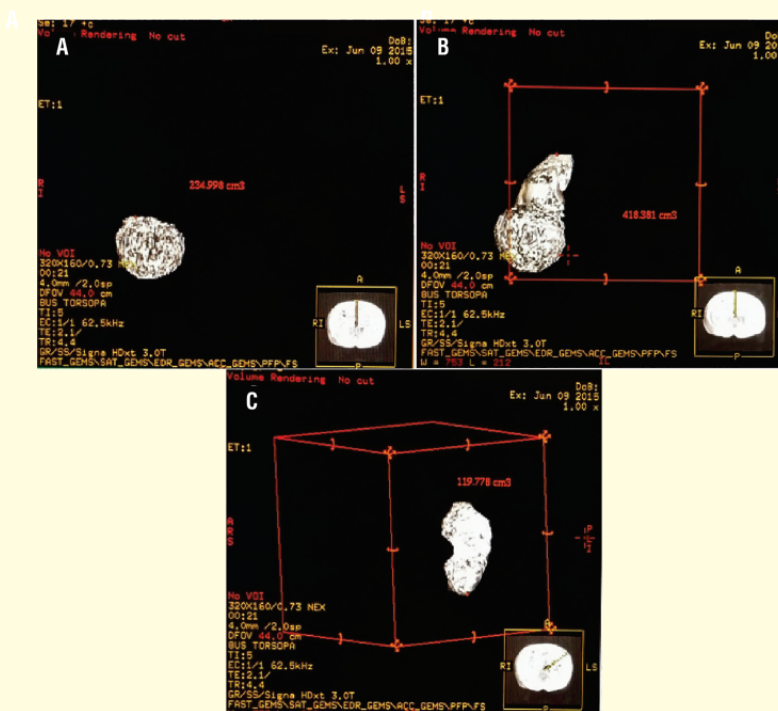


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 VOLUME 46, NUMBER 2, MARCH - APRIL, 2020



MR 3D volume reconstructed images showing (A) tumour volume, (B) affected kidney volume with tumour, and (C) unaffected kidney volume, in a patient planned for radical nephrectomy. (page 236).



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The March-April number of *Int Braz J Urol*, the second under my supervision, presents original contributions with a lot of interesting papers in different fields: Prostate Cancer, Renal Cell Carcinoma, Penile trauma, Bladder Cancer, BPH, Laparoscopy and Testicular Cancer. The papers came from many different countries such as Brazil, USA, Turkey, China, Korea, Colombia, India and Italy, and as usual the editor's comment highlights some of them. In the present issue we present two important reviews: in page 152 Dr. Barros and colleagues from Brazil (1) review in a nice narrative the urethral injury in penile cancer, and Dr. Li and colleagues from China (2) present in page 158 an important meta-analysis about preoperative serum total cholesterol is a predictor of prognosis in patients with renal cell carcinoma, but the bladder cancer is the highlight of this number.

Dr. Hamad and colleagues (3) supervised by Dra. Angela Smith of University of North Carolina - USA performed on page 169 a elegant review about bladder preservation therapies, patient selection criteria, and functional and oncologic outcomes for Bladder preservation therapies in muscle-invasive bladder cancer and concluded that the breadth of strategies that aim to preserve a patient's bladder while still optimizing local tumor control and overall survival and future areas for innovation include the use of predictive biomarkers and implementation of immunotherapy. The editor would like to highlight the following works too:

Dr. Ölçücü and colleagues from Turkey (4) on page 185 evaluate the effects of solifenacin, darifenacin, and propiverine on nasal-, subfoveal-, temporal choroidal thicknesses (NCT, SFCT, TCT), intraocular pressure (IOP) and pupil diameter (PD) in a 165 patients with overactive bladder (OAB) and concluded that solifenacin significantly reduced IOP, darifenacin significantly reduced NCT and propiverine significantly increased PD in patients with OAB who had normal ophthalmologic examinations after the twelve weeks of treatment. These findings can help to decide appropriate anticholinergic drug choice in OAB medical treatment for patients with eye-related disorders.

Dr Arda and Colleagues (5) from Turkey performed on page 216 in a interesting determined the utility of preoperative complete blood count (CBC) based systemic inflammatory markers in the prediction of testicular cancer and its prognosis in 182 patients and concluded that several systemic inflammatory markers, which are obtained by routinely performed cost-effective blood tests, could demonstrate incremental predictive and prognostic information adjuvant to preoperatively achieved testicular tumor markers.

Dr. Lal and Colleagues (6) from India performed on page 234 the study that is on the cover in this number. The authors assessed the role of MRI for predicting postoperative renal function by preopera-

tive estimation of renal parenchymal volume and correlation with glomerular filtration rate (GFR) in 30 patients with median tumor volume of 175.7cc. They concluded that preoperative residual parenchymal volume on MRI renal volumetry correlates well with postoperative GFR in patients with RCC undergoing radical nephrectomy or nephron sparing surgery.

Dr. Tae and Collegues (7) from Korea studied on page 244 the usefulness of natural killer cell activity (NKA) in diagnosing of prostate cancer (PC) in 102 patients and concluded that low NKA and high PSA levels were likely to be associated with a positive TRBx outcome. NKA detection was easy and improved the diagnostic accuracy of prostate cancer.

Dr. Reis Leonardo and Collegues (8) from Brazil shows on page 253 the role of laparoscopic pyeloplasty (LP) in children is less well defined and has slowly emerged as an alternative procedure in 38 children and suggested that LP has good functional and cosmetic results, not compromising the success of the open procedure, regardless patient's age.

We hope that readers will enjoy the present number of the *International Brazilian Journal of Urology*.

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## ARTICLE INFO

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# Urethral injury in penile fracture: a narrative review

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## ABSTRACT

**Objective:** To present the evolution and the recent data on the etiology, diagnosis, management and outcomes of penile fracture (PF) with concomitant urethral injury.

**Materials and Methods:** We searched the Pubmed database between 1998 and 2019 using the following key words: “penile fracture”, “fracture of penis”, “trauma to penis”, “rupture of corpora cavernosa”, “urethral injury”, “urethral rupture” and “urethral reconstruction”.

**Results:** The incidence of urethral lesion in patients with PF varies by geographic region and etiology. Blood in the meatus, hematuria and voiding symptoms are highly indicative of urethral rupture. The diagnosis of PF is eminently clinical and complementary exams are not necessary. The treatment consists of urethral reconstruction and the most common complications found are urethral stenosis and urethrocutaneous fistula.

**Conclusion:** PF is an uncommon urological emergency, particularly in cases with urethral involvement. Urethral injury should be suspected in the presence of suggestive clinical signs, and diagnosis is usually clinical. Urgent urethral reconstruction is mandatory and produces satisfactory results with low levels of complications.

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## INTRODUCTION

Penile fracture (PF) with associated urethral rupture is an extremely rare condition. The urethral lesion can be partial or complete and the incidence varies from 1% to 38%, depending the geographic region and etiology (1, 2).

Patients usually report a cracking sound with concomitant sudden swelling and ecchymosis of the penis followed by immediate detumescence. Blood in the meatus, hematuria and urinary retention may be experienced with urethral injury (3).

Studies have variously reported the usefulness of retrograde urethrocytography (RGU), ultrasound (USG), flexible cystoscopy and magnetic resonance imaging (MRI) in the diagnosis (4-7). PF and urethral injury should be treated by surgery with the goal of preserving sexual potency and regaining normal micturition function (8, 9).

It is important to address these issues in the urological literature. Therefore, in this review, we present the evolution and the recent data on the etiology, diagnosis, management and outcomes of PF with concomitant urethral injury.

## MATERIALS AND METHODS

We searched the Pubmed database between 1998 and 2019 using the following key words: “penile fracture”, “fracture of penis”, “trauma to penis”, “rupture of corpora cavernosa”, “urethral injury”, “urethral rupture” and “urethral reconstruction”. Special emphasis was given to relevant articles reporting the etiology, management and outcomes of PF with associated urethral rupture. All English papers were included and non-English papers were excluded.

## DISCUSSION

The incidence of urethral lesion in patients with PF was reported to be only 3% in Eastern European countries, Asia, and Africa, where the main cause was penile manipulation. In an Iranian study with 352 cases of PF, the main cause was the practice of *taqaandan* in 269 cases (76.4%). This is a self-inflicted injury, consisting of intentional forceful acute bending of part of the shaft of the erect penis in a downward, upward, or lateral direction while holding the other part stationary, to achieve detumescence of the penis, as a practice to release tension, among other reasons. In this series, there was combined penile and urethral rupture only in five cases (10). Et Atat et al. described their experience with 300 cases of PF, with masturbation as etiology in 180 (60%) cases. Concomitant urethral injury was found in only five (1.6%) patients, corroborating the theory that non-coital injury has a lower incidence of urethral involvement due to low-energy trauma (11).

On the other hand, the incidence reached 38% in western countries where sexual intercourse represented the main cause of PF (12). The incidence of urethral injury was higher in these countries, such as Brazil and the United States, because intercourse is generally associated with high-energy traumas. Nason et al. reported a retrospective analysis of 21 PF cases in Ireland and all fractures were the result of sexual misadventure (13). A Brazilian study evaluated the relationship between sexual position and severity of PF in 90 patients. According to the results, the positions with the “man on top” and “doggie style” were considered the most severe, present-

ing greater association with urethral and bilateral lesions of the corpora cavernosa (14) Figure-1.

Penile fracture generally causes a cracking sound followed by rapid detumescence, sudden swelling and ecchymosis of the penis, so that it acquires an aspect known as “eggplant deformity” (3) Figure-2. Blood in the meatus, hematuria and voiding symptoms are highly indicative of urethral rupture, but the absence of these findings does not exclude urethral lesions (15). A recently published systematic review found that 50% of cases of urethral injury were clinically asymptomatic and the lesion was found accidentally during USG or intraoperatively (16).

In suspected cases of urethral injury, RGU may demonstrate contrast leakage at the lesion site and reveal the exact point of urethral injury (17) Figure-3. Some authors consider RGU to be compulsory if diagnosis of urethral rupture is suspected (18). However, RGU can show false negative results in up

**Figure 1 - The figure shows a penile fracture with urethral injury and bilateral rupture of the corpora cavernosa.**



**Figure 2 - Typical eggplant aspect in a patient with penile fracture and urethral injury.**



to 28.5% of cases (17). Therefore, there is no consensus on the role of RGU in PF (15). Also, trying to assess the possibility of concomitant urethral injury, Kamdar et al. described the use of flexible cystoscopy at the same time as surgical repair, allowing direct visualization of the urethra without delaying treatment. However, not all emergency hospitals have a flexible cystoscope (5). Although the site of injury had 100% correlation with intraoperative findings, color Doppler ultrasound can miss urethral rupture (6). MRI is highly associated with intraoperative findings of tunical rupture, presenting 100% sensitivity and 77.8% specificity. On the other hand, MRI has lower accuracy for urethral lesions, with 60% sensitivity and 78.3% specificity (7). Therefore, the diagnosis of PF is eminently clinical and these complementary exams are not necessary, especially when urethral lesion is suspected and surgical intervention is always required (19).

The objective of treating PF with associated urethral injury is to preserve sexual potency and

**Figure 3 - The figure shows a urethrocytography of a patient with penile fracture and urethral injury.**



recover normal micturition function. The treatment consists of tension-free end-to-end anastomosis under a transurethral catheter. A circular subcoronal incision followed by further penile degloving is the best described surgical approach, allowing good exposure of the corpus cavernosum and urethra, besides identification and repair of any concomitant urethral injury (9). The corpus cavernosum is treated using interrupted 3-0 polyglactin sutures. Partial urethral tearing is primarily treated with simple 5-0 polyglactin sutures over an 18 French catheter. In cases of complete urethral injury, the treatment consists of tension-free end-to-end anastomosis after sufficient dissection of the urethra on both sides of the tear (8, 19). The postoperative duration of urethral catheterization depends on the complexity of observed lesions. Generally, the urethral catheter is left for 10-14 days in cases of partial injury and for 14-21 days in cases of complete lesion (8). Some authors recommend suprapubic cystostomy in cases of complete circumferential rupture. They believe that it is safer to place a suprapubic catheter and recommend keeping it closed for at least 3 days after urethral catheter removal to ensure adequate and normal voiding before its removal (4).

The main tools described in the literature to assess postoperative urinary function are the International Prostate Symptom Score (IPSS) questionnaire and uroflowmetry. While the IPSS question-

naire is subjective, uroflowmetry is a very objective way to determine urinary flow and screen for possible abnormalities. Some studies have observed urinary deterioration using IPSS in around 30% of patients with PF after urethral reconstruction (8, 12).

El-Assmy et al. used uroflowmetry in patients with urethral injury after surgical treatment of PF and found abnormal urinary flow due to urethral stenosis in only one case (20, 21). Raheem et al. observed similar results and only one of ten patients had abnormal flow (4). RGU is recommended when abnormalities are found in the IPSS questionnaire or uroflowmetry to identify possible urethral stricture or other complications. (8, 22-24). Short penile urethral stenosis can be treated with sequential dilatations (4, 21). Another complication is urethrocutaneous fistula. Usually patients experience deterioration in urinary function according to the IPSS questionnaire analysis and the diagnosis is confirmed through RGU. Small fistulas can be treated conservatively with a urethral

catheter for around 30 days (8). Some authors have suggested using grafting to interpose the suture to avoid fistulous trajectory formation. A subcutaneous abscess may occur in patients with a full urethral lesion who underwent end-to-end urethroplasty due to small extravasation of urine between the points, causing collection of urine, despite the use of the urethral catheter. This can be treated with percutaneous drainage and oral antibiotic therapy with a satisfactory outcome (8). Di Pierro et al. reported a case of urethral pseudodiverticulum after urethral injury in PF and management of the case conservatively with cystostomy for two months after surgery (22).

Although the treatment of urethral injury in PF is of interest to the urological community, we found in the literature review a number of quality case reports and small single institution case series, with few studies composed of larger series or providing details regarding follow-up and voiding function after surgery (Table-1).

**Table 1 – Findings of urethral injury in penile fracture and outcomes from selected series.**

Study	Total Pf	Confirmed Urethral Injury N (%)	Urethral Injury Cases Include On The Study	Urethral Bleeding	Partial/ Total Injury	Coital Etiology N	Preoperative Imaging Used	Treatment	Follow-Up N	Complications
Deiruche 2008	312	10 (3.2)	10	10	10/0	4	None	Primary urethroplasty	10	None
Ibrahim 2010	155	14 (9)	14	13	11/3	7	RGU was performed in three patients	Primary urethroplasty	12	One case of relative narrowing in the penile urethra
Raheem 2014	246	34 (13.8)	34	34	22/12	11	RGU was performed in all patients	Primary urethroplasty + Suprapubic catheter#	12+	One case of ring stricture in the anterior urethra
Barros 2018	175	27 (15.4)	13	10	9/4	13	None	Primary urethroplasty	13	One case of urethrocutaneous fistula and another of subcutaneous abscess

# = Suprapubic catheter insertion or not was determined by the surgeon's preference. + = Only in cases of complete urethral disruption.

## CONCLUSIONS

Penile fracture is an uncommon urological emergency, particularly in cases with urethral involvement. Urethral injury should be suspected in the presence of suggestive clinical signs, such as urethral bleeding, hematuria or urinary retention, and in cases with bilateral cavernosal rupture. Diagnosis is usually clinical and complementary diagnostic methods are not required. Urgent urethral reconstruction is mandatory and produces satisfactory results with low levels of complications.

## CONFLICT OF INTEREST

None declared.

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# Preoperative serum total cholesterol is a predictor of prognosis in patients with renal cell carcinoma: a meta-analysis of observational studies

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## ABSTRACT

**Purpose:** Several studies have demonstrated the strong correlation between the levels of preoperative serum total cholesterol (TC) and the survival of patients with surgically treated renal cell carcinoma (RCC). However, this association remains controversial. We performed a meta-analysis of published reports to evaluate the prognostic significance of the preoperative serum TC levels for patients with surgically treated RCC.

**Material and Methods:** The databases from MEDLINE (via PubMed), Embase, Web of Science and Cochrane Library were systematically searched to identify the eligible studies published before August 2019. Multivariate adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated through inverse variance by using random-effects models.

**Results:** Nine cohort studies comprising 15,609 patients were identified. Low preoperative serum TC levels were associated with poor cancer-specific survival (CSS; HR=0.98, 95% CI: 0.97-0.99; P=0.005; I<sup>2</sup>=74.2%) and progression-free survival (PFS; HR=0.69, 95% CI: 0.49-0.98; P=0.036; I<sup>2</sup>=80%) in patients with surgically treated RCC. However, no significant association was observed between low preoperative serum TC levels and shorter overall survival (HR=0.93, 95% CI: 0.87-1.00; P=0.057; I<sup>2</sup>=86.2%). Sensitivity analyses validated the reliability and rationality of the results.

**Conclusions:** Preoperative serum TC level is an independent poor prognostic factor for patients with surgically treated RCC, with lower levels associated with worse CSS and PFS. Hence, this parameter may provide additional guidance in the selection of therapeutic strategies to improve prognosis, considering that cholesterol is a broadly applied routine marker in clinical practice.

## ARTICLE INFO

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## INTRODUCTION

Renal cell carcinoma (RCC) has long been the third most common malignancy of the urinary tract and accounts for 2%-3% of adult malignant

tumours (1, 2). The incidence of RCC is increasing steadily worldwide, and a recent European study reported 115,000 new RCC cases and 31,000 cancer-related deaths (3, 4). Nephrectomy remains the standard treatment for clinically localised RCC,

but 10%-20% of cases may develop metastases (5, 6). The prognosis of advanced RCC after surgery remains poor despite the marked improvement in the survival outcomes of RCC after targeted therapy (7). Thus, appropriate predictors, especially serum biomarkers, are urgently needed to predict the prognosis of RCC.

Cholesterol is mainly synthesized by the liver, and malignant cells require excess cholesterol compared with normal cells (8). Serum high-density lipoprotein, including serum total cholesterol (TC), has been associated with the risk of breast cancer (9). Several clinical risk factors, such as body mass index and nutritional status, have also been considered as potential prognostic factors for RCC (10, 11). However, a comprehensive systematic review or meta-analysis of the association between levels of preoperative serum TC and survival outcomes of patients with surgically treated RCC has not been performed.

Few studies have directly suggested the association between preoperative serum TC levels with worse survival in patients with surgically treated RCC (12-14), but conflicting results have been reported (15). Comprehensive systematic review and meta-analysis are necessary to evaluate the prognostic value of preoperative serum TC levels in patients with surgically treated RCC. The results may be beneficial for treatment selection and postoperative monitoring.

## MATERIALS AND METHODS

Meta-analysis was conducted in accordance with the guidelines of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) (16) and Cochrane Collaboration criterion (17). Thus, ethical approval and patient consent were not required.

### Literature Search

We conducted a comprehensive literature search using the databases of MEDLINE (via PubMed), Embase, Web of Science and Cochrane Library to determine the relevant studies up to August 2019. The combination of medical subject headings (MeSH) and non-MeSH terms, such as 'renal cell carcinoma', 'renal carcinoma', 'renal cancer',

'kidney cancer' and 'cholesterol' were used, without region, publication type or language restrictions. We also manually searched the reference lists of all original studies recovered and those of previous review articles to identify additional relevant studies. The main search was completed by the senior author, and a professional librarian who directly assisted with the search and confirmed the search terms was recruited. Any discrepancy was resolved by consulting another investigator who was not involved in the initial procedure.

### Study Selection

Two independent investigators screened titles and abstracts to determine eligibility and comprehensively evaluated the full texts of the eligible records in case of uncertainty.

Eligible studies were included if they satisfied the following inclusion criteria: 1) pathologically confirmed diagnosis of RCC, 2) assessed serum TC levels prior to surgery (i.e. radical nephrectomy, cytoreductive nephrectomy and partial nephrectomy), 3) followed a prospective or retrospective study design and 4) directly reported the hazard ratio (HR) with corresponding 95% confidence intervals (CIs) or cases in which the data were available to recalculate risk estimates. If several trials pertained to an overlapping patient population, then the trial with the largest groups of patients was retained (where appropriate) to avoid duplication of information. Disagreements were resolved by consensus between the two investigators.

### Data Extraction and Quality Evaluation

The following data were extracted from all included studies into a standardised Excel (Microsoft Corporation) file: first author name, publication year, study design, research country, cancer site and stage, patient age, sample size and sex proportion, Fuhrman grade, follow-up duration, cut-off value, survival outcome types and HRs of the preoperative serum TC levels for survival outcomes and corresponding 95% CIs. Moreover, we contacted the corresponding authors for additional original data if the eligible records did not provide sufficient information. The accuracy of all extractions was checked by two independent

investigators. Disagreements were resolved via a discussion with a third investigator.

The quality of the observational studies was evaluated by two independent investigators using the Newcastle-Ottawa scale (NOS) (18), which consists of nine items to evaluate the representativeness of all included studies. The total score ranged from 0 to 9 and was categorized as follows: a score of 8-9 was considered as high quality, 6-7, moderate quality, 5 or lower, low quality. Disagreements were resolved through a discussion among the authors.

### Statistical Analysis

The prognostic value of different preoperative serum TC levels in patients with surgically treated RCC was assessed on the basis of HRs with corresponding 95% CIs via Stata version 15.0 (serial number: 10699393, StataCorp Wyb). An  $I^2$  test was conducted to evaluate the heterogeneity of the combined HRs, and significant heterogeneity of  $I^2 \geq 50\%$  warranted the use of random-effects models through inverse variance in line with the Cochrane Review guidelines (17). Otherwise, a fixed-effects model was applied. Moreover, pooled HR  $<1$  demonstrated a worse prognosis for patients with lower preoperative serum TC levels, whereas pooled HR  $>1$  suggested better prognosis when  $P < 0.05$ . The potential factors contributing to heterogeneity were analysed through subgroup analyses stratified by country and tumour type. Sensitivity analyses were conducted by omitting individual study at a time to assess the robustness of the results. Meta-regression analysis was performed to explore the possible sources of heterogeneity in several variables, and restricted maximum likelihood was applied in the analysis. However, the application of Egger (19) and Begg-Mazumdar (20) tests was limited due to the small number of studies evaluated.

## RESULTS

### Literature Search and Study Selection

A total of 497 publications were identified in line with the previously described comprehensive search strategy. Only 411 studies remained after

86 duplicates were removed. After screening the titles and abstracts of the 411 articles, only 12 articles were further assessed via full texts. Among these, three full-text articles were excluded because of the missing preoperative serum TC assessment in two studies and insufficient data for extraction in the other. Thus, nine retrospective cohort studies (12-15, 21-25) that comprised 15,609 patients were included in the meta-analysis. The flowchart of database search and study selection is depicted in Figure-1.

