified only in cases of high cardiovascular or blood coagulation "risk".

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Correspondence

Giuseppe Albino, MD
U.O.C. di Urologia, Ospedale "L. Bonomo", ASL BAT
C.so Istria, 1 - 76123 Andria, Italy
peppealbino@hotmail.com

Ettore Cirillo Marucco, MD
U.O.C. di Urologia,
Ospedale "L. Bonomo", Andria, ASL BAT, Italy

CASE REPORT

Spontaneous rupture of urinary bladder: A case report and review

Giuseppe Albino ¹, Francesco Bilardi ², Domenico Gattulli ², Pietro Maggi ³,
Antonio Corvasce ¹, Ettore Cirillo Marucco ¹

¹ U.O. di Urologia; ² U.O. di Chirurgia generale; ³ U.O. di Diagnostica per Immagini,
Ospedale "L. Bonomo", Andria, ASL BAT, Italy

Summary

Spontaneous rupture of the bladder is a rare event. The clinical presentation shows the signs and symptoms of peritonitis, but the diagnosis is made at the operating table. This event is burdened with a high mortality rate. We present a case report of a 73 year old man who came to our observation. He was a chronic carrier of urinary catheter, at least 7 times removed traumatically by himself. At the time of admission he showed drastic reduction in urine output, absence of hydronephrosis, normal functioning of the catheter, a tense and widely meteoric abdomen, the presence of air-fluid levels, normal kidneys, absence of free fluid in the abdomen. The CT showed a fluid collection of about 7cm diameter between the bladder and rectum. The explorative laparotomy found a small fissuration of the posterior wall of the bladder. For his severe conditions, the patient died a few hours after surgery, in intensive care unit. Although it is a rare event, since 1980, 177 cases of spontaneous rupture of the bladder are reported in the literature. Their causes may be essentially divided into two groups: for increase of intravesical pressure; or for weakening of the bladder wall. In most cases, the spontaneous rupture of the bladder takes place in presence of a urothelial neoplasm or after radiation therapy of the pelvic organs. The etiology of spontaneous rupture of the bladder in our case does not relate to a bladder tumor or radiotherapy. It may have been caused by repeated episodes of acute retention of urine with extreme bladder distension up to 3 liters. It is not easy to think of a bladder perforation in patients presenting signs of peritonitis without a history of bladder cancer or pelvic radiotherapy. A CT with intravesical contrast medium could help the diagnostic orientation.

KEY WORDS: Urinary bladder; Spontaneous rupture; Acute abdomen; Differential diagnosis.

INTRODUCTION

Spontaneous rupture of the bladder is a rare event. The clinical presentation shows the signs and symptoms of peritonitis, but the diagnosis is made at the operating table. This event is burdened with a high mortality rate.

MATERIALS AND METHODS

Case report

A patient of 73 years old came to our attention. He suffered from type II decompensated diabetes, uncontrolled hypertension with episodes of 200/100 mmHg of arterial

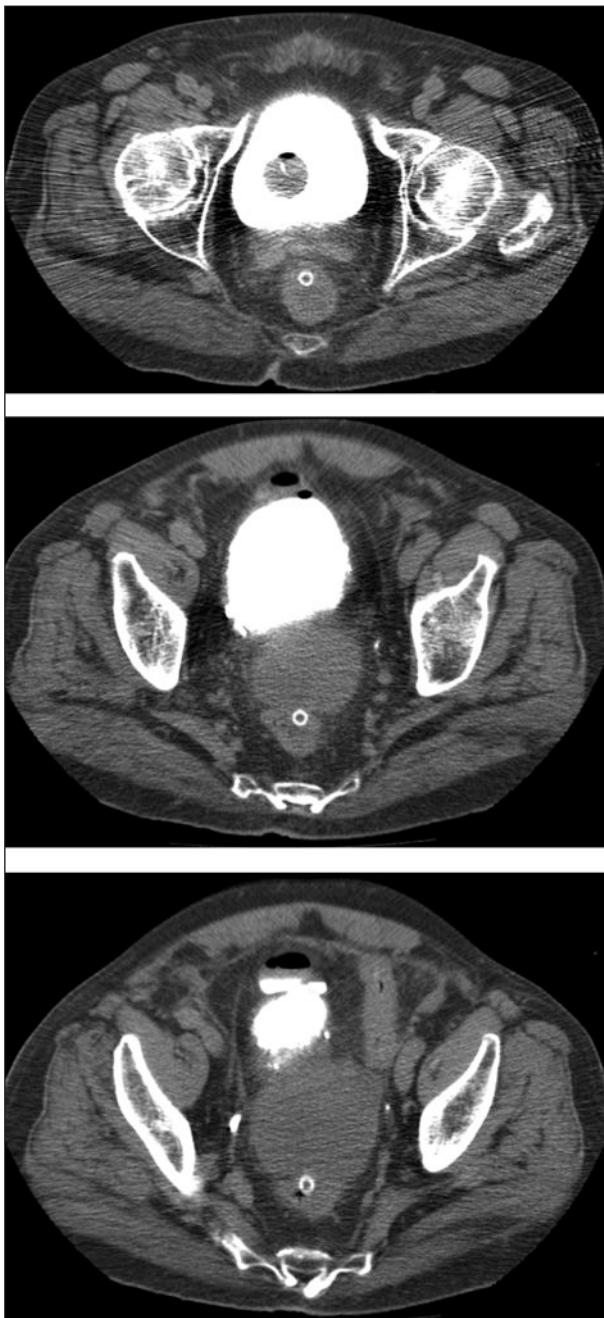
pressure, anterior left hemiblock and ventricular hypertrophy, chronic cerebral vascular disorders of walking, prostatic hyperplasia with prostate approximately 98 grams in weight and diverticulum on the anterior wall of the bladder. In the last 3 years 6 emergency room visits were recorded as consequences of accidental falls and at least 7 episodes of traumatic and accidental removal of the catheter, urethral trauma with hematuria, bilateral hydronephrosis and rising creatinine. About 3 months before he had undergone cystoscopy, negative for bladder cancer. Considering the general clinical condition, the patient decided not to perform a cervico-urethral dis-

obstruction surgery and chose to be a carrier of indwelling bladder catheter. Before the last access to the emergency room, with the catheter in place, the creatinine remained in the normal range (0.9 mg/dl) and kidneys showed no hydronephrosis. At the time of admission he showed drastic reduction in urine output (1000 ml 3 days), the absence of hydronephrosis, normal functioning of the catheter (verified by testing the filling and emptying, under ultrasonographic vision), a tense and

widely meteoric abdomen, the presence of air-fluid levels in the first CT without contrast, normal kidneys, absence of free fluid in the abdomen. The second CT performed after 4 hours with contrast medium into the bladder, showed a fluid collection of about 7 cm diameter between the bladder and rectum (Figure 1).

Figure 1.

The CT with contrast medium into the bladder, showed a fluid collection of about 7 cm diameter between the bladder and rectum.



RESULTS

Exploratory laparotomy revealed a sacculated collection secondary to a small fissuring of the posterior bladder wall. It was organized, with a pseudo wall of inflammatory origin easily removable. There was the presence of signs of peritonitis. A bladder wall repair was performed. The patient was transferred to intensive care unit for serious conditions, but he died a few hours after surgery.

DISCUSSION

Spontaneous rupture of the bladder is a rare event. Only a timely surgical repair offers the possibility of a favorable prognosis, but the conditions in which the clinical picture is presented almost never are clear and for this reason it is a clinical condition burdened with a very high mortality rate.

In most cases, the spontaneous rupture of the bladder takes place in presence of a urothelial neoplasm or after radiation therapy of the pelvic organs (1). Although it is a rare event in literature, since 1980, 177 cases of spontaneous rupture of the bladder are reported, the causes of which are essentially divided into two groups: 1) for increase of intravesical pressure; 2) for weakening of the bladder wall (2).

The etiology of spontaneous rupture of the bladder in our case does not relate to a bladder tumor or radiotherapy. It may have been caused by repeated episodes of acute retention of urine with extreme bladder distension up to 3 liters, as in an episode occurred the year before the fatal event. This is likely because it has been shown that prolonged overdistension can cause injury to the neural pathways responsible for micturition (3), can reduce the bladder elasticity, can alter the biochemical and neuronal responsiveness of the bladders (4). There is increasing evidence that ischaemia followed by reperfusion may be responsible for the progression of bladder dysfunction associated with overdistension (5). Hypoxia-reoxygenation and ischaemia-reperfusion lead to the generation of Reactive Oxygen Species (ROS) and the increased ROS may contribute to the voiding dysfunction by inhibition of bladder afferent and efferent nerve activity ATP- and acetylcholine-mediated contraction, and bladder cell apoptosis (6).

Three other episodes of acute urine retention due to the catheter dislocation occurred in the weeks before. It is possible that the bladder wall has been weakened by mechanical and metabolic, structural and cellular stress and probably this was the cause of a micro laceration, after which a flap-mechanism was created in the bladder wall (Figure 2).

In this way it is triggered the sequence of events that are gradually precipitates in the last 3 days before the patient death.

Figure 2.

A flap-mechanism was created in the bladder wall (hypothesis).



CONCLUSIONS

It is not easy to think of a bladder perforation in patients presenting signs of peritonitis without a history of bladder cancer or pelvic radiotherapy. A CT with intravesical contrast medium could help the diagnostic orientation.

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Correspondence

Giuseppe Albino, MD

U.O.C. di Urologia, Ospedale "L. Bonomo", ASL BAT
C.so Istria, 1 - 76123 Andria, Italy
peppealbino@hotmail.com

Francesco Bilardi, MD

Domenico Gattulli, MD

U.O. di Chirurgia generale,
Ospedale "L. Bonomo", Andria, ASL BAT, Italy

Pietro Maggi, MD

U.O. di Diagnostica per Immagini,
Ospedale "L. Bonomo", Andria, ASL BAT, Italy

Antonio Corvasce, MD

Ettore Cirillo Marucco, MD

U.O.C. di Urologia,
Ospedale "L. Bonomo", Andria, ASL BAT, Italy

ORIGINAL PAPER

PCA3 score accuracy in diagnosing prostate cancer at repeat biopsy: Our experience in 177 patients

Michele Barbera¹, Pietro Pepe², Quintino Paola¹, Francesco Aragona²

¹ Urology Unit - Giovanni Paolo II Hospital, Sciacca, Italy;

² Urology Unit - Cannizzaro Hospital, Catania, Italy.

Summary

Introduction: To evaluate PCA3 score accuracy in prostate cancer (PCa) diagnosis in patients undergoing repeat saturation prostate biopsy (SPBx).

Material and methods: From January 2010 to March 2012, 177 patients (median 64 years) with primary negative extended biopsy underwent a SPBx (median 28 cores) for persistent suspicion of PCa. The indications for repeat biopsy were: PSA > 10 ng/mL, PSA values between 4.1-10 or 2.6-4 ng/mL with free/total PSA < 25% and < 20%, respectively; moreover, before performing SPBx PCA3 score was evaluated.

Results: Median PSA was 9.5 ng/mL (range: 3.7-28 ng/mL): in 74 (41.8%) cases PSA was > 10 ng/mL, in 99 (56%) and 4 (2.2%) was included between 4-10 and 2.6-4 ng/mL, respectively. Median PCA3 score was equal to 52 (range 3-273); 140 (79%) and 100 (56.5%) patients had a PCA3 score greater than 20 and 35, respectively. A T1c PCa was found in 48 patients (27.1%); PCA3 score was 60 (median; range: 7-208) in the presence of PCa and 34 (median; range: 3-268) in the absence of cancer ($p < 0.05$). Diagnostic accuracy, sensitivity, specificity, PPV and NPV of PCA3 score cut-off of 20 vs 35 in PCa diagnosis were 43.5 vs 50.2%, 91.7 vs 73%, 25.6 vs 41.8%, 31.5 vs 35% and 89.5 vs 80.6%, respectively.

Conclusions: PCA3 score reduce number of unnecessary repeat SPBx; using a PCA3 cut-off of 20 vs 35 would have avoided 21% vs 37.8% of biopsies while missing 8.4% (4 cases) vs 27% (13 cases) of significant PCa, respectively.

KEY WORDS: PCA3 score; Prostate cancer; Saturation prostate biopsy; Repeat biopsy.

INTRODUCTION

The estimated rate of prostate cancer (PCa) at repeat prostate biopsy is equal to 22-41% (1, 2) and in an attempt to improve PSA specificity and reduce the number of unnecessary biopsies many molecular forms of PSA (i.e. free/total PSA, pro-PSA) have been brought into clinical practice, especially in the presence of PSA values lower than 10 ng/mL. Prostate Cancer Gene 3 (PCA3) score (a gene-based marker) has been used to select patients for repeat prostate biopsy (3-5); many Authors have reported a significant difference of PCA3 score in patients with positive or negative repeat biopsy (6, 7) and, recently, the PCA3 score has been incorporated into nomograms to assist in the decision to assignment of an individual risk of

PCa (8) in case of repeat biopsy. However a PCA3 cut-off of 35 seems to provide an optimal balance between sensitivity and specificity in diagnosing PCa (6, 7), a PCA3 cut-off lower than 20 reduce number of unnecessary repeat biopsy missing a little percentage of cancer (lower than 10%) (9) in comparison with PCA3 cut-off of 35; moreover, a PCA3 cut-off of 20 is highly predictive of pathological indolent PCa (pIPCa) especially in patients candidate to Active Surveillance (10) or in presence of a biopsy microfocus of PCa (11).

Our scope is to evaluate the accuracy of PCA3 score in PCa diagnosis in patients undergoing repeat saturation prostate biopsy (SPBx).

MATERIAL AND METHODS

From January 2010 to March 2012, 177 Caucasians patients (median age 64 years; range: 48-74) with primary negative extended biopsy (12-18 cores) and negative digital rectal examination (DRE) underwent a repeat SPBx (median 28 cores; range 24-39) for the persistent suspicion of PCa. The indications for repeat biopsy were: persistently high or increasing PSA values, PSA > 10 ng/mL, PSA values between 4.1-10 or 2.6-4 ng/mL with free/total PSA < 25% and < 20%, respectively (12). SPBx (2) was performed transperineally using a tru-cut 18 gauge needle (Bard; Covington, GA), a GE Logiq 500 PRO ecograph (General Electric; Milwaukee, WI) supplied with a biplanar transrectal probe (5-6.5 MHz) under sedation and antibiotic prophylaxis.

Before performing SPBx PCA3 score was evaluated: first-catch urine samples were collected following digital rectal examination (three strokes per lobe) and processed to quantify PCA3 and PSA mRNA concentrations using the PROGEN-SA PCA3 assay (Gen-Prob Inc. San Diego, CA USA) (13). The performance characteristics at different PCA3 score cut-off of 20 vs 35 were evaluated in terms of diagnostic accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV); moreover, a probability (p) value of less than 0.05 was considered statistically significant.

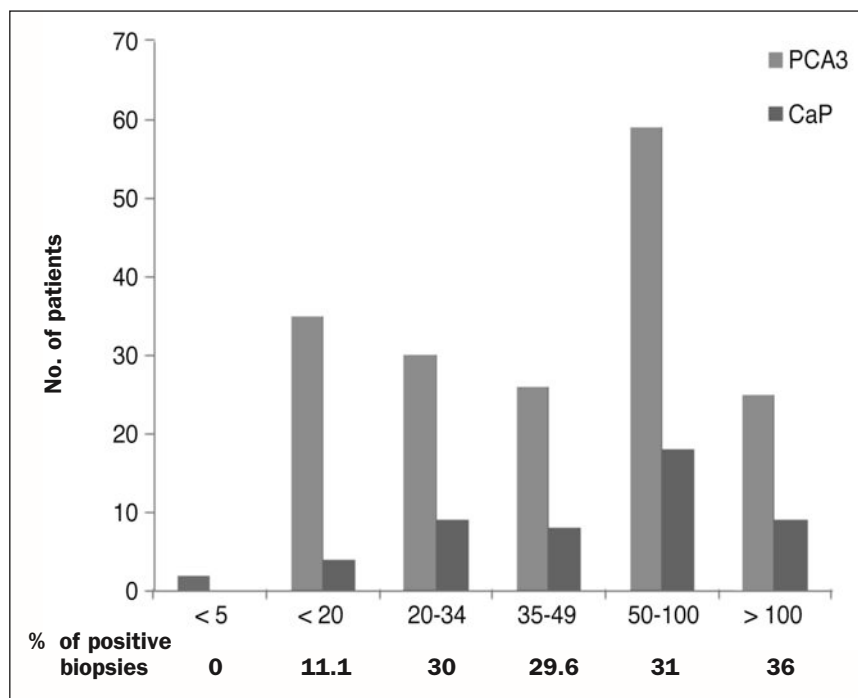
In presence of PCa either retropubic radical prostatectomy (RRP) with bilateral obturator and external iliac lymphadenectomy vs radiotherapy vs active surveillance (AS) was offered. The volume of cancer in the entire specimen was reported according to Bostwick (14); moreover, the incidence of PCa that fulfilled the Epstein criteria (15) for pIPCa (cancer volume less than 0.5 mL and no Gleason grade 4 or 5 disease) was recorded.

RESULTS

Median PSA was 9.5 ng/mL (range: 3.7-28 ng/mL): 74 (41.8%) had serum PSA > 10 ng/mL, 99 (56%) between 4-10 ng/mL and 4 (2.2%) between 2.6-4 ng/mL, respectively. In all patients an adequate concentrations of PCA3 and PSA mRNA was obtained; median PCA3 score was equal to 52 (range 3-273); 140 (79%) and 100 (56.5%) patients had a PCA3 score greater than 20 and 35, respectively. A T1c PCa was found in 48 patients (27.1%); median PSA was 13.4 ng/mL (range: 5-28 ng/mL): 22 and 26 men had a PSA > 10 and between 4-10 ng/mL, respectively. Gleason score was 6 in 38 cases (79.2%), 7 in 8 (16.7%) cases and 8 in 2 (4.1%) cases. The remaining 114 men (64.4%) had normal parenchyma, 5 (2.8%) had an ASAP and 10 (5.7%) an HGPIN.

Figure 1.

PCa detection by PCA3 score range in the 177 patients who underwent repeat saturation biopsy.



PCA3 score was 60 (median; range: 7-208) in the presence of PCa and 34 (median; range: 3-268) in the absence of cancer ($p < 0.05$); in presence of ASAP and HGPIN median PCA3 score was 109 (range: 42-273) and 40 (range: 27-148), respectively.

PCa detection rate increased from 11.1% with PCA3 score of less than 20 to 36% with scores greater than 100 (Figure 1); moreover, a PCA3 cut off of 20 and 35 found 44 (91.6%) and 35 (73%) PCa, respectively. Median PCA3 score in presence of Gleason score equal to 6, 7 and 8 was 60, 74 and 156, respectively. Setting a PCA3 cut-off at 20 vs 35, would have avoided 21% vs 37.8% of biopsies but 4 (8.4%) and 13 cases (27%) of cancer would have been missed, respectively.

Diagnostic accuracy, sensitivity, specificity, PPV and NPV of PCA3 score cut-off of 20 vs 35 are listed in Table 1. Among the patients with PCa 7 (14.7%) underwent radiotherapy and 4 (8.3%) followed AS protocol. No-one of the 37 (77%) patients submitted to RRP had a pIPCa (28

Table 1.

PCA3 score accuracy in diagnosing prostate cancer: cut-off 20 vs 35.

Accuracy	PCA3 > 20	vs	PCA3 > 35
Sensitivity	91.7%		73%
Specificity	25.6%		41.8 %
PPV	31.5%		35%
NPV	89.5%		80.6%
Diagnostic accuracy	43.5%		50.2%
PPV = positive predictive value; NPV = negative predictive value			

pT2cN0, 8 pT3aN0 and 1 pT3bN0) and median Gleason score was equal to 6.6 (6 in 25 cases; 7 in 10 cases; 8 in 2 cases).

DISCUSSION

Repeat prostate biopsy constitutes 20-30% of all performed procedures and certain clinical criteria for the selection of patients at high risk of developing PCa cancer are still lacking. In patients undergoing repeat biopsy Aubin (7), Haese (6) and Marks (4) reported positive biopsy probability (upon comparison of PCA3 score < 5-10 to PCA3 score equal to 100) as being 6 vs 12%, 12 vs 57% and 47 vs 50%, respectively. Aubin (7) demonstrated that a PCA3 cut-off equal to 35 predicts biopsy outcomes 2 years in advance resulting more accurate than PSA; moreover, Haese (6) at a PCA3 cut-off of 20 vs 35 reported a 44% vs 67% reduction of repeat biopsies missing 12 vs 21% of cancers with GS > 7.

Despite these interesting reports, PCA3 accuracy (cut-off 35) at repeat biopsy remains contradictory: sensitivity, specificity, PPV and NPV range between 47 to 76.6% (5), 66.6 to 78.6% (6), 39 to 74% (16) and 62.5 to 87% (17), respectively (4, 6, 9, 16, 17).

In our series, using a cut-off of 20 vs 35 NPV was the best parameter resulting equal to 89.5 vs 80.6% suggesting that PCA3 is more useful as an exclusion tool; moreover, a PCA3 cut-off of 20 vs 35 demonstrated an higher sensitivity (91.7 vs 73%) reducing the number of unnecessary repeat biopsy (21 vs 37.8% of the cases) and minimizing the risk of missing significant PCa (8.4 vs 27%).

Regarding our results some considerations need to be made. Firstly, we don't know if the false positive results correlate to SPBx false negatives or, conversely, could be predictive for future PCa detection (18): 5 men had an HGPN and 10 an ASAP; moreover, 25 patients with negative SPBx had a PCA3 score greater than 100 that allows a risk to detect a cancer at repeat biopsy equal to 30% (19). In conclusion, PCA3 score reduce the number of unnecessary repeat SPBx; using a PCA3 cut-off of 20 vs 35 would have avoided 21% vs 37.8% of biopsies while missing 8.4% (4 cases) vs 27% (13 cases) of significant PCa, respectively.

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Correspondence

Michele Barbera, MD
Urology Unit - Giovanni Paolo II Hospital
Via Pompei, Sciacca (AG), Italy
barbera.mic@tiscali.it

Pietro Pepe, MD
Francesco Aragona, MD
Urology Unit - Cannizzaro Hospital, Catania, Italy

Quintino Paola, MD
Urology Unit - Giovanni Paolo II Hospital, Sciacca, Italy

ORIGINAL PAPER

Incidence of abdominal aortic aneurysm during diagnostic ultrasound for urologic disease: Our experience

Lucio Dell'Atti

Urology Unit, Arcispedale "S. Anna", Ferrara, Italy.

Summary

Background: The prevalence of abdominal aortic aneurysms (AAA) is increasing because of increased life expectancy. There are none or few symptoms related to abdominal aortic aneurysm until rupture. After rupture, mortality rates are 60-80%, but with an elective operation.

Methods: We performed an observational study on 140 consecutive patients of age over 50 years (range 50-82), presented to our clinic to perform a routine ultrasound examination of the urinary tract. We consecutively evaluated in these patients the possible detection of abdominal aortic aneurysm.

Results: Ultrasonography of the abdomen is the test of choice for the detection of the disease, it is an examination of low-cost and non-invasive. It has a high diagnostic sensitivity 80%, in our study (result slightly less than the range reported by the literature 82-99%) and a specificity of 100%.

Conclusions: Because of its safety, low cost, ease of use, and wide availability, ultrasonography is the most commonly used clinical imaging modality. Ultrasonography is the standard method for screening and monitoring AAAs that have not ruptured. With the advance in 3-dimensional (3D) imaging, 3D ultrasonography has provided a new opportunity to acquire fast and reliable AAA measurements, which can not only shorten the time for a ultrasound exam but also reduce the workload of AAA surveillance.

KEY WORDS: Abdomen; Aortic aneurysm; Urologic disease; Ultrasonography.

INTRODUCTION

Abdominal aortic aneurysms (AAA) develop against a background of chronic deterioration and inflammation of the aortic wall. In up to 20% of all cases of AAA there is an underlying genetic predisposition, with a prevalence of AAAs of 13% to 19% among first-degree relatives of patients with an AAA (1).

In an arterial aneurysm, the artery is 1,5 times wider than normal. Since the infrarenal aortic diameter is usually about 2 cm, in epidemiological studies an aortic aneurysm is defined by a diameter of 3,0 cm or more. It needs to be remembered, however, that the aortic diameter increases with age, and is larger in men than in women. In everyday clinical practice, therefore, a diameter of 3 to 4 cm is often referred to as aneurismal widening of the infrarenal aorta, or ectatic abdominal aorta.

Prevalence figures for abdominal aortic aneurysm with a maximum diameter of at least 3.0 cm in screening programs are 5,5% (4% to 8%) for men over 65 and 1.3% (0,5% to 1,5%) for women over 65. In a quarter of all AAA cases, the diameter is 4 cm or more, and in about 10% of cases it is 5 cm or more (5-8).

The following clinical risk factors for development of an AAA have been identified:

- increasing age;
- family history of AAA;
- current or previous history of smoking;
- coronary heart disease;
- arterial hypertension.

Female sex, African ethnic origin, and diabetes mellitus all have a protective effect, probably via a genetic mechanism (2).

The average rate of growth of an AAA is 2 to 3 mm per year; it is higher in smokers, and can vary greatly between individuals (3). The risk of rupture of an AAA smaller than 4 cm is below 2% per year, but increases exponentially once a diameter of 5 cm is passed. Although women have a lower prevalence of AAA, when they have an AAA with a diameter of 5 to 6 cm the risk of rupture is three times as high as in men (4).

Apart from maximum diameter, risk factors for impending rupture include rapid increase in diameter (> 0,5 to 1 cm per year), family history of AAA, eccentric morphology of the AAA, and continued smoking (5, 6). Overexpression of MMP9 and lack of alpha1-antitrypsin have also been associated with an increasing risk of rupture (7, 8).

Ruptured AAA has an associated mortality rate of over 80% in industrialized nations, and is the tenth most frequent cause of death in men over 65 years of age.

The successful treatment of a ruptured abdominal aneurysm requires immediate recognition and prompt treatment otherwise untreated patients have a fatal outcome.

Patients with surgical repair of an AAA recover in 30 to 65 percent of the cases. (9)

The risk of an AAA rupturing increases exponentially with its diameter. Once the diameter has reached 5 cm, the risk is 3% per year; at 5 years the cumulative risk is 25%. More than 80% of patients with an AAA have no symptoms. For an AAA with a diameter of 5 cm or more, elective surgery is the only certain way to prevent rupture of the aneurysm.

At present most of the AAA is diagnosed incidentally during abdominal ultrasound.

Ultrasound screening for AAA leads to a significant reduction in AAA-related mortality after 3 to 5 years and in overall mortality at 7 to 15 years (10).

MATERIAL AND METHODS

During a period of three years, from January 2008 to December 2010, we performed an observational study on 140 consecutive patients of male sex and age over 50 years (range 50-82), came to our clinic to perform a routine ultrasound examination of the urinary tract.

We consecutively evaluated in these patients the possible detection of abdominal aortic aneurysm (Figure 1).

For the ultrasound examination was used ultrasound machine (G.E. - LOGIQ 7) equipped with a multifrequency convex probe. All examinations were performed by a single urologist expert in ultrasound.

With the patient in supine position after performing a standard ultrasound examination of urinary tract, the examination was carried out by moving the midline in the upper central quadrant of the abdomen, with longitudinal ultrasound scans on the umbilical line was possible to study the abdominal aorta until the bifurcation of the iliac vessels.

The abdominal aorta was considered aneurysmal if its maximum diameter in either transverse or antero-poste-

Figure 1.

B-mode ultrasound picture of abdominal aortic aneurysm.



rior planes was equal to or greater than 3 cm. During this period, any patient with a diagnosed aneurysm was subsequently referred to a consultant vascular surgeon for treatment or entry into the departmental surveillance programme.

RESULTS

Of the 140 patients studied in 10 it was not possible to visualize the abdominal aorta for obesity or bowel gas, in 8 there was an incidental finding of an aneurysm ≥ 3 cm, later confirmed by an ultrasound scan of the abdominal radiology specialist colleagues.

There were 6 patients with an aneurysm equal to or greater than 4 cm in diameter (Table 1).

In 2 patients but was detected 1 AAA ≥ 3 cm as incidental finding later after performing abdominal CT performed for the purpose of staging for cancer.

Ultrasonography of the abdomen is the test of choice for the detection of the disease, is an examination of low-cost, non-invasive and has a high diagnostic sensitivity 80%, in our study (result of slightly less than the range reported literature 82-99%), and a specificity of 100% (11).

The average execution time for each survey was about 2 minutes longer than the standardized urologic ultrasound.

Table 1.

Dimension and number of aneurysms detected by age.

Age	Number of patients	Number of aneurysms	Dimensions
50-60 years	48	2	< 3 cm
60-70 years	56	4	≥ 3 cm
70-80 years	27	3	> 3 cm
> 80 years	9	1	> 5 cm

DISCUSSION

All the mentioned facts and the fact that the incidence of abdominal aortic aneurysm is increasing have stimulated physicians to screen for the disease. Schilling did the first screening of abdominal aortic aneurysm in 1964 by lateral abdominal radiography (12).

Today, abdominal ultrasonography is the best tool to screen for abdominal aortic aneurysm (13).

Because of its safety, low cost, ease of use, and wide availability, ultrasonography is the most commonly used clinical imaging modality.

Ultrasonography is the standard method for screening and monitoring AAAs that have not ruptured. With the advance in 3-dimensional (3D) imaging, 3D ultrasonography has provided a new opportunity to acquire fast and reliable AAA measurements, which can not only shorten the time for a ultrasound exam but also reduce the workload of AAA surveillance (14).

The prevalence of abdominal aortic aneurysm has been different in various studies. The first reason is the fact that different definitions of aneurysm have been used by different authors.

Some authors have considered aorta "aneurysmal" when its diameter reaches 30 mm (13, 14). Some others have considered diameter more than 25 mm as aneurysm (15, 16). Morris *et al.* have defined aorta "aneurysmal" when infrarenal aortic diameter reaches 30 mm or more in patients aged 65 years or more and 25 mm or more in patients younger than 65 (17).

Because of the low prevalence of abdominal aortic aneurysm in our population, we chose "25 mm" as the cut-off point to increase the sensitivity of our study.

The study population is another factor affecting the prevalence of abdominal aortic aneurysm. Some studies have only included patients with cardiovascular risk factors, while other studies have evaluated elderly men (14, 17). Singh *et al.* studied 6386 men and women inhabitants of the Tromsø, Norway aged 25-84 years without considering the risk factors (19). At least one study has proved that ethnicity affects abdominal aortic aneurysm (northern European versus Mediterranean) (20).

A population-based study in eastern Australia confirmed that risk of abdominal aortic aneurysm was higher in men with northern European origin compared with those of Mediterranean origin (20).

There is only one report of abdominal aortic aneurysm from Turkey (21), which determined the prevalence of abdominal aortic aneurysm in "a mixed Turkish population, who were undergoing abdominal ultrasonographic examination for pathologies not involving aorta". The prevalence of abdominal aortic aneurysm was 0.6% in that study and the mean age was 48 years.

Our study had some limitations. We excluded 10 patients from the study because of gassy bowel. It was a trivial number of patients who could be re-evaluated after bowel preparation.

Another limitation was that we did not evaluate some other known risk factors such as peripheral vascular disease or family history of abdominal aortic aneurysm. Doppler ultrasonography of iliac and femoral arteries has been used for evaluation of peripheral arterial disease in patients with such aneurysm in other studies

(21). We ignored it because of the extra cost of lower limb Doppler study.

CONCLUSION

The ultrasound in the hands of a medical specialist is identified as a diagnostic strategy of fundamental interest, as it is possible to demonstrate the presence of a number of diseases in patients at risk even in the absence of an obvious symptoms so as to recognize and follow up at the time when the surgery is necessary, as in the case of the AAA.

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Correspondence

Lucio Dell'Atti, MD

U.O. Urologia

Azienda Ospedaliero-Universitaria Arcispedale "S. Anna"

Corso Giovecca 203 - 44100, Ferrara, Italy

dellatti@hotmail.com

CASE REPORT

Role of ultrasound in management of long-term complications after to radical cystectomy and orthotopic neobladder construction: Case report

Anna Mudoni ¹, Francesco Caccetta ¹, Maurizio Caroppo ¹, Fernando Musio ¹, Antonella Accogli ¹, Annalisa Noce ², Emiliana Ferramosca ³, Vitale Nuzzo ¹

¹ Nephrology and Dialysis, Hospital "Cardinale G. Panico", Tricase, Lecce, Italy;

² Department of Internal Medicine, Nephrology and Hypertension Unit, "Tor Vergata" University Hospital, Rome, Italy;

³ Department of Internal Medicine, Ageing and Renal Diseases, Division of Nephrology, Dialysis and Hypertension, "S. Orsola-Malpighi University Hospital", Bologna, Italy.

Summary

Radical cystectomy with urinary diversion is considered the gold standard treatment for bladder cancer.

We report a case of 66 years old male with long term complications, after radical cystectomy and an ileal neobladder according to Hautmann. He developed uroseptic episodes, stones, post-void residual, stenosis of the uretero-neobladder anastomosis, metabolic acidosis and progressive deterioration of renal function.

Renal ultrasound helped us to identify the dilation of the urinary tract, the grade of hydronephrosis and the presence of stones. During the follow-up, it is very important the collaboration between urologist and nephrologist and the role of ultrasound for an early correction of the hydronephrosis and the elective replacement of the stents in order to preserve the renal function.

KEY WORDS: Radical cystectomy; Long term complications; Hydronephrosis; Ultrasound.

INTRODUCTION

Bladder cancer is the fourth cause of deaths for cancer and its incidence is increasing in metropolitan areas. It is more frequent in Caucasian and males, and increases with age with a maximum peak at 65 years (1, 2).

The optimal treatment strategy for bladder cancer without any metastasis is still controversial, though radical cystectomy with urinary diversion is considered the gold standard (3, 4). The neobladder surgery, after radical cystectomy for bladder cancer, though is intended to restore bladder anatomy and function, is associated both with short and long-term complications, and sequelae on patients' quality of life.

The most frequent short-term complications are urinary fistulas (3-17%), pyelonephritis (5-15%), and enteric fistula (1-5%), as well as general complications (thrombophlebitis, pulmonary embolism, dehiscence of sutures). The long-term complications are intestinal obstruction,

renal failure, hernias, and stenosis of the stoma (7-15%) or uretero-neobladder anastomosis (5, 6).

CASE REPORT

We describe the clinical history of a 66 years old male, with an ileal neobladder according to Hautmann, for ten years. At 57 years, due to a bladder cancer, poorly differentiated and infiltrating the muscular tunica, the patient underwent a radical cystectomy with lymphadenectomy and urinary diversion. At that time his renal function was normal, with sCreatinine 0.9 mg/dl and cGFR 114 ml/min/m² (MDRD formula). Then he was submitted to cycles of adjuvant chemotherapy, during which there was a transient worsening of renal function.

Few months after the surgery, he developed a uroseptic episode, with fever and chills, complicated by acute renal

Figure 1.*Right Kidney with grade III-IV hydronephrosis.*

failure (ARF), resolved with appropriate antibiotic and fluid therapy. Renal ultrasonography showed only a moderate right pyelectasis.

From that time, the patient presented several renal colic episodes and ultrasound scans showed bilateral hydronephrosis, initially treated with placement of bilateral percutaneous nephrostomy, and subsequently of ureteral stents, albeit with normal renal function (cGFRc 120 ml/min/m², MDRD). At 63 years ARF (sCreatinine 13.5 mg/dl, cGFRc 5.4 ml/min/m², MDRD), with oliguria, electrolyte imbalance and severe metabolic acidosis, occurred.

Renal ultrasound showed: right kidney with grade III-IV hydronephrosis with thinning of the cortex (Figure 1). Left kidney with grade III hydronephrosis and normal cortico-medullary thickness. Presence of bilateral pyelo-bladder stent (Figure 2).

Heterogeneous and hypoechoic material floating in the

lumen of the neobladder, attributable to clot (Figure 3). After medical therapy, hemodialysis and replacement of stent due to bilateral stenosis of uretero-neobladder anastomosis, gradual and progressive improvement in renal function occurred (sCreatinine 3.5 mg/dl, cGFR 23 ml/min/m², MDRD), with restoration of an effective diuresis and correction of electrolyte imbalance and metabolic acidosis.

Later on, the patient underwent a regular clinical and ultrasound follow-up in our out-patient clinic, in order to early correct the hydronephrosis due to stenosis of the uretero-neobladder anastomosis, and to replace the stents when necessary.

To date, the patient suffers from a stage 3 renal failure (according to NKF KDOQI guidelines), with a sCreatinine 3.0 mg/dl and cGFR 37 ml/min/m².

Renal ultrasound scan shows the right kidney with grade III-IV hydronephrosis with thinning of the cortex and a

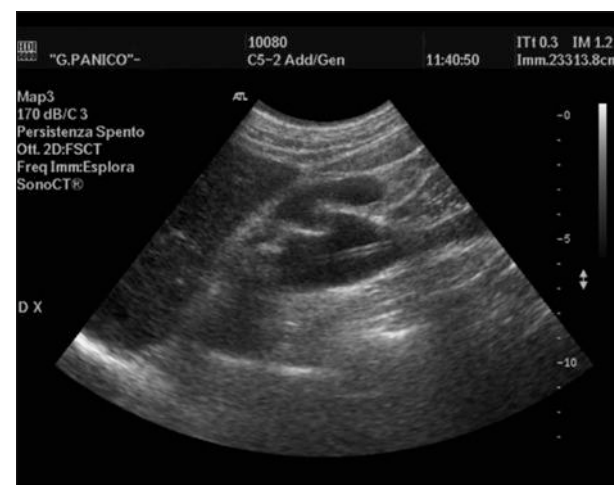
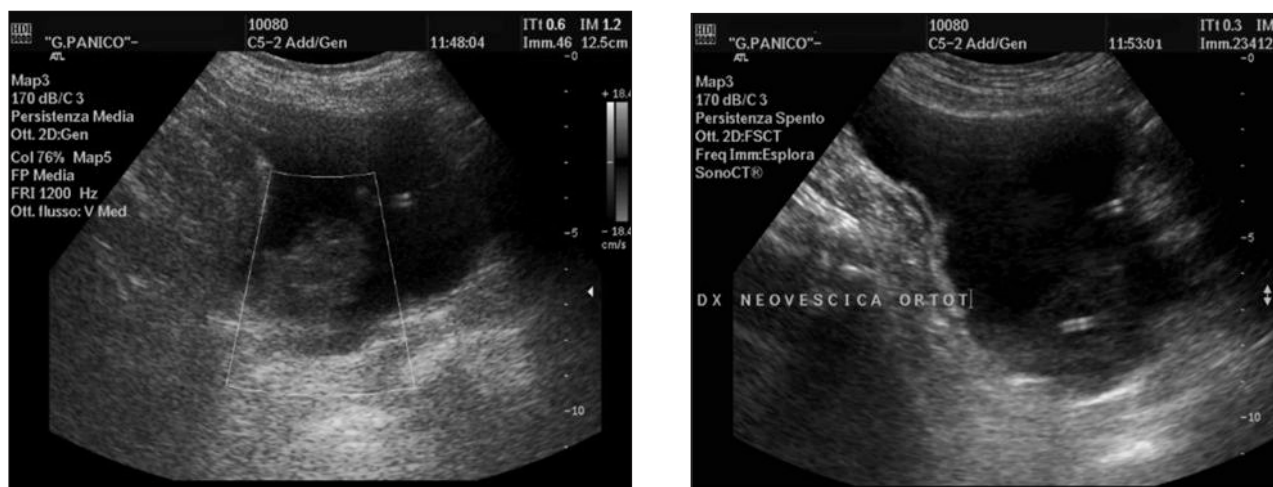
Figure 2.*Left kidney with grade III hydronephrosis. Presence of stent.*

Figure 3.

Heterogeneous and hypoechoic material floating in the lumen neobladder.



stone (Figure 4). The left kidney is normal, with a normal cortico-medullary thickness. Presence of bilateral pyelo-bladder stent (Figure 5).

Figure 4

Right kidney with grade III-IV hydronephrosis and a stone.

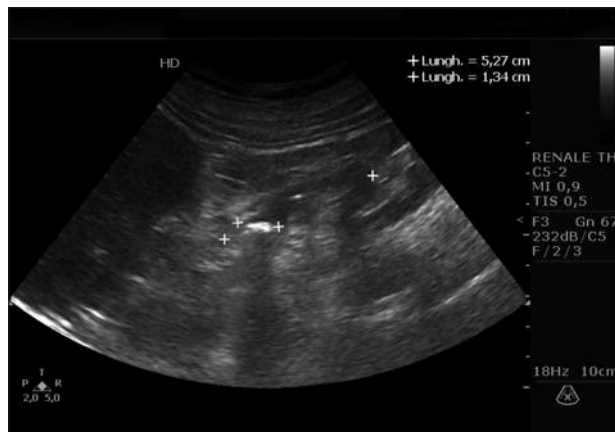


Figure 5

Left kidney with normal cortico-medullary thickness. Presence of stent.



DISCUSSION

The present case report focuses primarily on long-term complications of neobladder construction, particularly hydronephrosis, chronic sepsis, lithiasis, metabolic imbalance such as acidosis and renal function worsening. According to Lantz *et al.* (7), daytime and nighttime incontinence decreased during the follow-up, and an early development of hydronephrosis and progressive deterioration of renal function occurred. The worsening in renal function seems to be attributable to the chronic urinary tract infection, obstruction and/or high neobladder pressure. Furthermore, Hautmann *et al.* (8), by examining a 25 years experience with 1000 neobladders, have highlighted the high percentage of long-term complications especially hydronephrosis, uretero-neobladder anastomotic stenosis, sepsis, severe metabolic acidosis, and bowel obstruction. Other Authors, see Tollefson *et al.* (9), showed a higher rate of complications, with a higher incidence in uretero-intestinal stenosis and lithiasis, and a lower incidence in chronic renal failure. In almost all the patients metabolic alterations were present, going from mild to severe acidosis occurring in the course of severe dehydration.

CONCLUSION

Bladder cancer has a strong negative impact on the quality of life of the patient (loss of urinary continence, altered body shape, impairment of sexual function, etc.) affecting social and relational life (10). Therefore, patients with urinary diversion, in accordance with the European Guidelines, must be periodically subjected to blood tests, morphological and functional urinary tract evaluations (11, 12). The management of patients with orthotopic neobladder involves commitment and collaboration between urologist and nephrologist, using ultrasound which helps in identifying the complications of this disease (dilation of the urinary tract, stones, residual of urina, etc.) during follow-up in order to ensure a management such as to preserve as much as possible the renal function and improve the quality of life (13).

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Correspondence

Anna Mudoni, MD
Nephrology and Dialysis, Hospital "Cardinale G. Panico",
Via S. Pio X 4 - 73039 Tricase - Lecce, Italy
mudonia@libero.it

Francesco Caccetta, MD
Maurizio Caroppo, MD
Fernando Musio, MD
Antonella Accogli, MD
Vitale Nuzzo, MD
Nephrology and Dialysis, Hospital "Cardinale G. Panico",
Tricase, Lecce, Italy

Annalisa Noce, MD
Department of Internal Medicine,
Nephrology and Hypertension Unit,
"Tor Vergata" University Hospital, Rome, Italy

Emiliana Ferramosca, MD
Department of Internal Medicine, Ageing and Renal Diseases,
Division of Nephrology, Dialysis and Hypertension,
"S. Orsola-Malpighi University Hospital", Bologna, Italy

CASE REPORT

Nephrotic syndrome and abdominal arterial bruits in a young hypertensive patient: A case report

Maria Paola Canale¹, Valentina Rovella¹, Emiliano Staffolani¹,
Natascia Miani¹, Maria Silvia Borzacchi¹, Konstantinos Giannakakis²,
Annalisa Noce¹, Nicola Di Daniele¹

¹ Department of Internal Medicine - Nephrology and Hypertension Unit; University of Rome "Tor Vergata", Rome; Italy;

² Department of Radiology, Oncology and Pathology, University of Rome "La Sapienza", Rome; Italy.

Summary

We report the case of a 34-year old black African hypertensive woman who presented with nephrotic proteinuria, mild renal failure and abdominal bruits on physical examination. The renal Doppler ultrasound revealed bilateral artery stenosis. Thoraco-abdominal aortic nuclear magnetic resonance showed a restriction of proximal descending aorta with post-stenotic spindle dilation while abdominal aorta and iliac vessels appeared diffusely stenotic with atherosclerotic plaques and infrequent spindle dilations and right ostial renal artery stenosis. Renal angiography failed to reveal renal artery stenosis. Right renal biopsy showed type 1 membrano-proliferative glomerulonephritis in sclerotic evolution and severe arteriolosclerosis. The particularly early onset of the disease suggests that the pathogenesis of the membrano-proliferative glomerulonephritis may be multifactorial and related to vascular hypoplasia and chronic renal hypoperfusion leading to renin angiotensin system activation. Hyperlipidemia secondary to nephrotic syndrome may have accelerated systemic atherosclerosis and progression of renal disease.

KEY WORDS: Membrano-proliferative glomerulonephritis; Renal ischaemia; Vascular hypoplasia; Renin-angiotensin.

INTRODUCTION

Renal artery stenosis (RAS) is a cause of chronic renal hypoperfusion. Ostial RAS is due to atherosclerosis whereas mid portion localization is due to fibromuscular dysplasia. Duplex doppler ultrasonography (DDUS) is a non-invasive diagnostic test with very high sensitivity (more than 90 percent) and specificity (97 percent) (1). Here, we report the case of a 34-year old black African hypertensive woman who presented with nephrotic proteinuria, mild renal failure, abdominal bruits on physical examination and underwent renal biopsy in the suspicious of glomerulonephritis (GN).

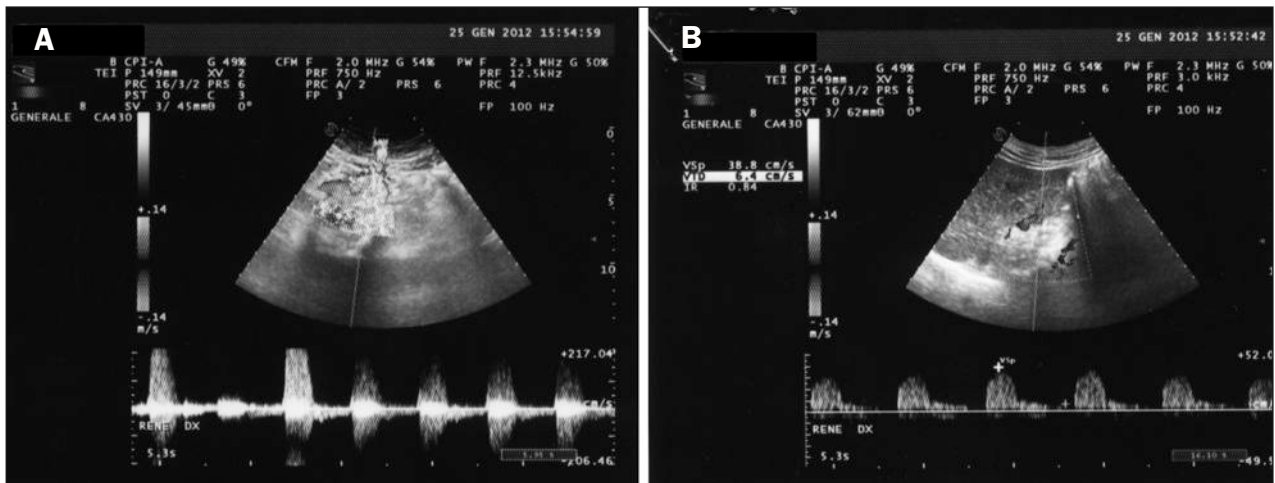
CASE PRESENTATION

A 34-year-old black African hypertensive woman was referred to our department during an hospitalization for

acute pontine ischemia complicating an atrial septal defect, for the occasional finding of renal failure (serum creatinine 1.8 mg/dl and glomerular filtration rate (GFR) 50 ml/min according to MDRD (Modification of diet in Renal disease study equation), hypercholesterolemia (serum total cholesterol: 300 mg/dl), hypoalbuminemia (2.4 g/dl) and nephrotic proteinuria (5 gr/day). Family and past personal history were unremarkable. Paraumbilical and iliac arterial bruits and absence of peripheral edema were reported on physical examination. She had full and symmetric pulses at the upper limbs and slight radial/femoral pulse delay. Decreased blood pressure (BP) values were observed at the lower limbs (110/70 mmHg) compared to upper limbs (125/80 mmHg). Continuous monitoring showed a good BP control under treatment with ramipril 5 mg/day (24-hour

Figure 1.

Duplex Doppler Ultrasound of renal arteries. Left panel (A) SPVs: > 200 cm/sec for the right renal artery. Right panel (B): parenchymal RI value (0.84), marked flattening of flowmetric layouts with reduced PSV and longer diastolic phase.



mean values for systolic and diastolic: 117 and 61 mmHg, respectively). Triglycerides were normal at 97 mg/dl. No inflammatory signs such as low-grade fever, cervical pain nor generalized malaise were present. Autoimmunological and inherited prethrombotic conditions workout were negative. Electrocardiogram and transthoracic echocardiogram showed signs of left ventricular hypertrophy. Fundoscopic examination revealed grade III hypertensive retinopathy. Renal color duplex doppler ultrasound (DDUS) showed a small right and a normal left kidney (longitudinal diameter 8.7 and 10.9 cm, respectively) with increased echogenicity, corticomedullar differentiation was reduced in the left and absent in the right kidney and parenchymal thickness reduced in the right kidney. On DDUS peak flow velocity was increased for both arteries (> 250 cm/sec for the right and 200 cm/sec for the left kidney, respectively)

(Figure 1A). Parenchymal resistance indexes (RI) were increased bilaterally (mean value: 0.79), with marked flattening of flowmetric layouts with reduced peak systolic velocities (PSV) and longer diastolic phase (Figure 1B) PSV measured at suprarenal abdominal aorta level was markedly increased (> 300 cm/sec), renal-aortic ratio was less than 3. Renography showed an asymmetric distributed reduction of GFR (left kidney: 61%, right kidney: 39%). Toraco-abdominal aortic nuclear magnetic resonance (NMR) showed a restriction of proximal descending aorta (21 x 20 mm) with post-stenotic spindle dilation while abdominal aorta and iliac vessels appeared diffusely stenotic with atherosclerotic plaques and infrequent spindle dilations, right ostial RAS was also present (Figure 2A and B). F-18-fluorodeoxyglucose positron emission tomography (FDG-PET) did not highlight inflammatory wall vessel lesions suggestive of vas-

Figure 2.

Toraco-abdominal aortic NMR showing restriction of proximal descending aorta (upper arrow) with post-stenotic spindle dilation (lower arrow) (A) and stenotic atherosclerotic abdominal aorta and iliac arteries with infrequent spindle dilations (B). Also, note right ostial RAS (as indicated by the arrow) (B).

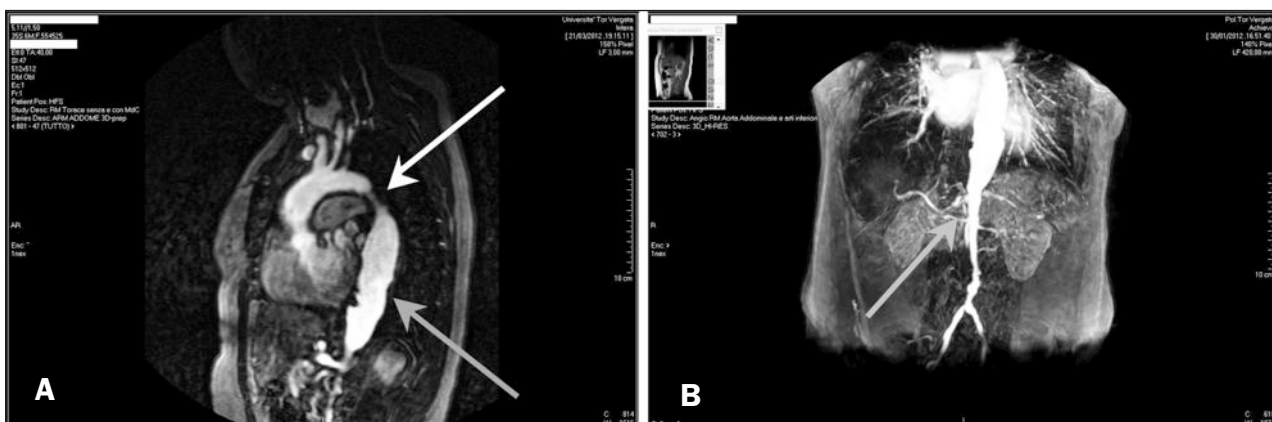
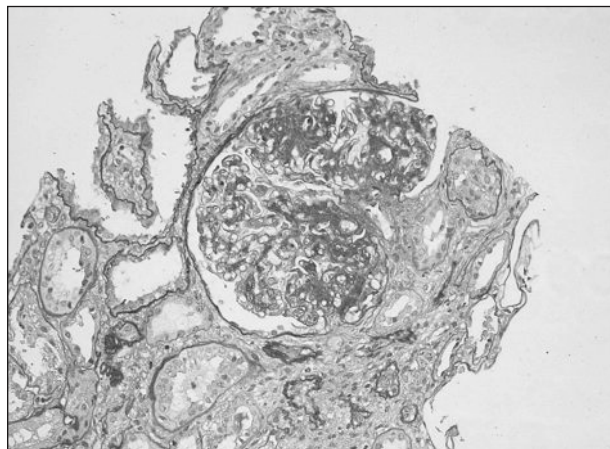


Figure 3.

Moderate mesangial proliferation with interposition in many capillaries, increased amount of intercellular substance and segmental sclerosis (PAS 200x).



culitis. Renal angiography failed to reveal RAS. Right renal biopsy showed type 1 membrano-proliferative glomerulonephritis (GN) in sclerotic evolution and severe arteriosclerosis (Figure 3).

DISCUSSION

Despite the DDUS and abdominal aortic NMR data, renal arteriography failed to reveal RAS. This finding was consistent with the clinical observation that renal failure did not occur after angiotensin-converting enzyme inhibitor (ACE-I) treatment was started. We suggest that vascular hypoplasia resulted in longstanding renal hypoperfusion. Renovascular disease also determines chronic renal hypoperfusion. Few cases of focal segmental glomerulosclerosis with non-nephrotic proteinuria (< 3 g/day) associated to renovascular hypertension are reported (2). Membrano proliferative GN is characterized by mesangial proliferation with interposition in many capillaries. Only a single case of mesangial proliferative GN without an immune response has been previously described in an elderly patient with diffuse atherosclerosis (3). To our knowledge, no previous cases of non immune membrano-proliferative GN have been described in the setting of chronic renal hypoperfusion due to RAS. Pretreatment BP values and cholesterol levels were not so high to determine such an early onset of severe atherosclerosis suggesting an insidious time course in this patient. It is possible that chronic renal hypoperfusion and renin angiotensin system (RAAS) activation induced severe glomerular endothelial damage leading to membrano-proliferative GN. RAAS is thought to be involved in the progression of GN into end-stage renal disease (ESRD) because of the observed renoprotective effects of ACEIs. ACEIs prevented the progression to ESRD by modulating the effects of Angiotensin II via Angiotensin II type 1 receptor on the production of TGF- β and collagen types I and III, as well as on intrarenal hemodynamics, in a rat model of

mesangial proliferative GN (4). Later on, Mahmood *et al.* demonstrated that local delivery of angiotensin receptor blocker into the kidney affects local RAAS and thus improves the renal injury and function in the potentially progressive glomerulosclerosis of rat model (5). Renally delivered aliskiren, a direct renin inhibitor recently showed a renoprotective effect on potentially progressive glomerulosclerosis in rat model by significantly suppressing mesangial matrix expansion and ameliorating the glomerular sclerotic index. Immunofluorescent studies revealed that pathological expressions of α -smooth muscle cell actin and type I collagen were remarkably decreased. Furthermore, local delivery of aliskiren significantly improved glomerular blood flow levels (6). A recent 10-year follow-up study indicated that early treatment with RAAS inhibitors at low doses favourably influences the long-term renal outcome in proteinuric patients with mesangial-proliferative GN (7). In this patient, membrano-proliferative GN showed a nephrotic pattern, not associated with inflammation on histologic examination, with proteinuria in the nephrotic range resulting in hypercholesterolemia and increase in low-density lipoproteins (LDL). Atherogenic lipoproteins induce formation of oxygen radicals not only in arteries but also in glomeruli and juxtaglomerular cells, causing an inhibition of nitric oxide mediated vasodilation, stimulation of renin disease, and modulation of mesangial cell growth and proliferation (8). Nishida *et al.* observed the proliferative action exerted by LDL and the effect of oxidated LDL on human mesangial cells in vitro (9). Kamanna *et al.* demonstrated that LDL oxidized forms within the glomerulus, through the activation of membrane receptor tyrosine kinase, activates the Ras and mitogen-activated protein (MAP) kinase signaling cascade leading to DNA synthesis and subsequent cell proliferation in murine mesangial cells (10). Moreover, oxidized LDL could induce oxidative stress and profibrotic gene expression in mesangial cells (11). Interestingly, infusion of angiotensin (1-7) reduced glomerulosclerosis through counteracting angiotensin II in experimental GN (12). Also, angiotensin II type I receptor blockade attenuated proteinuria and progressive glomerular remodeling via the suppression of glomerular RAAS activation in GN (13). Lastly, Hua *et al.* demonstrated that the transcription factor ETS-1 regulates angiotensin II stimulated fibronectin production in mesangial cells (14). The early onset of the disease in the absence of family history positive for hypertension and dyslipidemia strongly support our hypothesis.

CONCLUSIONS

The particularly early onset of the disease suggests that the pathogenesis of the membrano-proliferative GN may be multifactorial and related to vascular hypoplasia and chronic renal hypoperfusion leading to RAAS activation. Hyperlipidemia secondary to nephrotic syndrome may have accelerated systemic atherosclerosis and progression of renal disease. Finally, this case presentation stresses the importance of complete physical examination and to extend DDUS to the entire abdominal aorta when performing renal study.