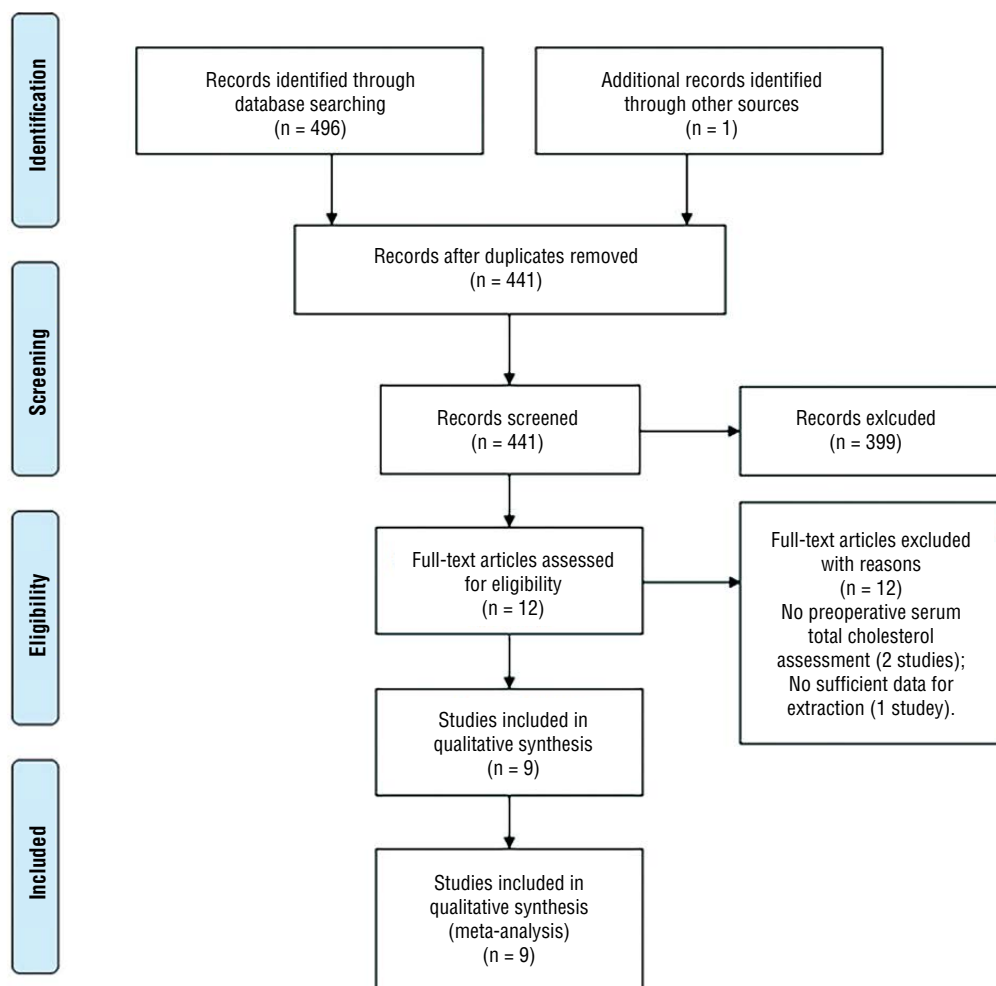
### Study Characteristics and Quality Evaluation

The basic clinical characteristics of the enrolled studies (12-15, 21-25) are provided in Table 1. For the study design, the nine included studies were retrospective cohorts and published from 2014 to 2019. The mean age ranged from 51.3 years to 64 years, and the mean follow-up duration ranged from 13 months to 81.1 months. The enrolled studies were performed in Korea ( $n=4$ ) (13, 14, 22, 23), China ( $n=2$ ) (12, 25), Austria ( $n=1$ ) (21), the United States ( $n=1$ ) (15) and Japan ( $n=1$ ) (24). Tumour types at diagnosis and main patient cancer characteristics (i.e. tumour stage and Fuhrman grade) varied. Few studies included only locally or metastatic RCC patients (14, 23), but most studies reported the inclusion of generalized RCC patients (12, 13, 15, 21, 22, 24, 25). Overall survival (OS) was reported in five studies (12-15, 23), cancer-specific survival (CSS) was assessed in six studies (14, 21-25), and progression-free survival (PFS) was evaluated in four studies (12, 14, 15, 25). Finally, HRs and corresponding 95% CIs were sufficiently provided by all included studies.

The qualities of the included studies were assessed on the basis of NOS. Six studies (12-14, 21, 22, 25) acquired 8 or 9 points and were considered as high-quality reports, and the other three studies (15, 23, 24) acquired 6 or 7 points and were considered of moderate quality. All these studies were included in the meta-analysis.

Five retrospective cohort studies comprising 9,929 patients reported the OS (12-15, 23). The results indicated no association between low preoperative serum TC levels and OS (HR=0.93, 95% CI: 0.87-1.00;  $P=0.057$ ;  $I^2=86.2\%$ ) (Figure 2). When stratified by different countries, the results

**Figure 1 - Flow diagram of literature searches according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.**



were inconsistent with the overall analysis except for the study performed in China (12) because of the limited number of studies evaluated. In the tumor type subgroup, low preoperative serum TC levels were significantly associated with worse OS of RCC, but not for patients with metastatic and localized RCC, except for the OS in the metastatic RCC group (Table-2) (23). In addition, the results of sensitivity analyses demonstrated the strength of our findings by omitting each single study in turn (Table-3). Finally, meta-regression analyses were conducted to further explore the significant heterogeneity among the studies, and the results indicated that none of the covariates (country,  $P=0.889$ , tumour type,  $P=0.969$ ) resulted in heterogeneity.

Preoperative serum TC levels and CSS and PFS in patients with surgically treated RCC.

Six retrospective cohort studies comprising 10,946 patients provided the CSS (14, 21-25). Low preoperative serum TC levels yielded a worse CSS (HR=0.98, 95% CI: 0.97-0.99;  $P=0.005$ ) in patients with surgically treated RCC, and significant heterogeneity was observed ( $I^2=74.2\%$ ). Therefore, a random-effects model was applied for the analysis (Figure 3). In the subgroup analysis according to different countries, low preoperative serum TC levels were associated with poor CSS in studies conducted in Austria (21) and China (25), whereas no significant association was observed in studies conducted in Korea (14, 22, 23) and Japan (24).

**Table 1 - Characteristics of the included studies.**

First author year	Study design	Country	Tumor type	Sample size (M/F)	Mean age of patients (range)	TNM stage (I/II/III/IV)	Fuhrman grade (I/II/III/IV)	Follow-up (months)	Survival analysis	Cut-off value	Multivariate analysis
de Martino M (21) 2015	Retrospective (2002-2012)	Austria	RCC	559/308	64 (54-72)	T: 503/364 (I-II/III-IV) N: 835/32 (NO/N+) M: 750/117 (MO/M1)	650/217 (I-II/III-IV)	Median 52	CSS	195mg/dL	Yes
Guo S (12) 2016	Retrospective (2000-2012)	China	RCC	526/260	51.3	T: 544/132/83/27 (I/II/III/IV) N: 729/57 (NO/N1) M: 755/31 (MO/M1)	198/278/67/8/235 (unkown)	Median 81.1	OS/PFS	200mg/dL	Yes
Haddad AQ (15) 2015	Retrospective (2000-2012)	United States	RCC	291/217	55 (20-87)	T: 300/197 (I-II/III-IV)	NR	Median 25	OS/PFS	161.5mg/dL	Yes
Jeong HC (13) 2019	Retrospective (1988-2015)	Korea	nmRCC	2.368/1.001	57	T: 2755/614 (I-II/III-IV)	1616/1753 (I-II/III-IV)	Median 38.8	OS	163mg/dL	Yes
Kang HW (22) 2018	Retrospective (1999-2011)	Korea	RCC	2.205/850	55.8	T: 2440/344 (I-II/III-IV)	1547/1468 (I-II/III-IV)	Median 37	CSS	156mg/dL	Yes
Lee H w(1)(14) 2017	Retrospective (1999-2016)	Korea	IRCC	3.515/1.507	56.9	T: 4029/445/527/21 (I/II/III/IV)	2681/2341 (I-II/III-IV)	Median 55	OS/CSS/PFS	161mg/dL	Yes
Lee H (2)(23) 2017	Retrospective (NR)	Korea	mRCC	185/59	59	T: 60/36/117/31 (I/II/III/IV)	34/210 (I-II/III-IV)	Median 13	OS/CSS	170mg/dL	Yes
Ohno Y (24) 2014	Retrospective (1990-2009)	Japan	CCRCC	273/91	60	T: 259/35/66/4 (I/II/III/IV)	278/86 (I-II/III-IV)	Median 71	CSS	150mg/dL	Yes
Peng D (25) 2017	Retrospective (NR)	China	RCC	952/408	55	T: 1015/113/225/7 (I/II/III/IV)	374/738/237/11	Median 67	CSS/PFS	148mg/dL	Yes

Regarding the tumour type, significant association was observed in patients with localized RCC, but negative results were found in those with RCC, metastatic RCC, and clear-cell RCC (Table-2). The sensitivity analyses indicated that the stability of results exhibited no significant change after each single study was deleted individually (Table-3). The meta-regression analyses revealed that none of the covariates (country, P=0.908, tumor type, P=0.698) resulted in significant heterogeneity among the included studies.

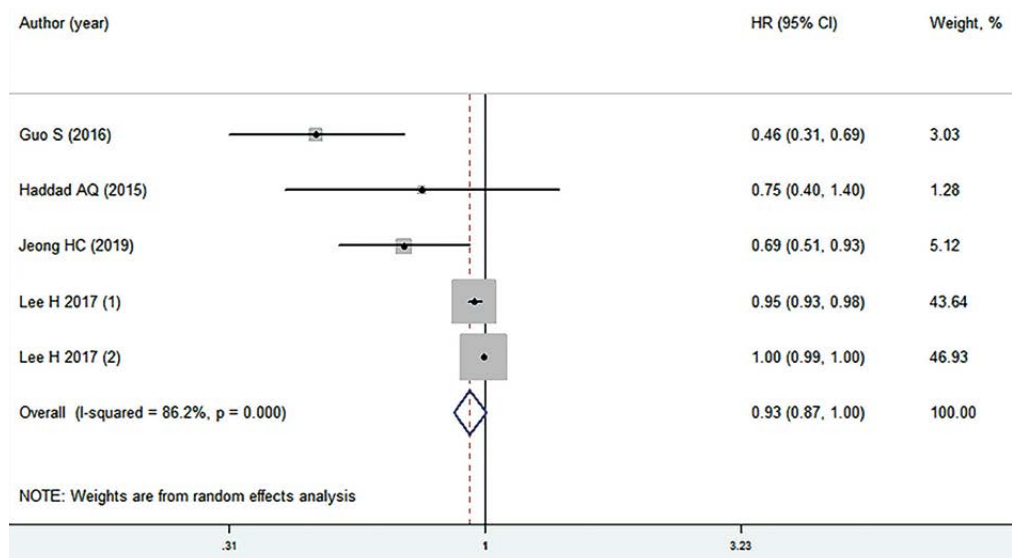
In the four studies (12, 14, 15, 25) involving 7.676 patients, low preoperative serum TC le-

vels were significantly associated with shorter PFS (HR=0.69, 95% CI: 0.49-0.98; P=0.036, I<sup>2</sup>=80%) (Figure-4). Considering that the number of eligible studies that assessed PFS was relatively small, we did not perform subgroup analysis for PFS.

## DISCUSSION

### Main findings

The meta-analysis included nine retrospective cohort studies that associated preoperative serum TC levels with survival outcomes in patients with surgically treated RCC. The results indicated

**Figure 2 - Preoperative serum TC levels and OS in patients with surgically treated RCC.**

**TC** = total cholesterol; **OS** = overall survival; **CI** = confidence interval; **HR** = hazard ratio

**Note:** individual studies are represented by a black square and a horizontal line, which corresponds to the point estimate and 95% confidence interval of the odds ratio. The size of the black square reflects the weight of the study in the meta-analysis. The solid vertical line corresponds to 'no effect' of treatment—a hazard ratio of 1. The diamond at the bottom and dotted line represent the combined or pooled hazard ratio of all five trials with its 95% confidence interval.

that low preoperative serum TC levels were significantly associated with worse CSS and PFS, whereas no significant difference was observed in the OS for patients with surgically treated RCC. For the subgroup analysis stratified by country and tumour type, the results were inconsistent with the overall analysis because of the limited number of studies evaluated. Nonetheless, sensitivity analyses indicated that the robustness of the results had no significant change after omitting each single study. Thus, the rationality and reliability of our analysis were validated. Finally, the meta-regression could not identify potential factors that might have substantially affected the heterogeneity between studies.

Most of the enrolled studies generally suggested an increased risk of shortened OS, CSS and PFS in patients with surgically treated RCC, whereas two studies yielded conflicting results (15, 23). Haddad AQ et al. (15) performed a retrospective cohort study comprising 508 patients with surgically treated RCC in the United States. The results showed no asso-

ciation between preoperative serum TC levels and OS or PFS. Lee H et al. (23) demonstrated that a low preoperative serum TC level is not an independent poor prognostic factor for patients with surgically treated RCC, particularly for OS and CSS. Moreover, our results revealed that low preoperative serum TC levels yielded a worse CSS from six retrospective cohort studies, whereas no significant association was observed in three of the studies. A HR of 0.98 and  $p=0.005$  have certain clinical utility, although the HR is close to 1. For instance, Ohno et al. (24) analyzed 364 subjects with clear cell RCC patients and concluded that low preoperative serum TC levels was associated with worse CSS, although the findings of their multivariate analysis were not statistically significant due to a limited number of cases. Hence, it is necessary to expand the sample size for more statistical power in the future study. Of note, when these studies were discarded from the meta-analysis, the results showed no significant changes, thus validating the reliability of our results.

**Table 2 - Results of subgroup analyses.**

OS	Studies, N	Participants, N	HR (95% CI)	p value	p of heterogeneity	I <sup>2</sup> (%)
	5	9.929	0.93 (0.87-1.00)	0.057	<0.001	86.2
<b>Country</b>						
China	1	786	0.46 (0.31-0.69)	<0.001	NA	NA
United States	1	508	0.75 (0.40-1.40)	0.368	NA	NA
Korea	3	8.635	0.97 (0.92-1.02)	0.187	0.001	85.8
<b>Tumor type</b>						
RCC	2	1.294	0.55 (0.35-0.88)	0.012	0.197	39.8
nmRCC	1	3.369	0.69 (0.51-0.93)	0.015	NA	NA
IRCC	1	5.022	0.95 (0.92-0.98)	0.001	NA	NA
mRCC	1	244	1.00 (0.99-1.01)	0.076	NA	NA
<b>CSS</b>						
	6	10.946	0.98 (0.97-0.99)	0.005	0.002	74.2
<b>Country</b>						
Austria	1	867	0.94 (0.91-0.98)	0.001	NA	NA
Korea	3	8.321	0.99 (0.99-1.00)	0.014	0.144	48.4
Japan	1	364	0.99 (0.98-1.00)	0.009	NA	NA
China	1	1.360	0.59 (0.40-0.88)	0.009	NA	NA
<b>Tumor type</b>						
RCC	3	5.282	0.95 (0.89-1.02)	0.181	0.001	86.6
IRCC	1	5.022	0.96 (0.92-0.99)	0.018	NA	NA
mRCC	1	244	0.99 (0.99-1.00)	0.023	NA	NA
CCRCC	1	364	0.99 (0.98-1.00)	0.009	NA	NA

**CCRCC** = clear cell renal cell carcinoma; **CI** = confidence interval; **CSS** = cancer-specific survival; **HR** = hazard ratio; **IRCC** = localised renal cell carcinoma; **mRCC** = metastatic renal cell carcinoma; **nmRCC** = non-metastatic renal cell carcinoma; **NA** = not available; **OS** = overall survival; **RCC** = renal cell carcinoma

### Implications for clinical practice

Cholesterol is a crucial part of the human cell membrane. This molecule is an important substitute for energy production and controlled by the feedback adjustment system and maintains homeostasis (26). A high serum TC level has been recently considered a poor prognostic predictor

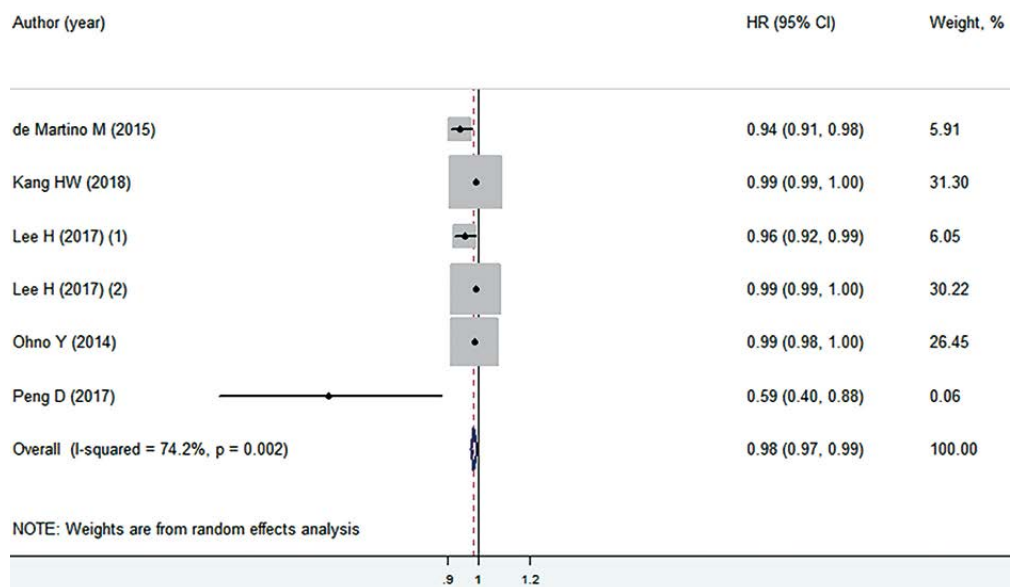
of cardiovascular disease and stroke. Thus, controlling the cholesterol level is an important issue for most clinicians. RCC is a metabolic disease with many risk factors, such as obesity, diabetes mellitus and nutritional status, which are closely associated with high risk of RCC or its prognosis (27-30). Histologically, a high level of cholesterol

**Table 3 - Results of sensitivity analyses.**

Study omitted	HR	95% CI	
<b>OS</b>			
Guo S 2016 (12)	0.96	0.91	1.02
Haddad AQ 2015 (15)	0.93	0.87	1.01
Jeong HC 2019 (13)	0.95	0.89	1.02
Lee H 2017 (1) (14)	0.72	0.49	1.05
Lee H 2017 (2) (23)	0.71	0.50	1.01
Combined	0.93	0.87	1.00
<b>CSS</b>			
de Martino M 2015 (21)	0.99	0.98	1.00
Kang HW 2018 (22)	0.98	0.96	1.00
Lee H 2017 (1) (14)	0.99	0.98	1.00
Lee H 2017 (2) (23)	0.98	0.96	0.99
Ohno Y 2014 (24)	0.98	0.97	1.00
Peng D 2017 (25)	0.99	0.98	1.00
Combined	0.98	0.97	0.99

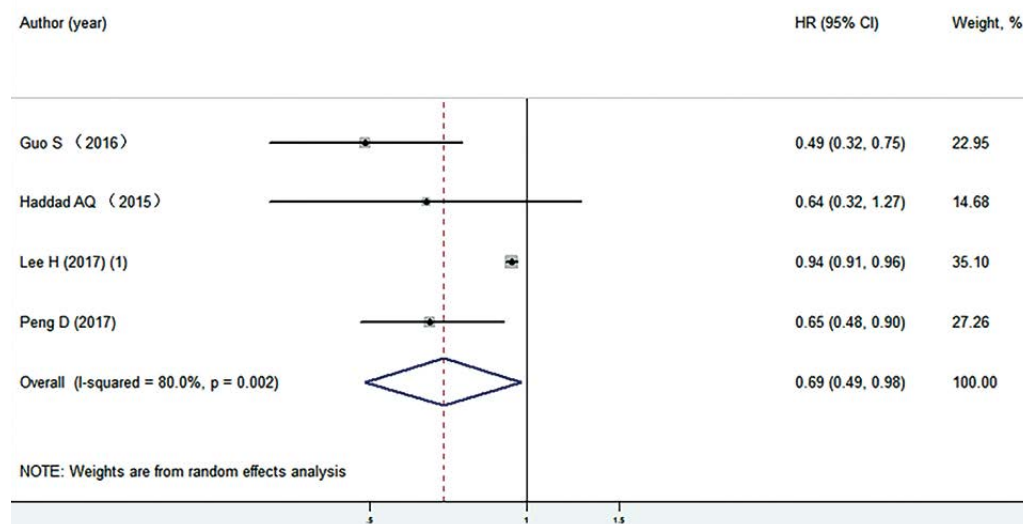
CI = confidence interval; CSS = cancer-specific survival; HR = hazard ratio; OS = overall survival

**Figure 3 - Preoperative serum TC levels and CSS in patients with surgically treated RCC.**



TC = total cholesterol; OS = overall survival; CI = confidence interval; HR = hazard ratio

**Note:** individual studies are represented by a black square and a horizontal line, which corresponds to the point estimate and 95% confidence interval of the odds ratio. The size of the black square reflects the weight of the study in the meta-analysis. The solid vertical line corresponds to 'no effect' of treatment-an hazard ratio of 1. The diamond at the bottom and dotted line represent the combined or pooled hazard ratio of all six trials with its 95% confidence interval.

**Figure 4 - Preoperative serum TC levels and PFS in patients with surgically treated RCC.**

**TC** = total cholesterol; **OS** = overall survival; **CI** = confidence interval; **HR** = hazard ratio

**Note:** individual studies are represented by a black square and a horizontal line, which corresponds to the point estimate and 95% confidence interval of the odds ratio. The size of the black square reflects the weight of the study in the meta-analysis. The solid vertical line corresponds to 'no effect' of treatment—an hazard ratio of 1. The diamond at the bottom and dotted line represent the combined or pooled hazard ratio of all four trials with its 95% confidence interval.

and glycogen accumulates in the clear-cell RCC (31). Saito K et al. studied 356 lipids and observed a significant difference in more than 70% of lipid levels. They distinguished the lipid profiles of RCC tissue from the clear-cell RCC tissue with normal parenchymal tissue (32). In addition, the lower serum TC levels in patients with advanced RCC may have been caused by increased storage of cholesterol in the cancer cells, and its application in the biosynthesis of new membrane has been suggested (33). However, whether serum TC can be used as a substitute for tumour cholesterol and whether these serum TC levels are pre-existing or tumour-causing remain unclear. Future studies should focus on the aforementioned complex relationship and address these interesting issues. The assessment of preoperative serum TC levels may provide a meaningful adjunct in clinical practice because cholesterol is a broadly applied routine marker. Our findings will help clinicians identify patients who suffer from RCC, undergo surgery and have a high risk of poor postoperative outcomes. Our findings will also aid in determining personalised therapeutic strategies after RCC surgery.

### Strengths and limitations

To the best of our knowledge, our meta-analysis is the first to deeply investigate the association between preoperative serum TC levels and survival outcomes in patients with surgically treated RCC in accordance with the PRISMA guideline. Moreover, multivariate-adjusted risk estimates were applied to minimize other relevant confounding factors that might affect the overall results. Finally, the results of sensitivity analyses and meta-regression validated the reliability and rationality of our meta-analysis.

This study had several limitations that should be considered. Firstly, only nine studies comprising 15,609 patients were included, and the sample size was relatively small. Secondly, the heterogeneity between the studies might affect overall results, although the meta-regression could not identify the potential factors. Thirdly, all included studies applied a retrospective design with disadvantages on potentially missing data and risk of bias. Finally, the included studies had diverse cut-off values which may affect the utility of our results. A unified cut-off value of preoperative se-

rum TC should be established. Further investigations regarding such an association in large-scale studies with greater statistical power are needed.

## CONCLUSIONS

In summary, preoperative serum TC levels is an independent prognostic predictor for patients with surgically treated RCC. Lower levels of this parameter were associated with worse CSS and PFS. Hence, the assessment of preoperative serum TC levels may be beneficial to stratify the risk and individualize treatment for patients with surgically treated RCC to improve prognosis. Further large-scale investigations on such association with greater statistical power are still required to confirm our findings.

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## CONFLICT OF INTEREST

None declared.

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# Bladder preservation in muscle-invasive bladder cancer: a comprehensive review

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## ABSTRACT

**Background:** Standard management of muscle-invasive bladder cancer involves radical cystectomy with pelvic lymph node dissection. However, patients may be ineligible for surgery or may wish to avoid the morbidity of cystectomy due to quality of life concerns. Bladder preservation therapies have emerged as alternatives treatment options that can provide comparable oncologic outcomes while maintaining patients' quality of life.

**Objective:** To review bladder preservation therapies, patient selection criteria, and functional and oncologic outcomes for BPT in muscle-invasive bladder cancer.

**Materials and Methods:** We conducted a comprehensive literature review of bladder preservation therapies in Pubmed and Embase.

**Discussion:** The ideal patient for BPT has low-volume T2 disease, absence of CIS, absence of hydronephrosis, and a maximal TURBT with regular surveillance. Technological advancements involving cancer staging, TURBT technique, and chemotherapy and radiation therapy regimens have improved BPT outcomes, with oncologic outcomes now comparable to those of radical cystectomy. Advancements in BPT also includes a heightened focus on improving quality of life for patients undergoing bladder preservation. Preservation strategies with most evidence for use include trimodality therapy and partial cystectomy with pelvic lymph node dissection.

**Conclusions:** This review highlights the breadth of strategies that aim to preserve a patient's bladder while still optimizing local tumor control and overall survival. Future areas for innovation include the use of predictive biomarkers and implementation of immunotherapy, moving the field towards patient-tailored care.

## ARTICLE INFO

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## INTRODUCTION

Bladder cancer is the ninth most common cancer worldwide, and the second most common genitourinary malignancy (1). At presentation,

approximately 70% of bladder cancer cases are non-muscle invasive and 30% are muscle-invasive (2). Whereas most first-line treatments for non-muscle invasive bladder cancer (NMIBC) are

bladder-conserving, the typical management of muscle-invasive bladder cancer (MIBC) includes bladder removal with bilateral pelvic lymph node dissection. The addition of neoadjuvant chemotherapy to MIBC treatment results in a 5% absolute improvement in survival at 5 years by reducing micro-metastatic disease at the time of surgery (3), with many regimens including cisplatin-based chemotherapy (e.g. cisplatin) (4, 5).