AUTHORS' CONTRIBUTIONS

MPC, VR, ES, NM and MSB examined the patients, interpreted the findings and were the major contributor in writing the manuscript. AN and ND designed and reviewed the manuscript. KG performed pathological diagnosis. AN performed, analyzed and interpreted radiologic examination findings. All authors read and approved the final manuscript.

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Correspondence

Nicola Di Daniele, MD
Department of Internal Medicine - Nephrology and Hypertension Unit,
University of Rome "Tor Vergata"
Viale Oxford 81 - 00133, Rome, Italy
didaniele@med.uniroma2.it

Maria Paola Canale, MD
Valentina Rovella, MD
Emiliano Staffolani, MD
Natascia Miani, MD
Maria Silvia Borzacchi, MD
Annalisa Noce, MD

Department of Internal Medicine
Nephrology and Hypertension Unit, University of Rome "Tor Vergata"
Viale Oxford 81 - 00133, Rome, Italy

Konstantinos Giannakakis, MD
Department of Radiology, Oncology and Pathology
University of Rome "Tor Vergata"
00133 - Rome, Italy

CASE REPORT

Ultrasound diagnosis of renal infarction: Case report and review of the literature

Lucio Dell'Atti ¹, Roberto Galeotti ², Gian Rosario Russo ¹

¹ Urology Unit, Arcispedale "S. Anna", Ferrara, Italy;

² Vascular and Interventional Radiology Unit, Arcispedale "S. Anna", Ferrara, Italy.

Summary

Renal infarction secondary to thromboembolism is usually a sequela of cardiac disease, the heart being the source of systemic arterial emboli in up to 94% of cases; the three major causes are: atrial fibrillation, myocardial infarction and rheumatic mitral stenosis. Renal infarction is often confused with other conditions due to similar presenting symptoms. This leads to delay in initiating treatment and significantly decreases the chances of renal salvage.

We report a sonographic diagnosis in 39-year-old man, with risk factors for thrombosis, without a prior history of thromboembolism.

KEY WORDS: Flank pain; Renal infarction; Atrial fibrillation; Embolism.

INTRODUCTION

Renal artery thrombosis is a rare, but serious and often misdiagnosed. In a series of over 14.000 autopsies, about 200 cases of kidney infarction were identified (1). Renal infarct is typically caused by blood or cholesterol clots occluding the renal artery or branch vessels. The source of blood clots is from atrial fibrillation causing thrombogenesis in the left atrium and left atrial appendage. Most kidney infarction results from emboli caused by atrial fibrillation or endocarditis (2), causing only partial occlusion of the renal artery or a branch. Rare causes reported include spontaneous renal artery dissection (3), dilated cardiomyopathy (4), paradoxical embolism (5) and involved multiple organs. Bilateral infarction has also been reported, including bilateral (global) renal infarction subsequent to dissecting aneurysms of the aorta (6), with septic emboli from endocarditis, lupus vasculitis or with sickle cell disease or fibromuscular dysplasia of the renal arteries. Reports of other causes associated with renal infarction include trauma, vasculitis, instrumentation, transplant, sepsis, sickle cell disease (7) and antiphospholipid antibody syndrome (8, 9), cocaine use (10), and subsequent to carotid artery dissection (11). In this case report is analyzed as a case of renal infarction supported by a renal artery thrombosis in a young-adult patients with risk factors for thrombosis, without a prior history of thromboembolism.

CASE REPORT

A 39-year-old man presented to the Emergency Room of 'Arcispedale "S. Anna" of Ferrara in February 2012 for the sudden appearance on the night of pain in left lumbar region, previously irradiated in the ipsilateral iliac fossa up to the testis. The pain occurred in a non-continuous and characterized by episodes of colicky, resistant to common painkillers.

The patient was without fever (T: 36.8°C), regular bowel function, no signs of nausea and vomiting, in the absence of symptoms of urinary obstructive or irritative.

His past surgical history included a left varicocele repair. His past medical history included a right ureteral lithiasis solved by spontaneous expulsion of stone and intervention of cardiac ablation for atrial fibrillation five years ago.

No home therapy was taken at admission. He did not smoke, use alcohol or illicit drugs. Hemocrome test, except for a slight increase in white blood neutrophils, appeared to be normal. Laboratory assessment revealed trace hematuria, creatinine of 1.1 mg/dL, mildly elevated lipase to 82/L, mild hyperglycemia and mildly elevated aspartate aminotransferase to 47 U/L. Coagulation profile was within normal limits. Lactate dehydrogenase (LDH) was not ordered at presentation, but obtained one day after admission, and was elevated 1.236 (normal range, 100-200 U/L).

Performed in emergency: an electrocardiogram, which proved to be normal and an abdominal CT without contrast-enhanced showed that the absence of stones, hydronephrosis, and signs of excess fluid in the abdomen. Given the non-remission of painful symptoms the patient was admitted to our urology department and was immediately subjected to abdominal ultrasound with color-Doppler study showed that the presence in the left renal parenchyma, exactly on the front lip of the median and a good part of the lower pole kidney, an area with a hypoechoic echotexture. This area did not appear vascularized through study color and power-Doppler (Figures 1, 2). The ultrasound image appeared to describe a renal infarction. Therefore to get a better definition of the clinical we proceeded to perform a CT abdomen with the contrast-enhanced in which it confirmed a large area of

the left kidney renal parenchyma due to vascular thrombotic process of the anterior branch of the ipsilateral renal artery.

The patient is sent by our Vascular and Interventional Radiology Unit, and through selective arteriography of the left renal. Showed a complete thrombosis of the branch prepielico, after placement of angiographic catheter within the artery concerned, they proceeded to thrombolysis with 100000 units of urokinase. The patient through the positioning of the angiographic catheter is subjected to thrombolytic therapy continuous perfusion for about 4 days. Subsequently selective arteriography were performed serial monitoring documented the third day of complete recanalization of the artery affected.

The patient was discharged on the tenth day after execution of ultrasound color-Doppler documenting signs of renal revascularization of the kidney.

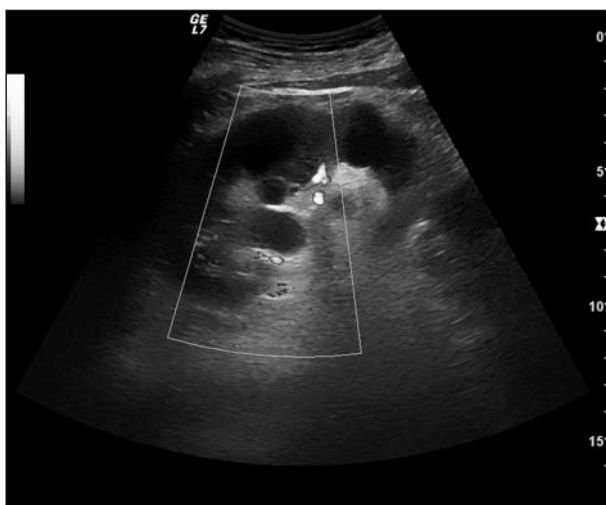
Figure 1.

Ultrasound picture of renal infarction.



Figure 2.

Ultrasound power-Doppler picture of renal infarction.



DISCUSSION

Acute renal infarction is rarely detected in clinical practice. This is reflected in the literature in which multiple scattered case reports are described but a prospective single or multi-center study of the condition is lacking. The earliest report of renal embolic disease appeared in 1856 by L. Traube from Germany and multiple case reports have been published since that time. In a series reported by Hoxie and Coggin, 205 cases of renal infarction were identified in 14,411 autopsies done at a major metropolitan hospital, an incidence of 1.4%; however the lesion was diagnosed clinically in only two cases (1). Lessman *et al.* 3 reported 17 cases (12), Korzets *et al.* (13) reported 11 cases, and Hazanov *et al.* reported 44 cases (14).

Renal infarction secondary to thromboembolism is usually a sequela of cardiac disease, the heart is the source of systemic arterial emboli in up to 94% of cases; the three major causes are: atrial fibrillation, myocardial infarction and rheumatic mitral stenosis (15). Renal infarction is often confused with other conditions due to similar presenting symptoms. This leads to delay in initiating treatment and significantly decreases the chances of renal salvage.

Patients with acute renal infarction commonly present with persistent abdominal, flank or low back pain. The pain is usually acute in onset, sharp and severe in nature and without radiation. Detection is often delayed or missed because the condition is rare and its clinical presentation is non-specific. Non-specific symptoms such as nausea, vomiting and fever are often present.

Physical findings in renal infarction may lead directly or indirectly to the diagnosis. Costovertebral angle or flank tenderness, when present, points to a kidney lesion.

The most sensitive (but not specific) laboratory test for renal infarction is lactate dehydrogenase (LDH) level. Elevation of more than 2,000 IU/ml can occur within 24 hours of renal infarction and can persist for up to 14 days. LDH 1 and 2 are the isoenzymes that are usually elevated. Urinary LDH can be helpful in differentiating the causes of serum LDH elevation (1).

Other laboratory abnormalities include leukocytosis, elevated serum CK and haematuria; since these are all com-

mon and nonspecific, they are therefore not helpful (16). The therapeutic guidelines of renal artery embolism are not established.

Generally treatment options include: systemic anticoagulation, intra-arterial thrombolytic therapy and surgical embolectomy. Treatment with anticoagulation should lead to reduced morbidity. Revascularization via surgical embolectomy or percutaneous transcatheter thrombolytic therapy during the first 24 hours can result in the complete reversal of renal failure and should be attempted, even when no significant collateral circulation is demonstrated.

CONCLUSION

We conclude that acute renal infarction secondary to atrial fibrillation is a rare clinical condition, and that its clinical picture is similar to that of renal stone; this resemblance may therefore delay its proper diagnosis and treatment. A high index of clinical suspicion and ultrasound (Figure 1) is important to increase the chance of renal salvage. The use of ultrasound with color-Doppler may, as in our case, helping to facilitate a rapid diagnosis, obtained with certainty by CT with contrast-enhanced, as reported in literature data. The most common finding is a hypoattenuated area with associated mass effect, sometimes accompanied by a cortical rim sign. The cortical rim sign represents opacification of a rim of functioning nephrons supplied via capsular collaterals surrounding an otherwise non-functioning kidney.

The cortical rim sign can be especially useful in differentiating ischemia (where it is sometimes seen, especially with global infarcts) vs. pyelonephritis (where it is not seen). Wedge-shaped focal infarcts, global infarcts and multifocal infarcts can also be seen with infarction.

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Correspondence

Lucio Dell'Atti, MD

U.O. Urologia

Azienda Ospedaliero - Universitaria Arcispedale "S. Anna"

Corso Giovecca 203 - 44100, Ferrara

dellatti@hotmail.com

Roberto Galeotti, MD

U.O. Radiologia Vascolare ed Interventistica

Azienda Ospedaliero - Universitaria Arcispedale "S. Anna"

Corso Giovecca 203 - 44100, Ferrara

gtt@unife.it

Gian Rosario Russo, MD

U.O. Urologia

Azienda Ospedaliero - Universitaria Arcispedale "S. Anna"

Corso Giovecca 203 - 44100, Ferrara

gianrosario.russo@ospfe.it

ORIGINAL PAPER

Ultrasonographic findings in dual kidney transplantation

Stefano Vittorio Impedovo, Pasquale Martino, Silvano Palazzo, Pasquale Ditunno, Michele Tedeschi, Fabrizio Palumbo, Ardit Tafa, Matteo Matera, Francesco Paolo Selvaggi, Michele Battaglia

Urology, Andrology and Kidney Transplantation Unit, Department of Emergency and Organ Transplantation, University of Bari, Bari, Italy

Stefano Vittorio Impedovo, Pasquale Martino and Silvano Palazzo have equally contributed to this work

Summary

Introduction: Organ shortage has led to using grafts from expanded criteria donors (ECD). Double kidney transplantation is an accepted strategy to increase the donor pool, using organs from an ECD which are not acceptable for single kidney transplantation (SKT). Aim of this retrospective study was to analyse the role of colour Doppler ultrasound (CDUS) in the diagnosis of major surgical complications in DKT, performed with unilateral or bilateral placement.

Materials and Methods: From 2000 to 2011 we performed 54 DKT. Unilateral placement of both kidneys was done in 26 patients and bilateral DKT in 28, through two separate Gibson incisions (18) or one midline incision (10). Each patient underwent at least 3 CDUS before hospital discharge. The main surgical complications, discovered initially thanks to ultrasound (US), were hydronephrosis from ureteral obstruction, lymphocele and deep venous thrombosis (DVT).

Results: Mean follow-up was 42.7 months. Good postoperative renal function was demonstrated in 25 patients (46.3%), while delayed graft function occurred in 29 (53.7%). US showed ureteral obstruction requiring surgery in 5 unilateral DKT while no patient subjected to bilateral DKT developed severe hydronephrosis. Lymphocele, surgically drained, was demonstrated in 6 bilateral DKT with a midline incision, 2 bilateral DKT with two separate incisions and 3 unilateral DKT. CDUS also enabled diagnosis of 2 cases of DVT in ipsilateral DKTs.

Conclusions: CDUS provides useful information in patients with DKT, allowing the detection of clinically unsuspected unilateral diseases. US study of our patients demonstrated that unilateral DKTs are more susceptible to the development of DVT and ureteral stricture, while the incidence of voluminous lymphocele is more frequent in bilateral DKT through a single midline incision. In this scenario, all patients undergoing DKT should be carefully monitored by US after surgery.

KEY WORDS: Expanded criteria donor; Dual kidney transplant; Colour Doppler ultrasound.

INTRODUCTION

Dual kidney transplant (DKT) is a safe strategy, with good results in terms of renal function and graft survival (1-11), adopted to combat the problem of organ shortage by using organs from an expanded criteria donor (ECD), which are not acceptable for single kidney transplantation (SKT).

However, DKT carries a potentially higher risk of surgical complications as compared to single kidney trans-

plantation, so it is very important to follow and screen these patients and carry out work-up that will determine the exact nature of the problem and rapidly establish the best treatment. The use of ultrasonography as a noninvasive technique to assess these complications has been suggested.

Aim of this retrospective study was to analyse the role of colour Doppler ultrasound (CDUS) in the diagnosis of

major surgical complications associated to DKT, performed by unilateral or bilateral placement.

PATIENTS AND METHODS

From October 2000 to July 2011, 54 DKT were performed at our Center, consisting of 26 ipsilateral and 28 bilateral DKT. Unilateral placement of both kidneys was done extraperitoneally through a single, longer paramedian incision; both ureters were anastomosed side-to-side at their spatulated ends and reimplanted into the bladder by the Lich-Gregoire technique. In bilateral DKT, kidney placement was performed extraperitoneally through two separate Gibson incisions 18 or one midline approach 10. All the ureters were stented by a pediatric double J stent 4.7Ch.

Delayed graft function was defined as the need for at least one dialysis in the early post-transplantation period. "Primary non-function" (PNF) of the graft was defined as no function at any time of the renal graft in the post-transplantation evolution, with the recipient continuing to require dialysis.

Immunosuppressive protocols included Tacrolimus or Cyclosporin A, mycophenolate mofetil and steroids; a IL2R inhibitor (Basiliximab) was used as induction therapy.

Each patient underwent at least 3 CDUS before hospital discharge. Colour Doppler examinations were performed with a phased array transducer in supine position. Surgical complications discovered initially thanks to US were hydronephrosis from ureteral obstruction, lymphocele, renal vein thrombosis and deep venous thrombosis. Kaplan Meier analyses were applied to calculate graft and patient survival.

RESULTS

Mean follow up time was 42.7 months. Non DKT was a retransplant. Donor and recipient characteristics are summarized in Table 1. Good postoperative renal function was demonstrated in 25 patients (46.3%), while delayed graft function requiring dialysis occurred in 29 (53.7%). Primary non-function (PNF) was observed in 1 man (1.8%). US scan showed severe ureteral stricture in 5 unilateral DKT, while no patient who had undergone bilateral DKT developed significant hydronephrosis. Lymphocele was demonstrated in 6 bilateral DKT with a midline incision, 2 bilateral DKT with two separate incisions and 3 unilateral DKT. CDUS also enabled diagnosis of 2 cases of deep vein thrombosis in ipsilateral DKT. Operation time was approximately the same for the three techniques, while hospital stay was longer for bilateral DKT with the midline approach.

Thanks to early detection of these complications by ultrasound, they could be promptly treated: patients affected by severe hydronephrosis underwent surgical correction of the ureteral stenosis with preservation of renal function, larger lymphoceles were initially treated by percutaneous drainage, but in two patients it was necessary to perform marsupialization, due to recurrence of the lymphocele.

Two patients underwent monolateral transplantectomy due to renal vein thrombosis after torsion. US also revealed a case of abscess near the left transplanted kidney, with pyelonephritis of the graft, so we immediately performed a monolateral transplantectomy.

Graft survival was 100%, 97.2% and 91% at 1, 3 and 5 years, respectively (Figure 1). Patient survival was 93% and 84%, 84% at 1, 3 and 5 years (Figure 2).

Table 1.

Baseline donor and recipient characteristics.

Donors	
Mean age (years)	70.9 ± 8.3 (33-83)
Male/Female	31/23
Cerebrovascular death (%)	80.3%
Mean estimated creatinine clearance by MDRD formula (mL/min)	52.2 mL/min ± 14.5 (16.6-83)
Mean serum creatinine (mg/dL)	1.2 mg/dL ± 0.63 (0.5-4.5)
Mean Remuzzi-Karpinsky score	4.5 ± 0.9
Mean Cold Ischemia Time (hours)	21.9 ± 4.3 (10-34)
Mean BMI (Kg/m ²)	25.7 ± 3.45 (17.6-32)
Recipients	
Mean age (years)	57.1 ± 5.0 (45-65)
Male/Female	28/26
Mean BMI(Kg/m ²)	25.1 ± 4.6 (18-40)
Mean time of dialysis before transplant (months)	72.6 ± 35.4 (10.2-135.1)
± SD (range)	
MDRD: Modification of Diet in Renal Disease	
BMI: body mass index	

Figure 1.

Kaplan-Meier estimates of graft survival in DKT.

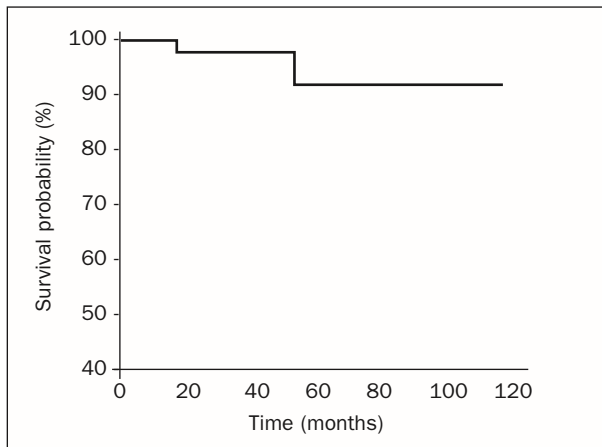
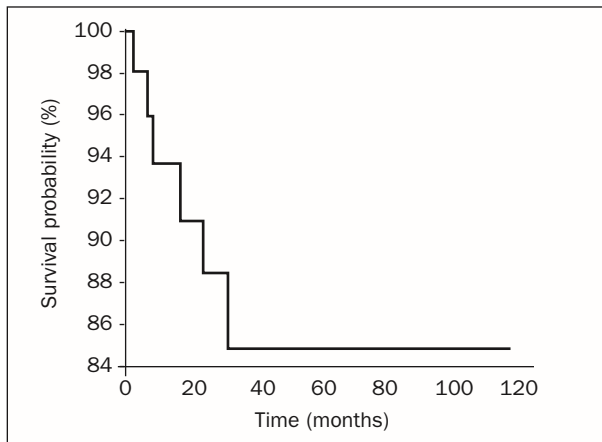


Figure 2.

Kaplan-Meier estimates of patient survival in DKT.



DISCUSSION

Organ shortage has led many transplant centers to accept kidneys from marginal deceased donors and to make increasing use of old-for-old allocation systems. DKT of marginal kidneys is a well established strategy to expand the donor pool (1-11).

Since 2000, at our center, DKTs have been performed successfully. Unilateral placement of the kidneys was initially the preferred technique because it allows the surgeon to operate through a single incision, to preserve the opposite vascular axis for a later retransplant, and it is an absolute indication in cases of a single vascular axis. On the other hand, it is more difficult to perform the second transplant, the ureteral anastomosis is more complex and also postoperative follow-up through US imaging is more complex. Today, the DKT technique is chosen based on the characteristics of the recipients and of the grafts: generally we do not perform monolateral DKT in obese patients and in cases of large grafts in small recipients.

The higher incidence of ureteral stricture in unilateral double transplants likely has an explanation of a mechanical nature, while in other cases, a Polyoma virus (BKV) infection seems to be a possible cause (12). Similarly, renal vein thrombosis occurred exclusively in unilateral DKT. Lymphocele seemed to affect bilateral DKT, in particular, performed with a midline incision. Thanks to assiduous US monitoring of these subjects, treatment was timely and often completely resolved the problem.

Regardless of the surgical technique, in our experience DKT poses a potentially greater risk of surgical complications as compared with single kidney transplantation (13). Frequently, these complications affect only one of the two grafts with no true worsening of the renal function and overall health of the patient, so they are clinically asymptomatic and occur late, when treatment is more difficult and sometimes ineffective.

CONCLUSIONS

Imaging evaluation of a graft kidney plays a critical role in the postoperative care of the renal transplant patient. Ultrasound, performed immediately at the clinical presentation, is the first step in the diagnostic evaluation of the transplanted kidney. The results of this study show that despite the high number of surgical complications after DKT, early detection of these events through CDUS allows early treatment, improving the quality of life and long term graft and patient survival.

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Correspondence

Stefano Vittorio Impedovo, MD
stefanovittorio@gmail.com

Pasquale Martino, MD
martino@urologia.uniba.it

Silvano Palazzo, MD
silvano.palazzo@alice.it

Pasquale Ditunno, MD
ditunno@urologia.uniba.it

Michele Tedeschi, MD
michele_tedeschi@live.it

Fabrizio Palumbo, MD

Ardit Tafa, MD

Matteo Matera, MD
materamatteo@libero.it

Francesco Paolo Selvaggi, MD
selvaggi@urologia.uniba.it

Michele Battaglia, MD
battaglia@urologia.uniba.it

Department of Emergency and Organ Transplantation
Urology, Andrology and Kidney Transplantation Unit
Piazza G. Cesare 11, 70124 Bari, Italy

CASE REPORT

Refractory hypertension and rapidly progressive renal failure due to bilateral renal artery stenosis: Case report

Annalisa Noce^{1,2}, Maria Paola Canale¹, Olga Durante^{1,2},
Simone Manca di Villahermosa¹, Valentina Rovella¹, Fulvio Fiorini^{2,3},
Claudia Parolini¹, Nicola Di Daniele¹

¹ Department of Internal Medicine - Nephrology and Hypertension Unit, University of Rome "Tor Vergata", Rome, Italy;

² Kidney Ultrasound Study Group - Italian Society of Nephrology (SIN-GSER);

³ Department of Nephrology and Dialysis, "S. Maria della Misericordia" Hospital, Rovigo, Italy.

Summary

Introduction: We report a case of refractory hypertension and acute renal failure with mild proteinuria due to an unreported bilateral Renal Artery Stenosis, who underwent renal biopsy in the suspicion of rapidly progressive glomerulonephritis.

Case presentation: A 51 year-old Caucasian male was admitted with refractory hypertension of recent onset and acute renal failure. Duplex Doppler Ultrasonography was performed and provided images highly suggestive for bilateral renal artery stenosis. The patient was referred to the department of interventional radiology, where bilateral selective renal angiography and percutaneous endovascular angioplasty and stenting were performed successfully.

Conclusion: Duplex Doppler Ultrasonography is thus suggested in patients presenting with refractory hypertension and acute renal failure, especially if atherosclerotic disease and clinical clues of RAS are present. Renal revascularisation with bilateral angioplasty and stenting may play a key role in the treatment of bilateral Renal Artery Stenosis, especially in patients unable to maintain renal function as systemic blood pressure is lowered.

KEY WORDS: Acute renal failure; Duplex Doppler ultrasound; Percutaneous angioplasty; Renal Artery stenosis.

INTRODUCTION

Renal artery stenosis (RAS) is a common cause of secondary hypertension; its incidence is 10 to 40 percent in patients with severe, refractory and acute hypertension. The major cause of RAS is atherosclerosis, that primarily affects men aged more than 45 and smokers, it usually involves the proximal segment of renal arteries. Bilateral RAS (or unilateral disease in a single viable kidney) can be associated with hypertension and progressive renal dysfunction (i.e. ischemic renovascular disease). Although no single non-invasive diagnostic test is sensitive enough to diagnose RAS, Duplex Doppler ultrasonography (DDUS) is a most accurate procedure in hemodynamically significant arterial stenosis of more than 75 percent, with 90 to 99 percent sensitivity and 97 percent specificity in skilful hands (1).

Treatment of bilateral RAS is still a matter of debate: the 2005 American College of Cardiology/American Heart Association (ACC/AHA) guidelines on peripheral arterial disease recommend medical therapy for the control of secondary hypertension in bilateral RAS but propose revascularisation (usually by percutaneous angioplasty and stenting) in case of resistant and/or malignant hypertension, or inability to tolerate hypotensive drugs (2).

Here we report the case of a young Caucasian man who presented severe, refractory hypertension and acute renal failure with mild proteinuria, due to an unreported bilateral hemodynamically significant RAS and underwent renal biopsy in the suspicion of a rapidly progressive glomerulonephritis (RPGN).

CASE PRESENTATION

A 51 year-old obese, heavy smoker Caucasian male with no family or personal history of hypertension was admitted into another hospital with refractory HBP of recent onset and acute renal failure (BUN 124 mg/dl, serum creatinine 5,78 mg/dl) with mild proteinuria (850 mg/24 h). B-mode kidney ultrasound showed bilateral normal shape and size (longitudinal diameter: left 108 mm and right 103 mm) with increased parenchymal echogenicity (grade I of Hricak's classification) and reduced cortico-medullary differentiation; right kidney showed cortical thinning localized between the upper and the lower pole (parenchymal thickness: right kidney 14 mm, left kidney 15 mm). Renography showed an equally distributed reduction of GFR (27,8 ml/min, left kidney 49,6%, right kidney 50,4%). In the suspicion of a RPGN patient underwent renal biopsy, that showed focal segmental glomerulosclerosis with moderate arteriolosclerosis.

At admission in our Department patient's systolic blood pressure (SBP) ranged between 190 and 220 mmHg and diastolic between 100 and 130 mmHg under treatment with irbesartan 300 mg and amlodipine 10mg daily. He had full and symmetric pulse in the upper and lower extremities with no radial/femoral delay. An intense abdominal systo-diastolic bruit was reported on auscultation.

No peripheral edema was noted. Fundoscopic examination revealed grade II hypertensive retinopathy and left ventricular hypertrophy was disclosed by echocardiography. Daily Ramipril 5 mg was added to therapy with slight reduction of blood pressure but a sharp increase in serum creatinine (up to 7,3 mg/dl) prompted the drug withdrawal.

DDUS was performed and provided images highly suggestive for bilateral renal artery stenosis: increased blood flow velocity (> 200 cm/sec) was observed at the ostial region of both renal arteries, together with renal aortic ratio (RAR) of 3.7, bilateral reduction of blood flow velocity and abnormal waveform of intra-renal vessels, "parvus tardus" pulse, loss of early systolic peak and reduction of parenchymal resistance index (RI = 0,52 for right and 0,53 for left kidney) (Figures 1, 2).

Magnetic resonance angiography confirmed DDUS findings and showed a severe ostial stenosis of both renal arteries (right 85%, left 75%).

We revised histological slides from the previous kidney core biopsy that showed focal and segmental glomerulosclerosis with moderate arteriolosclerosis. Eighteen of

Figure 1.

Duplex Doppler sonography of the right renal artery: a peak systolic velocity greater than 350 cm/sec is measured at the ostial tract.