Although radical cystectomy with neoadjuvant chemotherapy is considered standard treatment for MIBC, the associated morbidity and mortality remain significant concerns (6). The morbidity associated with cystectomy has spurred a growing interest in bladder conserving treatments, such as trimodality therapy (TMT) and partial cystectomy with neoadjuvant chemotherapy. Pooled analyses of prospective cohort studies demonstrated a 5-year overall survival (OS) of 57% and 5-year disease-specific survival (DSS) of 71% following trimodality therapy (7). Similarly, a meta-analysis published in 2015 demonstrated a 5-year OS of 56% with TMT, comparable to the OS seen following RC (8). TMT is also associated with higher quality of life scores, including better social, physical, sexual, and cognitive functioning compared to patients who underwent RC (9). With the growing body of research showing similar efficacy of TMT in properly selected patients, we identify the need to highlight TMT strategies and associated outcomes.

We present a comprehensive review of bladder preservation therapies (BPT) for MIBC, focusing on cT2-T4 N0M0 MIBC unless otherwise noted. Our objective is to review patient selection as well as oncologic and functional outcomes with BPT for MIBC.

## MATERIALS AND METHODS

We conducted a comprehensive search of PubMed and Embase databases on September 12, 2019. Our search included the following United States National Library of Medicine Medical Subject Headings (MeSH) terms: muscle-invasive bladder cancer, bladder preservation, bladder preserving treatments, and organ sparing treatments. We limited our search to articles written in En-

glish and excluded conference abstracts. We complemented this search by identifying additional articles referenced in the full-text review stage.

## RESULTS

### Patient Selection Criteria

Patients of two distinct categories have historically undertaken bladder preservation therapy: those who are medically inoperable (unfit for surgery) and those with organ-confined disease who have a strong preference to avoid radical surgery.

The National Comprehensive Cancer Network (NCCN) recommends bladder preservation over RC be reserved for patients whose tumors are small and solitary, lack lymph node metastases, lack carcinoma *in situ* (CIS), are without tumor-related hydronephrosis, and have favorable baseline bladder function (10). There is no absolute size cut-off for tumors amenable to bladder preservation, but it is generally agreed that tumors larger than 5 or 6 cm preclude bladder preservation. Patients with hydronephrosis have lower rates of complete response and 5-year DSS, as well as increased rates of salvage cystectomy, and thus are generally not candidates for bladder preservation (11). Other factors associated with complete response and successful BPT include low-volume T2 lesions, lesions amenable to complete TUR, and normal performance status (Table-1) (12-14). Completeness of TUR, both microscopically and macroscopically, is associated with improved patient outcomes (10), discussed in subsequent sections of this review.

**Table 1 - Bladder Preservation Patient Selection Criteria.**

Disease-related Factors	Patient-related Factors
Small, low-volume solitary tumors	Favorable baseline bladder function
T2 disease	
No CIS	
No hydronephrosis	
No lymph nodes metastases	Normal or favorable performance status
Tumor amenable to complete TUR	

With limited selection criteria outlined above, physicians may rely on clinical judgment for patient treatment selection, which can result in utilization disparities between RC and BPT. Analysis of Surveillance, Epidemiology, and End Results (SEER)- Medicare data of patients with cT2 MIBC found that older age at diagnosis and higher comorbidity were associated with decreased utilization of RC (15). Chronological age alone, however, should not preclude a patient from definitive therapy with RC or push a patient towards BPT, though it is often used as a proxy for fitness for surgery given increasing comorbidities with age. To better elucidate the prevalence of comorbidities in an elderly MIBC population, an evaluation of SEER data found that patients above the age of 75 with MIBC were more likely to have prior cancer diagnoses, cardiac disease, chronic anemia, and worse American Society of Anesthesiologists (ASA) Physical Status Classification, as compared to patients less than 75 years of age (16). As the number of comorbidities increases, so does the surgical risk. Thus, using comorbidities and performance status to predict outcomes instead of over-relying on chronological age allows clinicians and patients to make more informed treatment plan decisions.

There has been a surge in research investigating the role of biomarkers to predict a patient's response to treatment, however, to date, no biomarker has been incorporated into routine clinical decision making outside of clinical trials. Most studies analyzing associations of predictive biomarkers with clinical response in bladder preservation consist of retrospective reviews; thus, conclusions are limited in nature. Biomarkers have been categorized into apoptosis-related, cell proliferation-related, receptor tyrosine kinases, DNA damage response mediated, hypoxia markers, and by molecular sub-types (17). Delving into each of these categories is beyond the scope of this review, but we refer readers to two reviews covering the wide breadth of studied biomarkers in bladder preservation (17, 18). Incorporation of predictive biomarkers is likely a future direction for patient-tailored treatment of bladder cancer.

## SINGLE MODALITY THERAPIES

Experts generally agree that single modality therapies such as radical TUR, chemotherapy, and radiotherapy are less effective alone than in combination for the treatment of MIBC (10). However, some historical series demonstrate efficacy in highly selected patients.

### Maximal Transurethral Resection Alone

TURBT functions as both a diagnostic and therapeutic procedure in the management of bladder cancer. Maximal TURBT, defined as macroscopically complete resection of the bladder tumor when safely possible, is critical to successful treatment in mono- and multi-modality regimens. Guidelines for both NMIBC and MIBC emphasize conducting a maximal TURBT, with resection down to the detrusor muscle when feasible (4, 10, 19). Depending on the size and location of the tumor, however, maximal TUR may not be possible and requires special considerations (20).

Cohort studies of patients receiving TUR alone for T2 (B1 or B2) disease from the 1950s-1970s demonstrated inferior overall survival rates compared to RC, ranging from 31-38% at 5 years (21-23). Later studies documenting the use of TUR monotherapy showed efficacy in cohorts with very specific patient selection, with some studies revealing comparable 5-year survival rates to RC. Solsona and colleagues prospectively followed 133 patients with invasive bladder cancer who were treated with radical TUR and had negative biopsies of the tumor bed; 5- and 10-year cancer-specific survival rates were 80.5% and 74.5%, with bladder preservation rates of 82.7% and 79.6% at 5 and 10 years respectively (24, 25). After 15 years of follow-up in the same cohort, OS was found to be 73.7% at 5 years, 39.8% at 10 years, and 24.8% at 15 years. Although repeat TUR was not systematically performed, only 9 patients (6.7%) had their cancers under-staged, validating the study's selection criteria (26).

Similarly, Herr followed 99 patients treated with TUR alone for MIBC and 52 who underwent RC; 76% survived by 10 years of follow-up in the TUR group compared to 71% in the RC group (27). He found that mortality from a new invasive tu-

mor during follow-up was 31% for patients restaged as having persistent T1 disease compared with 11% for patients without residual cancer (T0) after restaging TUR (27). More recently, a retrospective review of 327 patients with MIBC treated at MD Anderson demonstrated that only 11% of patients qualified for bladder preservation with TUR. Qualification criteria included patients with no residual tumor on re-resection, normal exam under anesthesia, and absence of upper urinary tract pathology (28). BPT with TUR alone is thus appropriate for only a small proportion of patients with MIBC. Risk of recurrence following TUR monotherapy is shown to be anywhere from 38-56%, emphasizing the need for careful patient selection and regular cystoscopic follow-up (27, 28). Even with highly specific selection criteria, a high rate of recurrence leads to more salvage cystectomies, with a salvage cystectomy rate of 30% seen in the MD Anderson series (28).

If a patient receives TUR alone, NCCN guidelines recommend maximal repeat TUR within 4 weeks to ensure absence of residual disease. If negative, patients should be monitored with repeat cystoscopy and cytology every 3 months; if relapse occurs, the stage at re-resection determines subsequent management (10).

### Radiation Monotherapy

Radiation as a monotherapy for bladder preservation in MIBC was historically undertaken in patients unfit for RC, creating a barrier to comparison with RC outcomes. Fossa and colleagues retrospectively reviewed 263 patients who received RC and 271 patients deemed unfit or unwilling to undergo RC who received high-dose XRT. Five-year OS for the RC group was 48% compared to 22% in the RT group, noting that for each T stage group, survival rate for RC patients was twice that of XRT patients (29). A large retrospective series of 917 patients with transitional cell carcinoma of the bladder (T1-T4) undergoing XRT in the UK showed 5-year OS ranging from 11.6% (ages >79) to 50.4% (ages <60). Chung et al. stratified OS by stage, finding that OS steadily decreased with increasing stage: 48% T2a, 37% T2b, 21% T3b, 13% T4a, and 8% T4b at 5 years (30). Other series have shown similar rates of OS following RT monothe-

rapy, ranging from 22-40%, and notably all lower than those seen in RC series (30-35). Radiation monotherapy has also been studied as arms of overarching randomized trials. In these trials, radiation monotherapy shows comparable but lower OS compared to RC + radiation or TMT arms, and still remains a reasonable option for patients with comorbidities precluding treatment with modalities such as radical surgery or chemotherapy (36-38).

One study aimed to identify whether targeting radiation to the tumor-bearing region alone, as opposed to conventional whole-bladder radiation, could improve local disease control and thus overall survival while also limiting toxicity. The whole bladder radiation control arm had a 5-year OS rate of 61%, compared to 60% and 51% in the two partial bladder XRT trial arms ( $p=0.81$ ) (39). Kang et al. similarly found equivalent disease-free and OS in a smaller series comparing whole-bladder versus partial-bladder XRT, but they noted that hypofractionation with partial-bladder RT resulted in one-third reduction in both treatment duration and cost (40). In this study, patients receiving whole-bladder radiation had more acute and late toxicities than the partial-bladder group, although this series did not assess for statistical significance of this difference perhaps given small sample size. Dose escalation from the standard 64-66 Gy has not been found to improve survival and may impose a higher risk of toxicity (41).

Overall survival after XRT differs with location of treatment delivery. One study demonstrated that the composite National Comprehensive Cancer Network (NCCN) guidelines compliance rate of receiving TURBT before XRT, use of concurrent chemotherapy, and total dose of XRT was 48.0% at high-volume RT facilities versus 41.0% for low volume facilities ( $p<0.0001$ ), with a statistically significant difference in 5-year OS rates (high-volume facilities 24.8%, low volume facilities 20.7%,  $p=0.001$ ). Among patients whose treatment was compliant with all 3 NCCN parameters, OS remained statistically significantly higher at facilities with high XRT volumes ( $p=0.029$ ). Accounting for unmeasured socioeconomic confounders is a challenge but these studies raise questions regarding health disparities, as African American pa-

tients, rural community-dwelling patients, lower median household incomes, and lower education levels were more likely treated at low-volume RT facilities (42).

### Chemotherapy Monotherapy

There is a limited role for chemotherapy (CT) as the sole agent in the treatment of MIBC. As part of the standard non-preservation therapy for bladder cancer, chemotherapy is typically used in the neoadjuvant setting with RC. When combined with RC and PLND, cisplatin-based chemotherapy results in improved survival (5) with the greatest benefit seen in patients who achieve complete pathological response following NAC (43). There may also be a role for adjuvant chemotherapy following RC (10, 19).

Recently, presence of certain DNA damage response (DDR) gene mutations, associated with sensitivity to cisplatin-based chemotherapy, has spurred investigations into their use as predictive biomarkers of response to chemotherapy in bladder preservation (44). An Alliance for Clinical Trials in Oncology phase II trial at Memorial Sloan Kettering is currently studying whether patients with DDR mutations can forgo RC and PLND and be managed with cisplatin-based chemotherapy alone (45). Chemotherapy in the setting of BPT will be discussed in subsequent sections of this review.

## MULTIMODALITY THERAPIES

Modern multimodal bladder preservation typically involves some variation of maximal TUR with chemoradiation therapy. This is followed by regular cystoscopic evaluation to determine response to therapy, with prompt salvage RC should the patient not respond or have a muscle invasive recurrence.

### TUR + Chemotherapy

The addition of chemotherapy to maximal TUR was an attempt to improve local tumor control and reduce the risk of recurrence that is seen with TUR monotherapy. Early series examining TUR with chemotherapy were small and heterogeneous. One retrospective review examined 50

patients treated with maximal TUR followed by 2 to 6 cycles of adjuvant cisplatin-methotrexate (per the EORTC protocol 30851). Thirty-eight (76%) patients remained tumor-free at a median follow-up of 47 months. Ten patients (20%) relapsed with either Ta, T1 + CIS, or CIS at a median follow-up of 15.6 months, with 60% of these recurrences located at the original tumor site. Overall, the bladder was preserved in 37 (74%) of patients (46).

In a phase II nonrandomized trial, 75 patients with positive biopsies of apparently healthy tumor bed during TURBT subsequently received three cycles of cisplatin-based chemotherapy while the control group of 71 received RC. The bladder-sparing group had 5- and 10-year CSS rates of 64.5% and 59.8%, which were not statistically significantly different from the RC arm ( $p=0.544$ ). Among 51 patients who initially underwent BPT, 40 (53%) achieved a complete response to therapy, 16 (31.3%) developed recurrence, and 15 (29.3%) developed progression. Of the patients who achieved any clinical response (partial or complete), 56% developed progression or recurrence, resulting in a further 45% requiring RC (47). This series demonstrates that many patients' undergoing TURBT and chemotherapy will subsequently progress or recur, requiring escalation of therapy with salvage RC.

A systematic review that encompassed 18 publications and 518 patients who received systemic chemotherapy plus TURBT found that OS ranged from 20% to 87.5%, with a median follow-up range of 4 to 120 months. The 5-year OS rate for all patients in this review was 72% (95% CI 64%-82%). However, selection criteria across studies varied, with some patients selected due to lack of fitness for RC and others who elected for BPT (48).

### Trimodal Therapy

Trimodal therapy typically consists of maximal TURBT (as safely as possible) followed by chemoradiotherapy. Acceptance and implementation of TMT by the urologic community has been with caution due to concerns of cancer recurrence and need for salvage RC. This is likely perpetuated by the lack of randomized controlled trials comparing TMT to RC, exemplified by the Selective Bladder Preservation Against Radical

Excision (SPARE) trial ending early due to a failure to accrue patients (49). However, numerous retrospective and prospective studies have been conducted that contribute to a growing evidence base (prospective studies summarized in Table-2).

Regarding the delivery of TMT, chemoradiotherapy can be given as a single course of chemoradiation therapy or as a split-course. A split-course entails induction chemoradiation therapy followed by an interval cystoscopy and biopsy and, if a satisfactory response, consolidative chemoradiation therapy. In cases of persistent or recurrent MIBC, salvage cystectomy (with or without perioperative chemotherapy) is recommended, unless the patient has medical contraindications to radical surgery. Most series define complete response as the absence of: visible tumor, biopsy-proven bladder cancer, and tumor cells on urine cytology.

Radiotherapy administered in TMT has been studied in various approaches. One approach entails hypofractionation, in which a total dose of radiation is divided into larger fractions when given over a shorter time period. Hypofractionation protocols include variations in the total dose (Gy), the number of fractions, and the number of days radiation is administered. A prospective phase II trial evaluated the use of concurrent weekly gemcitabine with daily radiation for a total of 52.5 Gy in 20 fractions (50). Another approach involves intensity modulated radiation therapy (IMRT), in which the radiation delivered is manipulated to conform to the shape of a tumor in order to reduce toxicity and maximize the therapeutic ratio (51). A retrospective analysis of 2527 patients in the National Cancer Data Base who received XRT or CRT found that those who received IMRT had improved OS on multivariate analysis compared to those who did not (HR 0.85, 95% CI 0.75-0.97,  $p=0.02$ ) (51).

With respect to overall performance, TMT has produced comparable oncologic outcomes to RC in appropriately selected patients (8, 52, 53). A systematic review conducted in 2014 found 5-year CSS and OS with TMT to range from 50-82% and 26-74% respectively, with salvage RC rates of 25-30% (53). The similarity in outcomes is likely enabled by promptness of salvage cystectomy when TMT fails. An important distinction when evalua-

ting TMT series is whether patients included in the studies were cystectomy candidates (e.g. medically operable) or not.

A phase II Southwest Oncology Group trial (SWOG 9312) included patients who had surgically unresectable tumors (34%), were medically or surgically unfit (21%), or refused cystectomy (45%). Of note, only some patients received maximal TURBT (39%), with most having only a tumor biopsy conducted during resection (61%). Patients received 4 days of 5-fluorouracil with cisplatin on day 1; this was repeated every 28 days for two total courses during RT as well as two additional courses 4 to 8 weeks after RT was completed. Patients received RT 5 days a week for a total daily dose of 150-200Gy; 50Gy was delivered to the bladder, the prostate and prostatic urethra in men, the urethra in women, and external and internal iliac nodes. An additional 10Gy was delivered to the entire bladder and gross tumor volume. Of the 53 total patients, 26 (49%) achieved a complete response. Five-year OS was 32% for the entire cohort, and when stratified by reason for undergoing TMT, was 45%, 31%, and 20% for RC refusal, medically unfit, and surgically unfit patients, respectively. Patients with maximal TURBT had 38% 5-year progression-free survival, compared to only 14% for patients who only received biopsies during resection (54). This demonstrates the utility of maximal TURBT, when safely possible, and the importance of maximal TURBT in considering the prognosis of a patient undergoing TMT.

A multicenter prospective study (GETUG 97-015) stratified 53 patients into two groups: surgical candidates ( $n=38$ ) versus those who had a medical contraindication for surgery or who refused surgery ( $n=15$ ). Maximal TURBT was attempted for all patients but deemed complete for only 33 (66%) patients. All patients received RT with a 45Gy dose in 25 fractions over a period of 4weeks. Potentially operable patients underwent TUR after XRT ended, with salvage cystectomy if persistent tumor was present. Patients unfit for surgery, as well as patients without residual tumor on TUR, received an XRT boost of 18Gy to the bladder with concomitant cisplatin and 5-fluorouracil during weeks 1, 4, and 7 of XRT. Patients who were initially identified as surgical candidates had

**Table 2 - Prospective trimodal therapy studies.**

Series	Study Type & Trial Number	Patient Characteristics	Sample Size	Follow-up	Outcomes	Findings
Hussain et al. 2001 (54)	Prospective, single institution SWOG 9312	Unresectable tumors (34%)  Medically unfit for surgery (21%)  Refused cystectomy (45%)	N = 56	Not specified	Complete response N= 26 (49%)  5-year OS 32% entire cohort, 45% (RC refusal), 31% (medically unfit), 20% (surgically unfit)	Patients with best survival were ones who were fit for surgery but elected for TMT.  Patients who received maximal TUR, as opposed to just biopsies, had better progression free survival
Kaufman et al. 2009 (13)	Prospective, multi-institution RTOG 99-06	Medically operable	N = 80	Median: 49.4 mo	CR = 81%  Of the CR, 18 (28%) had local recurrence 5-year OS: 56%, Acute toxicity: Grade 3 (25%), grade 4 (1%)	Addition of paclitaxel to induction and consolidation resulted in greater cancer control, but more grade 3-4 toxicity.
Lagrange et al. 2011 (55)	Prospective, multi-institution GETUG 97-015	Medically operable (n=38); Medically unfit or refused RC (n=15)	N = 53	Median: 8 year	8-yr OS: 36% (overall), 45% (fit for surgery) and 13% (unfit for surgery); Metastasis = 43%; Mean QoL scores slightly improve 6 mo after TMT and maintained for 70% after 12 mo.	QoL found to be high; Patients fit for surgery have better survival than those unfit.
Mitin et al. 2016 (7)	Pooled prospective cohorts, multi-institution NRG Oncology/RTOG 99-06, 02-33	Medically operable	N = 119	Median = 5.9year	CR = 85%, near-complete = 15%; Recurrence rate = 34%; 5-year OS = 72% (complete responders) vs 61% (near-complete responders)	Even those with near-complete but not complete response may be appropriate for BPT.
Michaelson et al. 2017 (56)	Prospective, multi institution RTOG 05-24	Medically inoperable; Unfit for platinum-based CRT	N = 66	Not specified	CR = 72.2% (group 1) vs 67.6% (group 2)	Unfit population had comparable rates of CR and adverse events.

**OS** = overall survival; **DSS** = disease-specific survival; **CR** = complete response; **NAC** = neoadjuvant chemotherapy; **CRT** = chemoradiotherapy; **BPT** = bladder preservation therapy

statistically significantly improved 8-year overall survival of 45% (95% CI 28%-61%), compared to 13% (95% CI 2%-35%) in those who were unfit or refused radical surgery ( $p=0.001$ ) (55).

A prospective cohort (RTOG 0524) included 66 patients with T2-T4 NXM0 disease who were deemed medically inoperable. Treatment regimens were divided as followed: group (1) immunohistochemical (IHC) 2+ or 3+ expression of Her2/neu received RT + paclitaxel + trastuzumab ( $n=20$ ; 30%) and group (2) IHC negative or 1+ Her2/neu expression patients received RT+ paclitaxel ( $n=46$ ; 70%). XRT was done with daily 1.8Gy fractions, 5 days a week, for a total dose of 64.8Gy. All patients received “thorough” TURBT. Complete response rates at 1 year were 72.2% for group 1 and 67.6% for group 2. Treatment-related toxicities were seen in 35% of group 1 and 30% of group 2 patients, with notably low rates of cardiac and hematologic toxicities. Of note, patients were accrued over a seven year period in this study, highlighting the difficulty that such series have faced in accruing patients with medically inoperable bladder cancer (56).

Numerous retrospective and prospective series have studied TMT in medically operable patients. We include select reviews with 100 or more patients. From 1985 to 2001, the RTOG accrued 415 patients considered candidates for cystectomy, across 6 protocols (RTOG 88-12, 88-02, 89-03, 95-06, 97-06, 99-06). The protocols combined TURBT and RT, with varying combinations of cisplatin, methotrexate, vinblastine, paclitaxel, and gemcitabine given in split-course fashion. Complete response rates ranged from 59-75% with 5-year OS 49-52% (57). An updated and pooled analysis of the RTOG 99-06 and 22-03 protocols published in 2016 found that among 119 patients, 85% achieved a complete response (TO on restaging TURBT) and 15% achieved a near-complete response (Ta or Tis) after induction CRT. These patients then received consolidation XRT of at least 60Gy; incomplete responders proceeded to salvage RC. 36% of the complete responders versus 28% of the near-complete responders had a bladder cancer recurrence at a median follow-up period of 5.9 years, which was not a statistically

significant difference ( $p=0.52$ ). Among all 41 recurrences, 14 (34%) were invasive and resulted in salvage RC; there was no difference in invasive recurrence rates between the complete and near-complete responder groups. 5-year OS was 72% (95% CI 63-81%) for complete responders and 61% (95% CI 39%-84%) for near-complete responders ( $p=0.12$ ).<sup>7</sup> This analysis suggests that patients who have a near-complete response with Ta or Tis on restaging TUR are still appropriate candidates for selective bladder preservation, with no difference in recurrence or OS rates.

An unblinded, randomized controlled trial recruited 458 patients across 45 centers in the UK. Patients were randomized in 1:1 fashion to receive radiotherapy with or without synchronous chemotherapy (fluorouracil and mitomycin C) and either whole-bladder radiation or “modified-volume” radiation to the unaffected bladder. The study utilized two radiotherapy fractionation schedules, either 55Gy in 20 fractions over 4 weeks or 64Gy in 32 fractions over 6.5 weeks. The study did not note whether TURBT was maximal. Two-year local disease-free survival was 67% (95% CI 59-74) in the chemoradiotherapy arm compared to 54% (95% CI 46-62) in the radiotherapy arm. The chemoradiotherapy arm had a 2-year relapse rate of 18% compared to 32% in the radiotherapy group (HR 0.57, 95% CI 0.37-0.90,  $p=0.01$ ). This randomized study demonstrated the added benefit of chemotherapy and that this benefit was not significantly different between the two radiation schedules administered (38).

The Massachusetts General Hospital group retrospectively analyzed 475 patients who underwent TMT by choice and received maximal TURBT with split-course CRT. Only two of the included protocols incorporated NAC (MGH 180 and MGH 880/RTOG 8903 Arm 1), consisting of two methotrexate, vinblastine, and cisplatin (MVC) cycles. Most protocols used a 64-65 Gy RT dose. Seventy-five percent of patients achieved complete response to induction CRT. When stratified by completeness of TURBT, 84% of patients who had complete TURBT achieved CR versus 58% with visibly incomplete TURBTs. Five-, 10-, and 15-year OS rates were 57%, 39%, and 25% respectively.

Most patients had T2 disease (66%) and achieved a statistically significantly higher CR rate (83%) as compared to patients with T3-4 disease (63%) ( $p < 0.001$ ). This analysis also stratified outcomes by treatment decades (1986-1995, 1996-2005, and 2005-2013). The CR rate improved from 66% in the 1986-1995 cohorts to 88% in the patients treated from 2005-2013. Furthermore, 5-year OS increased from 53% to 75% from the earliest to latest treatment decades, attributed to improvements in cancer staging, TURBT technique, and chemotherapy and radiation therapy regimens. Salvage cystectomy rates decreased from 42% to 16% across this same time (58).

These series demonstrate comparable oncologic outcomes to RC. One major difficulty in comparing outcomes involves heterogeneous CRT regimens as well as varying surveillance protocols. At our institution, we have historically used a single-course of chemoradiation to 60-64Gy with either 5-fluoracil plus mitomycin or twice-

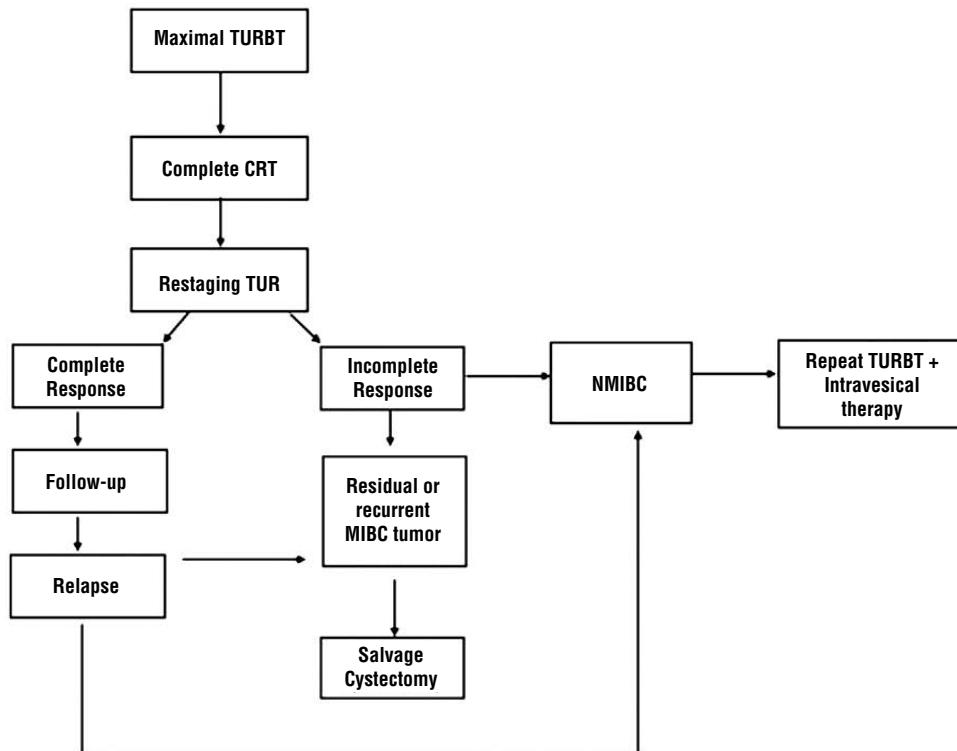
-weekly gemcitabine, based on available evidence (Figure-1) (38, 50, 59, 60). Our surveillance protocol consists of cystoscopy every three months for the first two years, every 6 months for years 3-5, and then annually until year 10.

**Partial Cystectomy**

The rationale for partial cystectomy (PC) rests in the ability to thoroughly resect bladder masses while still preserving a patient’s bladder and sexual function. With this procedure, as compared to maximal TUR, a surgeon has the ability to more completely assess surgical margins as well as perform PLND if indicated. Factors associated with poor oncologic outcomes following PC include presence of positive pelvic lymph nodes, lymphovascular invasion, need for ureteral reimplantation, and urothelial histology (61-63).

Early PC series produced questionable outcomes and tempered eagerness to pursue it as a bladder-sparing approach. For series conducted

**Figure 1 - Trimodal therapy treatment algorithm used at our institution, demonstrating an approach for continuous CRT and follow-up.**



in the 1970s-1980s, 5-year OS rates ranged from 25%-48% (64-66), while rates of local recurrence remained high around 54-78% (67-69). Latter PC series with more defined patient selection criteria revealed promising outcomes comparable to RC, although most series had small sample sizes. Across these series, 5-year OS ranged from 53.7% to 70%, and locally advanced tumor recurrence rates ranged from 18.5% to 38% (Table-3) (62, 63, 70, 71).

The Memorial Sloan-Kettering group published the largest available series consisting of 58 patients who received PC from 1995-2001, finding that 5-year OS was 69% at a mean follow-up of 33 months. Superficial recurrence occurred in 7 patients (12%) and was associated with CIS and tumor multifocality on univariate analysis. Advanced recurrence occurred in 15 patients (38%) and was associated with positive surgical margins and lymph node involvement on univariate analysis. Only concomitant CIS (odds ratio 7.05,  $p=0.004$ ) and lymph node involvement (odds ratio 4.38,  $p=0.031$ ) predicted advanced recurrence (62).

Because PC incurs a risk of leaving behind foci of cancer in the bladder with subsequent high rates of local recurrence, some series have attempted to combine PC with other modalities. A retrospective review included 36 patients who received neoadjuvant chemotherapy followed by partial cystectomy. Five-year OS was 63%, with 19 (53%) having recurrence at last follow-up and 22 (61%) maintaining an intact bladder. Positive lymph nodes on imaging and positive surgical margins at PC were associated with lower recurrence-free and OS on univariable analysis. Of note, this series only included patients with solitary tumors of less than 5 cm (72).

TUR with chemoradiotherapy followed by consolidative PC—sometimes referred to as tetramodal therapy—is gaining popularity for its multimodal approach in a highly selected patient population. In one bladder-sparing protocol consisted of debulking TUR and low dose chemoradiotherapy followed by partial cystectomy with PLND in 46 highly selected patients, five-year CSS and recurrence-free survivals

were 100%, although histologic examination of PC specimens revealed residual MIBC in 3 (7%) specimens. Median total International Prostate Symptom Scores (IPSS) from 33 of the PC patients was 5 (IQR 2-8.5), at a median follow-up time after PC of 23 months (IQR 10-53); this was reported to be noninferior to a similar population of community-based men in their 70s (73). More recently, a single-institution prospective cohort of 154 patients with T2-T3N0M0 disease initially provided patients with maximal TUR-BT followed by induction chemoradiotherapy (40Gy in 20 fractions with concurrent cisplatin). Patients who showed complete remission were then offered PC with PLND. Of the 107 who both qualified for and underwent PC, 19 (18%) experienced bladder cancer recurrence with 4 (4%) having MIBC recurrence. Five-year MIBC recurrence-free survival, CSS, and OS were 97%, 93%, and 91%, respectively. QOL survey of the patients who received PC revealed an average IPSS of 2, with the majority of patients mostly satisfied (74).

An analysis of Surveillance, Epidemiology, and End Results (SEER) data in 2009 consisted of 1573 patients treated with PC and 5670 patients treated with RC, covering a wide range of T(1-4)N(1-2)M0 bladder cancer. In this cohort, 5-year OS and CSS estimates for PC patients were 57.2% and 76.4% respectively. Five-year OS and CSS estimates for RC patients were 50.2% and 65.8% respectively. After matching for age, race, tumor stage, tumor grade, nodal status, and year of surgery, 5-year OS and CSS rates were 56.0% and 73.5% for PC, and 54.6% and 69.2% for RC. These data show that PC and RC have comparable oncologic outcomes at five years (75). In the Ontario Cancer Registry, 3320 patients received PC and 3139 patients received RC from 1994 to 2008. Factors associated with receiving PC included older age, having moderate comorbidities, and receiving surgery outside of a comprehensive cancer center (76). After adjusting for age, comorbidity score, stage, and presence of lymphovascular invasion, PC showed comparable and statistically nonsignificant differences compared to RC, with 5-year OS (HR 0.95, 95% CI 0.79-1.14) and CSS (HR 0.87, 95% CI 0.7-1.09).

**Table 3 - Partial cystectomy series identified in this review.**

Series	Study Type	Eligibility / Patient Characteristics	Sample Size	Follow-up	Outcomes	Findings
Holzbeierlein et al. 2004 (62)	Retrospective, single institution	Assessed cT/pT stage, age, size of primary tumor, concomitant CIS, margin status, multifocality, and systemic or NAC.	<i>N</i> = 58	Mean: 33 mo	5-year OS = 69%; Superficial recurrence = 12%; Advanced recurrence = 38%	Concomitant CIS and lymph node involvement predictors of advanced recurrence.
Ebbing et al. 2018 (63)	Retrospective, single institution	cT2 only; Medically unfit for RC or elected BPT	<i>N</i> = 27	Median: 36.5 mo	5-year OS = 53.7%; Local recurrence = 18.5%; Salvage cystectomy = 18.5%	Less stringent selection criteria showed worse but comparable outcomes.
Smaldone et al. 2008 (70)	Retrospective, single institution	solitary primary T2 (68%) or T1HG (32%)	<i>N</i> = 25	Mean: 45.3 mo	5-yr recurrence-free, DSS, and OS = 64%, 84%, and 74%, respectively. Locally advanced recurrence = 20%	Only tumor size at time of PC significantly associated with tumor recurrence.
Kassouf et al. 2006 (71)	Retrospective, single institution	Solitary tumor, no CIS, amenable to 2cm margin resection without need for ureteral reimplantation, normally functioning bladder	<i>N</i> = 37	Mean: 72.6 mo	5-year overall, disease specific and recurrence-free survival rates = 67%, 87% and 39%, respectively; Advanced recurrence = 24%	Highly selected cohort
Bazzi et al. 2014 (72)	Retrospective, single institution	Solitary tumor <5cm	<i>N</i> = 36	Median: 16.8 mo	CR to NAC = 58%; Downstaging after NAC = 74%; 5-year recurrence-free, advanced recurrence-free, and overall survival = 28%, 51%, and 63%; Advanced recurrence = 42%	NAC prior to PC associated with acceptable oncologic outcomes.
Kijima et al. 2019 (74)	Prospective, single institution	Tumor circumscription <25% bladder surface, absence of bladder neck involvement, absence of CIS, demonstrated CR to induction CRT	<i>N</i> = 107	Median: 48 mo	5-year DSS and OS = 93% and 91%; PC-related complications = 32%	Tetramodal therapy associated with excellent oncologic and QOL outcomes.

**OS** = overall survival; **DSS** = disease-specific survival; **NAC** = neoadjuvant chemotherapy; **CRT** = chemoradiotherapy; **PC** = partial cystectomy; **BPT** = bladder preservation therapy; **QOL** = quality of life.

### Adverse Effects and Quality of Life Considerations

Bladder preservation strategies come with their own set of complications and considerations. Most TMT series demonstrate acceptable toxicities, although some of the toxicities that do occur can become lifelong concerns of patients. On systematic review, rates of grade 3-4 acute toxicities ranged from 10% to 36%, although this was higher in studies that incorporated perioperative neoadjuvant or adjuvant chemotherapy. The majority of toxicities were gastrointestinal/genitourinary-related. Late grades 1 and 2 toxicities fell across a range of 10%-25% for genitourinary and 5%-6% for gastrointestinal among reporting studies. However, these ranges may underestimate the true prevalence of toxicities as these studies mostly involved physician-reported, as opposed to patient-reported, assessments (53).

Quality of life concerns have been one of the driving forces for studying bladder preservation strategies, and TMT studies have demonstrated comparable—if not superior—quality of life measures. This is largely driven by patients' ability to retain their native bladders, with bladder retention possible in 70% of patients treated with TMT in a large cohort detailed earlier (58). The GETUG cohort discussed above noted that 35% of their patients reported satisfactory bladder function at baseline before TMT, and at 6, 18, and 36 months after treatment, 43%, 57%, and 29% of patients reported satisfactory function respectively. The LENT-SOMA scale was also used, graded from 0 (no toxicity) to 4 (treatment-refractory toxicity). They reported no grade 4 toxicities; 90% of patients remained free from grade 1 side effects related to dysuria, hematuria, and incontinence after 6 months; 5% of patients had grade 2 urinary frequency (2-3 hour interval between urination) and 10% had grade 3 urinary frequency (1-2 hour interval between urination) (55). In one phase 3 trial, differences in grade 3 or 4 toxicities trended toward significance among patients who underwent CRT versus RT-only as part of their multimodal therapy, with 36% in the CRT group compared to 27.5% in the RT group ( $p=0.07$ ) (38).

A cross-sectional, bi-institutional study surveyed 226 patients with T2-T4 MIBC who were treated with TMT from 1990-2011, with a response elicited from 173 (77%). Multivariable analysis showed that TMT patients had a 9.7 point higher QOL (out of 100 points) compared to RC patients ( $p=0.001$ ). Furthermore, TMT patients had significantly higher physical, emotional, social, and cognitive functioning (6.6-9.9 points;  $p<0.04$ ), superior bowel function (+4.5 points;  $p=0.02$ ), and fewer bowel symptoms (-2.7-7.01 points;  $p<0.05$ ). This study was limited by nature of the heterogeneous follow-up times and not accounting for baseline QOL scores (9).

Finally, a comparative effectiveness analysis developed a Markov model to compare TMT with RC. This study found an increase in 0.59 quality-adjusted life years (QALYs) when undergoing TMT as compared to RC. Sensitivity analysis attributed this gain in QALY to significantly better quality of life associated with TMT in the presence of similar survival rates in the different treatment strategies (77). This study puts QOL into the measure of QALYs, which is important when considering the use of TMT versus RC at a population-level perspective.

### CONCLUSIONS

Interest in bladder preservation techniques has grown significantly over recent years as technological advancements improve BPT outcomes and the focus on improving quality of life heightens. This review highlighted the breadth of strategies that aim to preserve a patient's bladder while still optimizing local tumor control and overall survival. Trimodal therapy has the most evidence for its use, with newer series demonstrating promising oncologic outcomes including cancer-specific and overall survival. This holds especially true in cohorts of highly selected patients, with the ideal patient for BPT having low-volume T2 disease, absence of CIS, absence of hydronephrosis, and a maximal TURBT with regular surveillance. Although we are unlikely to see randomized controlled trials comparing TMT to RC, as evidenced by the SPARE trial failing to adequately accrue patients, there are many avenues to refine, advance and demonstrate the efficacy of TMT. Future directions and exciting areas of ad-

vancement include the use of tetramodal therapy, the use of predictive biomarkers such as DDR gene mutations, and the promise of immunotherapy (78) with subsequent bladder preservation. Regarding immunotherapy, several immune checkpoint inhibitors have gained approval in the last few years, with several trials underway studying combinations of immune-checkpoint inhibitors, their use with chemotherapy, and the potential use in a neoadjuvant setting (79).

## ABBREVIATIONS

NMIBC = non-muscle invasive bladder cancer

MIBC = muscle-invasive bladder cancer

RC = radical cystectomy

PC = partial cystectomy

NAC = neoadjuvant chemotherapy

TUR = transurethral resection

XRT = radiotherapy, radiation therapy

OS = overall survival

DSS = disease-specific survival

CSS = cancer-specific survival

TMT = trimodal therapy

BPT = bladder preservation therapy

IQR = Interquartile range

OR = odds ratio

CI = confidence interval

MVC = methotrexate, vinblastine, cisplatin

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## CONFLICT OF INTEREST

None declared.

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# Comparison effects of solifenacin, darifenacin, propiverine on ocular parameters in eyes: A prospective study

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## ABSTRACT

**Objective:** To evaluate the effects of solifenacin, darifenacin, and propiverine on nasal-, subfoveal-, temporal choroidal thicknesses (NCT, SFCT, TCT), intraocular pressure (IOP) and pupil diameter (PD).

**Materials and Methods:** Patients with overactive bladder (OAB) diagnosed according to The International Continence Society were administered with solifenacin, darifenacin or propiverine on a daily basis between November 2017 and May 2018. NCT, SFCT, TCT, IOP, and PD of these patients were measured and compared as initial, fourth and twelfth weeks.

**Results:** A total of 165 patients (330 eyes) with OAB were evaluated. Solifenacin (n=140) significantly reduced IOP from  $17.30 \pm 2.72$  mmHg to  $16.67 \pm 2.56$  mmHg ( $p=0.006$ ) and  $16.57 \pm 2.41$  mmHg ( $p=0.002$ ), at the fourth and twelfth weeks, respectively. Darifenacin (n=110) significantly reduced NCT from  $258.70 \pm 23.96$   $\mu$ m to  $257.51 \pm 22.66$   $\mu$ m ( $p=0.002$ ) and  $255.36 \pm 19.69$   $\mu$ m ( $p=0.038$ ), at the fourth and twelfth weeks, respectively. Propiverine (n=80) significantly increased PD from  $4.04 \pm 0.48$  mm to  $4.08 \pm 0.44$  mm ( $p=0.009$ ) and  $4.09 \pm 0.45$  mm ( $p=0.001$ ), at the fourth and twelfth weeks, respectively.

**Conclusion:** These findings can help to decide appropriate anticholinergic drug choice in OAB patients. We finally suggest further well-designed randomized prospective studies with a larger population to evaluate the anticholinergic-related complications in eyes.

## ARTICLE INFO

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## INTRODUCTION

Both sexes are affected by an overactive bladder (OAB), which is a common disorder with a reported prevalence between 11.8% and 16.9%. Symptoms of OAB include urgency, frequent urination, and nocturia with or without urge incontinence (1-3). Lifestyle modifications and behavioral therapies are the first steps taken into treatment, however, medical therapy constitutes

the mainstay method (4). Oral anticholinergics are the first-line drugs in medical treatment (5). Due to various settlements of cholinergic (muscarinic) receptors (M1-M5) in the body, the side effects of anticholinergics emerge in accordance with this (6). These drugs can cause side effects such as dry mouth, constipation, nausea, vomiting, headache, and confusion (7, 8).

There are extensive M receptors in iris sphincter muscle, ciliary muscle and trabecular

cells (9-11). Iris sphincter muscle and ciliary muscles are relevant with accommodation and changing of pupil diameter (PD) (12, 13). M3 receptors are most common cholinergic receptors than the other types in iris sphincter and ciliary muscle cells (10, 14). Trabecular cells control intraocular pressure (IOP) by changing the aqueous humor drainage (15). Blockage of these receptors may lead to blurred vision, dry eyes, and increased IOP in angle-closure glaucoma (16, 17). Choroid is one of the most vascularised areas in the body, allowing outer retina to become vascularised (18). Increased choroidal thickness (CT) can cause haemorrhage and exudation. Reducing this thickness can decrease blood flow of retina (18). Age-specific (haemorrhagic and exudated) choroidal thickening is known to be a poor prognostic factor in age-related macular degeneration. It is reported that choroidal layer contains smooth muscles with intense cholinergic innervations (18, 19).

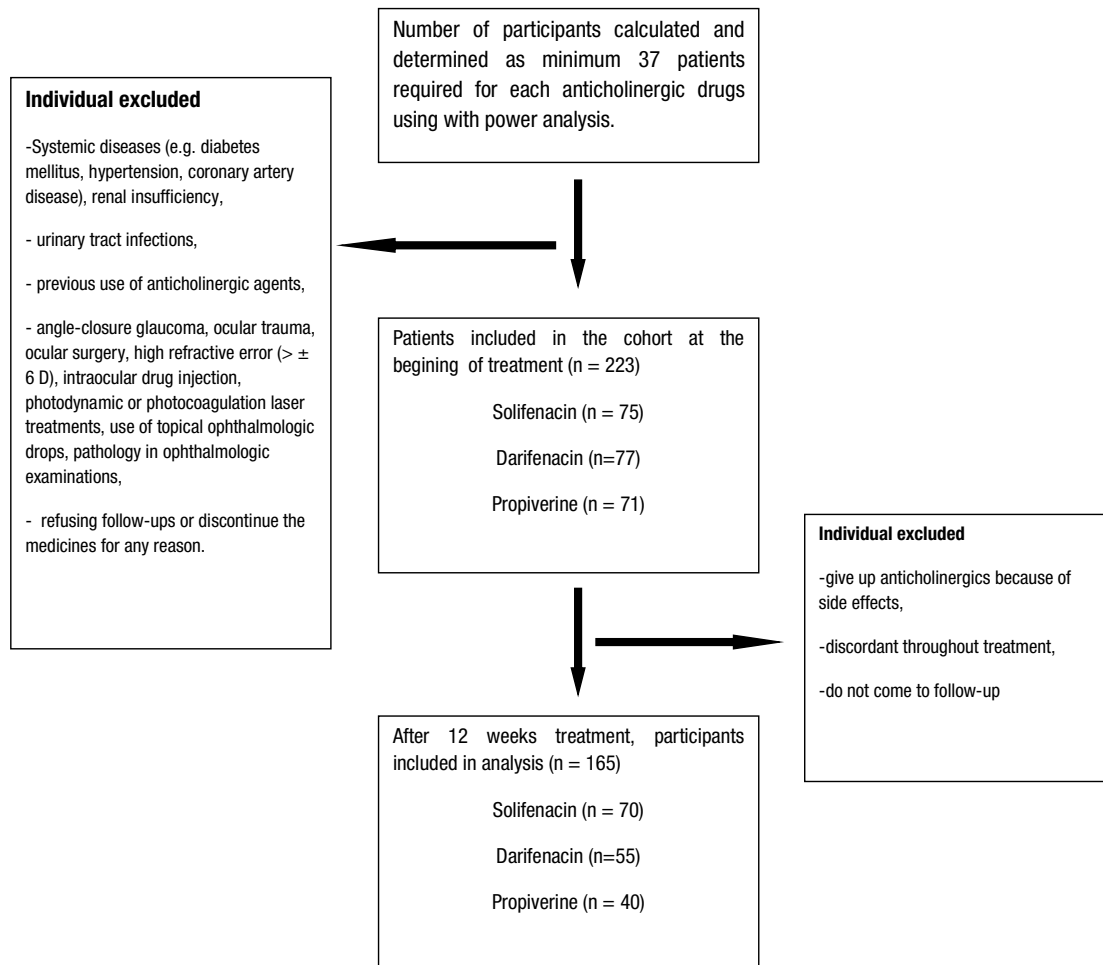
In this context, since anticholinergic drugs may affect ocular M receptors, we herein aimed to evaluate the effects of solifenacin, darifenacin, and propiverine on nasal-, subfoveal-, temporal CTs (NCT, SFCT, TCT), IOP and PD in the eyes.

## MATERIALS AND METHODS

The study was designed prospectively non-randomized in accordance with the Helsinki Declaration after approval of Erzurum Atatürk University Medical Faculty Ethics Committee (Approval Number: B.30.2.ATA.0.01.00/128). Patients who were diagnosed with OAB in urology clinic between November 2017 and May 2018 were included and referred to ophthalmologic clinic after receiving the informed consents from patients. The diagnosis of OAB was made according to the description described earlier by the International Continence Society (ICS) (20). Informed consent forms were obtained from patients who wanted to participate in the study. The costs of the drugs were paid by the patient's own health insurance. As a result of detailed urological and ophthalmological evaluations, patients with histories of any systemic diseases (e.g. diabetes mellitus, hypertension, coronary artery disease), renal insufficiency, urinary tract infections, previous use of anticho-

linergic agents, angle-closure glaucoma, ocular trauma, ocular surgery, high refractive error ( $> \pm 6D$ ), intraocular drug injection, photodynamic or photocoagulation laser treatments, use of topical ophthalmologic drops, pathology in ophthalmologic examinations and refusing follow-ups or discontinue the medicines for any reason were excluded from the study (Figure-1). No patient gave up on OAB treatment because of ocular findings or ocular side effects.