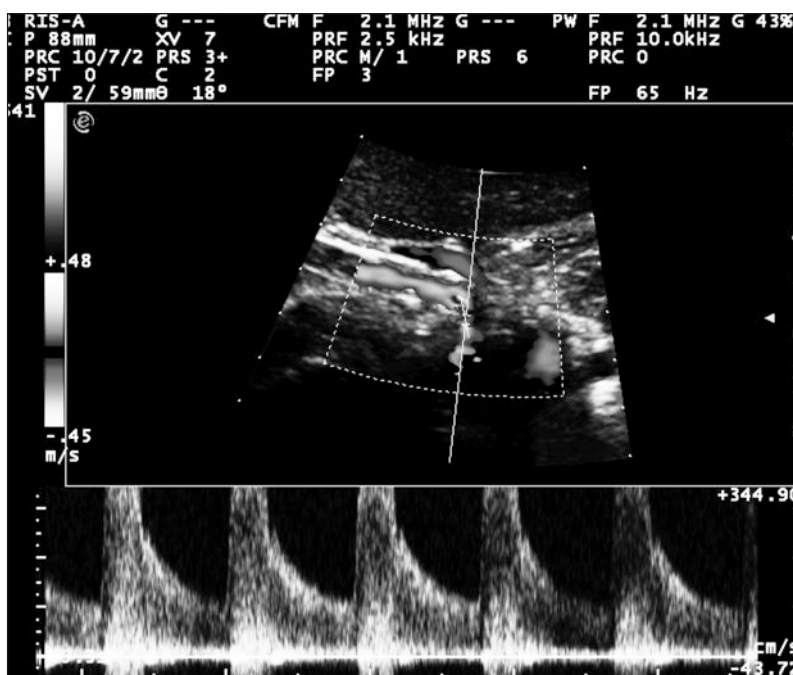
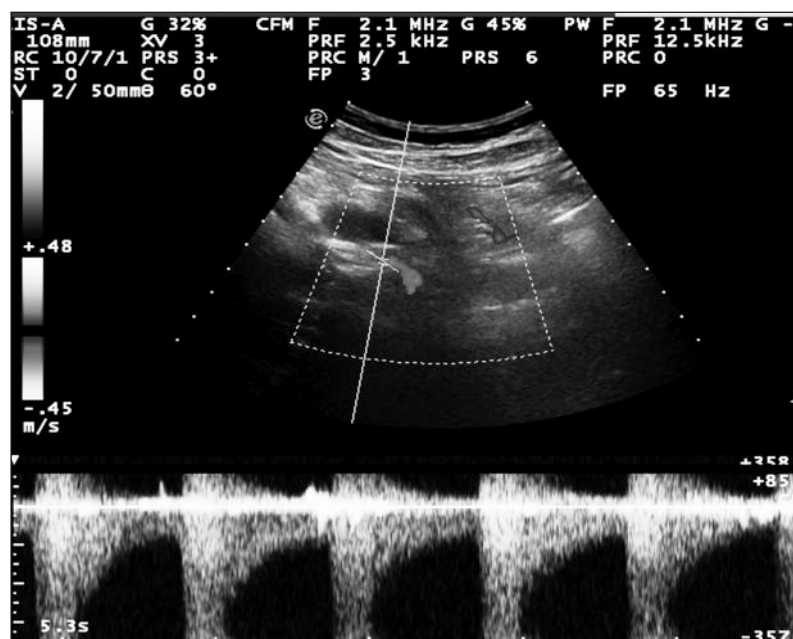


Figure 2.

Duplex Doppler sonography of the left renal artery: a peak systolic velocity greater than 370 cm/sec is measured at the median tract.

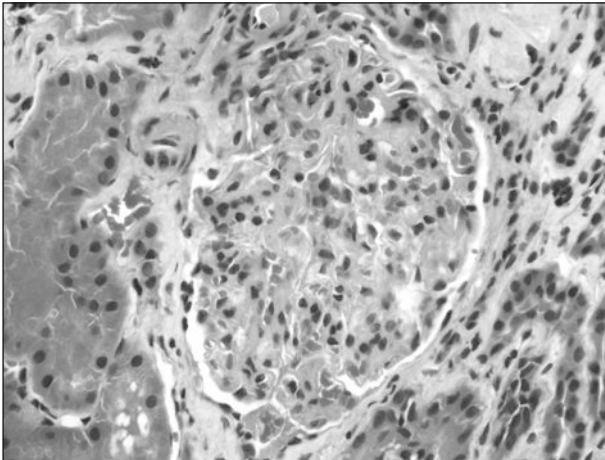


twenty glomeruli were ischemic and contracted, intimal fibrosis and focal disruption of the internal elastic lamina were also present. Final diagnosis was glomerulosclerosis with chronic ischemic injury (Figures 3, 4).

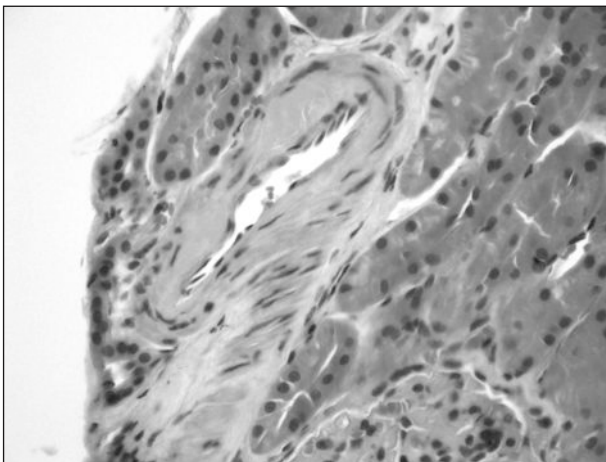
The patient was referred to the department of interventional radiology, where bilateral selective renal angiogra-

Figure 3.

Renal glomerulus showing mesangial scarring due to chronic hypertension and ischemic injury. Hematoxylin/eosin, original magnification 400X.

**Figure 4.**

Renal arterial vessel showing mild narrowing of the lumen due to fibrosis and muscular hyperplasia of the tunica media. Hematoxylin/eosin, original magnification 400X.



phy and percutaneous endovascular angioplasty and stenting were performed successfully. Anti-aggregation with Clopidogrel 75 mg and acetylsalicylic acid 100 mg daily was started before the procedure.

At 30-day follow up positive changes were evident: blood pressure was significantly improved (mean 150/85 mmHg) under the same hypotensive medications; renal function also improved as indicated by laboratory workout (serum creatinine dropped to 2,8 mg/dl and urinary protein excretion rate fell to 500 mg/24 h). Post-operatively DDUS showed a significant decrease of systolic peak velocity (80 cm/sec) at stent level, absence of turbulence and a well defined early systolic peak on parenchymal blood flow. There was also a significant increase of RI (mean 0.63, bilaterally) compared to pre-procedural values. At five-year follow up blood pressure

was maintained normal (120/80 mmHg) with only one hypotensive medication (irbesartan 300 mg/die), GFR, estimated by CKD-EPI formula was 65 ml/min, serum creatinine was stable at 1,5 mg/dl, DDUS findings were unchanged.

DISCUSSION

Renal failure secondary to ischemic renovascular disease is a potentially reversible disorder: hemodynamically significant high grade stenosis (more than 75%) of both renal arteries (or a stenosis in a solitary kidney) causes progressive parenchymal ischemia that involves the entire renal mass, resulting in organ insufficiency (3).

Ischemic renovascular disease should be suspected in case of acute, severe or refractory HBP associated to unexplained renal insufficiency or to acute renal failure after ACE-I or angiotensin II receptor blockers.

RAS may be asymptomatic or may present with a spectrum of clinical manifestations such as renovascular hypertension, congestive heart failure with or without progressive cardiovascular disease, stroke, ischemic nephropathy with or without progressive renal failure, secondary hyperaldosteronism (3).

Although part of these clinical clues were present in our patient, mild proteinuria, symmetric GFR reduction at renography and underestimation of ischemic pattern on biopsy specimen (prevalence of ischemic and contracted glomeruli, fibrosis of the vascular intima and focal disruption of the internal elastic lamina) led to the misdiagnosis of RPGN. Indeed, proteinuria of more than 1 g/24 h is common in patients with RAS and is positively related to active renin concentration, which reflects plasma angiotensin II concentration and glomerulosclerosis is also present in 30% of patients with RAS aged more than 65 (4, 5).

Since optimal treatment for bilateral RAS is still on debate, we chose renal artery angioplasty and stent implantation in this patient for the presence of significant bilateral renovascular disease with inability to maintain renal function after the systemic blood pressure was lowered, even with non-ACE inhibitor therapy (6). Although the incidence of clinical athero-embolic disease following renal artery angioplasty is probably higher in patients with bilateral RAS, significant improvement of blood pressure was observed after angioplasty rather medical therapy particularly in patients with bilateral disease.

CONCLUSIONS

The case reported suggests the necessity to suspect bilateral RAS in patients with HBP difficult to control presenting with acute renal failure or RPGN, especially in those patients with history of atherosclerotic disease and classical clinical clues of RAS (acute elevation of blood pressure, severe or refractory HBP, asymmetric renal size, increase in serum creatinine or unexplained progressive renal failure after ACE-I administration) and the importance to perform DDUS in these patients as well. Finally, renal revascularisation by means of angioplasty with stent implantation may play a key role in the treatment

of bilateral RAS, especially in patients with inability to maintain renal function after correction of HBP.

AUTHORS' CONTRIBUTIONS

AN, MPC and OD examined the patients, interpreted the findings and were the major contributor in writing the manuscript. SMV, VR and ND designed and reviewed the manuscript.

CP and FF performed, analyzed and interpreted radiologic examination findings.

All authors read and approved the final manuscript.

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Correspondence

Annalisa Noce, MD

Department of Internal Medicine - Nephrology and Hypertension Unit,
University of Rome "Tor Vergata"
Viale Oxford 81 - 00133, Rome, Italy
annalisa.noce@fastwebnet.it

Maria Paola Canale, MD

Olga Durante, MD

Simone Manca di Villahermosa, MD

Valentina Rovella, MD

Claudia Parolini, MD

Nicola Di Daniele, MD

Department of Internal Medicine - Nephrology and Hypertension Unit,
University of Rome "Tor Vergata", Rome, Italy

Fulvio Fiorini, MD

Department of Nephrology and Dialysis,
"S. Maria della Misericordia" Hospital, Rovigo, Italy

CASE REPORT

Bilateral native kidney neoplasia detected by ultrasound in functioning renal allograft recipient

Annalisa Noce¹, Giuseppe Iaria², Olga Durante¹, Daniele Sforza²,
Maria Paola Canale¹, Simone Manca Di Villahermosa¹, Veronica Castagnola¹,
Giuseppe Tisone², Nicola Di Daniele¹

¹ Department of Internal Medicine - Nephrology and Hypertension Unit; University of Rome "Tor Vergata", Rome, Italy;

² Department of Surgery, Transplant Surgery Unit - University of Rome "Tor Vergata", Rome, Italy.

Summary

We report the case of bilateral renal clear cell carcinoma in the native kidney, occurring four years after renal transplantation. Renal Doppler Duplex sonography revealed large solid bilateral neoformation. Total-body computed tomography confirmed the presence of bilateral kidney lesions and also showed the presence of concomitant gross dyscariocinetic lesion of left hemotorax. The patient underwent bilateral native nephrectomy and the histological diagnosis was renal cell carcinoma. Subsequent left upper lobectomy revealed necrotic keratinizing squamous cell carcinoma. Then, the patients was switched tacrolimus to everolimus treatment and mycophenolate mofetil was reduced.

KEY WORDS: Kidney transplantation; Everolimus; Renal Doppler duplex sonography; Renal clear cell carcinoma.

INTRODUCTION

Renal transplantation remains the best treatment option for patients with end-stage renal disease (ESRD). There is a significant increased risk of malignancies, most common skin malignancies and non-Hodgkin lymphomas, in renal transplant recipients as a result of the use of immunosuppressive medications (1). Kasiske and coworkers observed a twenty-fold incidence of Kaposi's sarcoma and non Hodgkin lymphomas in transplant patients compared to the general population (1). On the other hand, carcinoma of the native kidney accounts for less than 5% of all malignancies found in transplant recipients (2). After successful renal transplantation, the risk of developing renal cell carcinoma (RCC) in native kidneys is about 15 times higher than in the normal population (1). In the last years a 10 to 100-fold increase of native kidney tumors was also observed compared to the general population. Moreover, clear cell carcinoma of the native kidneys is quite more aggressive in renal allograft recipients compared to non immunosuppressed patients.

We report here the case of a bilateral native renal tumor in a transplant patient.

CASE REPORT

A 61-year-old ESRD Caucasian male under maintenance hemodialysis since 1999 for focal segmental glomerulosclerosis with clinical history of tonsillar neoplasia resected in 1997, colic diverticulosis and multiorgan vasculopathy underwent cadaveric renal allograft in 2007. Early post-transplant (PT) immunosuppression was basiliximab (day 0 and 4), mycophenolate mofetil (MMF) (1000 mg b.i.d.) and tacrolimus (Tac) (serum Tac between 6 and 10 ng/ml). In the postoperative period the patient suffered histologically proven acute tubular necrosis that resolved within five weeks. At two-month PT, prednisone (P) was started at 20 mg/day in the suspect of acute graft rejection. Corticosteroid therapy was withdrawn regardless of fair clinical conditions and renal function (serum creatinine 2.0 mg/dl) for the onset of PT diabetes mellitus. At 6-month PT, serum creatinine was 1.4 mg/dl, albuminuria was negative.

Immunosuppressive regimen was MMF 500 mg b.i.d. and Tac 0.5 mcg b.i.d. Renal function and immunosuppressive therapy were unchanged up to December 2011, when the patient complained episodes of gross hematuria during one week. Pre and PT renal ultrasound

Figure 1.

Right renal ultrasound showing solid non-capsulated hypoechoic neoformation of 36 x 37 mms with inhomogeneous (hypo-hyperechoic) structure.



Figure 2.

Abdominal Computed Tomography showing a dyscariocinetic lesion of 100 x 78 mms with necrotic and colliquative components in the left kidney and of a similar dyscariocinetic lesion of 36 x 37 mms in the right kidney (arrows).

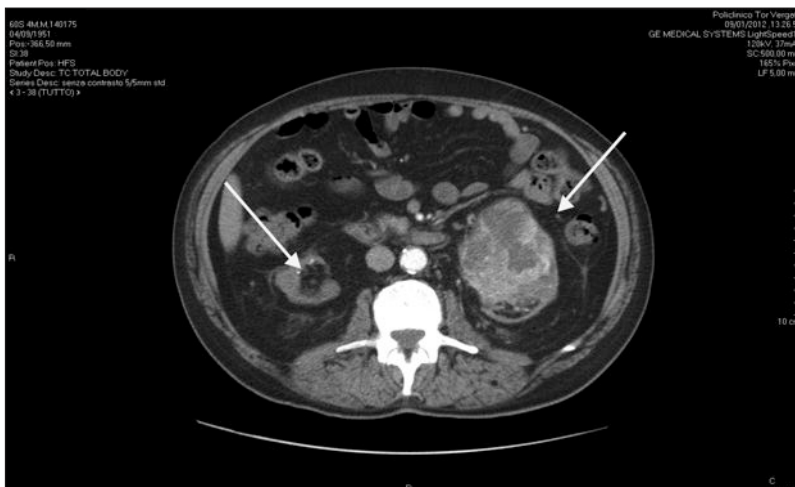
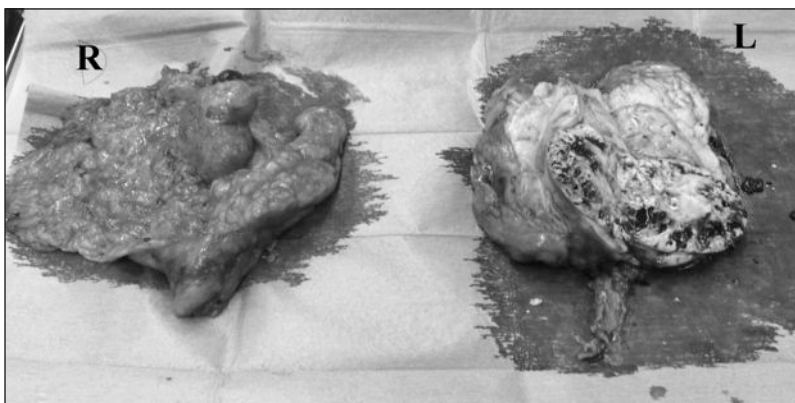


Figure 3.

Macroscopic appearance of resected native kidneys showing large tumor in the right kidney (R) and large lesion with necrotic and colliquative components in the left kidney (L).



examinations till July 2009 were negative for kidney neoplasms.

Renal duplex Doppler ultrasonography (DDUS) on December 2011 showed in the median third of the right native kidney the presence of a solid non-capsulated hypoechoic neoformation of 36 x 37 mm with inhomogeneous (hypo-hyperechoic) structure and intra and perilesional color signals showing low velocity and resistance on Doppler sampling (Figure 1). Analogous lesion of 100 x 78 mm was present at the lower pole of the left kidney.

Total-body computed tomography confirmed within the native organs of pyelonephritic appearance the presence of a gross dyscariocinetic lesion of 100 x 78 mm with wide necrotic and colliquative components in the left kidney and of a similar gross dyscariocinetic lesion of 36 x 37 mm in the right kidney (Figure 2). Moreover, a gross dyscariocinetic lesion of 53 x 48 mm was present in the left hemitorax. On January 2012 the patient underwent bilateral native nephrectomy (Figure 3). In both kidneys histologic diagnosis was RCC infiltrating the renal capsule (pT3).

Tac was switched to everolimus (serum everolimus about 8 ng/ml) and MMF was dropped to 500 mg/day. On March 2012 the patient underwent left upper lobectomy, with diagnosis of widely necrotic keratinizing squamous cell carcinoma without pleural infiltration at the bronchial resection edge (pT2b, N0). At the moment the patient is in fair clinical conditions, graft function is normal (serum creatinine: 0.8 mg/dl) and is in monotherapy with everolimus (serum everolimus about 7 ng/ml).

DISCUSSION

The incidence of RCC in native kidneys of renal transplant patients varies between 0.3 and 4.8%. Most RCCs in renal transplant patients are incidental low-stage, low-grade tumors with a good prognosis (3). In the new era of immunosuppression malignancy tends to appear earlier after transplantation. Recently, Watorek showed that malignancies occurred in 3,3% of patients on MMF+Tac+P treatment and appeared earlier compared to other regimens (4). With the improvement of life expectancy, cancer now becomes a major cause of death following renal transplantation. The cost-effectiveness of cancer screening including RCC is still debatable.

Inexpensive and noninvasive renal ultrasound still provides the best predictive value in screening and diagnosis of RCC in renal transplant recipients with a positive predictive value of 100% and a negative predictive value of 92-94% (5).

Following nephrectomy, the patient was switched to everolimus treatment because has been shown that the m-tor inhibitors have an antineoplastic activity (6).

CONCLUSIONS

Early diagnosis and aggressive treatment play a key role in the outcome of cancer in renal allograft recipients (7). We, thus, strongly suggest yearly DDUS of both renal allograft and native kidneys for early diagnosis and prompt management of renal cancer.

AUTHORS' CONTRIBUTIONS

AN, MPC, DS, GI and OD examined the patients, interpreted the findings and were the major contributor in writing the manuscript. SMV, GT and ND designed and reviewed the manuscript.

GI, DS and GT performed the surgical operation.

AN and VC performed, analyzed and interpreted radiologic examination findings.

All authors read and approved the final manuscript.

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Correspondence

Annalisa Noce, MD

Department of Internal Medicine - Nephrology and Hypertension Unit,
University of Rome "Tor Vergata"

Viale Oxford 81 - 00133, Rome, Italy

annalisa.noce@fastwebnet.it

Olga Durante, MD

Maria Paola Canale, MD

Simone Manca Di Villahermosa, MD

Veronica Castagnola, MD

Nicola Di Daniele, MD

Department of Internal Medicine - Nephrology and Hypertension Unit,
University of Rome "Tor Vergata",
Rome, Italy

Giuseppe Iaria, MD

Daniele Sforza, MD

Giuseppe Tisone, MD

Department of Surgery, Transplant Surgery Unit,
University of Rome "Tor Vergata", Rome, Italy

CASE REPORT

Torsion of a neoplastic intrascrotal testis: When the torsion reveals the mass. A case report and review

Giuseppe Albino ¹, Rosanna Nenna ², Antonio Corvasce ¹, Ettore Cirillo Marucco ¹

¹ U.O. di Urologia, Ospedale "L. Bonomo", Andria, ASL BAT, Italy;

² U.O. di Anatomia ed Istologia Patologica, Ospedale "L. Bonomo", Andria, ASL BAT, Italy.

Summary

Cases of torsion of the spermatic cord are rare in men over 30 years old. Testicular tumors manifest themselves rarely with symptoms of acute scrotum. We report the case of a 38 years old patient who presented for a suspected left testis torsion. On examination, the testicle was markedly increased in size and painful. The manual derotation made pain dramatically disappear. He came to our attention after about a month asking for an orchidopexy. During the surgery a biopsy was performed. The diagnosis was a Yolk Sac Tumor. A radical inguinal orchiectomy was performed with left hemiscrotal excision, "in block". He performed four cycles of chemotherapy and with no recurrence after 12 months of follow-up. In literature only seven cases of torsion of an intrascrotal testicle with cancer are reported. Our case is the eighth one.

KEY WORDS: Neoplastic testis torsion; Intrascrotal; Yolk sac tumor; In block excision.

INTRODUCTION

Cases of torsion of the spermatic cord are rare for men over 30 years old. From 20 to 30 years old, the case series report a prevalence between 33% and 52% of all patients with a diagnosis of acute scrotum in that age group (1), 4% between 30 to 35 years old (2), but cases of testicular torsion are also reported up to 68 years old (3). Although rare, testicular tumors can appear with symptoms of acute scrotum.

MATERIALS AND METHODS

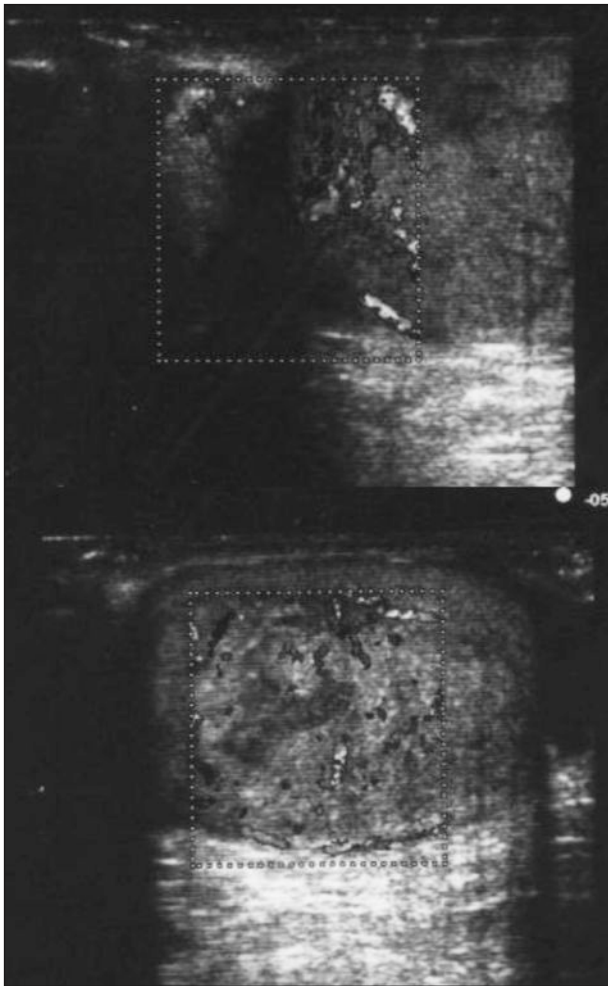
We report the case of a 38 years old patient who came to us for a suspected left testis torsion. He reported that the pain had manifested acutely 2 days before, and that he had succeeded in ending it by lifting and rotating the testicle inside the scrotum, but the pain had manifested itself again on the next morning when he had to go to the ER. On examination, the testicle was markedly increased in size if compared with the contralateral (x 2.5 times), it was increased of consistency and painful. The head of the epididymis is palpated posteriorly at the bottom, as for a rotation of 180°. The manual derotation made pain dramatically disappear. The Echocolor Doppler which was

performed after the manual derotation showed a disruption of the parenchymal tissue with accentuated vascularization. The U.S. pattern was interpreted as a reactive hypervascularization after inflammation caused by necrosis of some areas of the testis, which had frequently been subjected to sub torsions (Figure 1).

When we proposed the hospitalization in order to perform the orchidopexy, the patient refused surgery. He was again presented to our observation after about one month of recurrent episodes of sub torsion, and he accepted to be submitted to orchidopexy. At the opening of the scrotum the testicle appeared to be substantially increased in volume (x 2.5) and the albuginea had no injury, but it was in tension, and showed gross hemorrhagic areas, as leopard spots, the grossest ones charged to the upper pole. An incision of tunica albuginea was performed at the upper pole in order to reduce the internal pressure of the testis. The results was an evacuation of hemorrhagic necrotic material, which was sent for histological examination. After suturing the albuginea, an orchidopexy was performed, as it had already been. Unexpectedly, after a week, the histological diagnosis of sampled material highlighted the presence of a Yolk Sac

Figure 1.

The U.S. pattern was interpreted as a reactive hypervascularization.



Tumor. A radical inguinal orchiectomy was performed with left hemiscrotal excision, "in block" (Figures 2, 3).

Figure 2.

A radical inguinal orchiectomy was performed with left hemiscrotal excision, "in block" (incision).



Figure 3.

A radical inguinal orchiectomy was performed with left hemiscrotal excision, "in block" (closure).



RESULTS

Pathological findings. We examined specimen of left radical orchiectomy and left emiscrotum skin resection (Figure 4). On gross examination, testis was enlarged (7 x 6 x 4 cm) because of the presence within it of a large, solid, soft and pale gray-yellow mass (4,3 x 4 cm) with haemorrhage and necrosis (Figure 5). The testicular hilum was diffusely haemorrhagic. The tumor has focally invaded the adjacent tunica albuginea but not the epididymus, tunica vaginalis, spermatic cord and scrotum skin. On low-power microscopic examination, tumour showed a reticular-microcystic pattern, characterized by irregular loose spaces and anastomosing thin cords and tubules lined by flat or cuboidal cells. Also, papillary clusters of cells and many Schiller-Duval bodies were present (Figure 6). Peritumoral vascular lymphatic invasion occurred. All tumor cells are positive for Ck

Figure 4.

Left radical orchiectomy with left emiscrotum skin resection



Figure 5.

On gross examination, testis was enlarged (7 x 6 x 4 cm) for presence within it of large, solid, soft and pale gray-yellow mass (4,3 x 4 cm) with haemorrhage and necrosis.

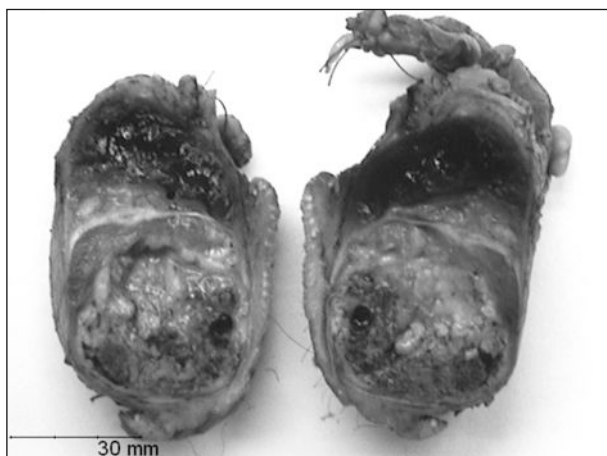


Figure 6.

Papillary clusters of cells and many Schiller-Duval bodies were present (Hematoxylin-Eosin x 10).

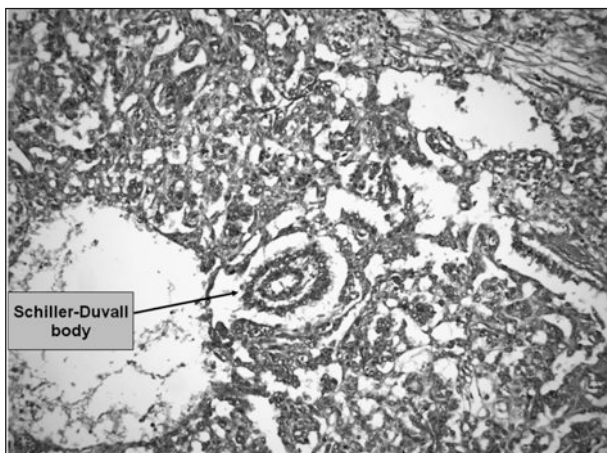
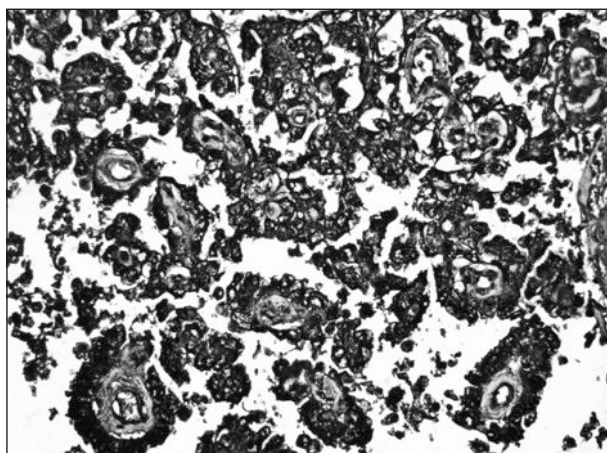


Figure 7.

Alpha-fetoprotein x 20.



AE1/AE3, Ck35BetaH11 and AFP (Figure 7), negative for CD30, PLAP, CD117 and BetaHCG. No other germ cell components are associated with this tumor. So, our diagnostic conclusion was "Pure Yolk Sac Tumour".

The Alpha-fetoprotein was (AFP) 2749 ng/ml before orchiectomy, and became < 4 ng/ml one month after surgery. The staging CT was negative for lymph nodes and distant metastases (N0, M0). He was subjected to 4 cycles of chemotherapy and there has been no recurrent disease after 12 months of follow-up.