Patients with OAB were administered with 5mg solifenacin 1x1, 7.5mg darifenacin 1x1 or 30mg sustained-release propiverine 1x1 on a daily basis. When we analyzed retrospectively, we found that the most preferred anticholinergics were solifenacin, darifenacin, propiverine, oxybutynin, and trospium, respectively in our clinic. Hence we aimed to compare the eyes of patients who were treated with most preferred three anticholinergics (solifenacin, darifenacin, propiverine) for OAB treatment. As known, the effects of anticholinergics are similar. But more adverse effects can be observed with some anticholinergics than others. Two urologists (MTO and KT) distributed the anticholinergics in a regular order to the patients with OAB. We did not make any randomization in this study. We tried to keep equally the number of groups. Some factors affected the number of participants who have finished the study among groups. Those factors included: patients who gave up the anticholinergic because of adverse effects, did not come to follow-up, and were discordant throughout treatment. In method, we have specified those factors as the excluded criteria described above. We observed more adverse effects in propiverine group. And it affected the number of propiverine group. The ophthalmologists who examined the patients did not know which anticholinergics were used by the patients. SFCT, NCT, TCT, IOPs, and PDs in eyes of the patients in the fourth and twelfth weeks were evaluated by ophthalmologists. CT was measured at 500-micron intervals of the section from 1mm nasal and temporal to the subfoveal center via an optical coherence tomography device (Topcon 3d Oct-2000 Fa Plus, Topcon Inc., Japan). IOP was measured with a computerized tonometer (Topcon Ct-800, Topcon Inc., Japan),

**Figure 1 - Flow-chart of the our prospective cohort study.**

and PD was measured by an autorefractometer (Topcon Kr-800, Topcon Inc., Japan).

When we assigned the statistical power as 0.8, the alpha as 0.05, effect size as 0.3 and group size as 3 the power analysis has shown minimum required sample size as 111. So a minimum of 37 patients were required for each anticholinergic drug. The mean values of the measurements for both eyes were recorded as data for each patient. The results were statistically analyzed with SPSS 15.0. Normality test was used to determine the pretreatment measurements among solifenacin, darifenacin, propiverine groups. Due to the data is normally distributed, ANOVA test was used to compare independent variables regarding those three groups. For the ages of the three groups, the

Kruskal Wallis test was used after the descriptive statistics, and two samples paired t-test was used to compare the values measured in the fourth and twelfth weeks for the same individuals depending on the medicines used. A value of  $p < 0.05$  was deemed statistically significant.

## RESULTS

One hundred sixty-five patients (330 eyes) who have completed 12 weeks follow-up received solifenacin (n=70), darifenacin (n=55), and propiverine (n=40) (Figure-1). A hundred eighteen (71.5%) patients were female and 47 (28.5%) were male. Female and male ratio for the solifenacin, darifenacin and propiverine groups were 59

(84.3%) vs. 11 (15.7%), 30 (54.5%) vs. 25 (45.5%), and 29 (72.5%) vs. 11 (27.5%), respectively. Total mean age was  $50.10 \pm 13.17$  years (ranging from 19 to 81) and observed as  $49.37 \pm 13.17$  (ranging from 19 to 76) in the solifenacin group, as  $50.49 \pm 12.50$  (ranging from 21 to 75) in the darifenacin group, and as  $50.87 \pm 14.31$  (ranging from 29 to 81) in the propiverine group. There was no significant difference between the mean age of the groups ( $p=0.848$ ). No statistically differences were determined between baseline pretreatment measurement of SCFT ( $p=0.587$ ), NCT ( $p=0.430$ ), TCT ( $p=0.365$ ) and PD ( $p=0.960$ ) among solifenacin, darifenacin, propiverine groups. However, baseline pretreatment values of IOP ( $p=0.010$ ) were statistically difference among those three groups (Table-1).

### Choroidal Thickness

Subfoveal Choroidal Thickness: No statistically significant differences were observed be-

tween the pretreatment and fourth week or between the pretreatment and the twelfth week for SCFT in the solifenacin-, darifenacin-, and propiverine-treated groups ( $p > 0.05$ ) (Table-2). Nasal Choroidal Thickness: The mean value of NCT slightly but statistically increased at fourth week in solifenacin group ( $p=0.042$ ). However, rising NCT regressed to approximately pretreatment levels at the twelfth week in these patients ( $p=0.849$ ). The darifenacin treatment gradually reduced the mean of NCT at the fourth and twelfth weeks compared to pretreatment levels. These decreases were significantly different at the fourth ( $p=0.002$ ) and twelfth weeks ( $p=0.038$ ) according to the pretreatment baseline. In propiverine group, the mean value of NCT was significantly reduced by the fourth week ( $p=0.012$ ). At the twelfth week, NCT had increased and reached approximately pretreatment levels ( $p=0.438$ ) (Table-2). Temporal Choroidal Thickness: In all three treatment groups (solifenacin, darifenacin, and propiverine), there was no statistically

**Table 1 - The pretreatment results of descriptive analysis regarding to three anticholinergic groups are presented.**

	Solifenacin (n=70)	Darifenacin (n=55)	Propiverine (n=40)	P
<b>Gender</b>				
Female (%)	59 (84.5%)	30 (54.5%)	29 (72.5%)	-
Male (%)	11 (15.5%)	25 (45.5%)	11 (27.5%)	
Age (mean $\pm$ SD)	$49.37 \pm 13.17$	$50.49 \pm 12.50$	$50.87 \pm 14.31$	0.848
Subfoveal choroidal thickness ( $\mu$ m) (mean $\pm$ SD)	$253.52 \pm 26.72$	$258.66 \pm 33.08$	$258.80 \pm 38.08$	0.587
Nasal choroidal thickness ( $\mu$ m) (mean $\pm$ SD)	$252.48 \pm 24.64$	$258.70 \pm 23.96$	$256.17 \pm 33.34$	0.430
Temporal choroidal thickness ( $\mu$ m) (mean $\pm$ SD)	$251.30 \pm 29.43$	$258.08 \pm 22.98$	$251.47 \pm 33.53$	0.365
Intraocular pressure (mmHg) (mean $\pm$ SD)	$17.30 \pm 2.72$	$17.05 \pm 3.40$	$15.50 \pm 3.02$	0.010*
Pupil diameter (mm) (mean $\pm$ SD)	$4.06 \pm 0.53$	$4.03 \pm 0.43$	$4.04 \pm 0.48$	0.960

The Kruskal Wallis test was used to compare the three treatment groups by age.

To compare independent variables regarding to those three groups, the ANOVA test was used.

\*  $p < 0.05$  value was accepted for the statistical difference.

**Table 2 - Measurement results of the sub-foveal, nasal-, and temporal- choroidal thicknesses, intraocular pressure and pupil diameter of the patients initial, 4th and 12th weeks after anticholinergic drug administration.**

	Solifenacin (n=70)				Darifenacin (n=55)				Propiverine (n=40)						
	Pretreatment	4th week	p <sup>1</sup> value	12th week	p <sup>2</sup> value	Pretreatment	4th week	p <sup>1</sup> Value	12th week	p <sup>2</sup> value	Pretreatment	4th week	p <sup>1</sup> value	12th week	p <sup>2</sup> value
Subfoveal choroidal thickness (µm) (mean ± SD)	253.52± 26.72	252.84± 26.05	0.215	254.45± 24.97	0.423	258.66± 33.08	259.93± 27.39	0.713	257.68± 21.82	0.748	258.80± 38.08	257.62± 39.13	0.144	258.82± 39.91	0.988
Nasal choroidal thickness (µm) (mean ± SD)	252.48± 24.64	252.87± 24.27	<b>0.042*</b>	252.57± 23.58	0.849	258.70± 23.96	257.51± 22.66	<b>0.002*</b>	255.36± 19.69	<b>0.038*</b>	256.17± 33.34	254.72± 32.81	<b>0.012*</b>	256.95± 33.91	0.438
Temporal choroidal thickness (µm) (mean ± SD)	251.30± 29.43	250.74± 29.70	0.429	249.80± 28.45	0.133	258.08± 22.98	257.49± 22.01	0.218	254.87± 16.59	0.138	251.47± 33.53	251.93± 32.27	0.186	252.41± 34.37	0.490
Intraocular pressure (mmHg) (mean ± SD)	17.30± 2.72	16.67± 2.56	<b>0.006*</b>	16.57± 2.41	<b>0.002*</b>	17.05± 3.40	17.87± 3.24	<b>0.007*</b>	17.53± 3.09	0.097	15.50± 3.02	16.06± 3.00	0.050	15.78± 3.23	0.224
Pupil diameter (mm) (mean ± SD)	4.06± 0.53	4.06± 0.50	0.501	4.07± 0.50	0.329	4.03± 0.43	4.04± 0.45	0.609	4.04± 0.43	0.693	4.04± 0.48	4.08± 0.44	<b>0.009*</b>	4.09± 0.45	<b>0.001*</b>

p<sup>1</sup>: The p value of the statistical difference between the initial and end of the 4th week. (Two sample paired t-test was used)  
 p<sup>2</sup>: The p value of the statistical difference between the initial and end of the 12th week. (Two sample paired t-test was used)  
 \* p<0.05 value was accepted for the statistical difference.

significant difference in the fourth and twelfth weeks when compared to the pretreatment period ( $p > 0.05$ ) (Table-2).

#### Intraocular Pressure

Four and twelve weeks after solifenacin treatment, when compared to the mean level of pretreatment, the mean values of IOP were significantly reduced ( $p=0.006$  and  $p=0.002$ , respectively). The results at four weeks after darifenacin treatment showed a significant increase in mean IOP when compared to the mean pretreatment level ( $p=0.007$ ). The mean IOP level in patients treated with darifenacin after twelve weeks was lower than after the four-week treatment period, and it also did not have any statistically significant difference when compared with the pretreatment IOP levels ( $p=0.097$ ). In propiverine group, the IOP changes were not found to be statistically significant when compared to the pretreatment levels at fourth and twelfth weeks ( $p > 0.05$ ) (Table-2).

#### Pupil Diameter

The changes of PD with solifenacin and darifenacin, according to pretreatment levels, were not significantly different at fourth and twelfth weeks ( $p > 0.05$ ). Unlike solifenacin and darifenacin, propiverine treatment significantly increased PD at the fourth ( $p=0.009$ ) and twelfth weeks ( $p=0.001$ ) when compared to pretreatment levels (Table-2).

## DISCUSSION

M2 receptors are the most intensive muscarinic receptor types in the bladder and mostly M2 and M3 receptors play a role in OAB physiopathology (21). It is known that darifenacin and solifenacin are more selective for M3 than M2 receptors (6). Propiverine, oxybutynin, fesoterodine, and trospium are nonselective anticholinergics (22, 23). It has also been reported propiverine serves as a calcium channel blocker and increases relaxation in smooth muscles, making it more efficient in treating symptoms of OAB (23). In studies conducted by evaluating the effects of systemic anticholinergics on eyes,

it has been emphasized that attention should be paid to the use of these medicines in patients with ophthalmologic diseases, especially dry eye and angle-closure glaucoma (24, 25). We considered these suggestions when choosing criteria for patient's inclusion in the study.

Telek et al. studied 61 OAB patients and the effects of three months of 1x1 daily oral administration of sustained-release tolterodine on SFCT, NCT, TCT, IOP, and PD (7). When the values before and after treatment and the p-values were compared, it was observed that SFCT ( $p=0.862$ ), NCT ( $p=0.658$ ), TCT ( $p=0.497$ ), IOP ( $p=0.732$ ), PD ( $p=0.711$ ) had no differences. The results demonstrated that there was no statistically significant difference on the parameters before and after treatment. However, it was stated that these findings should be supported by other studies.

Turkoglu et al. evaluated daily 1x1 administration of oral trospium to 80 female OAB patients and IOP changes before treatment as well as in the fourth and twelfth weeks of treatment. No significant difference was found in the study for IOP changes in the fourth and twelfth weeks compared to pretreatment ( $p=0.251$ ,  $p=0.340$ , respectively), however, it was reported that trospium significantly reduced tear secretion (26). Likewise, in another study conducted by Turkoglu et al. in 2015, no significant difference was observed in IOP values at commencement, the fourth week, or the twelfth week of daily 1x1 oral solifenacin in 93 female OAB patients (27). It was also emphasized in this study that solifenacin did not affect tear secretion. Sekeroglu et al. compared the IOPs of 60 female OAB patients who used solifenacin for four weeks and a control group of 30 healthy females at commencement and four weeks (28). They found no significant difference in either group ( $p=0.864$  and  $p=0.160$ , respectively), and, hence, they reported solifenacin does not affect IOP. In these two studies, effect of solifenacin on CT, IOP, and PD is not statistically significant. However, in these studies, it was observed that solifenacin decreased IOP even though it was not statistically significant in some individuals. In our study, we concluded that solife-

nacin significantly decreased IOP at the fourth week, and this decline was more pronounced in the twelfth week. Even though IOP significantly decreased in those who used solifenacin, it remained within normal limits (9-22mmHg) in our study.

Altan-Yaycioglu et al. conducted a study on 52 OAB patients, administering oral tolterodine to 28 of them and oxybutynin to remaining 24. The authors then compared the patient's IOPs and PDs with the initial values at the four-week follow-up. No significant difference was found among the initial values except for PD in dark light in the group that used tolterodine (3.72 vs. 4.16mm,  $p=0.025$ ) (29). In this study, neither agent affected tear secretion.

Although it is generally recommended that anticholinergics should not be used in OAB patients with angle-closure glaucoma, it was concluded by a randomized, double-blind, placebo-controlled study conducted by Gatchev et al. in 2016 that propiverine does not change IOP in patients with angle-closure glaucoma (30). This study suggested that propiverine could increase PD in patients with wide-angle and angle-closure glaucoma compared to a placebo (28). In our study, we concluded that propiverine did not alter IOP and significantly increased PD at the fourth week and twelfth week.

An important finding of our study is the effect of darifenacin on NCT. According to the results we obtained, usage of darifenacin for twelve weeks progressively decreases NCT. It is reported that the perfusion pressure is important for blood supply to this area (31). Therefore, factors that might spoil ocular blood flow may lead to decreased NCT (32). However, the reason for this finding should be investigated in more detail.

Furthermore, there was a statistically significant difference in the fourth week, and some parameters that improved in the twelfth week also attracted attention in our study. NCT significantly increased and then returned to normal levels for those who used solifenacin, IOP significantly increased and then returned

to normal levels for those who used darifenacin, and NCT significantly decreased and then returned to normal levels for those who used propiverine. Perhaps this situation may be related to some adaptation mechanisms in the eye.

This work has several limitations. A major lack of this study is its non-randomized design and the fact that the groups were not evenly distributed. Additionally, even if some baseline characteristics like CT and PD of treatments groups were homogenously distributed, pretreatment IOP from three groups was statistically different. Another notable limitation, anticholinergic-related complications like dry mouth, constipation, and confusion were not mentioned in this cohort. Further works are needed to evaluate the anticholinergic-related complications in collaboration with some parameters for eye and to compare the treatment groups, which have similar baseline characteristics.

In conclusion, solifenacin significantly reduced IOP, darifenacin significantly reduced NCT and propiverine significantly increased PD in patients with OAB who had normal ophthalmologic examinations after the twelve weeks of treatment. These findings can help to decide appropriate anticholinergic drug choice in OAB medical treatment for patients with eye-related disorders. We suggest these findings should be supported by further well-designed randomized prospective studies with larger populations for better reliability.

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## CONFLICT OF INTEREST

None declared.

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# Profile of renal artery embolization (RAE) for renal trauma: A comparison of data from two major trauma center

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## ABSTRACT

**Objective:** To evaluate usage of renal artery embolization (RAE) for renal injuries and discuss the indications for this treatment.

**Materials and Methods:** A retrospective study was performed evaluating the electronic medical records of all patients with renal trauma admitted to two major comprehensive hospitals in Shantou city from January 2006 to December 2015.

**Results:** There were 264 and 304 renal traumatic patients admitted to hospital A and B, respectively. LGRT was the reason for presentation in the majority of patients (522, 91.9%). A total of 534 (94.0%) patients were treated conservatively. RAE was performed in 9 patients from 2012 to 2015 at hospital A, including in 6 patients (6/9, 66.7%) with LGRT, and 3 patients (3/9, 33.3%) with HGRT. No patient underwent interventional therapy (RAE) at hospital B during the same period. No significant differences in the operative rate of hospital A were observed between the two time periods (2006-2011 and 2012-2015). The operative rate for LGRT between the two hospitals from 2006 to 2011 and 2012 to 2015 was not significantly different. Hospital A showed a significant decrease in the rate of conservative treatment for patients with LGRT. In the univariate and multivariate analyses, the AAST renal grade both were significantly associated with undergoing RAE.

**Conclusions:** LGRT was present in the majority of patients, and most cases of renal trauma could be treated with conservative treatment. RAE was well utilized for the treatment of renal trauma. However, some patients with LGRT were treated with unnecessary interventional therapy.

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## INTRODUCTION

The kidney is the most frequently injured genitourinary organ in 1-5% of all trauma patients (1, 2). Approximately 245,000 cases of renal trauma occur worldwide per year (3), with an incidence ranging from 10.25 to 48.9 per million population (4, 5). Nearly three-quarters of patients

with renal trauma are young and male (6). As the most common type of injury, blunt trauma remains a significant cause of morbidity and mortality in the population, accounting for 80-95% of renal trauma in Western countries caused by motor vehicle accidents, pedestrian accidents and falls (6-9), which is consistent with the findings of a study in China (10), although penetrating in-

juries are becoming more frequent due to an increase in violence, gunshot wounds and stabbing wounds. Given the well-protected anatomic location of the kidney, only major external forces lead to significant kidney injury.

Derived from clinical observations, the American Association for the Surgery of Trauma (AAST) kidney injury severity scale (Table-1) (11), which is based on computed tomography (CT) scan findings, classifies kidney injury into five grades, mainly including low-grade renal trauma (LGRT, I-III) and high-grade renal trauma (HGRT, IV-V); the AAST grade is the most important predictive variable of an increasing need for intervention (including vascular interventions and open surgery), and this tool is a useful practical instrument for clinicians to treat renal trauma properly.

With advances in imaging and treatment strategies, most cases of renal trauma can be managed conservatively to decrease the need for surgical intervention and increase organ preservation (12, 13). According to the guidelines of American Urological Association (AUA) (2) and European Association of Urology (EAU) (14) most patients with grade

I-III renal trauma and even those with hemodynamically stable grade IV-V renal trauma can initially undergo conservative treatment (15-20). In particular, recent literature has provided more support for the application of conservative treatment in patients with HGRT to achieve good outcomes.

Renal artery embolization (RAE) was popularized in the 1970s by Almgard et al. (21). This technique has been increasingly applied to patients with renal trauma. According to the guidelines of the EAU (14), angiography or embolization can be used to diagnose and treat patients with stable hemodynamics, and good outcomes can be achieved, especially in patients with renal injury above grade III (15-17).

However, there is still no consensus on the selection principles for interventional therapy. The literature (22) has reported differences in the use of interventional therapy between interventional physicians and urologists, especially in patients with LGRT and some cases of overuse of interventional therapy. Furthermore, due to the inevitable risk and complications of interventional therapy, such as ectopic embolization and hemorrhage, it is of great significance to understand the appropriate application of and indications for interventional therapy in patients with renal trauma. This research will review the situation of renal trauma patients in two tertiary hospitals in the region in the past 10 years and elucidate the application and effects of interventional therapy for renal injury according to the different treatment methods of the two hospitals (one of which did not apply interventional therapy to treat renal trauma). We discuss the indications for RAE.

## MATERIALS AND METHODS

This study was approved by the 2<sup>nd</sup> Affiliated Hospital of Shantou University Medical College Ethics Committee.

A retrospective study was performed on the electronic medical records of all patients with renal trauma collected from January 2006 to December 2015 in two hospitals (hospital A and hospital B) in Shantou city. The two hospitals are the major comprehensive hospitals affiliated with the medical university in Shantou city. These regional trauma

**Table 1 - AAST renal injury grading scale (11).**

Grade*	Description of injury
1	Contusion or nonexpanding subcapsular hematoma No laceration
2	Nonexpanding perirenal hematoma Cortical laceration < 1 cm deep without extravasation
3	Cortical laceration > 1 cm without urinary extravasation
4	Laceration: through corticomedullary junction into collecting system or Vascular: segmental renal artery or vein injury with contained hematoma, or partial vessel laceration, or vessel thrombosis
5	Laceration: shattered kidney or Vascular: renal pedicle or avulsion

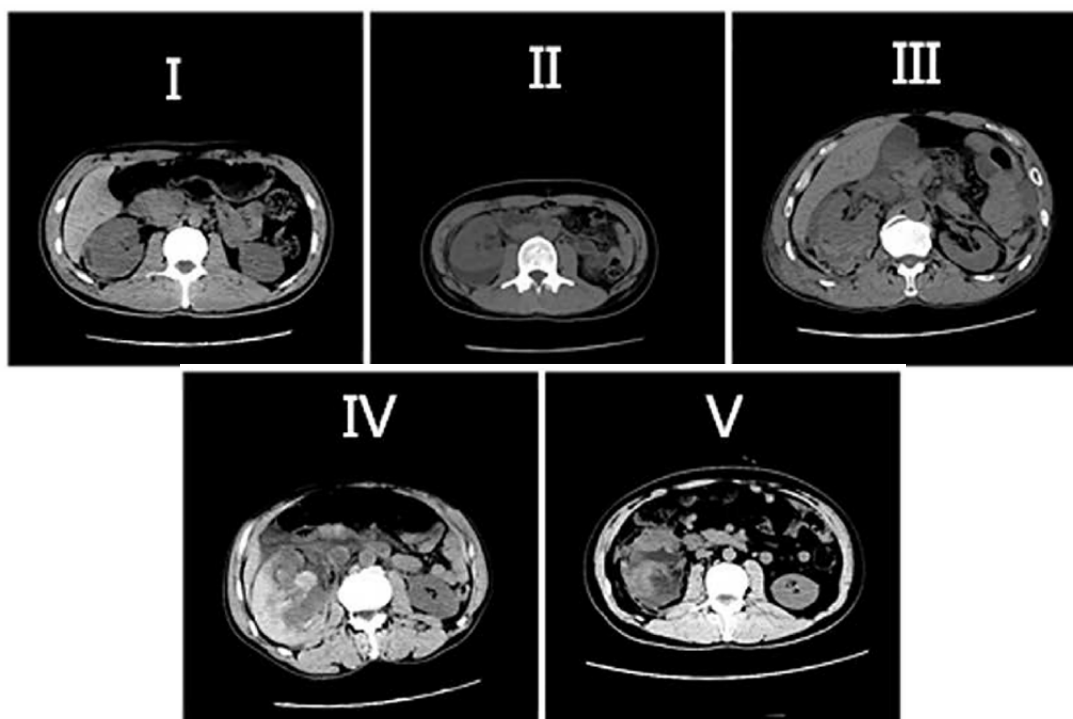
\*Advance one grade for bilateral injuries up to grade III.

centers have all medical capabilities, similar to the level I trauma centers described by the American College of Surgeons, Committee on Trauma (ACS-COT) (23). To provide standardization of the population, trauma patients were defined as any patient with an International Classification of Diseases, Tenth Revision, Clinical Modification code (ICD-10-CM) discharge diagnoses of S35.400-S35.402 and S37.001-S37.012. Patients with no renal injury (coding error) or iatrogenic renal trauma (as a complication) were excluded. In hospital A, the indication of treatment was obtained after consultation between urologists and interventionalists, mainly according to the hemodynamic situations of the patients. If the hemodynamics was stable, yet the patients having progressive bleeding, such as progressive decrease of hemoglobin or progressive hematuria, IR treatment was given. If the patient had hemodynamic instability, renal exploration was performed. The rest of the stable patients were treated conservatively. In the hospital B, the indication of treatment was determined by the surgeons to determine whether to perform a renal

exploration based on the hemodynamic condition. The treatment of renal trauma was categorized as renal-related operative management (RROM, including the following: nephrectomy (55.5), partial nephrectomy (55.4), renorrhaphy (55.81), nephrostomy tube placement (55.02-55.03), RAE or angioembolization (39.7928) and conservative treatment (including treatments in addition to the above two groups of renal injury patients). Conservative treatment was considered successful if renal-related surgery or RAE was avoided, even in patients who underwent surgery or interventional therapy that was unrelated to the kidney.

Data on gender, age, characteristics and mechanism of renal trauma, length of hospital stay (LOS), hematuria, clinical findings on presentation (blood pressure, heart rate), CT or ultrasonography findings, associated injuries, management and outcomes were recorded. Imaging for all patients was retrospectively reviewed by a radiologist experienced in renal trauma and graded using the AAST organ injury severity scale (Table-1) (Figure-1) (23).

**Figure1 - Renal trauma staging.**



Descriptive statistics were conducted to estimate the characteristics of all patients. Continuous data that were normally distributed (i.e., age) were expressed as the mean and standard deviation (SD), and those that were not normally distributed (i.e., LOS) were described using the median (interquartile range, IQR), and the between-group differences were assessed with independent-sample t tests. Categorical variables are presented as numbers and percentages and tested for differences using the Pearson  $\chi^2$  test.

Hospital A began to perform RAE for renal trauma in January 2012, but hospital B had not applied RAE for renal trauma in the same period. We therefore performed the following statistical analyses: (1) between-group comparisons of the operative rate of RROM at hospital A between 2006-2011 and 2012-2015 (Pearson  $\chi^2$  test); (2) comparison of the conservative treatment rates for LGRT at hospitals A and B between 2006-2011 and 2012-2015 (Pearson  $\chi^2$  test); and (3) relevant factors for interventional therapy (multivariate logistic regression analysis after the Pearson  $\chi^2$  test and independent-samples t-test). The association of relevant factors with interventional therapy stratified by renal AAST injury grade was determined by logistic regression analyses, with low-

-grade as the reference category. Statistical analyses were performed using SPSS software package (SPSS 23.0 for Windows; SPSS, Chicago, IL, USA), and statistical significance was determined at two-sided  $p < 0.05$ .

## RESULTS

There were 264 and 304 renal trauma patients admitted to hospitals A and B, respectively, over the 10-year period. On average, approximately 26 and 30 patients with renal trauma presented per year to hospitals A and B, respectively. There was no statistically consistent change in the number of admissions per year over this study period ( $P > 0.05$ ).

Table-2 presents the outcome data for all patients with renal trauma treated at the two hospitals. Of the 434 men and 134 women included in the study, the mean age was 33.11 years. The mechanism of injury was blunt in 87.9% of patients and occurred secondary to the following three causes: falls (38.9%), road traffic-related injury (36.3%) and injury due to being hit by a blunt object (12.7%). A total of 69 (12.1%) patients presented with penetrating renal trauma. The above data were not significantly different between the two hospitals.

**Table 2 - Basic information of the renal trauma patients admitted to hospitals A and B during 2006-2015.**

	Hospital A (N=264)	Hospital B (N=304)	<i>p</i>
Male(%)	200 (75.8)	234(77)	0.733
Age, mean(SD), year	33.59(17.13)	32.63(16.69)	0.499
Hematuria	207(78.4)	220(72.4)	0.096
<b>AAST, (%)</b>			<b>&lt;0.001</b>
I-III	252(95.5)	270(88.8)	
IV-V	12(4.5)	34(11.2)	
LOS, median (IQR), day	20.5(14.00,34.00)	16.0(9.00,30.00)	<0.001
Cost, median (IQR), RMB	16483.7(7888.72,43857.72)	15950.9(8408.51,33042.57)	0.189
Associated lesions, (%)	159(60.2)	253(83.2)	<0.001
<b>Mechanism of injury, (%)</b>			<b>0.533</b>
Blunt	233(88.3)	263(86.5)	
Penetrating	31(11.7)	41(13.5)	

The mean LOS for renal trauma patients over the 10-year study period was 20.5 and 16.0 days at hospitals A and B, respectively. There was no consistent change in the mean LOS per year over this study period.

According to the AAST renal injury grading system, the patients were classified as grade I, II, III, IV and V renal injury in 245 (43.1%), 186 (32.7%), 91 (16.0%), 35 (6.2%), and 11 (1.9%) patients, respectively. The majority of the patients (72.5%) had associated injuries.

Of the 568 renal trauma patients, 534 (94.0%) were treated conservatively (including the patients who underwent surgery and interventional therapy that was unrelated to the kidney). No patient treated with observation underwent renal-related surgery or RAE. All patients with grade I trauma were managed

conservatively. The renal-related surgery rate increased from 1% among patients with AAST grade II injuries to 7.7% in those with grade III injuries to 22.9% in those with grade IV injuries to 72.7% in those with V injuries. RAE was performed in 9 patients from 2012 to 2015 at hospital A, including 6 patients (6/9, 66.7%) with LGRT, and 3 patients (3/12, 33.3%) with HGRT. No patient underwent interventional therapy (RAE) at hospital B during the same period.

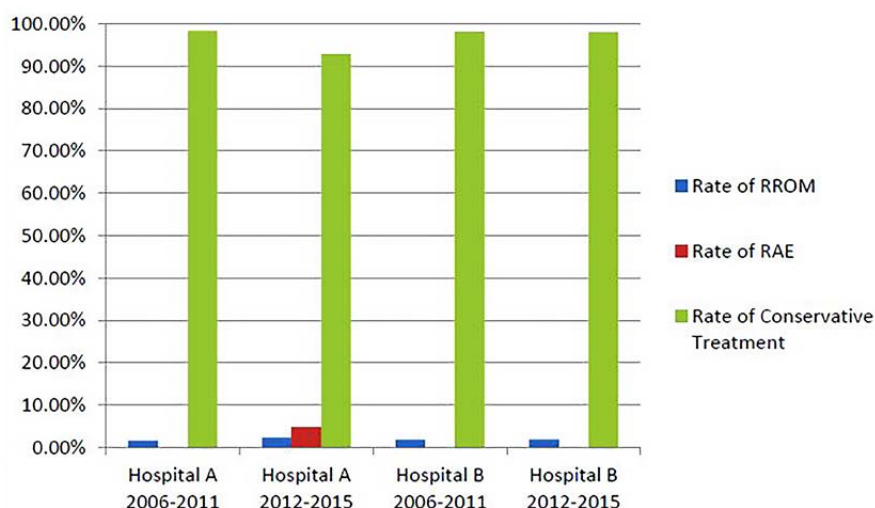
As presented in Table-3, there were no significant differences in the operative rate at hospital A between the two time periods (2006-2011 and 2012-2015) ( $p < 0.05$ ). At the same time, the operative rate for LGRT between two hospitals in 2006 to 2011 and 2012 to 2015 was not significantly different (all  $p < 0.05$ ) (Figure-2). The operative rate for LGRT was not reduced due to the

**Table 3 - Comparison of the operative rates of patients with renal injury between 2006-2011 and 2012-2015 at hospital A.**

	2006-2011 N=133, n(%)	2012-2015 N=131, n(%)	<i>p</i>	$\chi^2$
Treatment			0.683	0.22
Non-RROM*	131 (98.5)	128 (97.7)		
RROM	2(1.5)	3(2.3)		

\*including RAE and NOM.

**Figure 2 - Comparison of the nonoperative rates for LGRT at hospitals A and B between 2006-2011 and 2012-2015. The conservative treatment rates of hospital A decreased from 98.41% to 92.86% ,with significantly different between two periods ( $p=0.008, \chi^2=9.761$ ). The conservative treatment rates of hospital B were not significantly different between two periods ( $p=0.557, \chi^2=0.345$ ).**



implementation of interventional therapy. However, hospital A showed a significant decrease in the rate of conservative treatment for patients with LGRT, which may be the reason for some patients undergoing interventional therapy.

In the univariate analyses, the AAST renal grade was significantly associated with undergoing RAE. Additionally, in the multivariate analysis, only the AAST renal grade (odds ratio [OR], 13.56; 95% confidence interval [CI], 2.91-63.06) was significantly associated with undergoing RAE (Table-4).

## DISCUSSION

Conservative treatment is currently the standard of care for LGRT and is increasingly recommended for majority of patients with HGRT if they are hemodynamically stable. Our findings from this 10-year retrospective review including data from two major comprehensive hospitals show that approximately 94.0% of renal trauma patients are managed conservatively (including patients who underwent surgery and interven-

tional therapy that was unrelated to the kidney). No one patient required conversion for further treatment.

Patients with LGRT had a higher success rate with conservative treatment (96.94%). This is consistent with the results of previous literature (15-20) as well as the guidelines (2, 14) on the choice of treatment for renal trauma. Furthermore, we found that patients with HGRT (27/46, 58.70%) also had good outcomes. However, all the patients who were successfully managed with conservative treatment had grade IV renal injury; one patient with grade V renal injury died due to multiple organ trauma, and the rest required surgical treatment (9 cases) or interventional treatment (1 case).

Interventional therapy as an effective treatment for renal trauma has been widely used. The application of interventional therapy enables the patient to avoid the risk of kidney resection and retain as much renal function as possible while reducing trauma to the patient. The EAU guidelines recommend that angioembolization has a central role in the nonoperative

**Table 4 - Univariate and Multivariate Logistic Regression Model for Predicting RAE.**

Characteristics	Univariate OR(95% CI)	<i>p</i>	Multivariate OR(95% CI)	<i>p</i>
Age, y	0.98(0.94-1.02)	0.34	-	-
LOS, mean, d	1.00(1.00-1.01)	0.51	-	-
Sex	2.63(0.32-21.40)	0.37	-	-
Hematuria (yes/no)	2.25(0.28-18.38)	0.45	-	-
Cost	1.00(1.00-1.00)	0.23	-	-
Associated lesions (yes/no)	0.52(0.14-1.97)	0.33	-	-
<b>Mechanism of injury</b>				
Blunt	1.00(ref.)		-	-
Penetrating	0.94(0.11-7.76)	0.95	-	-
Shock (yes/no)	0.54(0.06-4.59)	0.57	-	-
Tachycardia (yes/no)	2.00(0.52-7.64)	0.31	-	-
AAST renal grade				
LGRT	1.00(ref.)		1 (ref.)	
HGRT	13.677(2.94-13.58)	0.001	13.56(2.91-63.06)	0.578~2.215

management of blunt renal trauma in hemodynamically stable patients (15-17). Currently, there are no validated criteria to identify patients who require angioembolization, and its use in renal trauma remains heterogeneous. Generally accepted CT findings indicating angioembolization are active extravasation of contrast, arteriovenous fistula and pseudoaneurysm (24). The presence of both active extravasation of contrast and a large hematoma (>25 mm depth) predict the need for angioembolization with good accuracy (24, 25). In fact, angioembolization has been utilized in the nonoperative management of patients with all grades of renal trauma; however, it is likely to be most beneficial in the setting of HGRT (AAST >3). According to our results, we found that RAE can be used as an effective treatment for renal trauma, even HGRT. Two patients with grade IV trauma and one patient with grade V trauma were treated with RAE and had good outcomes. The same findings were described by Hotaling (26), who believed that patients with HGRT could receive interventional therapy if they were hemodynamically stable and that good results could be obtained. However, close observation of vital signs should be ensured, and secondary embolization or surgical treatment should be performed in a timely manner if necessary. This is a significant change from the previous view that patients with HGRT are not suitable for interventional therapy.

However, we also compared the operative rate before and after the application of RAE to the treatment of patients with renal trauma at hospital A ( $p < 0.05$ ) and found no significant difference. The application of RAE did not significantly reduce the operative rate of patients with renal trauma at hospital A. In the patients who were treated with interventional therapy, 66.67% (6/9) were LGRT patients. We compared LGRT patients who underwent conservative treatment at the two hospitals during different periods. Hospital A utilized interventional therapy for some LGRT patients, so the conservative treatment rates decreased significantly ( $p = 0.008$ ,  $\chi^2 = 9.761$ ). At the same time, hospital B maintained the original treatment, and the conser-

vative treatment rates were not significantly different ( $p = 0.557$ ,  $\chi^2 = 0.345$ ) (Figure-2). The above results suggest that RAE did not reduce the operative rate of patients with renal trauma, especially those with LGRT, and reduced the conservative treatment rate of patients with LGRT. Thus, some patients with LGRT may have unnecessarily undergone interventional therapy. According to the literature (22, 27), different diagnoses and treatment protocols may be used or different clinicians may have different understandings of the indications for interventional therapy based on their own experience, which may lead to unnecessary interventional therapy for some patients.

This result leads us to think about which are the relevant factors for RAE. We performed a statistical analysis of single and multiple factors related to RAE and found that the AAST grade was an independent factor associated with RAE for renal trauma. Multivariate analysis showed that only the AAST grade was associated with RAE for renal trauma. Previous literature and guidelines have highlighted the same perspective and suggested that HGRT (AAST >3) should be a relevant factor for RAE. Therefore, we prefer to recommend interventional treatment in patients with HGRT.

Although RAE is a minimally invasive technique with decreased trauma and improved repeatability, there are still inevitable complications that may impart significant morbidity to trauma patients. Complications of RAE, such as pain, infection, hemorrhage, ectopic embolization, pseudoaneurysm, arteriovenous fistula, and arterial dissection have been reported (28-30). Although complications were not found in our study, some patients still bear the risk of complications. Furthermore, the average hospitalization cost for interventional therapy patients and other patients was 61337.3 RMB and 37006.2 RMB, respectively. The average LOS for interventional therapy patients and other patients was 43.22 days and 31.42 days, respectively. Patients who underwent RAE incurred higher expenses and had a longer LOS than those who underwent other treatments, although there was no significant difference between them.

## CONCLUSIONS

The results of this study showed that LGRT accounted for the majority of patients, and most renal trauma patients could be successfully treated with conservative treatment. RAE is a minimally invasive technique that is well utilized for the treatment of renal trauma. Good outcomes can be achieved in HGRT patients, and HGRT is also recommended as an indication for RAE. However, some patients with LGRT who should receive conservative treatment were treated with unnecessary interventional therapy. This may lead to increased hospital costs and LOS.

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## COMPLIANCE WITH ETHICAL STANDARDS

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

## CONFLICT OF INTEREST

None declared.

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# Training of Brazilian Urology residents in laparoscopy: results of a national survey

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## ABSTRACT

**Objectives:** To evaluate the familiarity of Brazilian urology residents with laparoscopy, methods of training and perspectives.

**Material and methods:** a questionnaire with 23 questions was sent by e-mail to all urological residents of 86 Urology Residence Programs certified by the Brazilian Society of Urology (BSU).

**Results:** 225 valid answers (85% of all residents) responded. Most residences belong to academic hospitals mainly in the Southeast region of Brazil. Women account for 5% of residents and 82% of programs perform less than 100 procedures per year. Residents have access to LESS, RAL and 98% to surgical laparoscopy and 87% of these participate actively at the surgery, but 84.9% do not have access to RAL. The most common laparoscopic procedure is radical nephrectomy (73.2%), but only 28.8% of residents acted as surgeons, and third year residents (R3) are those that mainly performed this procedure (statistical significance,  $p < 0.05$ ). 61% of residents do not participate in hands-on courses or fellowship in laparoscopy, among those who attended these fellowships, 23.47% were sponsored by BSU in equal regions of the country. Although there are several opportunities of training in laparoscopy, 42% of residents do not have access to any kind of preparation and 52% have no structured specific program. R3 perception of laparoscopy experience is significantly higher than R2 and R1 residents. Almost 30% of them affirms that they are prepared for professional life regarding urologic laparoscopy.

**Conclusion:** Brazilian urologic residents have access to laparoscopy and actively participate in the learning process. Robotic surgery is expanding in the country, although still very far from residents. Brazilian resident, at the end of medical residency, is motivated to perform laparoscopic procedures.

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## INTRODUCTION

Over the last 20 years, laparoscopic surgery has gained popularity in Urology, reducing morbidity, convalescence period and with improving results, and has become the gold standard treatment of many urologic diseases (1-3). However, until

nowadays training in laparoscopy is challenging in underdeveloped countries, frequently, public health services do not provide this treatment and availability of experienced urologist is insufficient (4, 5). With consolidation, more complex procedures were incorporated, and Urology Residence Programs (URP) could not accompany this evolution. Part

of the problem is caused by the learning process based on Halsted (1889): “see one, do one, teach one”. This aphorism is very useful to open surgery, but for laparoscopy is inadequate, since the procedure requires acquisition of skills, and a more step-by-step model must be used. This is challenging to most Brazilian URPs (6, 7). There are several evidences that an adequate training helps achieving proficiency in laparoscopy (6-8). Therefore, it is ideal that a residence program contains a well-structured learning skill program in urologic laparoscopy, that performs most of available procedures (3, 9, 10).

In Brazil, most urology residents do not have access to laparoscopic training (11). Therefore, it is important to know the reality of training in urologic laparoscopy among Brazilian residents in order to improve and develop resources for better training (1).

The objective of the present study is to evaluate the access of Brazilian urology residents to laparoscopy surgery and the pattern of training in urologic laparoscopy.

## **PARTICIPANTS AND METHODS**

A question form containing 23 questions was proposed, based on the study of Furriel et al. (7). After review of the Teaching and Learning Commission of Brazilian Society of Urology (TLC-BSU), the questionnaire was published in an online questionnaire specialized website ( Survey-Monkey™, Palo Alto, USA) that was sent by email to all residents of the 86 Residence in Urology Programs (URP) certified by BSU. The question forms were sent again three times every 15 days. It was established a period of 6 months (July 2016 to January 2017) for answer.

The questionnaire evaluated five main aspects: i. Personal and professional characteristics of residents: ii: resident access to laparoscopy, iii: resident experience with laparoscopy, iv: training in laparoscopy and v: motivation and future perspectives.

The answers were included in a database and analyzed by descriptive statistical methods using IBM SPSS Statistics Version 21.0 software (IBM, New York, USA).  $X^2$  test was used to com-

pare quantitative variables among groups.  $P < 0.05$  was considered statistical significant.

## **RESULTS**

Among 265 residents of all URP certified by BSU at the time of the study, 225 (85%) answered the questionnaire.

### **Personal and professional characteristics of Urology residents**

Demographic data are presented at Table-1. Women are less than 5% of residents, most are from Southeast region and in academic hospitals (68%). Almost half of responders (48.9%) are last year residents and 16% of first year. Around 82% of URPs perform less than 100 laparoscopic procedures/year for resident training and 5% more than 250 procedures/year.

### **Access of residents to laparoscopy**

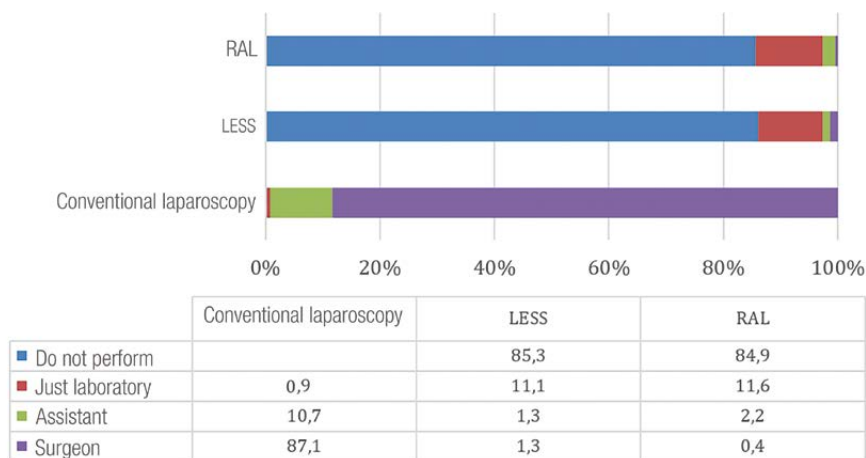
Brazilian residents follow different surgical techniques such as conventional laparoscopy, single site laparoscopy (LESS) and robotic surgery (RAL), a sub-analysis of laparoscopic techniques showed that almost all residents (98%) accompany conventional laparoscopy and only one resident answered that did not have access to laparoscopy (Figure-1). Considering this URPs characteristic, residents are able to participate in laparoscopic procedures as auxiliary surgeon or as first surgeon in up to 87% of procedures. Also, 85.3% and 84.9% of residents have no access to LESS and RAL, respectively.

### **Experience of residents in laparoscopy**

Residents were asked about their experience as surgeons in specific procedures (Table-2). Most performed laparoscopy procedure was radical nephrectomy (73.2%) but only 28.8% acted as surgeon. Next, it was informed pyeloplasty (56.8%) and marsupialization of renal cyst (54.4%). Less performed surgeries included radical cystectomy, probably due to its high complexity, and sacrum-promontory-fixation. Procedures that require higher skills such as partial nephrectomy and radical prostatectomy were not performed by 56.7% and 69.9% of residents, respectively.

**Table 1 - Demographics and services characterization.**

Variable	Frequency	%
<b>Sex</b>		
Male	212	95,5%
Female	10	4,5%
No reply	3	
<b>Age years</b>		
26-30	109	49,1%
31-35	105	47,3%
36-40	5	2,3%
>40	3	1,4%
No reply	3	
<b>Hospital Type</b>		
Academic	151	68,0%
Non-academic public	45	20,3%
Private	26	11,7%
No reply	3	
<b>No. of PRU residents</b>		
1-3	52	23,3%
4-6	112	50,2%
7-9	39	17,5%
>9	20	9,0%
No reply	2	
<b>What is your year of residence in Urology? (Outside General Surgery)</b>		
1st year	36	16%
2nd year	77	34,2%
3rd year	110	48,9%
No reply	2	
<b>How many urological laparoscopic procedures are performed on the PRU per year?</b>		
None	2	0,9%
1-50	94	42,3%
51-100	88	39,6%
101-250	27	12,2%
>250	11	5,0%
No reply	3	

**Figure 1 - Participation of residents in surgeries.**

LESS = Laparo-endoscopic single site; RAL = Robotic Assisted

According to year of residency, when residents performed laparoscopic procedures as first surgeons (Table-3), third year residents are the most frequent to perform radical nephrectomy as first surgeon, with statistical significance ( $p < 0.05$ ). If we consider marsupialization of renal cyst, there are no statistical difference between R3 and R2, although significantly different of R1.

#### Laparoscopic Training of Residents

The study asked residents about the available opportunities to attend hands on or fellowship in urologic laparoscopy. As shown in Figure-2. 61% of residents do not participate in any training during their URP. Among those who attended, 23.47% are promoted by BSU and it is important to draw attention to the fact that 11.22% attended those trainings promoted by other medical societies.

When they were asked about the structure of their services, 52% of residents responded that there was no specific laparoscopy training program during residence.

Most opportunities of training are parted, as shown in Figure-3, however, almost 42% of residents have no access to any training in laparoscopy.

When analyzed according to the region of Brazil, there is no statistical difference among residents that attend BSU courses, demonstrating

an equal distribution of trainings among different regions of Brazil (Table-4).

#### Motivation and future perspectives

Residents were also questioned about their current laparoscopic experience (at the time of questionnaire) (Figure-4a). R3 perception, as expected, had more answers of "satisfactory", "good" and "very good", significantly different of R2 and R1s. However, at the end of residence, 15.5% of R3 answered "very poor" or "poor" (21.6%), indicating that 37.1% judged themselves unprepared for urologic laparoscopy.

Finally, they were asked about their expectations of laparoscopic experience at the end of residence (Figure-4b). It is observed that there are no statistical differences between R1 and R2, and R3. Both groups have good expectations at the end of residence.