DISCUSSION

Yolk Sac Tumour (YST) (or Endodermal Sinus Tumour) is a testicular non-seminomatous germ cell tumour (NSGCT) characterized by numerous patterns that recapitulate the yolk sac, allantois and extraembryonic mesenchyme (4). In the testis YST is seen in two distinct age groups, infants and young children (from birth to 5 years) and postpubertal males. In young children YST is almost always present in pure form and it accounts for 75-80% of all childhood testicular neoplasms. In adults, YST is found in approximately 40% of NSGCT and the pure form is very rare because it usually occurs as a component of mixed germ cell tumours. Alfa-Fetoprotein levels are elevated in 90 percent of cases (5, 6). On gross examination, the enlarged testis contains a poorly defined, lobulated, white-gray or gray-yellow tumor ranging in size from 2 to 6 cm in diameter. It may be focally cystic or a solid mass with variable consistency, and haemorrhage and necrosis may be present. The cut surface often has a mucinous texture. Microscopically, the key to the recognition of YST is the simultaneous presence of myriad histologic patterns. The reticular-microcystic pattern is most common. The most distinctive pattern is the one forming Schiller-Duval bodies, considered a hallmark of YST, in which a central fibrovascular core is surrounded by malignant from cuboidal to columnar epithelioid cells. Other variations include macrocystic, papillary, glandular-alveolar, solid, myxomatous, polyvesicular vitelline, hepatoid and enteric patterns. Intracellular and extracellular hyaline Pas-positive globules are characteristic of yolk sac differentiation. Pediatric tumors are not associated with ITGCN (Intratubular Germ Cell Neoplasia); in contrast, almost all adult tumors with yolk sac tumor occurring as a component of MGCT (Mixed Germ Cell Tumors) have ITGCN. Tumor cells are positive for AFP, CK AE1/AE3, CK35BetaH11 and negative for CD30, CD117, PLAP and BetaHCG. There are two groups of prognosis predictive factors:

Clinical criteria:

- Age does not appear to be prognostically important, even though patients less than 2 years old have the best prognosis;
- Clinical stage of disease at initial presentation and degree of AFP elevation are important prognostic factors.

Morphologic criteria:

- Histologic patterns of YST have not a prognostic value;
- Lymphovascular invasion is associated with a worse prognosis.

In adults with yolk sac differentiation as a part of NSGCT, the prognosis varies with the stage of disease, but its presence does not appear to affect outcome adversely when current therapeutic modalities are used. Since pure YST in adults is very rare, little is known about its behavior at this time (7).

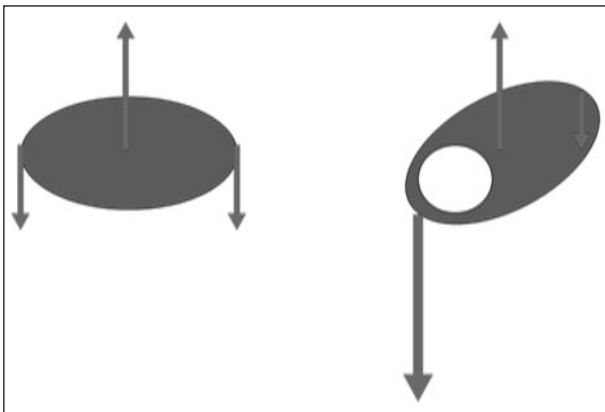
In literature there are 39 cases of torsion of undescended testes with cancer (8, 9), while there are only 7 cases of intrascrotal testicular torsion with cancer (10, 11). Our case is the eighth one. The reason because the torsions of the intra-abdominal testicles with cancer are more prevalent than the intrascrotal ones lies in the fact that the diagnosis of intrascrotal testicular neoplasm is made occasionally thanks to self examination or to a routine medical examination before it happens a possible torsion, while the presence of a neoplasm of an undescended testis in the abdomen, on which a torsion occurs, acquires greater clinical relevance to be mentioned by a case report. It should make us reflect the fact that in a series of 48 elective laparoscopic explorations to remove the cryptorchid testicle, none of the histopathological examination revealed the presence of tumor (12), whereas of 41 case reports of intra-abdominal testicular torsion, only 2 cases showed no malignancy, but 1 of the 2 cases showed hydrocele (13); in the other 39 cases there was a tumor.

CONCLUSIONS

There seems to be a strong correlation between the presence of a testicular mass and the possibility that a torsion takes place spontaneously in the abdomen, probably because of the asymmetrical distribution of the parenchymal weight caused by a testicular mass (Figure 8).

Figure 8.

The presence of a mass changes the center of gravity of the testis and promotes its rotation.



If this explication seems to be likely in the abdomen, it would be even more likely for the intrascrotal testicles, who enjoy a greater degree of freedom of rotation. These considerations should push to investigate the possible presence of a misunderstood testicular tumor, even for the obvious cases of torsion of the spermatic cord.

ACKNOWLEDGMENTS

We thank Lucia Vitofrancesco for her contribution.

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Correspondence

Giuseppe Albino, MD
U.O.C. di Urologia, Ospedale "L. Bonomo", ASL BAT
C.so Istria, 1 - 76123 Andria, Italy
peppealbino@hotmail.com

Rosanna Nenna, MD
U.O. di Anatomia ed Istologia Patologica,
Ospedale "L. Bonomo", Andria, ASL BAT, Italy

Antonio Corvasce, MD
Ettore Cirillo Marucco, MD
U.O.C. di Urologia,
Ospedale "L. Bonomo", Andria, ASL BAT, Italy

ORIGINAL PAPER

Comparison between ultrasound-guided and digital-guided anesthesia before prostatic biopsy

Giuseppe D'Eramo, Daniela Fasanella, Francesca Di Quilio, Peter Molnar, Stefano Salciccia, Alessandro Sciarra, Vincenzo Gentile

Department of Urology "U. Bracci", University Sapienza, Rome, Italy

In memory of prof. Franco Di Silverio

Summary

Objective: Our target in this study is to evaluate the efficacy of ultrasound (US)-guided anesthesia in comparison it to the digital-guided one, considering pain and discomfort reduction, during prostate biopsy.

Materials and methods: We analyzed 150 patients that underwent prostate biopsy between March 2011 and January 2012; conditions to enter the sample were: elevated PSA levels and/or psa ratio free/total less than 15% and/or detection of alteration via ultrasound examination and/or a positive outcome of a digital rectal examination. Patients were randomized into two groups. In 75 patients (Group A) was performed local US-guided anesthesia with a dose of 10 ml of mepivacaine 1%, in the other 75 patients (Group B) a local digital-guided anesthesia was performed, again with an equal dose of 10 ml of mepivacaine 1%. After the biopsy patients were kept under observation for two hours, afterthat they were asked to provide description of the pain experienced during biopsy, using a 10-point visual analog scale (Visual Analogue Scale; 0 for no pain, 10 for excruciating pain).

Results: In Group A, 49 patients scored a VAS value of zero, 23 a value of 1 and 2 a value of 3. On the other side, in Group B, 9 patients scored a VAS value of 1, 36 a value of 2, 28 a value of 3 and 2 a value of 4. In comparison patients in Group A scored VAS values statistically lower than patients in Group B (t Student Test, $p < 0,01$).

Conclusions: The ultrasound-guided prostatic anesthesia is preferable to the digital-guided, because it considerably reduce the pain related to this procedure.

KEY WORDS: Prostatic biopsy; Digital-guided anesthesia; Ultrasound-guided anesthesia; VAS score.

INTRODUCTION

The prostate biopsy is currently the diagnostic method used to assess the presence or absence of a tumor disease. Being an invasive technique, it is important this be done under a targeted and appropriate local anesthesia, in order to significantly reduce the patient's discomfort and pain during the biopsy. It has been used a dose of 10 ml of 1% Mepivacaine hydrochloride, a potent local anesthetic and drug of first choice in diagnostic anesthesia for its absence of induced vasodilatation, low tissue toxicity, limited spread, fast-acting and long-lasting anesthetic effect. The study conducted at our center aims to demonstrate that ultrasound-guided anesthesia of the

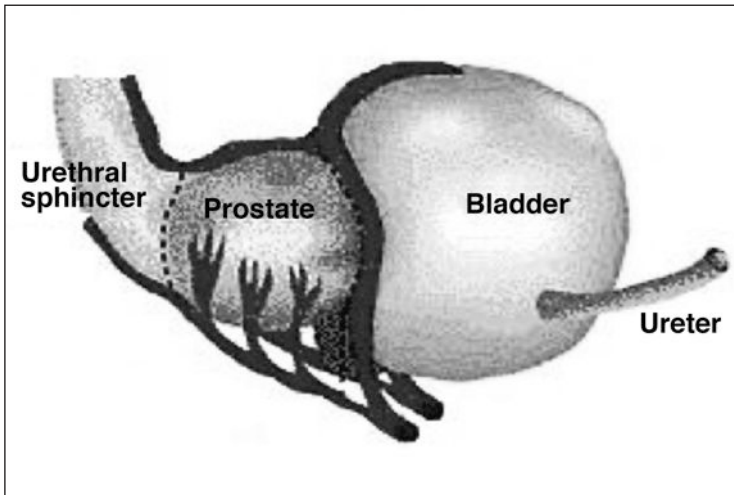
periprostatic neurovascular bundles significantly reduces pain in this procedure.

MATERIALS AND METHODS

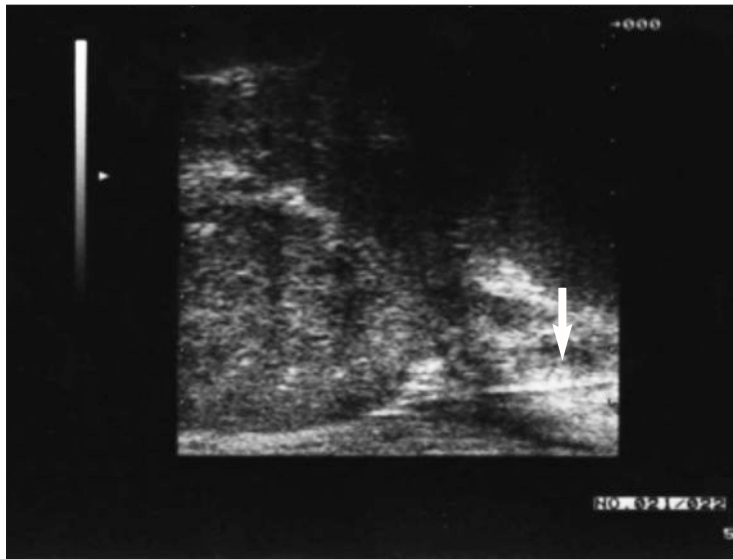
Between March 2011 and January 2012 150 patients presenting elevated PSA levels and/or psa ratio free/total less than 15% and/or detection of alteration via ultrasound examination and/or a positive outcome of a digital rectal examination undergone prostate biopsy. Studied Patients had an age range between 45 and 75 years; patients at risk for bleeding hemorrhoids, chronic

Figure 1.

Needle positioning for injection of the anesthetic solution along the neurovascular bundles.

**Figure 2.**

Transrectal ultrasound, longitudinal scanning, during execution of local periprostatic anesthesia (arrow indicates the site of injection).



pelvic pain syndrome and thrombocytopenic (platelet count $< 50000/\text{mm}^3$) were excluded from the study. Patients treated with antiplatelet agents were asked to discontinue about 10 days before surgery and a replacement therapy was prescribed to patients treated with anticoagulants. All patients started antibiotic therapy the day before the procedure and performed a cleansing enema on the morning of the biopsy. They also signed informed consent. Patients were randomized into two groups. In 75 patients (Group A) was performed local US-guided anesthesia with a solution of 10 ml of 1% mepivacaine, injected on each side of the prostate, near the junction of the seminal vesicles with the base of the gland along the neurovascular bundles (Figure 1).

To properly view the site for injection and separation of periprostatic tissue planes, we used an high frequency (7 MHz) biplanar probe TRUS-guided (Figure 2). In the other 75 patients (Group B) was performed a local digital-guided anesthesia with a solution of 10 ml of mepivacaine 1% on each side of the prostate. After the anesthesia, the biopsy is carried forward with patient in lithotomic position.

The biopsy technique chosen involves use of automatic guns with 18 gauge needle, able to pick up, with a quick release mechanism, small chips of prostatic tissue. We took a minimum of 14 to a maximum of 18 samples (in the paramedian apical, middle and cranial) on each patient. After the biopsy, every patient spent at least two hours in a recovery room and they have been asked to provide description of the experienced pain using a scale of 1 to 10 (VAS scale). The statistical analysis was performed using t Student test and PASW Statistics 18 software.

RESULTS

In Group A, 49 patients expressed a VAS value of zero, 23 of them a value of 1 and 2 marked a value of 3. On the other side, in Group B, 9 patients marked a VAS value of 1, 36 a value of 2, 28 marked 3 and 2 patients expressed a value of 4.

Patients in Group A, subjected to biopsy under local US-guided anesthesia, reported average VAS significantly lower ($0,38 \pm 0,57$) compared to Group B ones ($2,31 \pm 0,72$), which underwent biopsy after a local digital-guided anesthesia (Figure 3).

The comparison patients in Group A expressed VAS values statistically lower than patients in Group B (t Student Test, $p < 0,01$).

Hematuria manifested in 87 subjects; 13 patients had a vasovagal episode.

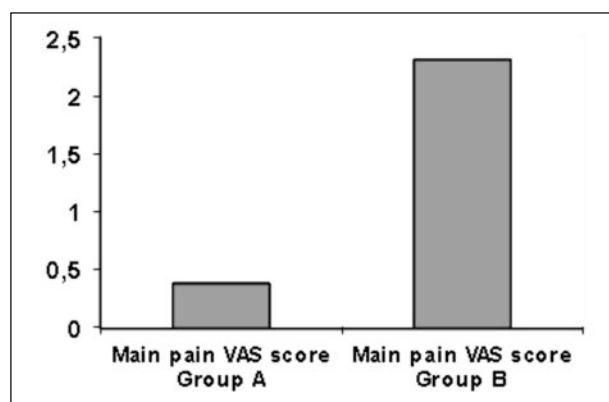
There has been only one episode of acute urine retention, patient underwent ladder catheter positioning. No patients reported lower urinary tract infections and/or rectal bleeding (Table 1).

DISCUSSION

The results obtained clearly demonstrate a significant pain reduction in transrectal prostate biopsy after performing ultrasound-guided anesthesia. Patients in group B gave higher VAS scores than group A, stating that they experienced discomfort and/or pain during the test. On the other side the majority of patients in group A reported that they experienced no pain or discomfort of any kind and that the procedure, as a whole, has been painless. The VAS (Visual Analogue Scale) visually represents the magnitude of pain that a patient believed to feel. The amplitude is represented by a line, usually 10 cm long, in which one end indicates the absence of pain, while the other represents the worst pain imaginable (Figure 4). The scale is marked off by the patient, who is asked to draw a line on the value

Figure 3.

Main values of VAS score in Group A ($0,38 \pm 0,57$) and Group B ($2,31 \pm 0,72$).

**Table 1.**

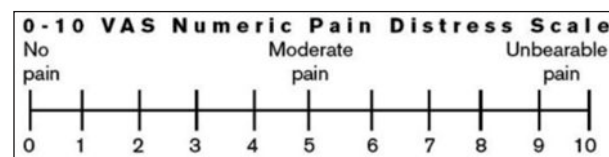
Complications of prostate biopsy.

Complication	Incidence (%)
Gross hematuria	58 (87)
Vasovagal syncope	8,7 (13)
Acute retention	0,7 (1)
Febrile UTI	0 (0)
Rectal bleeding	0 (0)
Total	67,4 (101)

that represents the level of experienced pain. This scoring technique has an approximate value, it expresses an opinion extremely subjective, therefore it cannot be evaluated in an absolute manner. However, we decided to use the VAS scale for its ease of use and evaluation.

Figure 4.

VAS (Visual Analogue Scale). The scale is completed by the patient who is asked to draw a line on the sign that represents the level of pain experienced.



CONCLUSION

Based on the results obtained in our study, we believe that use of ultrasound executing a prostatic anesthesia, has proved very effective reducing pain and discomfort in patients undergoing biopsy, since it allows to identify more precisely the periprostatic neurovascular bundles.

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Correspondence

Giuseppe D'Eramo, MD
Department of Urology, University Sapienza,
Viale dell'Università 33 - 00185 Rome, Italy
giuseppederamo@inwind.it

Daniela Fasanella, MD
Francesca Di Quilio, MD
Peter Molnar, MD
Stefano Salciccia, MD
Alessandro Sciarra, MD
Vincenzo Gentile, MD
Department of Urology, University Sapienza,
Viale dell'Università 33 - 00185 Rome, Italy

ORIGINAL PAPER

Modifications of the bladder wall (organ damage) in patients with bladder outlet obstruction: Ultrasound parameters

Andrea Benedetto Galosi ¹, Daniele Mazzaferro ², Vito Lacetera ²,
Giovanni Muzzonigro ², Pasquale Martino ³, Giacomo Tucci ⁴

¹ Division of Urology, Area Vasta 4, ASUR Marche, "Augusto Murri" General Hospital, Fermo;

² Institute of Urology, Polytechnic University of Marche, Azienda OU Ospedali Riuniti, Ancona;

³ Institute of Urology, Dept. DETO, University of Bari, Italy;

⁴ Urinary Incontinence Unit, Division of Urology, "Murri" General Hospital, Fermo, Italy.

Summary

Introduction: Progressive changes in the bladder wall are observed in men with lower urinary tract obstruction secondary to benign prostatic enlargement (BPE). The high pressure voiding causes initially an increase in the proportion of smooth muscle (hyperplasia/hypertrophy of the detrusor) that develops to major changes in the advanced stages of bladder decompensation (fibrosis), hyperactivity and decreased functional capacity. Early identification of bladder changes by noninvasive transabdominal ultrasound can suggest therapeutic choices that can prevent further organ damage in the bladder wall. Aim of our study is to review ultrasound (US) parameters, that could be considered reliable and reproducible, in order to demonstrate the damage of the bladder wall.

Methods: We performed a literature review to detect reported US parameters according to our aims. Our clinical experience was evaluated in retrospective manner to detect feasibility and limitations of the evaluation of these parameters in men with different degrees of bladder damage secondary to BPE.

Results: Measurement of the Bladder Wall Thickness (BWT) or Detrusor Wall Thickness (DWT) by US is reliable, with at least 3 measurements of the anterior bladder wall taken at a filling volume of 250 ml. In particular, the DWT [thickness of the hypoechoic muscle between two hyperechoic layers corresponding to serosa and mucosa] is considered the best diagnostic tool to measure detrusor hypertrophy using cut-off value > 2.9 mm in men. US derived measurements of bladder weight (Estimated Bladder Weight, EBW) is another noninvasive tool for assessing bladder modifications in patients with Bladder Outlet Obstruction (BOO) with a cut-off value of 35 gr. Technique for measuring the BWT and EBW relies on conventional US 7.5-4 MHz using the automatic system of computation (BVM 6500 3.7 MHz). The variability of intra-operator (4.6 to 5.1%) and inter-operator measurements (12.3%) is acceptable. Also conventional US detects established signs of bladder damage: diverticulosis, trabeculations in the bladder wall (pseudo-diverticula), calculi and post-void residual urine (PVR) (> 50cc). Furthermore the Intravesical Prostate Protrusion (IPP), easily measured by transabdominal ultrasound, is strongly correlated to obstruction in men with BPE (cut-off 12 mm). Measurement, scoring and monitoring of the cervico-urethral obstruction in men with symptomatic BPE is possible by the non-invasive US of the bladder wall. Early identification by measuring DWT and EBW in addition to established US parameters has the advantage of suggesting the adoption of therapeutic measures sufficient to prevent progression of bladder damage.

Conclusions: US derived measurements of DWT and EBW are reproducible and reliable. Transabdominal US also detect established bladder damage such as diverticula, stones and PVR, while IPP measurement seems to be correlated to BOO. US bladder parameters are considered potential noninvasive clinical tools for baseline assessment of patients with BOO. In particular noninvasive US parameters could be useful for longitudinal studies monitoring men with lower urinary tract obstruction secondary to BPE.

KEY WORDS: Prostatic hyperplasia; Urinary bladder; Urinary bladder neck obstruction; Ultrasonography; Prostate.

INTRODUCTION

The obstruction of the lower urinary tract secondary to benign prostatic hyperplasia (BPH) causes progressive changes of the bladder wall (1, 2). The high pressure of voiding, as demonstrated by urodynamic findings, initially causes an increase in the proportion of smooth muscle (hyperplasia/hypertrophy of the detrusor) that develops to major changes for advanced stages of bladder decompensation (fibrosis), hyperactivity or decreased functional capacity. Damage of the bladder wall is defined as the presence of at least one of the following conditions: detrusor hypertrophy (> 5 mm), fibrosis of the bladder wall, bladder stones, bladder diverticula, pseudodiverticula associated with large muscle bundles of the bladder wall, post-void residual urine (PVR) > 50 ml up to urinary retention. Hypertrophy of the bladder detrusor may be due to both obstruction of the bladder neck (prostatic or urethral obstruction) and detrusor overactivity (overactive bladder syndrome) or neurogenic bladder (1, 3).

In the initial diagnostic work up of the patient with low urinary tract symptoms (LUTS), it has to be taken into account that detrusor hypertrophy may have different causes (obstruction, detrusor overactivity, rarely a neurological cause).

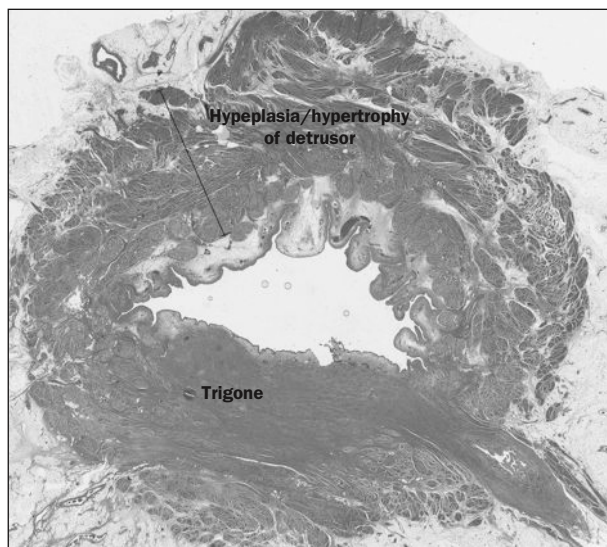
In men with obstructive symptoms associated with an enlarged prostate, hypertrophy of the detrusor is a parameter that allows to predict the degree of obstruction of the bladder neck if correlated with other clinical data (PVR, uroflowmetry and gland volume) (4).

The hypertrophy of the detrusor is a parameter to be monitored to assess changes during or after medical therapy (5). Early identification of changes induced by the obstruction of the bladder neck can induce therapeutic choices which may prevent the progression of organ damage of the bladder wall.

The aim of our study was to codify and disseminate the ultrasound (US) parameters, considered reproducible and reliable, in order to demonstrate noninvasively the changes of the bladder wall.

Figure 1.

Histologic macrosection demonstrating detrusor hypertrophy.



METHODS

We performed a literature review and on the basis of our clinical experience, we evaluated a series of clinical cases of prostatic hypertrophy with varying stages of organ damage secondary to bladder neck obstruction secondary to BPH.

Histological sections from patients suffering from obstructive disease were analyzed and compared with those of cases without obstructive disease (Figures 1-3). We referred to the following definitions: Bladder Outlet Obstruction (BOO) generally defines all forms of obstruction to bladder outflow (including BPH and urethral strictures); Benign Prostatic Enlargement (BPE) indicates an enlarged prostate. This is a presumptive diagnosis based on the size of the gland benign prostatic; Benign Prostatic Obstruction (BPO) indicates an obstruction confirmed by

Figure 2.

Histologic macrosection demonstrating normal bladder.

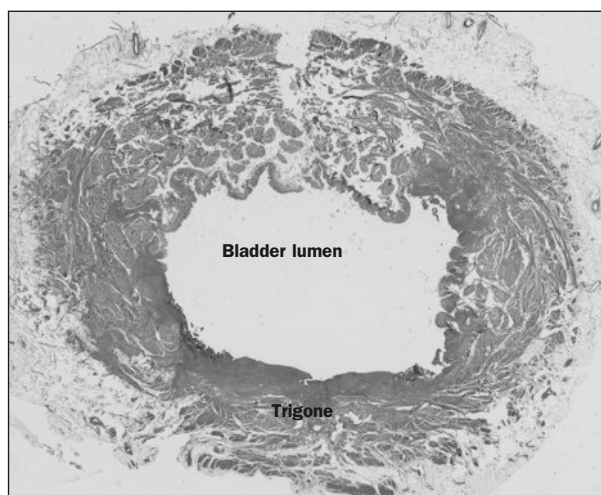
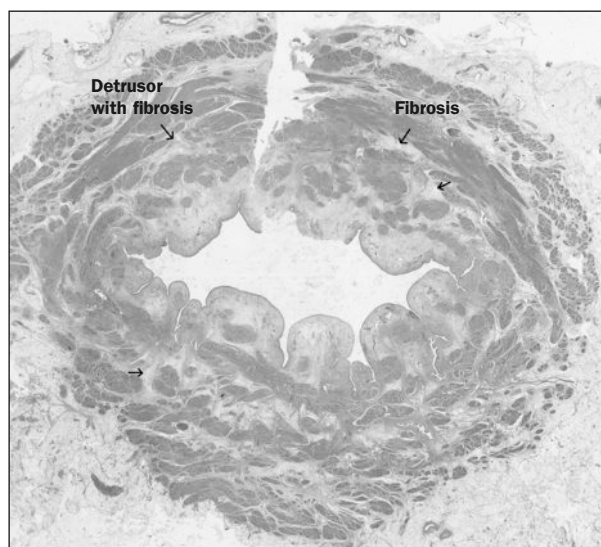


Figure 3.

Histologic macrosection demonstrating fibrotic bladder changes and hypertrophy of the detrusor.



a pressure-flow study or strongly suspected on the basis of uroflowmetry associated with pathological enlargement of the prostate gland.

RESULTS

Bladder wall thickness (BWT)

One study in a normal population found a median value of 2.3 mm (CI 25-75: 1.8-2.7 mm) with a 9.8% variability (CI 25-75: 4.9%-14%). Urodynamic evaluations show a high correlation (88%) with obstructive disease for BWT values > 5 mm, values included between 3.1 and 5 mm detect obstruction in 37%. BWT > 2.9 mm are to be considered suspicious and abnormal (6). The limitations of this measurement are related to variables that make studies disomogeneous, therefore the definition of a clear cut-off has not been uniformly accepted (7, 8).

Estimated bladder weight (EBW)

The calculation of the bladder weight (EBW, Estimated Bladder Weight) is less affected by the degree of bladder distension and has been introduced in order to make more reliable the echographic evaluation (9). It correlates significantly with the degree of bladder neck/urethral obstruction (10). The computation is performed with the following formula: $SA \times BWT \times 0.957 \text{ g/ml density}$.

The computation can be performed by an automatic system or by a standard ultrasound examination.

A recent study analyzed by automatic evaluation a population of normal subjects so detecting a median value of 48.5 g (IC 25-75: 43.7 to 53) and a variability of 7.9% (CI 25-75: 4-11%). Therefore values > 48 g obtained by the automatic device Bladderscanner can be considered abnormal (11, 12). The computation performed by ultrasound has as cut-off 35 g (13). Of particular interest is to study the extent to which EBW is changed after prostatectomy: EBW significantly decreases from 52.9 ± 22.6 to 31.6 ± 15.8 gr 3 months after prostatectomy (14). This demonstrates the reversibility of the modifications of the bladder wall induced by BOO.

Miyashita *et al.* (15) measured the EBW in men with and without acute retention of urine demonstrating that 90% of patients with retention had a value of EBW > or = to 35 gr compared to 41% of patients without retention. In a multivariate analysis, age and EBW correlated to urinary retention. In addition, a value of EBW > or = to 35 gr was associated with a 4.13 times greater risk of developing acute urinary retention. In a longitudinal study with the use of

an alpha-blocker for LUTS, the EBW was > or = to 35 grams in about half of individuals (16).

Echographic technique of measurement

It is used using the standard ultrasound method with a linear abdominal probe placed at suprapubic level using frequencies 9-4 MHz. You can also use an automatic ultrasound device with a dedicated computing system (BVM 6500 3.7 MHz scanner).

Both methods work, but in 2-14% of cases the automatic system does not allow a reliable calculation.

Resolution depends from the frequency of the probes: from 7.5 to 3.5 MHz the resolution obtained is 0.13 and 0.3 mm, respectively. The manual measurement remains more reliable than the automatic, but it requires more time and skill. The measurement is made on the anterior wall of the abdomen at a bladder filling of about 250 cc, by calculating the thickness of the hypoechoic muscle between the two hyperechoic layers of serosa and mucosa. The final value is the average of at least 3 measurements. Some have proposed to measure the posterior bladder wall using transrectal probes because no difference in the thickness of various parts of the bladder were demonstrated. The variability of intra (4.6 to 5.1%) and inter-operator measurements (12.3%) is acceptable.