#### DISCUSSION

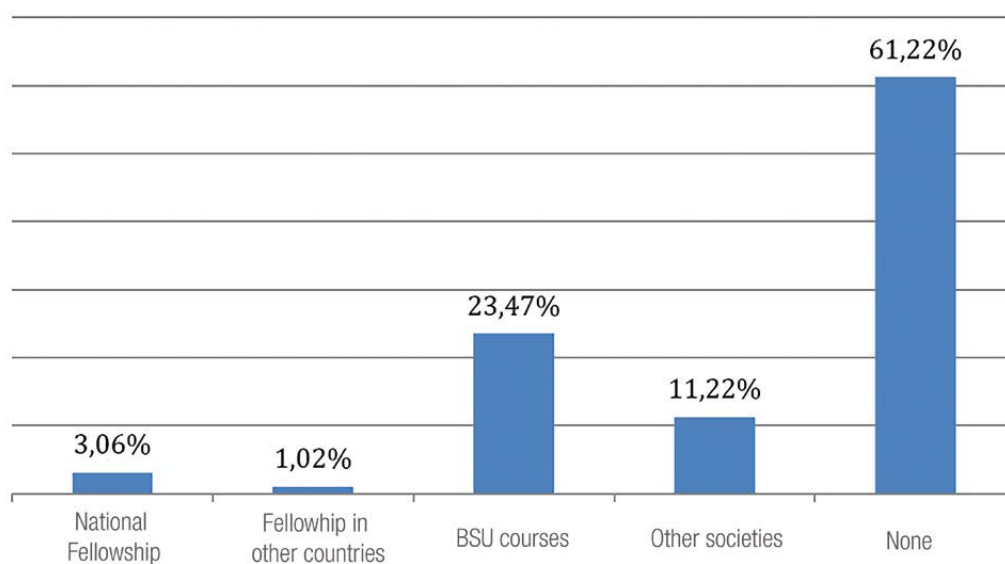
In order to change Brazilian urology, to incorporate new technologies, it is important to invest in medical learning in Brazilian URPs. It is challenging to introduce laparoscopic training in a poor underdeveloped country, particularly in public health services URPs. The need is overwhelming, as demonstrated by the high answer of

**Table 2 - Laparoscopic surgeries performed by residents as a surgeon.**

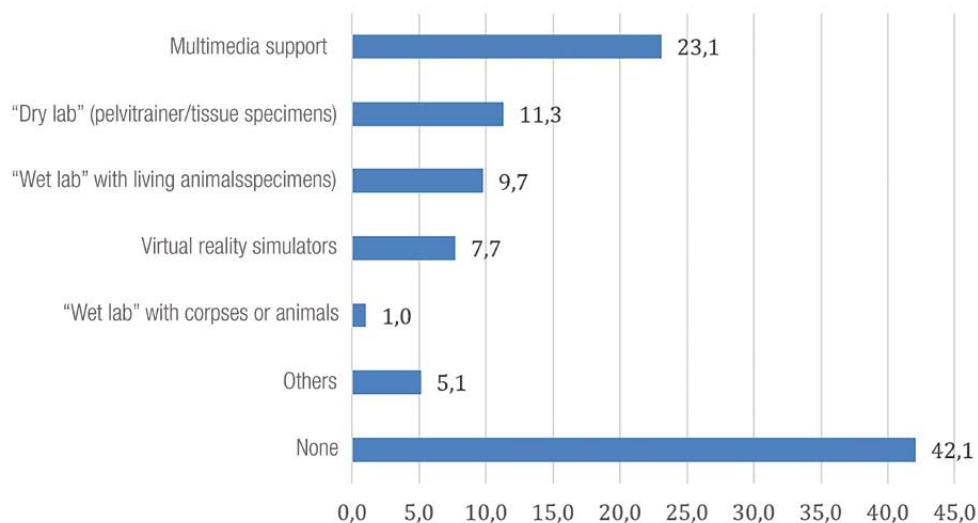
Procedure	Number of procedures	Residents	
		Frequency	%
<b>Total nephrectomy</b>	None	43	26.9
	1 a 10	71	44.4
	> 10	46	28.8
<b>Partial Nephrectomy</b>	None	80	56.7
	1 a 10	57	40.4
	> 10	4	2.8
<b>Renal cryoablation</b>	None	107	93.0
	1 a 10	8	7.0
<b>Pyeloplasty</b>	None	63	41.4
	1 a 10	86	56.6
	> 10	3	2.0
<b>Adrenalectomy</b>	None	79	56.4
	1 a 10	61	43.6
<b>Renal cyst marsupialization</b>	None	68	45.6
	1 a 10	79	53.0
	> 10	2	1.3
<b>Radical prostatectomy</b>	None	93	69.9
	1 a 10	28	21.1
	> 10	12	9.0
<b>Radical cystectomy</b>	None	108	90.8
	1 a 10	10	8.4
	> 10	1	0.8
<b>Promonto-fixation</b>	None	100	85.5
	1 a 10	16	13.7
	> 10	1	0.9
<b>Varicocelectomy</b>	None	98	79.0
	1 a 10	23	18.5
	> 10	3	2.4
<b>Orchidopexy</b>	None	90	66.2
	1 a 10	41	30.1
	> 10	5	3.7
<b>Lithiasis surgery</b>	None	64	43.2
	1 a 10	61	41.2
	> 10	23	15.5

**Table 3 – Year of residence in which the resident performs the procedure as a surgeon.**

	Year of first procedure			Responders
	1st year	2nd year	3rd year	
Total nephrectomy	5.8%	33.1%	61.2%	103
Partial Nephrectomy	6.0%	22.0%	72.0%	50
Renal cryoablation	50.0%	12.5%	37.5%	8
Pyeloplasty	7.9%	21%	70.1%	76
Adrenalectomy	5.9%	15.7%	78.4%	51
Renal cyst marsupialization	12.9%	37.2%	50%	70
Radical prostatectomy	-	31.2%	68.8%	32
Radical cystectomy	-	20.0%	80.0%	10
Promonto-fixation	17.6%	35.3%	47.1%	17
Varicocelectomy	34.8%	30.4%	34.8%	23
Orchidopexy	23.1%	30.7%	46.2%	39
Lithiasis surgery	11.6%	34.8%	53.6%	69

**Figure 2 - Hands on or fellowship in urologic laparoscopy.**

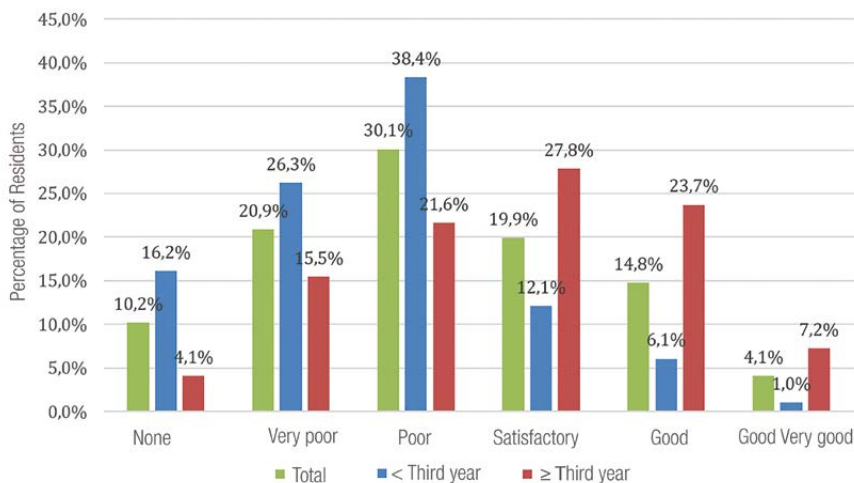
**Figure 3 - Available trainings at residence.**

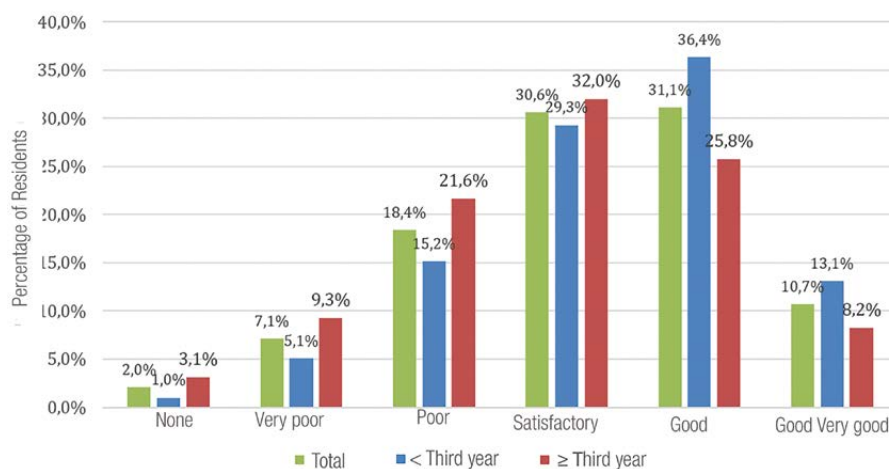


**Table 4 - Participation of residents distributed by region.**

	Region					
	Total	North	Northeast	Midwest	Southeast	South
Fellowship in national hospital	3.1%	0.0%	2.6%	5.6%	3.6%	0.0%
Fellowship other countries Hospital	1.0%	16.7%	0.0%	0.0%	0.9%	0.0%
Course promoted by SBU	23.5%	33.3%	25.6%	22.2%	24.1%	14.3%
Course promoted by other societies	11.2%	0.0%	12.8%	11.1%	10.7%	14.3%
I never attended a course or fellowship	61.2%	50.0%	59.0%	61.1%	60.7%	71.4%

**Figure 4a - Laparoscopic experience at the time of questionnaire.**



**Figure 4b - Expectations of laparoscopic experience at the end of residence.**

Brazilian residents (85%), compared to Italy (72.6%), Portugal (71.6%), Spain (68%), Germany (65%) and only 3.1% in European Community (1, 7, 12).

It was shown that there is a higher concentration of residents in the southeast region of Brazil. That region presents the higher demographic density and higher concentration of hospitals and teaching institutions (13). As in Europe, the higher number of residents belong to academic institutions (68%), reinforcing the teaching bias of medical residence (7). Mean age of residents was 26 to 30 years, mainly males. In Italy and Portugal, 22% and 13% respectively are female (1, 14), while in Brazil only 4.5% are female. Otherwise, in Germany, most urology residents are female (55%) (15).

The amount of laparoscopic training (access to laparoscopy training offered by URP) reflects the future integration of the professional with advanced laparoscopic skills, characteristic of the specialty (16-18). Our results indicate that most residents (98%) have access to laparoscopy, but only 87% participate as surgeon. Therefore, in 12% of URPs there are laparoscopic surgeries but not training, the residents act only as auxiliary surgeons and only 1% attend only laboratory. This difference is related to the fact that the preceptor has a learning curve (institutional learning) and/or the preceptor is responsible for the patient and not the URP (11). In Europe, 78.8% of

residents have access to laparoscopy, 56% in Germany, 25.8% in Italy and 100% in USA (1, 16, 12). 14.7% and 15.1% of Brazilian residents have access to most recent technologies such as LESS and RAL, similar to 17% of European residents (7). In USA and Canada, countries with a great number of platforms, 54% and 36% have robotic training (16, 19). It is important to stress that in the year when the questions forms were applied, in Brazil there were only 10 da Vinci® platforms; at present, there are 41 robotic platforms with a perspective of 15% of year growth (industry data).

On the other hand, Brazilian residents act more as surgeons (87%) if compared to European residents (27%) and Portuguese residents (32.7%) (1, 7). This huge difference may be related to the methodology of the question form, that may be interpreted differently in the different countries of European Community and lack of clear definition of which participation percentage as surgeon is related to this denomination. Another possible explanation is that we reproduce the teaching methodology of open surgery, where “doing” is sooner (“see one, do one, teach one”).

General surgery residence (GS) initiates surgical learning, including laparoscopy, and is mandatory for urologic training. At present, most Brazilian GS residences include training in initial laparoscopy (11). Only 6.3% of residents answered that they had no training in laparoscopy during

general surgery residence, but among those 93% that experienced it, 26% indicated a bad training. The others evaluated positively their laparoscopic preparation before joining an urology residence. Therefore, almost one third (27.7%) of residents that joined the URP have an inadequate initial laparoscopic training. Those must be identified and offered complementary training to overcome this deficiency to not jeopardize the urology laparoscopic training. Hands on courses and immersion programs may help this task.

This study shows that the main form of teaching in Brazil is still direct training in patients of URP programs, under the supervision of preceptors, as observed in other studies (20), therefore, the learning curve of most urologic procedures is slower, since it is not possible to have an equal number of procedures (21, 22), and the number of laparoscopic procedures is very important to acquisition of skills. It is worrisome that 42.3% of URPs of Brazil do not perform more than 50 laparoscopic procedures/year. In 82%, less than 100 procedures/year. Also, it must be taken in consideration that there are at least two residents (R2 and R3) to share laparoscopic procedures and that only 30% of URPs have 1 resident/year, 48.8% have 2 residents/year, 11.2% have 3 residents/year, and there are residences with up to 8 residents/year (BSU Teaching and Learning Commission data). Training must include several procedures. Borgmann et al. referred that in order to increase exposition of residents to laparoscopy, the best way is to reduce the number of residents/year (15).

The time of access to learning is important during resident training (22). That study indicated that 33%, 34% and 33% of residents have experience as first urology laparoscopy surgeon during R1, R2 and R3, respectively. This equal distribution means a priori that a step-by-step approach is being implemented at the URPs in relation to laparoscopic training. Two other aspects may explain this high number during first year of residence: they finish GS training with adequate skills and incorporated less complex procedures to laparoscopic techniques.

The most performed procedure, as in the European study, was laparoscopic radical nephrec-

tomy (LRN), since this procedure is the gold standard for the treatment of renal tumors, when it is not possible to perform partial nephrectomy (PN) (2). This information may direct URPs to which procedure adopt to initiate laparoscopic training. In Brazil, LRN is performed by 61.2% and 33.1% of R3 and R2, respectively. This may raise a discussion about if LRN may be performed by R2 as prerequisite for R3 LPN. In Brazil, 73.2% of residents perform at least one LPN during their residence, in contrast to one third of European residents (7).

In sequence, the most performed procedures are pyeloplasty, marsupialization of renal cyst, and stone laparoscopic surgery. A possible explanation is that these are abdominal surgeries similar to those learned during general surgery residence. In this context, more difficult technical procedures, specially pelvic surgeries, such as radical prostatectomy and cystectomy are performed by less number of residents. Also, partial nephrectomy is not performed by more than 50% of residents. This fact may be explained that this is a complex procedure and was recently considered gold standard for T1 and T2 tumors (2).

Ideally, training programs must develop several basic skills in order to the residents feel comfortable to perform laparoscopy in their subsequent practice (9, 6). In Brazil, more than 80% of URP do not evaluate proficiency in laparoscopy before surgery in humans and less than half of services have a specific teaching laparoscopy program (5). These data corroborate the difficulty of URPs to change the teaching methodology to a step-by-step approach, maintaining the traditional Halsted approach for open surgery.

An alternative for this change of teaching paradigm is training in simulator laboratory. It improves significantly the resident skills and is associated to several advantages, including speed and quality, particularly in this initial phase of training in special if present in the URP itself (3, 6, 9, 22-24). In our study, 42% of URPs do not have any training facility for laparoscopy. In Portugal, it is observed in 35.7% of URPs and in 41.7% of European Community URPs (1, 7).

A little more than 20% have a video database, drylab (11%), wetlab (9%) and virtual reality simulators (7%). Even when available, 76%

of support laboratories are not structured to teach programs. The final objective of a simulator program is to show the possibility of transference of acquired skills at the laboratory for the clinical scenario, allowing for objective quantification of operational clinical performance following the simulator training (24).

In a recent analysis about laparoscopic training in GS residences in Brazil, Nácúl et al. (11) affirmed that the failure of a good professional training is related to the lack of a pedagogic model based on intensive courses. It not provides surgical experience for an adequate and safe laparoscopic performance. This modality, that should have been used for punctual situations, is been used for replacement of insufficient training (25).

The lack of a facility is related that most residents never attended to hands on or fellowship laparoscopic courses, but most answers were pointed by R1 and R2 residents. Those who attended any course were sponsored by Brazilian Society of Urology and most were R3. Most residents, particularly R3, are motivated to perform laparoscopic surgeries at the end of the course. In this scenario, 60% of residents intend to join a fellowship at the end of residence, in order to complement training with more advanced procedures/techniques or as a sign of unprepared training.

Teaching process premises a constant feedback with the student (22). Most residents negatively evaluate their current experience in laparoscopy. This initial worrisome fact is observed in all residents, including R1, that are initiating their laparoscopic urological training. However, according to the year of residence, R3 are more positive, indicating confidence and skill gain. At the end of the course, 72% had a positive estimative.

One limitation of the present study is that the questionnaire was responded by all residents and not only by R3, underestimating the skills. Most responders were first year residents indicating a bias on the performance of laparoscopy. However, it is important to remind that those same residents will have opportunities to improve their skills over residence. Another aspect is that all answers were individual and subjected to individual interpretation, the differences among Bra-

zilian regions diffculted an homogeneous question form answer.

## CONCLUSIONS

Urologic residents in Brazil, in general, have access to laparoscopy and participate actively in the learning program, although with a limited number of procedures. With the expansion of robotic surgery in Brazil, and the inevitable replacement as main surgical modality, it is expected that residence programs also include this new reality in their teaching programs.

Although there are pedagogic errors based on the old model of learning or surgical techniques, with the endorsement of Brazilian Society of Urology and other medical societies, that incentive the attendance to preparatory courses of laparoscopic surgeries, the Brazilian resident, at the end of his program, is motivated to perform laparoscopic procedures.

## CONFLICT OF INTEREST

None declared.

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## Editorial Comment: Training of Brazilian urology residents in laparoscopy: results of a national survey

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Over the last two decades we have seen the development of the minimally invasive surgery (MIS) on the Urology field and laparoscopy was the main part of it, considered as a great option for many of the urological conditions.

The laparoscopic procedures, as in other specialties, became popular by reducing morbidity, convalescence period and showed good results at the literature, becoming attractive for most of urologists.

On this paper, the authors evaluate the access of Brazilian urology residents to laparoscopy surgery, methods of training and perspectives (1).

The Brazilian paper showed a nice response rate (85% of residents) and most of the medical doctors were from the academic hospitals. The most common laparoscopic procedure was radical nephrectomy (73.2%), but less than one third (28.8%) of residents acted as surgeons.

On other nice study about the same issue, surgeons from Portugal compared themselves training with the rest of Europe, showing that all of them had good access to laparoscopic procedures, mostly as assistant (2).

Among the Europeans, the most commonly performed procedure was total nephrectomy also. Most residents rate their motivation to perform laparoscopy in the future as “High” or “Very High”, and plan performing a post-residency fellowship in this field.

On Brazil, 61% of residents did not participate in hands-on courses or fellowship in laparoscopy and almost 30% of them affirms that they are prepared for professional life regarding urologic laparoscopy. A number that is suboptimal for the urology market after the learning period.

Van der Poel et al. (3) also studied the training in minimally invasive surgery at the European Association of Urology. As the Brazilian authors, they showed that the training in MIS has shifted from ‘see-one-do-one-teach-one’ to a structured learning, from e-learning to skills laboratory and modular training settings (4).

The authors concluded that Brazilian urologic residents have access to laparoscopy and actively participate in the learning process and that this should be encouraged.

There is new scenario at the surgery specialties. Robotic surgery has become the new revolution in modern surgery, combining all the benefits of minimally invasive surgery with the advantage of three dimensions (3D) and better intracorporeal instrumentation. It is rapidly expanding in South America, mainly in Brazil, although still very far from most of the hospitals. The Urology staff must be prepared to teach our future residents at this new technology.

### CONFLICT OF INTEREST

None declared.

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# Predictive and prognostic impact of preoperative complete blood count based systemic inflammatory markers in testicular cancer

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## ABSTRACT

**Purpose:** To determine the utility of preoperative complete blood count (CBC) based systemic inflammatory markers in the prediction of testicular cancer and its prognosis.

**Material and Methods:** Between 2008-2017 the data of all testicular tumor patients undergoing radical orchiectomy were retrospectively analyzed. Patient baseline characteristics (age, tumor stage, tumor markers, etc.) and results of routine preoperative blood tests including mean platelet volume (MPV), red cell distribution width (RDW), lymphocyte ratio (LR) and neutrophil ratio (NR) were retrieved. In addition, neutrophil to lymphocyte ratio (NLR) was calculated.

**Results:** Mean age of the tumor and control group was  $36.0 \pm 15$  and  $30.50 \pm 11$  years, respectively. Mean RDW, NR and NLR were significantly higher in the tumor group with  $p$  values  $< 0.001$ ; whereas LR and MPV were significantly higher in the control group ( $p < 0.001$ ). Receiver Operating Characteristic (ROC) analyses of LR, NR, RDW, MPV, and NLR are shown in Table-3. The cut off values for RDW and NR were found as 13,7 (Area under the curve (AUC): 0.687, sensitivity = 42.2%, specificity = 84.8%) and 55.3 (AUC:0.693, sensitivity 72.2%, specificity 62%), respectively. Area under the curve for NLR in tumor group was 0.711, with a threshold value of 1.78 and sensitivity=81.8% and specificity=55.4% (AUC:0.711/sig<0.001) that together with RDW exhibited the best differential diagnosis potential which could be used as an adjuvant tool in the prediction of testicular tumor and its prognosis.

**Conclusion:** Several systemic inflammatory markers, which are obtained by routinely performed cost-effective blood tests, could demonstrate incremental predictive and prognostic information adjuvant to preoperatively achieved testicular tumor markers.

## ARTICLE INFO

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## INTRODUCTION

Testicular cancer is the most common malignancy in men between the ages of 20-40 and constitutes about 1-1.5% of all cancers. Mainly, it can be classified as germ cell, sex cord-gonadal stromal and secondary testicular

tumors (1). Clinical admission, in daily urology practice, is usually due to painless testicular mass, while serum tumor markers (human chorionic gonadotropin (HCG), alpha-fetoprotein (AFP) and lactate dehydrogenase (LDH) and scrotal ultrasonography are used for definitive diagnosis (2).

Studies investigating the relationship of inflammation and cancer, by revealing different mechanisms of influence, are increasing in recent years. It has been reported that tumor cells are triggering cancer-related inflammation, and increasing tumor promoting effect, by secreting chemokines, cytokines and prostaglandins (3). Particularly, in various urinary tract malignancies such as renal cell carcinoma (RCC), bladder cancer and prostate cancer, it has been claimed that cancer-related inflammation plays an important role in disease progression and prognosis (4). In addition, a recent study showed that chronic inflammatory processes such as orchitis-epididymorchitis can influence the formation of testicular malignancy (5). Therefore, taken into account the role of inflammation in tumor biology, using inflammatory markers such as neutrophil ratio (NR), lymphocyte ratio (LR) and/or neutrophil to lymphocyte ratio (NLR) in predicting the occurrence and prognosis of the disease, is of great importance (6). Among these markers, it has been suggested that, especially NLR reflects immune response and can be used as a prognostic marker, in many urologic malignancies (7). Nowadays, as a result of previously accomplished studies, the European Urological Association approved NLR as a prognostic parameter for RCC (8).

Even though inflammatory processes comprise a more important role in testicular tissue than other urinary tract organs, there are only a few studies showing the relationship between inflammatory markers and testicular cancer.

Based on the above mentioned hypothesis, we aimed to determine the utility of preoperative complete blood count (CBC) based systemic inflammatory markers in the prediction of testicular cancer and its prognosis.

## MATERIAL AND METHODS

Between 2008-2017, the data of all testicular tumor patients, who underwent radical orchiectomy in two University Hospitals in the Region of Trakya (Turkey) were retrospectively examined. Histopathologically proven testicular germ cell tumor patients of stage pT1-T4 including any regional lymph node positivity

without distant organ metastasis, and healthy unoperated grade 1 varicocele individuals with peripheral blood count results, were included in the study and defined as tumor and control group, respectively.

Patient baseline characteristics (age, tumor stage, etc.) and routine preoperative blood test results were retrieved from both hospitals electronic data base. Biochemical analyses included testicular tumor markers (AFP, HCG, LDH) and CBC-based systemic inflammatory markers such as mean platelet volume (MPV), red cell distribution width (RDW), LR and NR. Additionally to the extracted CBC based markers, NLR was calculated to compare between the groups.

The following exclusion criterias for both groups were used: i) men with a secondary malignancy: ii) presence of another active infection: iii) disease causing increased inflammatory response (e.g. familial mediterranean fever): iv) hematologic diseases affecting blood count: and/or v) receiving chemotherapy, meanwhile.

Definition of cancer specific survival (CSS) was the time period (in months) involving time of surgery to cancer related death. Postoperative follow-up of testicular tumor patients in both clinics were routinely performed according to the EAU guideline protocol (9). Informed consents were taken and institutional review board was approved by the hospital ethics committee.

## Statistical analysis

Statistical analyses were performed by R version 3.5.3 (2019-03-11). Continuous variables were expressed as means (standard deviation (SD)) or median (interquartile range (IQR)) where appropriate, categorical variables were expressed as frequencies and percentages. Variables were compared for statistical significance between groups by Student t-test or Mann Whitney U test. The association between categorical variables was tested using Fisher's exact test. Kaplan Meier analysis was used to correlate NLR with CSS. Receiver operating characteristic (ROC) curve analyses were performed to assess the discriminative ability of the biomarkers for testicular cancer. The cut-off points for biomarkers were determined by a

criterion based on Youden’s Index defined as  $Y I(c)=\max(c)(Se(c)+Sp(c)-1)$  and the corresponding specificity-sensitivity levels were provided.

For all analyses, the p value of  $p < 0.05$  was considered statistically significant.

## RESULTS

After determining inclusion/exclusion criterias, a total of 182 patients were included in the study and divided into two groups, as tumor and control groups, with 90 and 92 patients each, respectively. Descriptive properties and their distribution with respect to groups are summarized in Table-1.

Mean age of the tumor and control groups was  $36.0 \pm 15$  and  $30.50 \pm 11$  years, respectively. Pathological subtypes consisted of 90 germ cell tumors including 42 seminomas (46.6%), 48 non-seminoma (53.4%), with a mean follow-up period of 39.83 months. According to the TNM classification, patients comprised of 56 (62.2%) pT1, 28 (31.1%) pT2, 4 (4.4%) pT3 and 2 (2.2%) pT4 patients (Table-2). Mean RDW, NR and NLR were significantly higher in

the tumor group with p values  $< 0.001$ , whereas LR and MPV were significantly higher in the control group ( $p < 0.001$ ). During follow-up, postoperative 68 patients of the tumor group got an additional treatment such as chemotherapy (n=62), radiotherapy (n=3) or chemoradiotherapy (n=3).