Intravesical prostatic protrusion (IPP)

The IPP is not an expression of organ damage of the bladder, but since it has a high correlation with other functional parameters of bladder neck obstruction, it seems appropriate to introduce it in the non-invasive ultrasound evaluation. It is evaluated with an abdominal probe through a longitudinal suprapubic scan measuring the height (protrusion) of the prostate from the circle line that the bladder defines at the base of the prostate (Figure 4). As proposed by Tan and Foo, one can identify 3 groups of patients according to the degree of IPP: IPP-grade 1 = < 5 mm, grade 2 = 5-10 mm, and grade 3 = > 10 mm (17). Tubaro *et al.* identified as the ideal cut-off a value of 12 mm to have the maximum correlation with the BOO (18).

Figure 4.

On the left, the stars indicate muscle bundles of the bladder wall with pseudodiverticula (arrows), on the right the line measures intravesical prostatic protrusion.

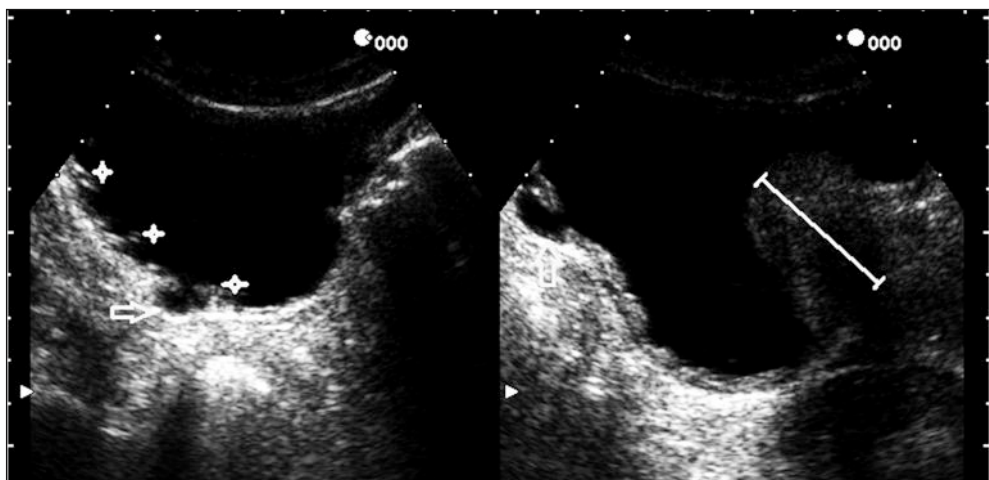
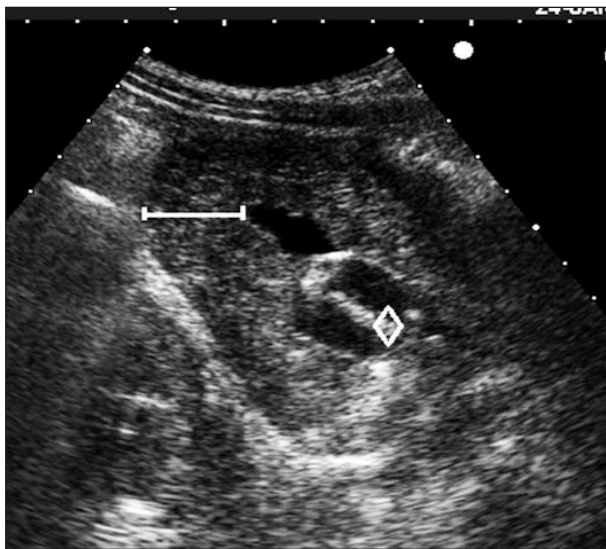
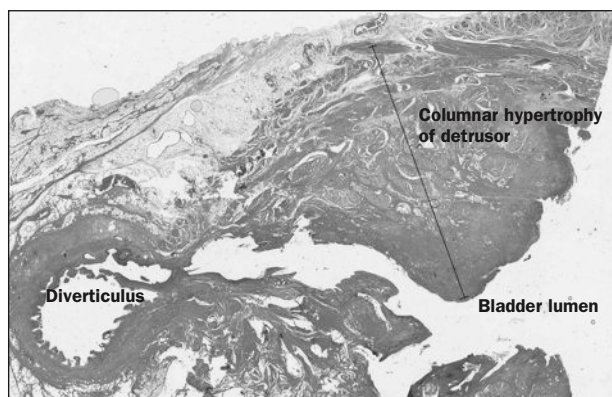


Figure 5.

An extreme condition of thickness of the bladder wall (line) in a patient with acute urine retention and indwelling catheter (diamond).

**Figure 6.**

Histologic macrosection demonstrating bladder with diverticulum and columnar hypertrophy of the detrusor.



Standard abdominal ultrasonography

This identifies the presence of diverticula, pseudodiverticula and larger bundles of the bladder wall, bladder stones and can be used to measure PVR. The presence of diverticula, stones and larger bundles of the bladder wall are signs of overt organ damage in the bladder (Figures 4-6). PVR is clinically relevant for values > 50 ml. The latter has to be considered as a decrease in functional bladder capacity and should be expressed as a percentage of total bladder volume. PVR measurement should be made avoiding overdistension of the bladder. Focal thickening of the bladder wall must be distinguished from diffuse thickening of the bladder wall: focal thickening can be related to the presence of cancer, acute or glandular cystitis, tuberculosis, endometriosis, inflammatory lesions.

DISCUSSION

Our study highlights the role of ultrasonography in the

evaluation of parameters which are the expression of the bladder changes in the bladder wall in patients diagnosed with BPO. Therefore these changes can define organ damage, which can be either reversible irreversible. For example the EBM decreases significantly from 52.9 ± 22.6 g to 31.6 ± 15.8 g 3 months after prostatectomy (15).

The previous published works have focused on diagnostic accuracy of ultrasound parameters for the non-invasive diagnosis of bladder neck obstruction as an alternative to the urodynamic pressure-flow study.

Instead, our review is based on the use ultrasound parameters as a measure and quantification of changes of the bladder wall due to obstruction.

These findings are related to a population of patients diagnosed with clinical benign prostatic enlargement and predominantly obstructive symptoms.

The urodynamic study remains the gold standard for the diagnosis of bladder neck/urethral obstruction.

We do not want to stress the diagnostic capability of ultrasound parameters when rather demonstrate the ability to identify the modifications of the bladder and to offer a reliable and reproducible monitoring an individual patient over time. These parameters can be used also to monitor the effectiveness of therapy (5).

The ultrasound parameters (measurable and quantifiable) should then be useful for the initial evaluate the patient with symptomatic BPH and then to monitor it over time, identifying any benefit or worsening associated with the development of the disease and its treatment.

Currently no longitudinal clinical trials have been conducted but the application of these parameters seems to be ideal for evaluation along time of the clinical course of the disease and of its symptoms limiting the use of urodynamics in selected cases and only in the early stages. These concepts have been recently expressed by a research group of the *International Consultation on Incontinence-Research Society* (2).

In the initial diagnostic phase of the patient with BPH, the computation of the weight and thickness of the bladder detrusor are potentially useful for evaluating the severity of the bladder neck/urethral obstruction or the detrusor overactivity, limiting the indications to the urodynamic study. As echocardiography evaluates the extent of cardiac organ damage in the patient suffering from high blood pressure so ultrasound evaluates the extent of bladder organ damage in patients with bladder neck obstruction. This comparison, first suggested by *Tubaro and Miano* in 2002 although proposed in order to diagnose obstruction, is still valid and actual. The bladder ultrasound is used today to measure the damage induced on the bladder wall by high voiding pressures while not neglecting its capability to diagnose obstruction.

The bladder damage evolves towards two conditions: the first is the bladder failure which is characterized by urinary retention (acute or chronic) and measured by PVR and the second is the fibrotic involution (Figure 3) of the bladder wall, which is characterized by the reduction of compliance and capacity, involving concomitant both symptoms of the filling phase and obstructive. The early identification of bladder damage has the advantage of taking therapeutic measures sufficient to prevent a further increase of the bladder damage and thus to reduce the uri-

nary symptoms or at least make them reversible. A limitation for the calculation of the DWT and EBW is given by the difficulty of performing the ultrasound evaluation at setted volume of bladder filling. A simple and easy solution in clinical practice could be to do these tests should be done before uroflowmetry. The combination of these tests could be named "echo-urometry".

Kessler *et al.* (19) first suggested to measure the DWT and IPP parameters with full bladder immediately before uroflowmetry and obviously to measure residual urine after urination.

CONCLUSIONS

The ultrasound parameters of bladder injury are reproducible, reliable and non-invasive. The implementation in the clinical practice of these parameters can help in early diagnosis and prevent progression of the damage of the bladder wall. The option to use ultrasound will allow us perform monitoring studies in patients with bladder neck/urethral obstruction secondary to BPH.

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Correspondence

Andrea B. Galosi, MD, PhD

Chief Division of Urology, Dept of Surgery,
ASUR Marche, "A. Murri" General Hospital
Via Murri 18, I-63900 Fermo, Italy
galosiab@yahoo.it

Giacomo Tucci, MD

Urologist, Urinary Incontinence Unit,
Division of Urology, "Murri" General Hospital, Fermo, Italy
tucci.giacomo@virgilio.it

Daniele Mazzaferro, MD

Resident in Urology
Institute of Urology, A.O. Ospedali Riuniti, Ancona, Italy
danim33@katamail.com

Vito Lacetera, MD, FEBU,

Urologist, A.O. Ospedali Riuniti, Ancona, Italy
vlacetera@gmail.com

Giovanni Muzzonigro, MD

Professor of Urology, Chief Institute of Urology,
A.O. Ospedali Riuniti, Ancona, Italy
g.muzzonigro@univpm.it

Pasquale Martino, MD

President SIEUN, Institute of Urology, University of Bari, Italy
martino@urologia.uniba.it

ORIGINAL PAPER

Comparison of ESWL outcome between Wolf Piezolith 3000 vs Storz Modulith SLK. It is the man who makes efficient the machine

Giuseppe Albino, Ettore Cirillo Marucco

U.O.C. di Urologia, Ospedale "L. Bonomo", Andria, ASL BAT

Summary

Aim of the Study: The choice of an extracorporeal lithotripter for extracorporeal shock wave lithotripsy (ESWL) of urinary stones must be done with efficacy criteria. It is easy to demonstrate the advantages of the third-generation lithotripters compared to previous generations of lithotripters. This study has the purpose of evaluate whether it is possible to establish differences in effectiveness between two third generation lithotripters.

Methods and Results: We report about the last 100 ESWL treatments carried out with the Wolf Piezolith 3000 and the last 100 with the Storz Modulith SLK, performed by the same single operator. Stones were stratified by site and size. Comparison was made considering the number of shock waves per session and the number of sessions and the outcomes. The results showed no statistically significant differences. In fact, the cumulative stone-free rate was 93% for the Wolf Piezolith and 91% for the Storz Modulith.

Conclusions: The technical differences between lithotripters concern the energy delivered, the shape of the acoustic focus, the depth of focus, the coupling surface, the mobility of the head, the alignment mode and the simultaneous use of ultrasonography and radiological pointing. These differences are never obtained from published series. Furthermore data of patients and stones that have not been treated for the difficulty of stone targeting due to the depth of acoustic focus (high BMI), the limited inclination of the head or to the patient intolerance to shock waves are not usually reported.

The results obtained by the same operator are comparable even when are obtained with different machines of the same generation. The real differences could arise if we would take into account also the patients which were excluded from evaluation because, for the same generation of lithotripters, the results depend on the operator, while the eligibility to treatment of the patient depends on the characteristics of the machine.

KEY WORDS: ESWL; Effectiveness and efficiency; Third-generation lithotripters; Single operator.

INTRODUCTION

The choice of an extracorporeal lithotripter for ESWL of urinary stones must be effected with efficacy criteria, which are translated into efficiency for the company. For clinicians, leading priority is a system allowing complete disintegration of the stone with the minimum number of shock and low re treatment rate. One of the prerequisites of this system is a powerful shock wave generator, but "power" is a complex definition in lithotripsy and depends from the pulse intensity in the acoustic focus and the size of the focal zone (1). Other important factors are the possibility of X-ray and ultrasound pointing, in-line or off-line, the possibility of contemporary X-ray and ultrasound pointing, the mobility of the shock wave generator head.

It is easy to demonstrate the advantages of the third-generation lithotripters compared to previous generations of lithotripters. This paper has the purpose of checking if it is possible to establish whether there are differences in effectiveness between two third generation lithotripters taking into account the respective case series of stones underwent to ESWL.

MATERIALS AND METHODS

We have taken into account the last 100 consecutive stones undergoing ESWL with the Wolf lithotripter Piezolith 3000 (Figure 1) and the last 100 consecutive

Figure 1.
Wolf Piezolith 3000.



Figure 2.
Storz Modulith SLK.



stones with Storz Modulith SLK (Figure 2). The Piezolith lithotripter has a piezoelectric generator that can deliver Shock Wave from 6 MPa to 132 MPa in the acoustic focus; the Modulith SLK lithotripter has an electromagnetic generator that can deliver Shock Wave from 6 MPa to 120 MPa in the acoustic focus. In both cases the generator is mounted on a movable arm and owns an “in line” ultrasound probe. With both lithotripters is possible to point by X-ray: with an isocentric off line X-ray generator C-arch mechanically connected to the Piezolith lithotripter; with an infrared connection and manual alignment using dedicated software for the Modulith lithotripter. All treat-

ments were conducted by the one single operator. The stones were stratified by location and size. The number of sessions and successful outcomes (stone free or insignificant residual fragments < 4 mm) were compared (2). The statistical analysis of results was performed by the “chi-square” (χ^2) test, having regard to the homogeneity between the two groups to be compared.

RESULTS

The results reported in the tables did not show statistically significant differences (both for strata both global-

Table 1.
Renal stones results.

Renal stones								
	Wolf Piezolith 3000				Storz SLK			
Size (mm)	< 10	10 ÷ 15	> 15	All	< 10	10 ÷ 15	> 15	All
Stone (nr)	18	9	8	35	7	13	6	26
Average size (mm)	7.4	11.4	18.4	11.1	7.6	12.8	21.0	13.3
sessions/stone	2.7	1.9	5.9	3.2	2.3	3.1	4.3	3.1
Loss at follow up	//	//	1	1	//	1	//	1
Stone free	17/18	9/9	6/7	32/34	6/7	10/12	5/6	21/25
Rate %	94%	100%	86%	94%	86%	83%	83%	84%

Table 2.
Ureteral stone results.

Renal stones								
	Wolf Piezolith 3000				Storz SLK			
Size (mm)	< 10	10 ÷ 15	> 15	All	< 10	10 ÷ 15	> 15	All
Stone (nr)	39	18	8	65	33	31	10	74
Average size (mm)	6.9	12.4	18.9	9.9	7.4	11.3	18.0	10.5
sessions/stone	1.9	3.0	7.1	2.8	1.5	2.6	5.8	2.6
Loss at follow up	//	//	1	1	//	1	1	2
Stone free	37/39	16/18	7/8	60/65	33/33	28/30	6/9	67/72
Rate %	95%	89%	87%	92%	100%	93%	67%	93%

Table 3.
All stone comparison.

All stones		
	Wolf	Storz
Stones (nr)	100	100
Average size (mm)	10.3	11.2
Sessions/stone	2.9	2.7
Loss at follow up	1	3
Stone free	92/99	88/97
Rate %	93%	91%

ly). In fact, the stone-free rate of all treatments was 93% for the Wolf Piezolith and 91% for the Storz Modulith (Tables 1-4).

Table 4.
Statistical comparison.

	WP 3000	Storz SLK	χ^2	
Renal				
< 10 mm	17/18 (94%)	6/7 (86%)	4.2e^-06	n.s.
10 ÷ 15 mm	9/9 (100%)	10/12 (83%)	0.147	n.s.
> 15 mm	6/7 (86%)	5/6 (83%)	0.655	p < 0.50 (n.s.)
<i>All renal</i>	32/34 (94%)	21/25 (84%)	0.009	n.s.
Ureteral				
< 10 mm	37/39 (95%)	33/33 (100%)	0.119	n.s.
10 ÷ 15 mm	16/18 (89%)	28/30 (93%)	0.003	n.s.
> 15 mm	7/8 (87%)	6/9 (67%)	0.414	n.s.
<i>All ureteral</i>	60/65 (92%)	67/72 (93%)	0.366	n.s.
All treatment	92/99 (93%)	88/97 (91%)	0.429	n.s.

DISCUSSION

The novelty of this report is that it was built using the personal series of one single operator and not of a team. The operator, on the basis of his personal experience, used energy levels that corresponded to the same MPa in the acoustic focus for both Shock Wave generators. This means that the operator has delivered similar doses of Effective Energy (3) for stones similar in size, position in the urinary tree and their presumed composition (as radiolucent or Hounsfield Unit at CT). This enabled the operator to reach a comparable outcome. After a sufficient period of training, the operator will get similar results with similar stones on both machines, indifferently. What differs between the two machines is the depth of acoustic focus (165 mm and 150 mm for the Piezolith for Modulith), the coupling surface (560 cmq for Piezolith

and 255 cmq for Modulith) with tolerance of the patient to the shock wave inversely proportional to the coupling surface, but also the possibility to direct the head with handling similar to that of the ultrasound probe when the coupling surface is smaller. The Piezolith combined system of pointing offers the advantage of being able to obtain an X-ray isocentric image starting from the ultrasound imaging; unfortunately such an isocentric configuration between ultrasound probe and X-ray image gives a lower degree of freedom of the arm on which the shock waves generator is installed; on the contrary, the tracking system of the Modulith enables the isocentric ultrasound verification of a X-ray pointed stone, but it is hard to have an isocentric X-ray image starting from an ultrasonographically pointed stone, however, the Modulith tracking system offers the advantage of a greater degree of freedom of the arm on which the generator of shock waves is installed. Allow me

to express this concept with a figurative example: it is as if the operator was Robin Hood and the lithotripter were represented together by the bow and the slit on the walls of a castle; the arrows represent the shock waves and enemy soldiers out of the castle are the stones (Figure 3).

Figure 3.

Robin Hood and the window.



Robin Hood will strike the same percentage of enemies on which he will aim, whether the slit is large and whether the slit is narrow. This is because Robin Hood is always Robin Hood, with any bow and any slit. So the real difference is not in the objectives are struck, but in the objectives which are seen; through the largest slit Robin Hood will be able to see much more enemies than those he will be able to see through a narrow slit, but anyway he will strike all enemies on which he will be able to take aim. The real difference, therefore, is not in the percentage of struck enemies, but in the number of the enemies on which he can take aim. The same situation take place during extracorporeal shock wave lithotripsy: the use of two different lithotripters gives no significant differences of outcome, because all the stones, on which it was possible to perform the pointing, will be treated with the same efficacy, based only on the experience of the operator who takes aim. But in all series the only recorded data are those of the treated patients. What really makes the difference are the data of the patients who do not fall into the series because it was not possible to point the stone owing to the depth of position, as in case of obesity, or to the inclination of the head in case of orthopedic abnormalities of the trunk or to the difficult position of the stone in the urinary tree. All series, both the early (4) and the latest (5), report only the number of patients undergoing ESWL and many of them have been submitted to alternative procedures because of ESWL failure, but they never report the number of patients who were submitted to alternative procedures because of pointing difficulties.

CONCLUSIONS

The technical differences between lithotripters are well documented and include the delivered energy, the shape of the acoustic focus, depth of focus, the coupling surface, the mobility of the head, the alignment mode and simultane-

ous use of ultrasonography and X-ray for pointing. But these differences are not deducible from the case series of the same operator who, based on his experience, will deliver the same energy, as he considers safe, into the acoustic focus, even if the machines have energy range of different width. On the contrary, the series will not report the patients and the stones that have not been treated for the difficulty of pointing due to the depth of acoustic focus (high BMI), the inclination of the head or intolerance to shock waves. Therefore, the results obtained by the same operator are comparable even if obtained with different machines (of the same generation).

The differences may arise if one takes into account the patients who were excluded because, for a given generation of lithotripters, the results depend on the operator, while the eligibility of the patient and the stone to the treatment depends on the characteristics of the machine.

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Correspondence

Giuseppe Albino, MD
U.O.C. di Urologia, ASL BAT
C.so Istria, 1 - 76123 Andria, Italy
peppealbino@hotmail.com

Ettore Cirillo Marucco, MD
U.O.C. di Urologia, ASL BAT

ORIGINAL PAPER

Transrectal ultrasound (TRUS) and TRUS-biopsy accuracy in potential candidates for PRIAS active surveillance protocol

Vito Lacetera¹, Andrea Benedetto Galosi², Ubaldo Cantoro¹, Francesco Catanzariti¹, Daniele Mazzaferro¹, Daniele Cantoro¹, Luigi Quaresima¹, Alessandro Conti¹, Rami Raquban¹, Rodolfo Montironi³, Giovanni Muzzonigro¹

¹ Institute of Urology, Polytechnic University of Marche, Azienda O.U. Ospedali Riuniti, Ancona;

² Division of Urology, Area Vasta 4, ASUR Marche, "Augusto Murri" General Hospital, Fermo;

³ Institute of Pathology, Polytechnic University of Marche, Azienda O.U. Ospedali Riuniti, Ancona, Italy.

Summary

Aim: Evaluate the transrectal ultrasound (TRUS) and TRUS-guided Biopsy (TRUS-Bx) accuracy in patients with low risk prostate cancer (PCA) that were potential candidate for PRIAS active surveillance (AS) protocol but underwent to immediate radical prostatectomy (RP).

Methods: 616 men were extracted from our institutional RP database. We selected the patients who met PRIAS inclusion criteria. The primary outcome was to evaluate the positive predictive value (PPV) and the specificity of suspected lesions at TRUS. The secondary outcome was to evaluate the TRUS-Bx accuracy in term of pathological upstaging and pathological upgrading with respect of RP specimen pathology report.

Results: 147 men of 616 (23,8%) in our RP database met PRIAS criteria; in this group we found 66 suspected lesions at TRUS examination (66/147: PPV 44,8%). Prostate cancer was really present in the biopsy specimen in only 32/66 of suspected lesions; in 28/66 the suspect lesion at TRUS was in the same position of the index lesion at final pathology. TRUS/biopsy specificity was 48% and TRUS/surgical specimen specificity 39%. TRUS-Bx staging accuracy: upgrading between biopsy and RP was recorded in 57/147 (38%) whereas 30/147 (20%) were upstaged on final pathology up to N1.

Conclusions: TRUS and TRUS-Bx are insufficient tools to detect the grade, the location and the extent of PCA. New emerging techniques, such as US-MRI fusion biopsy and 3D template-guided transperineal saturation biopsy are promising to minimize the risk of misclassification and therefore to better select the best option of treatment (radical treatments or focal therapies or active surveillance) in each patient with low risk prostate cancer.

KEY WORDS: Transrectal ultrasound; Active surveillance; Low risk prostate cancer; Prostate biopsy; Staging accuracy.

INTRODUCTION

In Europe, the cancer of the prostate (PCA) is the most frequently diagnosed solid tumor: in 2008 the incidence was estimated at 111 cases per 100,000 inhabitants, accounting for 20.3% of total cancer incidence (1).

Even in Italy, according to the findings from the 2009 Report of the Italian Cancer Registry (AIRTUM), the PCA is the most frequently observed malignancy in the male population, constituting 10.1% of all cancers in the general population and 20.3% of cancers of men with

more than 65 years (2). The percentage of deaths related to PCA increased from 5.5% in 1955 to 7.2% in 1994 and according to 2009 data reported by AIRTUM, is now 8.5%, being the third leading cause of cancer-related deaths (2).

This means that one man out of 7 is at risk of having a diagnosis of PCA in the course of its life (cumulative risk of incidence) and 1 out of 33 will die because of PCA (cumulative risk of mortality).

Today most prostate carcinomas are diagnosed at organ-confined stage with Gleason score of 6 and there is an increase of the cases with smaller cancer volume (migration stage) that are suspected in asymptomatic patients on the basis of the increased blood levels of PSA and of its kinetic.

It is estimated that the diagnosis of indolent tumors (which would never be clinically evident in the absence of the PSA assay) can vary from 20 to 84% (overdiagnosis) depending on the used definition of indolent disease (3-4).

The overdiagnosis almost always involves a not necessary active treatment (overtreatment) with an unavoidable impact on the quality of life in particular related to urinary continence and sexual potency.

It is estimated that up to 40% of the patients with low-risk CAP would be eligible to conservative strategies (active surveillance or watchful waiting) but only 8% of patients in the U.S. (1% in Italy) choose this option, a percentage that is decreased compared to the '90 (5-6).

Active Surveillance (AS) is a treatment option for patients with low risk CAP that meet certain criteria for inclusion in the chosen protocol and accept a deferred treatment in case of progression. The major limitation of all protocols is the proper selection of patients using conventional tools for diagnosis and staging such as transrectal echo-guided prostate biopsy and mapping.

Even in more selective protocols about 1 out of 5 patients is erroneously included and exits from AS at the first biopsy follow-up. They are not to be considered as progression but this means that in about 25% of patients CAP is underestimated (misclassification risk category) and that diagnosis and treatment with curative intent is postponed with consequences not always predictable. The aim of our study was to test the diagnostic accuracy of ultrasound of the prostate (TRUS) and of transrectal bioptic mapping (TRUS-bx) with end-fire probe in subjects eligible for the PRIAS active surveillance protocol but treated with immediate radical prostatectomy.

METHODS

We selected from our database the cancer patients who underwent radical retropubic prostatectomy in the period 2005-2009 with clinical and bioptic features of potential candidates for the PRIAS active surveillance protocol (inclusion criteria: clinical stage T1-T2, PSA \leq 10, PSA density \leq 0.2, Gleason score < 7 , ≤ 2 positive biopsy cores).

In this group of patients, we evaluated how many had suspicious hypoechoic lesions at transrectal ultrasound with end-fire probe performed before or simultaneously to transrectal bioptic mapping (predictive positive value of TRUS).

We then evaluated the matching between the hypoechoic areas demonstrated at TRUS with the sites of positive biopsies (TRUS / biopsy specificity) and then with the final histological examination (TRUS / final histology

Figure 1.

TRUS: hypoechoic area in the middle left side of biopsy in a patient with negative DRE and PSA = 4.8 and PSA Density = 0.15.



specificity) with reference to the main neoplastic focus (index lesion) (8).

Finally, we evaluated the accuracy of staging by transrectal bioptic mapping in terms of upstaging (defined as pathologic stage $> pT2$ and/or $pN1$) and upgrading (defined by the presence of Gleason score > 6 at final histology).

Figure 2.

A 7 mm focus of prostatic adenocarcinoma GS 3 + 3 = 6 in the site corresponding to hypoechoic area (1/12 positive biopsy).

Patient eligible for the PRIAS protocol but subjected to RP.

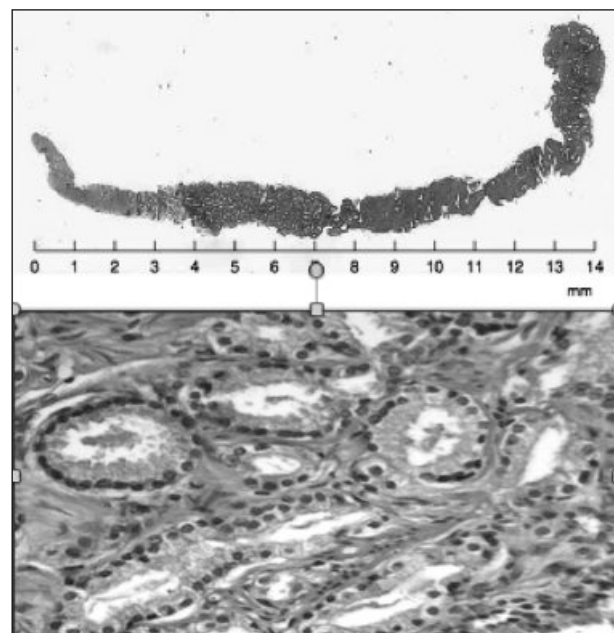


Table 1.
Results of the study.

Number of patients potentially eligible for PRIAS	147/616 (23.8)
Suspicious hypoechoic lesions	66/147 (VPP 44.8%)
TRUS/biopsy specificity	32/66 (48%)
TRUS/histology PR specificity	28/66 (39%)
Upstaging TRUS-bx/final histology	29/147 (20%)
Pathological stage	
pT3a	26/29
pT3b	3/29
pN1	2/29
Upgrading TRUS-bx/final histology	57/147 (38%)
Pathological Gleason Score	
3 + 4 = 7	48/57
4 + 3 = 7	8/57
4 + 5 = 9	1/57

RESULTS

147 of 616 (23.8%) patients who were treated with retropubic radical prostatectomy in the period 2005-2009 were potentially eligible for the PRIAS protocol. Mean age was 64.1 (range 42 to 72), mean PSA 6.2 ng/ml (range 0.5 to 9.9), mean volume 53.1 ml (range 19 to 124) and mean number of biopsy cores 12.3 (range 8 to 16).

In this group of patients, transrectal ultrasound reported a suspicious hypoechoic area in 66 out of 147 patients: the positive predictive value of TRUS was 66/147 44.8%.

The specificity of these hypoechoic areas in relation to

the positive locations at biopsy was 32/66 (TRUS/biopsy specificity = 48%) while the specificity in relation to the index lesion at final histology after surgery was 28/66 (specificity TRUS /final histology = 39%) (Figure 1-2).

The evaluation of diagnostic accuracy of transrectal biop-
tic mapping with end-fire probe in terms of correct evaluation of stage and grade of the disease compared to the final histology demonstrated an overall upstaging of 20%. In fact out of 147 patients judged as organ-confined PCA (< = pT2) 26 cases with extraprostatic extension (pT3a), 3 cases with seminal vesicles involvement (pT3b) and 2 cases with lymph node metastases (pN1) were observed. A Gleason score greater than 6 in the surgical specimen was shown in 57/147 patients (3 + 4 = 7 in 48/57, 4 + 3 = 7 in 8/57, 4 + 5 = 9 in 1/57) with a total upgrading of 38%. (Table 1, Figure 3).

DISCUSSION

The positive predictive value of the hypoechoic lesions at TRUS and the sensitivity and specificity in relation to biop-
tic and definitive histology of the surgical specimen are very low (20-37%) as known by literature and reported in the European Guidelines (9, 10): for this reason the biopsies of target lesions can be only an implementation of random mapping of the entire prostate gland with a number of samples varying between 10 and 16.

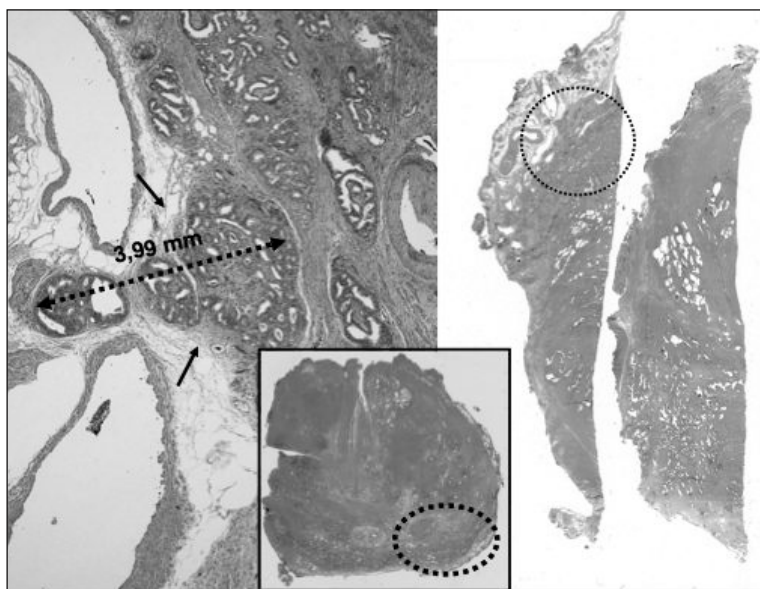
This limitation is amplified in patients with low risk PCA eligible to programs of AS and makes inclusion in the protocols and subsequent follow-up at risk of underestimation the real clinical entity of PCA. For the same reason the number of samples of target lesions at TRUS for diagnosis and follow-up of PCA can not be reduced.

In literature, we found only one study by *Hruby et al.* in which the accuracy of TRUS is evaluated in patients eligible for a conservative strategy: of 174 patients enrolled, 28 were switched to active treatment owing to a clinical progression during follow-up and only in 7/28 of them TRUS had showed a hypoechoic lesion suspect for a T3. The Authors conclude that the TRUS is an insufficient tool for the follow-up of patients with PCA (11).

Many more studies in the literature evaluated the upgrading and upstaging of patients eligible for AS and instead treated with radical prostatectomy. In particular, with reference to patients eligible to PRIAS protocol, Suardi et al. reported a rate of upgrading of 29.4% and upstaging in 7.1% (12), while Van den Bergh et al. of 20% and 8%, respectively (13). The positive predictive value of TRUS and the rate of upgrading in our study are consistent with the data of the literature, whereas the rate of upstaging was significantly greater (20% vs. 7-8%). Also other studies reported high-risk disease (pT3b and/or pN1 and/or Gleason 8-10) in patients eligible for PRIAS. The limitations of our study are the number of operators (urologists and/or radiologists) who performed TRUS and detected hypoechoic areas (interopera-

Figure 3.

Final histology: the index lesion was located in the left basal site with a volume of 0.33 cc but with extraprostatic not focal extension for 3.99 mm beyond the capsule. GS = 3 + 4 = 7 (Upstaging and Upgrading of the PCA).



tor variability), and the variability in the choice of the scheme for mapping and number of biopsy samples.

CONCLUSIONS

Our study confirms the low PPV and specificity values of TRUS with particular reference to patients with low risk cancer eligible for PRIAS active surveillance protocol. The transrectal bioptic mapping in these patients has an insufficient accuracy of staging and correct assessment of a low Gleason score that implies a risk of upstaging and upgrading respectively of 20% and 38%. We therefore evaluate the traditional diagnostic tools (TRUS and TRUS-bx) as insufficient for a correct diagnostic and prognostic evaluation of prostate cancers especially in relation to a conservative strategy.

New techniques such as biopsy with fusion of RMN-TRUS images (14) or the transperineal biopsy with template (15) seem to be promising in order to minimize these risks and to select more carefully patients for radical therapy, focal therapy or active surveillance.

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Correspondence

Vito Lacetera, MD, FEBU

Urologist Institute of Urology, A.O. Ospedali Riuniti,
Via Conca 71, I-60020 Ancona, Italy
vlacetera@gmail.com

Giovanni Muzzonigro, MD

Professor of Urology
Chief Institute of Urology, A.O. Ospedali Riuniti, Ancona, Italy
g.muzzonigro@univpm.it

Andrea B. Galosi, MD, PhD

Chief Division of Urology, Dept of Surgery,
ASUR Marche, "A. Murri" General Hospital, Italy
galosiab@yahoo.it

Rodolfo Montironi, MD

Professor of Pathology, A.O. Ospedali Riuniti, Ancona, Italy
r.montironi@univpm.it

Ubaldo Cantoro, MD

Resident in Urology
Institute of Urology, A.O. Ospedali Riuniti, Ancona, Italy
ubymaior83@gmail.com

Francesco Catanzariti, MD

Resident in Urology
Institute of Urology, A.O. Ospedali Riuniti, Ancona, Italy
fracatanzariti@libero.it

Daniele Mazzaferro, MD

Resident in Urology
Institute of Urology, A.O. Ospedali Riuniti, Ancona, Italy
danim33@katamail.com

Daniele Cantoro, MD

Resident in Urology
Institute of Urology, A.O. Ospedali Riuniti, Ancona, Italy
danidoc2580@alice.it

Luigi Quaresima, MD

Resident in Urology
Institute of Urology, A.O. Ospedali Riuniti, Ancona, Italy
luigiquaresima@yahoo.it

Alessandro Conti, MD

Resident in Urology
Institute of Urology, A.O. Ospedali Riuniti, Ancona, Italy
alessandro.conti@hotmail.com

Rami Raquban, MD

Resident in Urology
Institute of Urology, A.O. Ospedali Riuniti, Ancona, Italy
dott.ramiraquban@hotmail.it

CASE REPORT

Pancake polycystic kidney: Case report

Marco Heidempergher, Nicoletta Landriani, Cristina Airaghi, Monique Buskermolen, Maria Teresa Barone, Daniele Scorza, Paola Cuoccio, Francesco Genderini, Luciana Scandiani, Augusto Genderini

Nefrologia - Dialisi Ospedale "L. Sacco", Milano, Italy

Summary

Pancake kidney is a very rare fusion abnormality, characterised by the presence of a renal parenchymal mass located in pelvic site, generally with two pelvises and two ureters and without an intervening fibrous septum. The case here reported describes a condition of "pancake kidney", eventually associated with polycystic disease and abnormous vascular supply. Hypertension and microscopic hematuria were the only clinical signs.

KEY WORDS: Pancake kidney; Polycystic kidney disease; Congenital renal anomalies.

CASE REPORT

A 57-years old man was referred for a casual ultrasound finding of kidney anomalies. In his past history, besides smoking habits, he referred hypertension from about seven years without an appropriate treatment in the last 6 months.

For this reason the patient was submitted to further diagnostic procedures at the Hypertension Centre of our Hospital: laboratory tests were within normal range, in particular normal renal function, microscopic hematuria in absence of proteinuria. The above mentioned ultrasound abdominal evaluation, performed elsewhere,

described a wrinkled right kidney and an undetectable left kidney. He was hospitalized in our Department.

A renal ultrasound examination disclosed absence of kidneys in their physiological position, but we could observe an oval mass in pelvic site, highly suggestive for renal parenchyma, without a clear profile and without a cortico-medullary differentiation. Several hypo- or unechogenic areas with variable sizes were detected, defined as simple cysts. A complete derangement of the parenchymal structure was observed. The pelvic sinus was undetectable (Figure 1).

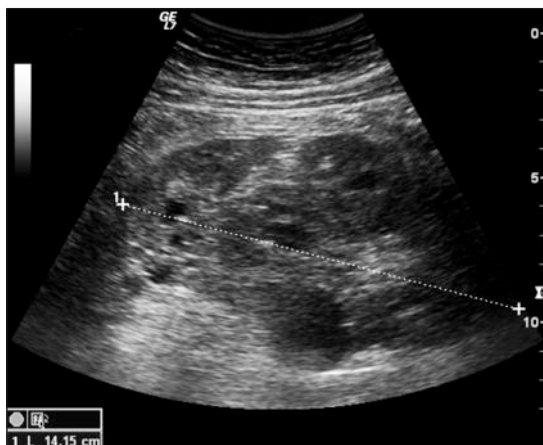
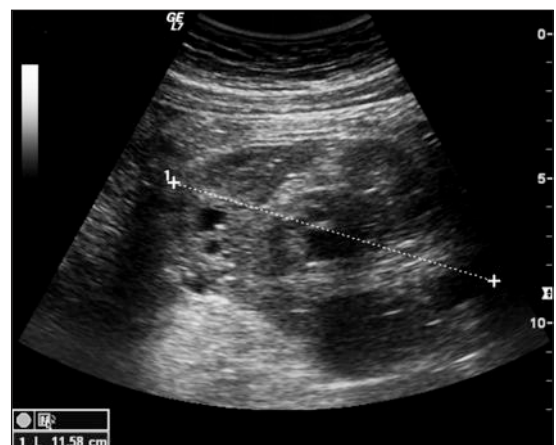


Figure 1.
Pelvic mass
recognizable
by renal
ultrasonography.



EchoColorDoppler examination revealed a difficult sampling of renal arteries; resistance indexes were normal. The whole pattern was evocative of pelvic renal polycystic disease. In addition, the patient was submitted to an abdominal angio-NMR (nuclear magnetic resonance), which showed an anomaly involving both kidneys, which were fused together in one solid horizontal mass in pelvic location. The abnormal structure was characterized by multiple cystic images containing a hemorrhagic fluid. The typical renal parenchymal aspect was lacking and the excretory system was undetectable. The renal arteries were not clearly seen in their usual site. By contrast, it was possible to identify two arterial-like structures, connected to the large pelvic mass, deriving from the proximal segment of the iliac trunk (Figure 2).

Figure 2.

Angio-NMR shows the large pelvic mass and its vascular supply.

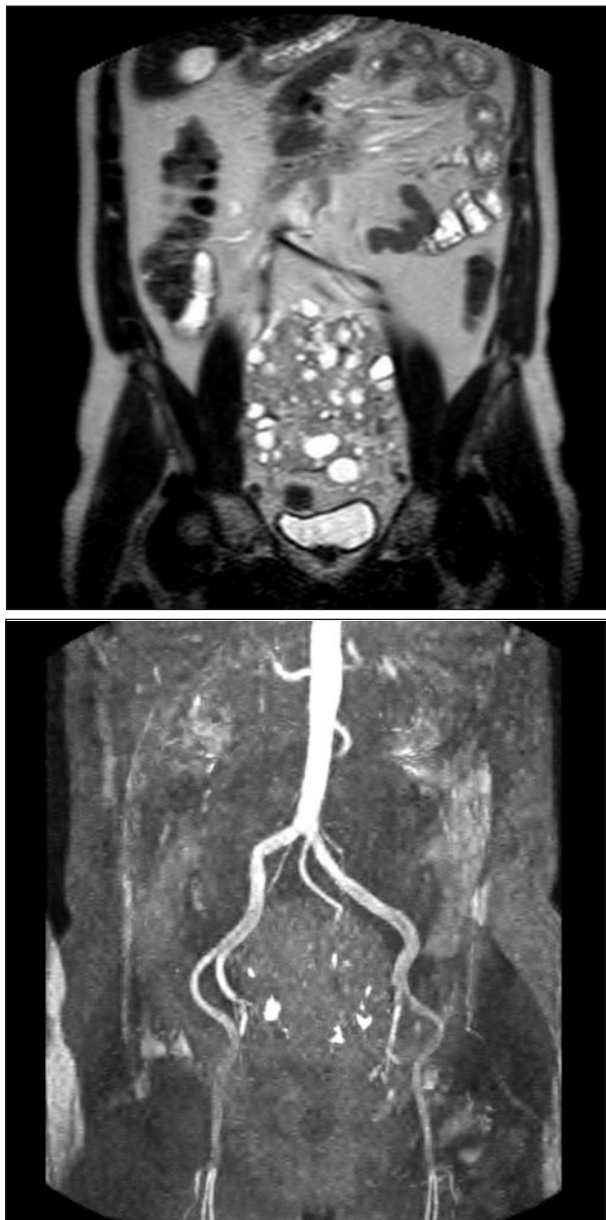


Figure 3.

CT shows pelvic polycystic renal mass and accessory hilar spleen.



Finally, the patient was submitted to abdominal computed tomography (CT) with contrast medium and the picture of renal ectopic localization with fusion abnormality was confirmed. The cystic aspect was also confirmed. Cysts' size was ranging from a few millimetres to 3.5 centimetres. Some had an exophytic expansion and some other had an hemorrhagic content. CT examination better showed the arterial supply of the mass; renal arteries derived as follows: the left side from the distal tract of iliac artery and the right side from the iliac fork. Moreover, excretory system could be identified with two slightly ectatic pelvis, directed forward and regularly channelled until the bladder (Figure 3). Collateral detection of one accessory hilar spleen and bilious cysts.

DISCUSSION

Among the renal fusion anomalies the horseshoe kidney is one of the most frequent (prevalence 0.25% of gener-

al population). In these cases, during the embryonic development of the kidney there is a malrotation and a fusion of the lower renal poles with a fibrous isthmus, generally located on the median line. The ureters leave the kidney medially. The kidney has a typical "U" shape and either pelvic or lumbar location (1).

Polycystic horseshoe kidney is a rare event; about 20 cases are described in the Literature and its incidence ranges from 1 over 134.000 to 1 over 8.000.000 live births (2).

Pancake kidney is a more rare condition with a real incidence yet undefined. It is characterized by lobulated renal masses located in the pelvis, produced by the fusion of two renal parenchymas, without a fibrous sept. In fact, during early ascent in the embryonic development, a metanephric fusion takes place and excludes the migration process. Each parenchyma has its own collecting system with short ureters jutting in bladder at their normal site. Frequently an abnormal vascularization from common iliac artery or terminal aorta can be found (1, 3).

We are not aware of any Literature report of pancake plus polycystic kidney.

CONCLUSIONS

For the case here described we accept the above mentioned definition, considering the intrinsic characteristics of the described renal mass. The pelvic site and the shape of the mass are in favour of "pancake kidney" rather than "horseshoe kidney". Cysts' type and their random location are consistent with polycystic kidney. Double excretory systems exclude single pelvic kidney. Peculiar vascular supply further confirms the congenital renal anomaly. Diagnostic precise definition has been achieved through ultrasound test, performed in a specialized nephrologic structure.

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Correspondence

Marco Heidempergher, MD
Nefrologia - Dialisi Ospedale "L. Sacco"
Milano, Italy
heidempergher.marco@hsacco.it

Nicoletta Landriani, MD
Cristina Airaghi, MD
Monique Buskermolen, MD
Maria Teresa Barone, MD
Daniele Scorza, MD
Paola Cuoccio, MD
Francesco Genderini, MD
Luciana Scandiani, MD
Augusto Genderini, MD
Nefrologia - Dialisi Ospedale "L. Sacco"
Milano, Italy

ORIGINAL PAPER

Value of the resistive index in patient and graft survival after kidney transplant

Stefano Vittorio Impedovo, Pasquale Martino, Silvano Palazzo, Pasquale Ditunno, Michele Tedeschi, Floriana Giangrande, Carlos Miacola, Saverio Forte, Francesco Paolo Selvaggi, Michele Battaglia

Urology, Andrology and Kidney Transplantation Unit, Department of Emergency and Organ Transplantation, University of Bari, Bari, Italy

Stefano Vittorio Impedovo, Pasquale Martino and Silvano Palazzo have equally contributed to this work

Summary

Introduction: The Resistive Index (RI) obtained by performing doppler sonography is a hemodynamic index commonly used to measure flow resistance within an organ to assess if there is a vascular disease associated with that organ. It is a well-known predictor of kidney transplant outcome.

The purpose of this study was to analyze the impact of RI values on patient and graft survival, as well as kidney graft function during 5-year follow-up.

Materials and Methods: We retrospectively investigated 761 kidney transplant recipients from cadaveric donors performed between 1998 to 2011. RI was measured at hospital discharge after the kidney transplant. All the patients were divided into tertiles, according to the baseline RI value (Group 1: RI < 0.70, Group 2: RI between 0.70 and 0.79 and Group 3: RI > 0.80).

Results: Patients with a low RI (<0.70) showed the lowest incidence of delayed graft function (DGF) compared to the other two groups (20.2% vs 32.2% vs 33%). Recipients with low RI values displayed significantly better creatinine clearance (70 vs 55 vs 35ml/min, respectively) than those with medium or high RI values at 5-year follow-up. Kaplan-Meier estimates of cumulative graft survival were significantly worse in patients who had a RI of 0.70 or more than in patients with a RI of less than 0.70 ($p = 0.02$). Cumulative patient survival showed the same behavior (0.01).

Conclusions: Low RI values measured in segmental arteries in the very early post-transplant period predict better kidney graft function and reduce the risk of all-cause graft loss, including patient death in a 5-year follow-up period.

KEY WORDS: Kidney transplant; Doppler sonography; Resistive index; Graft survival; Patient survival.

INTRODUCTION

The role of kidney transplantation in the treatment of end-stage renal disease is now well-established, improving the quality of life and long term survival. After transplantation, it is essential that any graft-related complication be diagnosed early to ensure quick treatment and optimal survival of both the graft and the patient (1). Doppler sonography is one of the most important techniques used postoperatively in kidney surveillance, and allows early detection of medical and surgical complications.

The Resistive Index (RI) obtained by performing doppler sonography is a hemodynamic index, commonly used to measure flow resistance within an organ, and has been proposed as a non-invasive method to evaluate renal allograft dysfunction. At our Center the measurement of intrarenal resistance indices plays an important role in the follow-up care of renal transplant patients.

The purpose of this study was to analyze the impact of RI values on patient and graft survival, as well as kidney graft function during 5-year follow-up.

PATIENTS AND METHODS

We retrospectively investigated 761 kidney transplant recipients from cadaveric donors performed between February 1998 and July 2011. Intrarenal resistance indices were measured by duplex ultrasound at hospital discharge after the kidney transplant. Doppler spectra were obtained from the segmental arteries at three separate locations. For each spectrum obtained, the resistive index (RI) was calculated, using the system software, from the Doppler wave form according to the following formula:

$$RI = (\text{peak systolic frequency shift} - \text{minimum diastolic frequency shift}) / \text{peak systolic frequency shift}$$

All the patients were divided into tertiles, according to the baseline RI value: Group 1: RI < 0.70 (n = 334), Group 2: RI between 0.70 and 0.79 (n = 369) and Group 3: RI ≥ 0.80 (n = 58).

The donor variables collected from the database were: age, body mass Index (BMI), serum creatinine levels, clearance at the time of death and biopsy by the Remuzzi-Karpinsky score. Recipient variables were: age, BMI, time on dialysis, cold ischemia time, delayed renal function incidence, hospital stay, incidence of acute rejection, actuarial graft and patient survival.

Kidney rejection was monitored by laboratory findings. Delayed graft function was defined as the need for at least one dialysis in the early post-transplantation period. Statistical analyses were performed by MedCalc software. The values of continuous variables are expressed as mean ± standard deviation and those of qualitative variables as proportions. Differences in donor and recipient variables were evaluated using unpaired Student's t-test when comparing two continuous variables and the ANOVA test when comparing more than two continuous vari-

ables. Graft and patient survival were calculated by Kaplan Meier analyses. The log-rank test was used to compare survival curves; p < 0.05 was considered statistically significant.

RESULTS

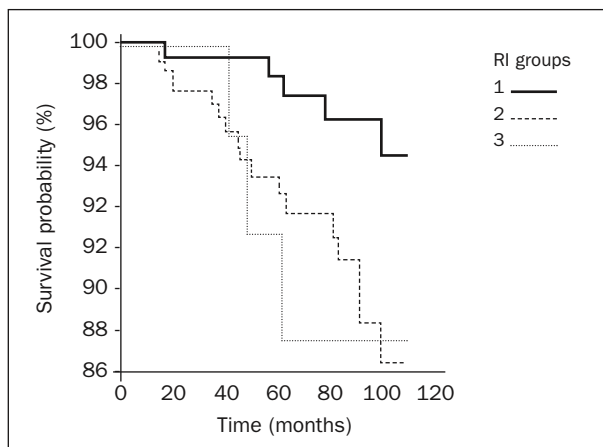
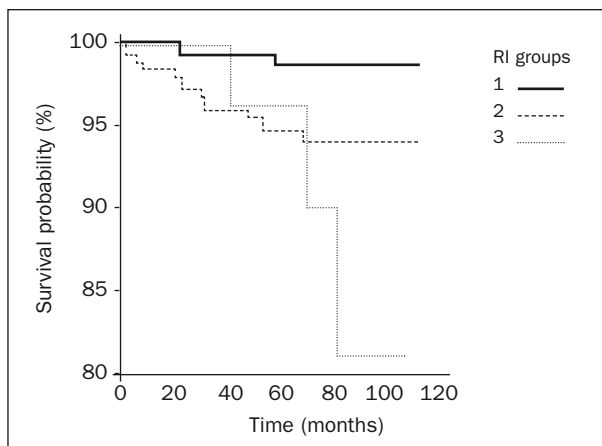
In our transplant centers, 761 kidney transplant from cadaveric donors were performed. Mean follow-up time was 60.1 (± 38.5) months. Table 1 shows the main characteristics of donors and recipients according to RI groups.

After transplantation, patients with a RI lower than 0.70 showed the best graft function and lowest incidence of delayed graft function (DGF) as compared to the other two groups (20.2% vs 32.2% vs 33%; p: 0.05). Similarly, the first group displayed significantly better creatinine clearance values than those with medium or high RI values at 5-year follow-up (70 vs 55 vs 35 ml/min; p < 0.001). Acute rejection occurred in 18 patients in group 1 (5.3%), in 15 in group 2 (4.0%) and 6 in group 3 (10.3%), but this difference between the 3 groups did not reach statistical significance.

The mean durations of post-transplant hospital stay were 13.2, 16, 15.8 days in groups 1, 2 and 3, respectively (p: 0.02). At univariate analysis, RI was associated with donor and recipient age, mean Remuzzi-Karpinsky score of the graft, mean cold ischemia time and recipient's history of CMV disease in the first year after transplant, with an incidence of 5.3%, 9% and 17.2% in groups 1, 2 and 3 respectively. Otherwise, we did not find any significant correlation between resistance indices and body mass index of donors and recipients, or mean time of dialysis before transplant.

Table 1.
Baseline donor and recipient characteristics.

Donors	Group 1 (RI < 0.70)	Group 2 (70 ≤ RI ≤ 0.79)	Group 3 (RI ≥ 0.80)	P
Mean Age (years)	40.9 ± 17.3 (12-79)	49.0 ± 17.9 (13-83)	54.2 ± 16.2 (19-78)	< 0.001
Cerebrovascular death (%)	47.6%	52.7%	48.1%	n.s.
Mean estimated creatinine clearance by MDRD formula (mL/min)	86.3 mL/min ± 30.1 (20-240)	82.4 mL/min ± 35.6 (17-214)	74.0 mL/min ± 31.2 (27-147)	n.s.
Mean serum creatinine (mg/dL)	1.1 mg/dL ± 0.52 (0.4-3.9)	1.1 mg/dL ± 0.4 (0.4-2.7)	1.4 mg/dL ± 0.4 (0.9-2.4)	0.04
Mean Remuzzi-Karpinsky score	1.36 (0-6)	1.9 (0-6)	2.5 (0-5)	< 0.001
Mean Cold Ischemia Time (hours)	14.4 ± 5 (6-32)	15.9 ± 5.5 (7-34)	18.4 ± 6.6 (6-32)	0.003
Mean BMI (Kg/m ²)	25.1 ± 4 (12.8-40.4)	25.6 ± 3.9 (13.3-40.4)	25.2 ± 3.9 (16.5-31.2)	n.s.
Recipients				
Mean Age (years)	41.4 ± 10.8 (10-62)	49.2 ± 8.9 (18-65)	55.2 ± 6.1 (35-65)	0.001
Mean BMI(Kg/m ²)	22.9 ± 4.0 (12.2-37)	23.5 ± 3.9 (15-36)	24.9 ± 4.8 (17.3-35)	n.s.
Mean time of dialysis before transplant (months)	75.2 ± 56.0 (2-264)	78.8 ± 56.1 (5-339)	81.8 ± 58.5 (3.4-236)	n.s.
± SD (range)				
MDRD: Modification of Diet in Renal Disease				
BMI: body mass index				

Figure 1.Kaplan-Meier estimates of graft survivals ($P: 0.02$).**Figure 2.**Kaplan-Meier estimates of Patient survivals ($P: 0.01$).

Kaplan-Meier estimates of cumulative graft survival were significantly worse in patients who had an RI of 0.70 or more than in patients with an RI of less than 0.70 ($p = 0.02$) (Figure 1). Cumulative patient survival showed the same behavior ($p: 0.01$) (Figure 2).

DISCUSSION

After kidney transplantation, several complications may occur. For many years, research has been focused on non-invasive diagnostic techniques that would reliably predict the outcome of transplantation and graft function. Doppler ultrasonography is a useful tool for early evaluation of the kidney vasculature and function (2). However, a rise in the RI value is not pathognomonic of any one clinical condition and may occur whenever peripheral vascular resistance is increased due to constriction of peripheral arteries, indirectly when renal parenchyma is compressed, e.g. by increased intrarenal

interstitial pressure as in acute rejection, but also in acute tubular necrosis (3), or by direct vasoconstriction.

Doppler ultrasonography has been steadily improving over the past 10 years and is now frequently used as the first-line screening test for kidney transplant recipients (3-7).

In agreement with previous studies (7-10), clinical parameters associated with increased RI were older donor and recipient age and vascular compliance. We also found that RI was associated with the mean Remuzzi-Karpinsky score of the graft, mean cold ischemia time, recipient's history of CMV disease in the first year after transplant. A better histological score correlates with a lower RI, probably because of good vascular compliance of the kidney, while we believe that a lower cold ischemia time might reduce the ischemia-reperfusion damage and consequently early kidney dysfunction. As to the correlation with CMV disease, both animal models and epidemiologic studies suggest a role of Cytomegalovirus in atherogenesis (11-13) so in agreement with these data, CMV might contribute to endothelial dysfunction and vascular aging in recipients.

Finally, the prognostic value of RI for subsequent graft loss is still controversial. Some authors found elevated RI to be predictive of graft failure (10, 14) but other studies did not confirm these results (7, 15). In the present study, Kaplan-Meier estimates of graft survivals showed an increased rate of graft loss in patients with a substantial increase in intrarenal RI, so that a RI value of 80 or higher was a strong predictor of both allograft failure and death with a functioning graft.

CONCLUSIONS

Doppler sonography is a non-invasive diagnostic method which provides flowmetric quantitative parameters for hemodynamic evaluation of the graft. An increase in RI values is not indicative of a particular graft disease; in fact, it might occur in acute rejection but even in other parenchymal pathologies. Nevertheless, in our experience, RI values measured in segmental arteries in the early post-transplant period show a good correlation with the clinical evolution of the kidney and can predict better kidney graft function and reduce risk of all-cause graft loss, including patient death in a 5-year follow-up period.

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Correspondence

Stefano Vittorio Impedovo, MD
stefanovittorio@gmail.com

Pasquale Martino, MD
martino@urologia.uniba.it

Silvano Palazzo, MD
silvano.palazzo@alice.it

Pasquale Ditunno, MD
ditunno@urologia.uniba.it

Michele Tedeschi, MD
michele_tedeschi@live.it

Floriana Giangrande, MD
giangrandefloriana@libero.it

Carlos Miacola, MD

Saverio Forte, MD
saverio.forte@gmail.com

Francesco Paolo Selvaggi, MD
selvaggi@urologia.uniba.it

Michele Battaglia, MD
battaglia@urologia.uniba.it

Department of Emergency and Organ Transplantation
Urology, Andrology and Kidney Transplantation Unit
Piazza G. Cesare 11, 70124 Bari, Italy

ORIGINAL PAPER

Indication to renal biopsy in DM2 patients: potential role of intrarenal resistive index

Monica Insalaco¹, Pasquale Zamboli², Fulvio Floccari³, Fulvio Marrocco³, Simeone Andrucci⁴, Francesco Logias⁵, Luca Di Lullo⁶, Fulvio Fiorini⁷, Antonio Granata¹

¹ Nephrology and Dialysis Unit - "San Giovanni di Dio" Hospital, Agrigento, Italy;

² Nephrology and Dialysis Unit - Second University, Napoli, Italy;

³ Nephrology and Dialysis Unit - "San Paolo Hospital, Civitavecchia, Italy;

⁴ Nephrology and Dialysis Unit - "A. Manzoni" Hospital, Lecco, Italy;

⁵ Nephrology and Dialysis Unit - "San Francesco" Hospital, Nuoro, Italy;

⁶ Nephrology and Dialysis Unit - "Parodi Delfino" Hospital, Collesano, Italy;

⁷ Nephrology and Dialysis Unit - "S.Maria della Misericordia" Hospital, Rovigo, Italy.

Summary

Diagnosis of diabetic nephropathy is generally based, rather than on histological confirmation, on clinical criteria (long history of diabetes, presence of proteinuria, diabetic retinopathy or peripheral neuropathy). This clinical approach has perhaps limited utility in DM2 patients, because only 50% of them show microvascular complications in presence of nephropathy. Eco-colour-Doppler sampling of interlobular renal arteries and determination of their resistance indices (RI), was proposed in the differential diagnosis of numerous nephropathies. Aim of this study was to evaluate whether RI can be useful in discerning non-diabetic renal disease (NDRD), in order to better define indications to perform renal biopsy among proteinuric DM2 patients. All patients were submitted to: echo-colour-Doppler study of renal vessels; systematic screening for diabetic retinopathy; needle renal biopsy. RI resulted to be significantly higher in diabetic glomerulosclerosis (GSD) group as compared with NDRD group, while no significant difference was found with respect to NDRDs overlapping GSD (overlapping group). The last one showed however median RI significantly higher than isolated NDRD group. Normalized chi square Pearson for the hypothesis that RI can predict GSD resulted 0.73, while it resulted 0.43 for the hypothesis that diabetic retinopathy can predict GSD. Echo-colour-Doppler can significantly contribute, more than the other parameters proposed (nephritic or nephrotic syndrome, hematuria, diabetic retinopathy), to the identification of underlying nephropathy in DM2 subjects. In the light of our experience, it seems that the detection of RI values > 0.72 suggests the diagnosis of GSD or mixed forms, reducing the indications to renal biopsy only in presence of values < 0.72.

KEY WORDS: Intrarenal resistive index; Doppler ultrasound; Renal biopsy; Type II diabetes mellitus.

INTRODUCTION

The number of patients affected by type-2 diabetes, on a world scale, is growing all the time, and it is expected to reach 438 million people by 2030 (1-5).

Diabetic nephropathy (DN) is a common complication (2), being the most common secondary cause of glomerular pathology (3). It affects about 40% of diabetic patients (2) and it is responsible for end-stage renal disease (ESRD) in 40% of uraemic patients in the United

States and in 15-20% of patients in Italy (4, 5). Diabetic glomerulosclerosis (GSD) is characterised by diffuse or nodular mesangial sclerosis and thickening of the basal glomerular membrane, accompanied by tubular atrophy, interstitial fibrosis and arteriosclerosis (6). Proteinuria is the classical sign, ranging from microalbuminuria to overt proteinuria (2, 8, 9).

Diagnosis of diabetic nephropathy is generally based,

rather than on histological confirmation, on clinical criteria such as a long history of diabetes, presence of proteinuria and evidence of another microvascular complications such as diabetic retinopathy or peripheral neuropathy (3, 6, 7). This clinical approach has perhaps limited utility in DM2 patients, because only 50% of them show microvascular complications in presence of nephropathy (1, 6).

On the other side, histology does not ever match with clinical criteria, with a GSD prevalence ranging from 7 to 57%. This datum depends probably on study cohort composition and on criteria adopted to prescribe biopsy, with 30-50% of these proteinuric DM2 patients showing other nephropathies, isolated or overlapping GSD (6-10).

Predictors of non-diabetic renal disease (NDRD), in proteinuric DM2 patient, include a short history of diabetes, the presence of microhematuria, the absence of retinopathy, immunological anomalies (2-10). Differential diagnosis is obviously crucial to allow affordable prognostic evaluation and correct subsequent therapeutic choices (8).

Eco-colour-Doppler sampling of interlobular renal arteries and determination of their resistance indices (RI), was proposed in the differential diagnosis of numerous acute and/or chronic nephropathies (11). This is a rapid, non-invasive, repetitive method to study intrarenal blood flow. RI is generally higher in vascular and tubulo-interstitial pathologies, and not in pure glomerular ones (12).

Higher values are generally correlated with risk factors for macroangiopathy (body mass index, mean arterial pressure, total cholesterol and LDL), and therefore with intrarenal arteriosclerosis, while they generally do not correlate with microalbuminuria, a consequence of glomerular damage (12, 13).

In many studies, patients affected by diabetic nephropathy reported higher RI as compared with other nephropathies. The frequent histological finding of atherosclerotic glomerulosclerosis perhaps well correlates with this increase, directly correlating with elevated pulse wave velocity (PWV) between carotid and femoral artery, index of arterial stiffness consequent to atherosclerosis (10-15). Aim of this study was then to evaluate whether RI can be useful in discerning NDRD, in order to better define indications to perform renal biopsy among proteinuric DM2 patients.

SUBJECTS AND METHODS

A monocentric observational study was conducted on DM2 patients, reporting proteinuria > 1 gr/24 hour and arterial hypertension (> 140/90 mmHg or already on antihypertensive therapy with ACE-I, ARB and/or calcium-antagonists). Patients affected by DM1 or other secondary nephritic syndromes were excluded.

All patients were submitted to:

- an echo-colour-Doppler study of renal vessels (registering RI, systolic peak velocity, end diastolic velocity);
- systematic screening for diabetic retinopathy, through fundus examinations;
- an ultrasound guided, needle renal biopsy.

RI were calculated on three different interlobular arteries

for each kidney, on the upper, median and lower third of the organ, using the following equation

$$RI = 100 \times [1 - (V_{min}:V_{max})]$$

Renal biopsy was performed using real-time ultrasound-fixed guidance (3.5 MHz convex probe, Technos MP; Esaote, Italy), and 16-gauge automated spring-loaded gun. In all cases the lower pole of the left kidney was used for biopsy, sampling from each patient two frustules. The tissue was observed by optical microscope after colouring with hematoxylin-eosin, and with UV for immunofluorescence by the same pathologist. Statistical analysis was performed using Statistica 10.0 (Statsoft Inc.) software. Data were, case by case, presented as mean \pm DS, median \pm DS or percentage, as reported in legends. Two-way ANOVA test was used to test statistical significance. $P < 0.05$ was considered as threshold of statistical significance. Normalized χ^2 Pearson was used to test the hypothesis that RI and diabetic retinopathy can predict GSD or not.

RESULTS

62 DM2 patients (37 mean and 25 women) were enrolled. Median age was 55 ± 9.3 years. Median duration of DM2 from first diagnosis to renal biopsy was 6.2 ± 2.9 years. Median glomerular filtration rate, estimated using CKD-EPI, was 37 ± 7.6 ml/min/1.73 m². Median 24 hours proteinuria was 5.1 ± 4.3 gr.

Demographic data are reported in Table 1.

Table 1.

Demographic data of the study population.

Population (n = 62)	
Sex: male/female (n)	37/25
Age (years)	55.0 \pm 9.3
Creatinine clearance sec. CKD-EPI (ml/min/1.73 m²)	37.0 \pm 7.6 (88-21 ml/min)
Blood creatinine (mg/dl)	1.3 \pm 0.4
Proteinuria (gr/24 h)	5.1 \pm 4.3
Duration of diabetes (years)	6.2 \pm 2.9

The population was stratified in three groups, according to the anatomo-pathological picture emerging from renal biopsies (Figure 1):

Figure 1.

Stratification of the population (62 patients) by anatopathological picture.

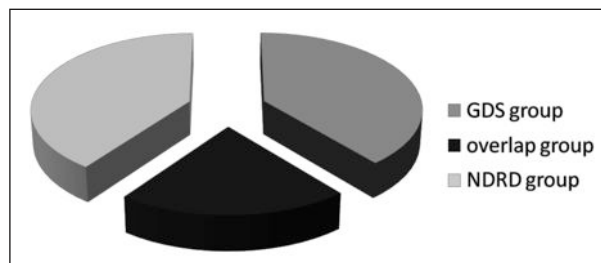


Table 2.
Histological findings in groups II and III.

	Group II NDRD+GSD (n = 13) (21%)	Group III NDRD (n = 24) (39%)
IgA nephropathy (n) (%)	3 (23)	8 (33)
Membranous GN (n) (%)	1 (8)	6 (25)
Primary FSGS (n) (%)	0	5 (21)
HT nephrosclerosis (n) (%)	9 (69)	0
ANCA-associated vasculitis (n) (%)	0	3 (13)
Acute interstitial nephritis (n) (%)	0	2 (8)

- 40% (n = 25) presented GSD (GSD group);
- 21% (n = 13) was affected by NDRDs overlapping GSD (overlapping group);
- 39% (n = 24) were isolated cases of NDRDs (NDRD group).

Between 13 patients belonging to overlapping group, histological investigation showed IgA nephropathy (23%, n = 3), membranous glomerulopathy (8%, n = 1) and nephroangiosclerosis (69%, n = 9). Of the 24 patients belonging to NDRDs group, 33% (n = 8) presented an IgA nephropathy, 25% (n = 6) a membranous glomerulopathy, 21% (n = 5) a primitive focal segmental glomerulosclerosis (FSGS), 13% (n = 3) an ANCA-associated vasculitis and 8% (n = 2) an acute interstitial nephritis (Table 2).

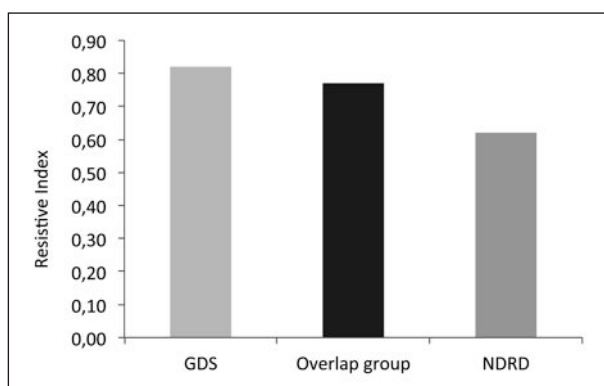
RI resulted to be significantly higher in GSD group as compared with NDRD group (0.82 vs 0.62, $p < 0.01$), while no significant difference was found with respect to overlapping group (0.82 vs 0.77, $p > 0.05$). The last one showed however median RI significantly higher than isolated NDRD group (0.77 vs 0.62, $p < 0.01$) (Figure 1).

Diabetic retinopathy was presented in 29 of 62 patients, equally distributed in GSD (12 pts, 48%), overlapping (6 pts, 46%) and NDRD group (11 pts, 45.8%).

No significant difference was detected between the three groups concerning the actual age expressed in years, the duration of diabetes and the number of antihypertensive medications used.

Figure 2.

Resistive Index in GSD, Overlap, and NDRD groups.



Normalized χ^2 Pearson for the hypothesis that RI can predict GSD resulted 0.73, while it resulted 0.43 for the hypothesis that diabetic retinopathy can predict GSD.

DISCUSSION

Owing to the progressive and rapid increase in the number of patients affected by NIDDM, diabetic nephropathy is becoming one of the most common cause of renal disease (1).

In many Centres the diagnosis of diabetic nephropathy is based on clinical criteria, rather than on histological investigation. In the case of DM2, these criteria have lesser relevance, owing to the greater heterogeneity of clinical outcome and the weaker correlation between diabetic nephropathy and retinopathy.

The diagnosis of non-diabetic renal disease (NDRD) in DM2 patient is important above all with a view to the therapeutic decisions.

In a study by *Soni et al.* (2), 72.5% of 160 DM2 patients presented isolated or overlapping NDRD, and the most common causes were membranous glomerulonephritis, FSGS, acute interstitial nephritis and post-infective glomerulonephritis.

Bi et al. (6) reported a 45.5% of NDRD overlapping GSD, IgA Nephropathy being the most common cause, followed by membranous glomerulonephritis.

Both studies confirmed the absence of retinopathy as a strong predictive factor of NDRD, especially if associated with proteinuria or hematuria, confirming the set of several diagnostic criteria takes on a more sensitive predictive role as compared with a single criterion.

In our work we included Caucasian patients with a mean age equal to 55 years, affected by NIDDM for 4 years, with arterial hypertension, moderate IRC with FGR of 37 ml/min and nephritic syndrome.

All of them were submitted to the Eco-colour-Doppler study of the renal arteries with determination of the resistance indices (RI) and subsequently to renal biopsy. From the study of the renal biopsies, the prevalence of NDRD, isolated or overlapping with GSD, resulted equal to 60%, in line with the literature reports.

The patients were subsequently stratified into three groups, the first of which included 40% of the patients affected by isolated GSD. In 21% of the patients, belonging to the second group, an NDRD overlapping with GSD was detected, and the most frequent causes were nephroangiosclerosis in 69% of the cases and 23% IgA nephropathy. Thirty-nine per cent of the patients, belonging to the third group, presented an isolated NDRD, whose most common causes were IgA nephropathy in 33% of the cases and membranous glomerulonephritis in 25%.

From a study by *Haider et al.* performed in 2011 (8) on a Caucasian population of 567 patients affected by IDDM and NIDDM there was instead an NDRD incidence, isolated or overlapping with GSD, equal to 30%, with no differences in regard to the type of diabetes; the most commonly observed causes were glomerulonephritis from immune complexes and FSGS, followed by IgA nephropathy. From our study, in line with the literature reports (2, 6, 8), what emerges, then, is the need to better consider the chances of a non-diabetic nephropathy

as the cause of renal damage in patients with NIDDM, and to submit them to renal biopsy.

Within the scope of diabetic nephropathy an important diagnostic role can be played by the Echo-Colour-Doppler study of the renal arteries (11), which evidences a pathological pattern with an increase in RI, understood as a predictive factor of a worsening in renal function (4). The increase in RI is correlated with intrarenal arteriosclerosis, which characterises the GSD apart from the glomerular damage responsible for the microalbuminuria. The study by *Nosadini et al.* in 2006 (4) on patients affected by NIDDM, evidences the association between $RI \geq 80$ at the Doppler test with a more rapid decrease in the renal glomerular filtrate (FGR) and a lower regression from microalbuminuria to normoalbuminuria.

The evaluation of intrarenal RI thus seems to perform a non-negligible role in predicting the evolution of renal function in the microalbuminuria diabetic patients, even when GFR is still in the normal range (4).

According to *Boeri et al.*, in a study dated 1998 (12), RI seem to be a marker of intrarenal arteriosclerosis and can be used as a rapid and non-invasive method of investigation of the intrarenal flow.

From our work another important fact emerges: RI resulted to be significantly higher in patients with isolated GSD as compared with patients with isolated NDRD (0.82 and 0.62, respectively, $p < 0.01$); a significant difference was also observed among the patients with mixed forms GSD + NDRD and those with isolated NDRD (0.77 and 0.62, respectively, $p < 0.01$). Normalized χ^2 Pearson confirmed the hypothesis that RI can predict GSD, with a predictive value (0.73) higher than that observed (0.43) for the predictivity of diabetic retinopathy for GSD.

Our work, in line with the literature (14, 15), thus contributes to confirming the fact that the RI, measured at the level of the interlobular renal arteries in patients with diabetic nephropathy, are significantly higher as compared with those measured in patients with another type of nephropathy, and reflect the systemic vascular damage caused by diabetes.

CONCLUSIONS

Echo-colour-Doppler, by means of the determination of the RI, represents an investigation that can significantly contribute, more than the other parameters hitherto proposed (nephritic or nephrotic syndrome, hematuria, diabetic retinopathy), to the identification of the underlying nephropathy in the subjects affected by NIDDM.

In the light of our experience, it seems that the detection of elevated RI values (> 0.72) suggests the diagnosis of GSD or mixed forms, reducing the recommendation of renal biopsy only to cases in which the values of RI < 0.72 support the suspicion of an NDRD.

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Correspondence

Antonio Granata, MD

Via F. Paradiso 78/a I-95024 Acireale, Catania, Italy
antonio.granata4@tin.it

Monica Insalaco, MD

Nephrology and Dialysis Unit - "San Giovanni di Dio" Hospital, Agrigento, Italy

Pasquale Zamboli, MD

Nephrology and Dialysis Unit - Second University, Napoli, Italy

Fulvio Floccari, MD

Fulvio Marrocco, MD

Nephrology and Dialysis Unit - "San Paolo Hospital, Civitavecchia, Italy

Simeone Andrulli, MD

Nephrology and Dialysis Unit - "A. Manzoni" Hospital, Lecco, Italy

Francesco Logias, MD

Nephrology and Dialysis Unit - "San Francesco" Hospital, Nuoro, Italy

Luca Di Lullo, MD

Nephrology and Dialysis Unit - "Parodi Delfino" Hospital, Colleserferro, Italy

Fulvio Fiorini, MD

Nephrology and Dialysis Unit - "S.Maria della Misericordia" Hospital, Rovigo, Italy

ORIGINAL PAPER

Ureteral strictures after kidney transplantation: Risk factors

Pasquale Martino, Stefano Vittorio Impedovo, Silvano Palazzo, Pasquale Ditunno, Vito Ricapito, Gabriele Alberto Saracino, Giuseppe Lucarelli, Michele Tedeschi, Carlo Bettocchi, Michele Battaglia

Urology, Andrology and Kidney Transplantation Unit, Department of Emergency and Organ Transplantation, University of Bari, Bari, Italy

Stefano Vittorio Impedovo, Pasquale Martino and Silvano Palazzo have equally contributed to this work

Summary

Introduction: Ureteral obstruction is one of the most commonly reported urological complications after kidney transplantation often occurring within the first 3 months after surgery. Ischemia is the most frequent cause of ureteral stenosis and is the result of excessive hilar dissection and a poor anastomotic technique. Aim of this study was to identify the main risk factors for ureteral stenosis after kidney transplantation from cadaveric donors and to assess their impact on both graft survival and patient.

Materials and Methods: We retrospectively investigated 761 kidney transplants from cadaveric donors performed between 1998 to 2011. In all the patients, the ureteroneocystostomy was stented with a double J stent 4.7Ch x 12 cm held in place for an average time of 4-6 weeks post-operatively. Each patient underwent at least 3 ultrasound scans during hospital stay and subsequently during follow-up. All patients with severe hydronephrosis were followed by sequential renal scintigraphy with MAG3 and diuretic stimulus.

Results: After a mean follow-up of 60.1 (\pm 38.5) months, severe ureteral stenosis was discovered in 21 patients (2.76%), with exclusive involvement of the vesicoureteral junction. No statistically significant correlation was found with donor age and the incidence of delayed graft function, whereas a significant correlation between ureteral obstruction and unilateral placement of both grafts in dual kidney transplantation (DKT) ($p < 0.001$) was found. These patients had a longer mean hospital stay than the control group, but there was no influence on survival of the organ or patient.

Conclusions: ureteral obstruction after renal transplantation often features subtle and late symptoms. Early ultrasound monitoring is therefore essential and in the presence of severe hydronephrosis, scintigraphic confirmation of the obstruction. In fact, early resolution of the stenosis appears to provide optimal graft and patient survival.

KEY WORDS: Kidney transplant; Hydronephrosis; Ultrasound scan; Ureteral obstruction.

INTRODUCTION

Hydronephrosis is very common after kidney transplantation and can be readily detected by sonography, but its significance should be interpreted in conjunction with renal function and clinical data (1). It is often the result of denervation of the organ with a reduction in renal pelvis tone, and so does not require any treatment. In some cases, however, it may be secondary to ureteral obstruction, usually caused by ureteral ischemia, extrin-

sic compression due to lymphocele, hematoma, abscess, ureteral kinking, intrinsic obstruction by calculi and clotting or a tumor.

In a native kidney, hydronephrosis is associated with colicky pain while in a transplanted kidney it is often asymptomatic, and manifests by a reduced diuresis and worsening of renal function; hence the prominent role of ultrasound.

Aim of this study was to identify the main risk factors for ureteral stenosis after kidney transplantation from cadaveric donors, and to assess their impact on both graft and patient survival.

PATIENTS AND METHODS

All 761 consecutive patients who underwent kidney transplantation from a cadaveric donor between February 1998 and July 2011 at the Kidney Transplant Unit of Bari (Italy) were included in this retrospective study. Single kidney transplants (707, 92.9%) were performed through an extraperitoneal approach in the iliac fossa. The renal vein was anastomosed to the external iliac vein, and the renal artery was anastomosed to the external iliac artery. The method used to establish urinary continuity was extravesical ureterocystostomy (Lich-Gregoir method). Starting from October 2000, 26 unilateral and 28 bilateral dual kidney transplants were performed. Unilateral placement of kidneys was done extraperitoneally through a single Gibson incision; both ureters were anastomosed side-to-side at their ends and reimplanted into the bladder by the Lich-Gregoire technique. In the case of bilateral double kidney transplantation (DKT), kidney placement was performed extraperitoneally through two separate paramedian incisions (n = 18) or one midline approach (n = 10); two separate extravesical ureterocystostomies were executed. In all patients, the ureteroneocystostomy was stented with a double J stent 4.7Ch x 12 cm held in place for an average time of 4-6 weeks post-operatively. Each patient underwent at least 3 ultrasound scans during hospital stay and subsequently during follow-up. All patients with severe hydronephrosis were followed by sequential renal scintigraphy with mercapto-acetyl-tri-glycine

(MAG3) and diuretic stimulus, as well as monitoring serum parameters of renal function.

The risk factors for the development of a ureteral stenosis considered were: donor age, type of transplantation (single transplant vs dual unilateral vs bilateral transplant), and the appearance of delayed graft function (DGF) post transplant.

RESULTS

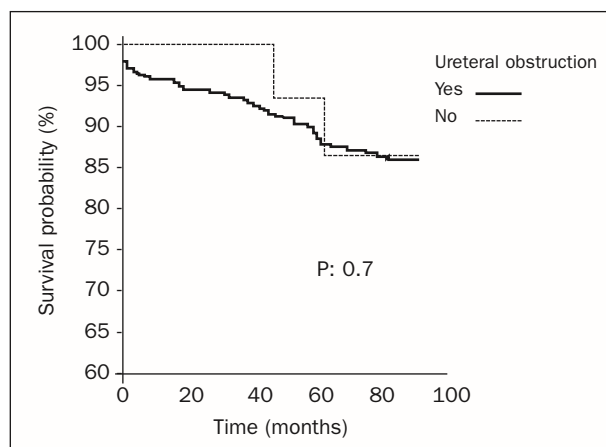
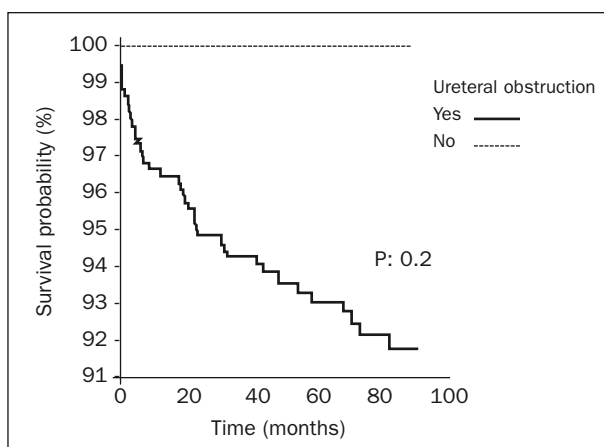
In a mean follow-up of 60.1 (\pm 38.5) months severe ureteral stenosis was discovered in 21 subjects (2.76%), with exclusive involvement of the vesico-ureteral junction. Donors and recipients characteristics are shown in Table 1. Among the analyzed factors, a statistically significant correlation was found between ureteral obstruction and unilateral placement of both DKT grafts ($p < 0.001$). No statistically significant correlation was found with donor age ($p: 0.3$) or the incidence of delayed graft function ($p: 0.8$). Early detection of the ureteral stenosis allowed prompt intervention and all these patients underwent endoscopic or open surgical correction of the obstruction. These patients had a longer mean hospital stay than the control group ($P = 0.01$), but there was no influence on survival of the organ or patient. (Figures 1-2).

DISCUSSION

Urological complications are an important source of morbidity, and sometimes mortality, after kidney transplantation. Ureteral obstruction occurs in 2-10% of renal transplant recipients (3), occasionally presenting with nausea, vomiting, contraction of diuresis and worsening of renal function (4). This kind of complication may occur in the early post-surgery period or later; the

Table 1.
Donor and recipient characteristics.

Donors	No ureteral obstruction	Ureteral obstruction	P
Mean age (years)	45.8 \pm 17.6 (12-83)	49.5 \pm 14.9 (18-76)	0.3
Cerebrovascular death (%)	55.6%	70.0%	0.2
Mean estimated creatinine clearance by MDRD formula (mL/min)	82.4 mL/min \pm 31 (20-240)	72.4 mL/min \pm 33.2 (19-140)	0.2
Mean serum creatinine (mg/dL)	1.0 mg/dL \pm 0.46 (0.4-4.5)	1.1 mg/dL \pm 0.36 (0.6-1.8)	0.3
Mean Remuzzi-Karpinsky score	1.9 (0-6)	2.3 (0-6)	0.3
Mean Cold Ischemia Time (hours)	14.9 \pm 5.3 (6-34)	16.6 \pm 4.0 (12- 24)	0.2
Recipients			
Mean Age (years)	46.1 \pm 10.9 (10-65)	50.3 \pm 8.7 (32-65)	0.09
Mean BMI(Kg/m ²)	23.8 \pm 4.0 (12.2-39)	25 \pm 6.1 (17.6-36)	0.1
Delayed graft function(%)	31.5	30	0.8
Mean Hospital stay (days)	15.2 (5-82)	21.2 (7-60)	0.01
\pm SD (range) MDRD: Modification of Diet in Renal Disease BMI: body mass index			

Figure 1.Kaplan-Meier estimates of graft survivals ($P: 0.7$).**Figure 2.**Kaplan-Meier estimates of Patient survivals ($P: 0.2$).

causes of obstructive hydronephrosis in the early post transplant period are blood clots within the ureter or bladder and edema at the ureteroneocystostomy, although the systematic use of ureteral stents has significantly reduced the incidence. Late obstruction generally occurs in distal ureter secondary to ureteral stricture, as a result of ischemia, infection due to cytomegalovirus (CMV), and polyoma virus and rejection (5-7).

Other, less common causes are extrinsic compression by pelvic fluid collection like hematoma, urinoma, lymphocele, abscess, periureteral fibrosis and a pelvic tumor (8). Obstruction due to calculi is a rare cause. Some recent studies have suggested an ischemic component related to advanced age of the donor, the higher incidence of DGF and abnormal organ revascularization at declamping (9), although in our study this correlation was not confirmed, probably due to the protective effect of the ureteral stent. Sometimes hydronephrosis is not

obstructive and is determined by vesicoureteral reflux, decreased ureteral tone secondary to denervation or rejection.

Hydronephrosis can be readily identified by ultrasound scan but its significance should be interpreted in conjunction with renal function and clinical data. All patients with severe hydronephrosis underwent sequential renal scintigraphy with MAG3 and diuretic stimulus. Furosemide was administered, approximately 20 minutes after tracer injection of MAG3. A quick washout of the radionuclide was shown in stasis without an anatomic obstruction. No change in the amount of radioactivity in the renal collecting system after the diuretic was characteristic of a complete obstruction.

Early treatment of the ureteral obstruction consists of percutaneous nephrostomy, which is the procedure of choice for temporarily relieving the obstruction (10). There is controversy as to whether definitive treatment should be endoscopic or by open surgery. In accordance with other Authors we reserve minimally invasive endoscopic techniques for cases of short segment stenosis treated within 3 months. Open surgery is the gold standard treatment for ureteral obstructions which are lengthy and of long duration, or that recur after endoscopic failures, and seems to guarantee a global success rate of 85% (11).

CONCLUSION

The clinical picture of ureteral obstruction after kidney transplantation is characterized by subtle, late symptoms. Early ultrasound monitoring is therefore fundamental and in the presence of severe hydronephrosis, scintigraphic confirmation of the nature of the obstruction. The early resolution of stenosis appears to provide an optimal graft and patient survival.

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Correspondence

Pasquale Martino, MD
martino@urologia.uniba.it

Stefano Vittorio Impedovo, MD
stefanovittorio@gmail.com

Silvano Palazzo, MD
silvano.palazzo@alice.it

Pasquale Ditunno, MD
ditunno@urologia.uniba.it

Vito Ricapito, MD

Gabriele Alberto Saracino, MD

Giuseppe Lucarelli, MD
giuseppe.lucarelli@inwind.it

Michele Tedeschi, MD
michele_tedeschi@live.it

Carlo Bettocchi, MD
bettocchi@urologia.uniba.it

Michele Battaglia, MD
battaglia@urologia.uniba.it

Department of Emergency and Organ Transplantation
Urology, Andrology and Kidney Transplantation Unit
Piazza G. Cesare 11, 70124 Bari, Italy

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