Receiver Operating Characteristic (ROC) analyses of LR, NR, RDW, MPV and NLR are shown in Table-3 and Figure-1. The cut off values for RDW and NR were found as 13.7 (Area under the curve (AUC): 0.687, sensitivity = 42.2%, specificity = 84.8%) and 55.3 (AUC: 0.693, sensitivity = 72.2%, specificity = 62%), respectively. Area under the curve for NLR in tumor group was 0.711, with a threshold value of 1.78 and sensitivity=81.8% and specificity=55.4% (AUC: 0.711/sig  $< 0.001$ ) that together with RDW exhibited the best differential diagnosis potential which could be used as an adjuvant tool in the prediction of testicular tumor and its prognosis (Table-3).

Distribution of descriptive properties and comparison of clinical parameters between the patients with respect to NLR cut-off values

**Table 1 - Descriptive statistics and comparisons of CBC based parameters with respect to groups.**

Variables	Tumor group (n=90)	Control group (n=92)	P value
Age (years)	36 (15) min:20; max:76	30.50 (11) min:16; max:54	<b>&lt;0.001</b>
LR (%)	26.15 (14.23) min:5.5; max:80	33.90 (11.78) min:11.10; max:13.30	<b>&lt;0.001</b>
NR (%)	63.20 (13.10) min:6; max:87.2	53.95 (13.65) min:33.6; max:81.9	<b>&lt;0.001</b>
NLR (%)	2.37 (2.02) min:0.33; max:15.85	1.6 (1.05) min:0.58; max:7.38	<b>&lt;0.001</b>
MPV ( $10^3/uL$ )*	8.35 (1.17) min:6.02; max:11.4	9.09 (2.33) min:6.10; max:13.3	<b>&lt;0.001</b>
RDW ( $10^3/uL$ )	13.50 (1.47) min:11.50; max:25.80	12.9 (0.85) min:11.6; max:17	<b>&lt;0.001</b>

LR = Lymphocyte ratio; MPV = Mean platelet volume; CBC = Complete blood count; NLR = Neutrophil/Lymphocyte ratio; RDW = Red cell distribution width; NR = Neutrophil ratio

\*: The variables with asterisk are described by mean (standard deviation), and the corresponding p value is based on t-test, otherwise the variables are described by median (interquartile range) and the corresponding p value is based on Mann Whitney U test.

**Table 2 - Tumor Classification and Pathological Stage**

Subtypes of Tumor	Number (n)	Percentage (%)
<b>Seminoma</b>		
pT1	26	28.9
pT2	15	16.7
pT3	-	-
pT4	1	1.1
<b>Mix germ cell</b>		
pT1	25	27.8
pT2	13	14.4
pT3	3	3.3
pT4	1	1.1
<b>Yolc sac</b>		
pT1	2	2.2
<b>Immature teratoma</b>		
pT1	2	2.2
<b>Mature teratoma</b>		
pT3	1	1.1
<b>Germ cell neoplasia</b>		
pT1	1	1.1

**GERM CELL TUMORS (n=90)**

**Table 3 - Optimal cut-off values and ROC analyses for LR, NR, RDW, MPV and NLR.**

Variables	AUC	Cut-off	Sensitivity	Specificity	PPV	NPV
<b>Preop RDW</b>	0.687	>13.7	42.2%	84.8%	73.1%	60%
<b>Preop NLR</b>	0.711	>1.78	81.8%	55.4%	64.3%	76.1%
<b>Preop NR</b>	0.693	>55.3	72.2%	62%	65%	70%
<b>Preop LR</b>	0.698	<28.7	62.2%	70%	67%	65%
<b>Preop MPV</b>	0.636	<33.4	78.9%	44.6%	58.2%	68.3%

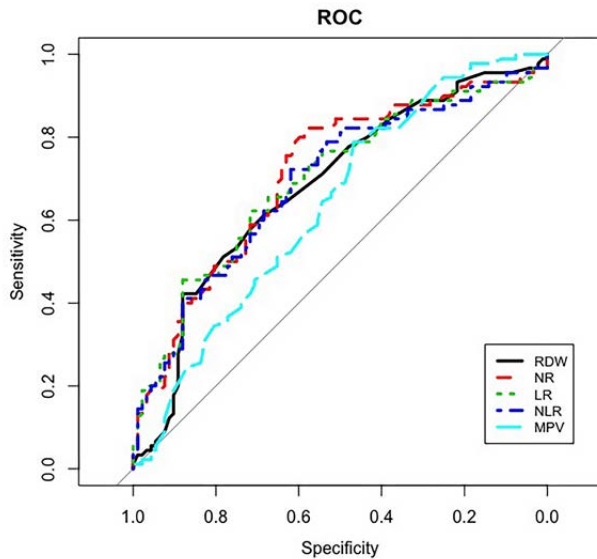
**RDW** = Red cell distribution width; **NR** = Neutrophil ratio; **NLR** = Neutrophil to Lymphocyte ratio; **MPV** = Mean platelet volume; **LR** = Lymphocyte ratio; **AUC** = Area under the curve; **PPV** = Positive Predictive Value; **NPV** = Negative Predictive Value; >: greater than, <: smaller than

(<1.78 and ≥1.78) are shown in Table-4. Except HCG, NR, LR and NLR no statistically significant difference was found between both groups.

Mean NLR of 42 patients with stage pT1, and 48 patients with stage ≥pT2, was 3.06 and 3,15, respectively. Neutrophil to lymphocyte ratio was quantitatively higher in patients with a

stage ≥T2, however no statistically significant difference between both groups was observed (p=0.107). Retroperitoneal lymph node metastases, at the time of disease diagnosis, was revealed in two of 25 patients (8.00%) with a NLR <1.78 and in nine of 65 patients (13.85%) with a NLR ≥1.78.

**Figure 1 - Optimal cut-off values and ROC analyses for LR, NR, RDW, MPV and NLR.**



Mean CSS of all patients was calculated as  $84.78 \pm 4.89$  months, whereas median CSS was found 96 month showing no difference between the groups according to NLR cut-off value ( $p=0.378$ ) (Figure-2) In addition, five year overall survival rates for patients with NLR  $<1.78$  and  $\geq 1.78$  were found as 54.00% and 48.00%, respectively.

## DISCUSSION

Immune mechanisms, such as the role of neutrophils as a promoter in tumor formation and the presence of antitumoral activity of lymphocytes have been reported to be associated with malignancies (10). Studies have shown that systemic inflammatory markers, including cytokines, C-reactive protein (CRP), albumin, serum amyloid A and leukocytes, may be independent prognostic factors in cancer patients (11). Recently, in addition to those markers, NLR and platelet lymphocyte ratio (PLR) have been extensively investigated and their relation to the formation and progression of malignancy were reported (10). Especially in urinary system malignancies like prostate, bladder and kidney cancers, the role and efficiency of NLR has been shown in several studies (6, 12-14).

Researchers investigating the relationship between tumor size and NLR in patients with RCC, demonstrated that NLR was significantly higher in patients with a tumor size larger than 4cm (15). Considering that RCC's larger than 4cm are upstaged according to the TNM classification, it was thought that NLR may correlate with tumor stage. Based on this suggestion, the obtained results of our testicular tumor patients revealed a significant correlation between tumor stage and the NLR cut off value, supporting previously accomplished studies (15, 16). Apart from this, a study evaluating ovarian mature cystic teratoma patients, it was reported that NLR was significantly higher in patients that showed malignant transformation (7). Interpreting our results, besides the similarity of embryological origin and exposition of frequent inflammatory processes identical to the testes, this finding could contribute to the literature in terms of showing the association of NLR and genitourinary related malignancies.

We sought to describe the potential association between preoperative CBC-based blood count parameters and testicular cancer patients who underwent radical orchiectomy. The major findings of the present study are that: i) RDW, NR and NLR are significantly higher in testicular tumor patients compared to healthy control subjects, and ii) especially NLR and RDW could be used as a predictive and/or prognostic factor showing the highest sensitivity and specificity, respectively.

In a study comparing 36 patients with localized testicular cancer and 36 control subjects, it was shown that NR and NLR were significantly higher in the tumor group, whereas LR was higher in the control group, which was in agreement to our findings (4). However, ROC analysis revealed a significantly lower NLR cut off value and sensitivity compared to our results, which we believe to be caused due to the small sample size of this study.

Jankovich et al. (17), studied 103 testicular germ cell tumor (GCT) patients and evaluated the prevalence of their histopathology, metastatic status and tumor stage according to NLR  $<4$  or NLR  $\geq 4$ . Despite that, NLR cut off value was considera-

**Table 4 - Distribution of descriptive properties and comparison of clinical parameters between the patients with respect to NLR of <1.78 and  $\geq 1.78$ .**

Variables	NLR <1.78 (n=25)	NLR $\geq 1.78$ (n=65)	P value
<b>Age (years), Median (IQR)</b>	36.00 (12.00)	36.00 (16.00)	0.576
<b>Tumor size (cm<sup>3</sup>), Median (IQR)</b>	6.00 (45.40)	13.50 (67.00)	0.313
<b>Follow-up (months), Median (IQR)</b>	36.00 (36.00)	24.00 (48.00)	0.282
<b>Stage, n(%)</b>			0.475
T1	17 (68.00%)	38 (58.46%)	
n $\geq$ T2	8 (32.00%)	27 (41.54%)	
<b>Tumor markers, Median (IQR)</b>			
Preop AFP (U/mL)	4.50 (10.28)	5.10 (147.14)	0.385
Preop HCG (mIU/mL)	1.00 (4.65)	5.00 (41.00)	<b>0.047*</b>
Preop LDH (U/L)	310.00 (242.00)	335.00 (386.00)	0.859
<b>CBC based markers, Median (IQR)</b>			
Preop NR (%)	52.00 (11.00)	68.10 (11.00)	<b>&lt;0.001*</b>
Preop LR (%)	36.30 (6.70)	22.10 (10.60)	<b>&lt;0.001*</b>
Preop NLR (%)	1.38 (0.42)	3.12 (2.27)	<b>&lt;0.001*</b>
Preop MPW (10 <sup>3</sup> /uL)	8.00 (1.90)	8.20 (1.60)	0.491
Preop RDW (10 <sup>3</sup> /uL)	13.30 (2.10)	13.50 (1.20)	0.695
<b>Lymph node metastasis at the time of diagnosis, n (%)</b>	2 (8.00%) 23 (92%)	9 (13.85%) 56(86.15%)	0.721
<b>Prognostic factors related to occult metastatic disease*, n (%)</b>	8 (32.00%) / +17 (62.00%) /-	27 (41.54%) / + 38 (58,36%) / -	0.475
<b>CSS, n (%)</b>	19 (76.00%)	48 (73.38%)	1
Survived Ex	6 (24.00%)	17 (26.62%)	

**AFP** = Alfa fetoprotein; **HCG** = Human chorionic gonadotropin; **LDH** = Lactate dehydrogenase; **LR** = Lymphocyte ratio; **NR** = Neutrophil ratio; **MPW** = Mean platelet volume; **NLR** = Neutrophil/Lymphocyte ratio; **RDW** = Red cell distribution width.

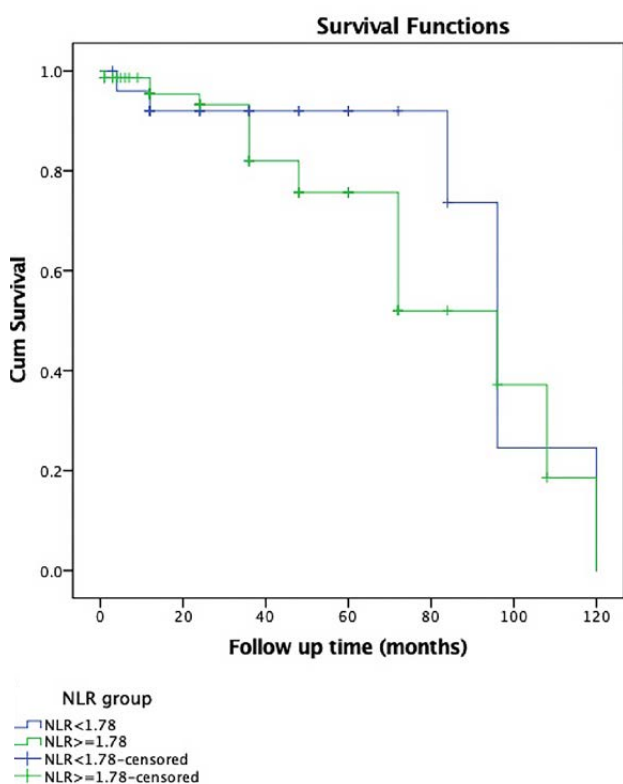
\* Rete testis invasion, Lymphovascular invasion

bly higher than ours, no statistically significant difference according to these parameters was observed, which was supported by our findings.

In another study conducted by Bolat et al., patients were divided and compared according to the NLR threshold value of <3.55 and  $\geq 3.55$ , to investigate its potential impact on the prognosis of testicular GCT. Similar to our

findings, no significant relation between NLR and tumor stage or prognostic factors related to occult metastasis, like rete testis invasion and/or lymphovascular invasion, was obtained. However, the average sample size and inclusion of distant organ metastatic patients to such a small group, made the clinical evaluation of their data difficult and query (18).

**Figure 2 - Kaplan-Meier curves used to evaluate the correlation between neutrophil-to lymphocyte ratio and CSS.**



Despite the adequate patient size, the retrospective nature and the inability of comparing extensively matched metastatic and non-metastatic patients, according to NLR and other inflammatory markers, are considered the main limitations of the present study. Additionally, due to treatment strategies of testicular masses we could not consider the circadian rhythm of neutrophils and lymphocytes during blood sample collection. Apart from these, it could be interesting to evaluate preoperative to postoperative alterations of NLR and other CBC based inflammatory parameters after tumor removal and to compare the sensitivity and specificity against established routine testis tumor markers.

## CONCLUSIONS

Several systemic inflammatory markers, which are obtained by routinely performed cost-

-effective blood tests, could demonstrate incremental predictive and prognostic information adjuvant to preoperatively achieved testicular tumor markers. However, further research is needed.

## CONFLICT OF INTEREST

None declared.

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# Bladder cancer trends and mortality in the brazilian public health system

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## ABSTRACT

**Introduction:** Considering the lack of data on BC trends in Brazilian population, mainly as a result of the difficulty on gathering data, the present manuscript provides an overview of bladder cancer incidence, hospitalization, mortality patterns and trends using the Brazilian Data Center for The Public Health System (DATASUS).

**Materials and Methods:** All hospital admissions associated with BC diagnosis (ICD-10 C67) between 2008 and 2017 were analyzed. Distributions according to year, gender, age group, ethnicity, death, length of hospital stay, and costs were evaluated. Demographic data was obtained from the last Brazilian national census.

**Results:** From 2008 to 2017 there were 119,058 public hospital admissions related to BC. Patients were mostly white males aged 60 to 79 years-old. Mortality rates for patients who have undergone surgery was 6.75% on average, being 7.38% for women and 6.49% for men. Mortality rates were higher when open surgeries were performed compared to endoscopic procedures (4.98% vs 1.18%). Considering only endoscopic procedures, mortality rates were three times higher after urgent surgeries compared to elective ones (2.6% vs 0.6%). Over the years the cystectomy/transurethral bladder resection (C/T) ratio significantly decreased in all Brazilian Regions. In 2008, the C/T ratio was 0.19, while in 2017 it reduced to 0.08.

**Conclusions:** Despite BC relatively low incidence, it still represents a significant social economic burden in Brazil, as it presents with recurrent episodes that might require multiple hospitalizations and surgical treatment. The set of data collected might suggest that population access to health care has improved between 2008-2017.

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## INTRODUCTION

According to American Cancer Society, in the United States in 2018, approximately 81,190 patients were diagnosed and about 17,240 deaths occurred due to bladder neoplasm (1). Data retrieved from the Surveillance, Epidemiology and End Results Program from National Cancer Institute (SEER), recollects that rates for new bladder cancer (BC) cases have been falling on average

1.0% each year over the last 10 years. Nevertheless, BC remains as the 6<sup>th</sup> more common type of cancer in the United States, accounting for 4.7% of all new cancer cases (2).

Worldwide, about 549,393 new diagnosis were made and 199,922 deaths were attributed to BC in 2018, which corresponds, respectively, to 3% of all cancer diagnosis and 2.1% of cancer-related deaths (3). In Brazil, where BC figures as the seventh most common malignancy in men

and the 14<sup>th</sup> in women, it is estimated a yearly diagnosis of 6.43 new cases per 100.000 men and 2.63 per 100.000 women (4). Whilst more frequent in men, BC tend to be found more clinically significant and in more advanced stages in women (5). As BC manifests primarily with gross or microscopic hematuria and has a recurrent pattern, patients who have been diagnosed with the disease frequently require multiple procedures and hospitalizations, both elective or urgent, in order to achieve either cure or at least control the disease. Despite having a relatively low incidence, clinical characteristics of this neoplasms results in a relevant social and economic burden to Brazilian government. In 2014 alone, 27.738 life years were lost due to BC deaths, US\$ 29.879.165 were directly spent with BC treatment and an indirect loss of US\$76.996.523 was estimated (6).

It is well known that the incidence of BC varies geographically with higher incidence rates in Western Europe and North America and lowest rates in Eastern Europe and Asia (7). There is data recollecting that the disease incidence may vary significantly even within a country, in the United States there are lower incidence rates in Utah and Hawaii compared to the Northeastern states (8). Studies assessing mortality and incidence of BC found that more than 60% of cases and over half of the deaths occur in less developed countries (3).

Bladder cancer occurrence is strongly related to environmental factors and aging. Smokers are 2-4 times more likely to develop BC and this association seems to be related to smoking intensity (9, 10).

Workplace exposure to carcinogens may account to approximately 10-20% of BC cases (11).

Metal workers, painters, rubber industry and textile workers and cement or mine workers are professionals with higher risk for BC due to exposure to polycyclic aromatic hydrocarbons (12, 13).

Considering social and demographic characteristics along with BC treatment impact on Brazilian Public Health System, it is imperative that caregivers be aware of BC epidemiology in the Brazilian population. The present manus-

cript provides an overview of BC incidence, hospitalization, mortality patterns and trends using the Brazilian Data Center for The Public Health System (DATASUS).

## MATERIALS AND METHODS

Brazilian Public Health System Information Database was used as the primary data source for our study. DATASUS represents the primary effort of Brazilian Federal Government to collect data from the national health system. This database includes information from all public health hospitals throughout the country, guaranteeing health support to about 170 million Brazilians.

All hospital admissions associated with BC diagnosis (ICD-10 C67) between 2008 and 2017 were analyzed. Distributions according to year, gender, age group, ethnicity, death, length of hospital stay and costs were evaluated.

Additionally, another search was performed according to surgical procedure. All procedures directly associated with BC surgery were evaluated, and divided into endoscopic surgery (codes: 0409010383-BLADDER TUMOR ENDOSCOPIC RESECTION, 0416010172-ONCOLOGIC BLADDER TUMOR ENDOSCOPIC RESECTION) and open surgery (codes: 0409010022-PARTIAL CYSTECTOMY, 0409010030-RADICAL CYSTECTOMY, 0409010049-SINGLE STAGE RADICAL CYSTECTOMY AND URINARY DIVERSION, 0409010057-CYSTOENTEROPLASTY, 0416010024-ONCOLOGIC SINGLE STAGE RADICAL CYSTECTOMY AND URINARY DIVERSION, 0416010032-ONCOLOGIC RADICAL CYSTECTOMY AND SIMPLE URINARY DIVERSION). For this second search, data evaluated included year, geographic region of Brazil, death rate, length of hospital stay and characteristic of hospital admission (elective vs. urgent).

Demographic data from the Brazilian population during the studied period were obtained from the last national census, realized in 2010 and trends in the rate of BC diagnosis and treatment from 2008 to 2017 were described.

Statistical analysis was performed using SPSS 13.0 (SPSS for Mac OS X, SPSS, Inc., Chicago, Illinois). Groups were compared with Pearson's

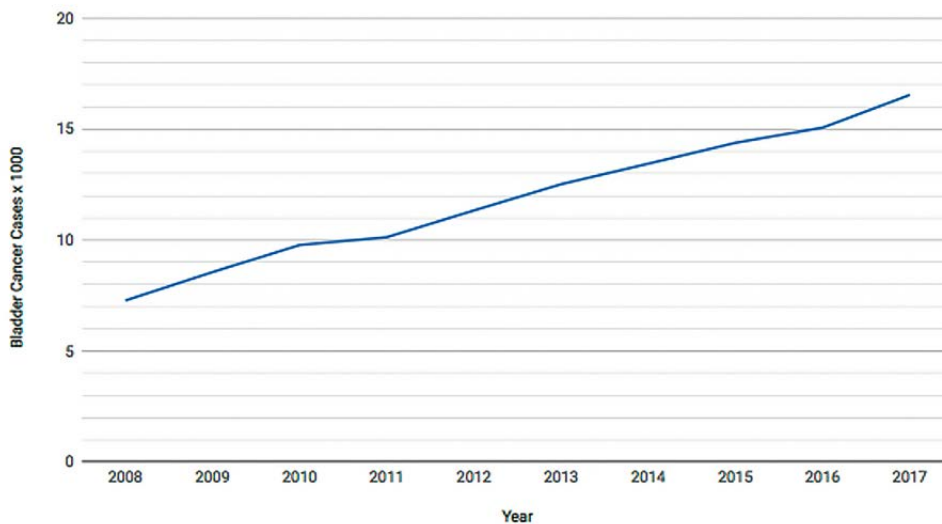
chi-square test and ANOVA. Statistical significance was determined at  $p < 0.05$ .

**RESULTS**

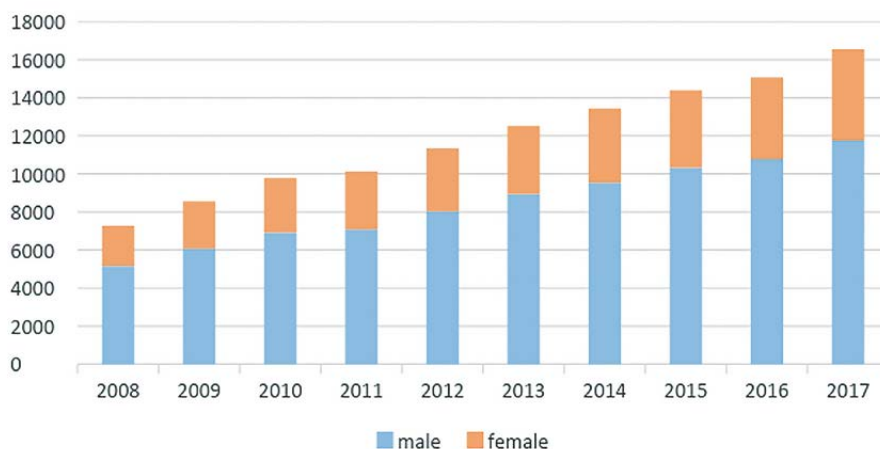
From 2008 to 2017, the population that relies on Brazilian Public Health System has increased 6.3% reaching 162 million people in 2017 and there were 119,058 patients admitted to public hospitals in Brazil with diagnosis of BC along those years. The number of hospital admissions

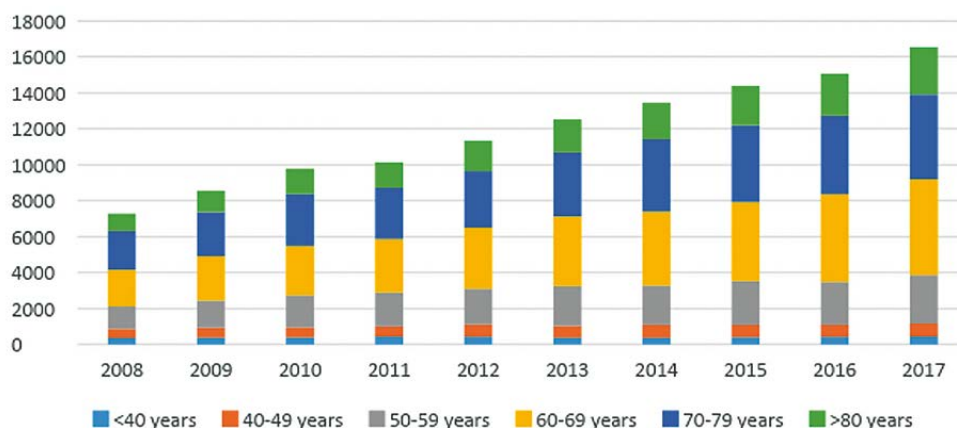
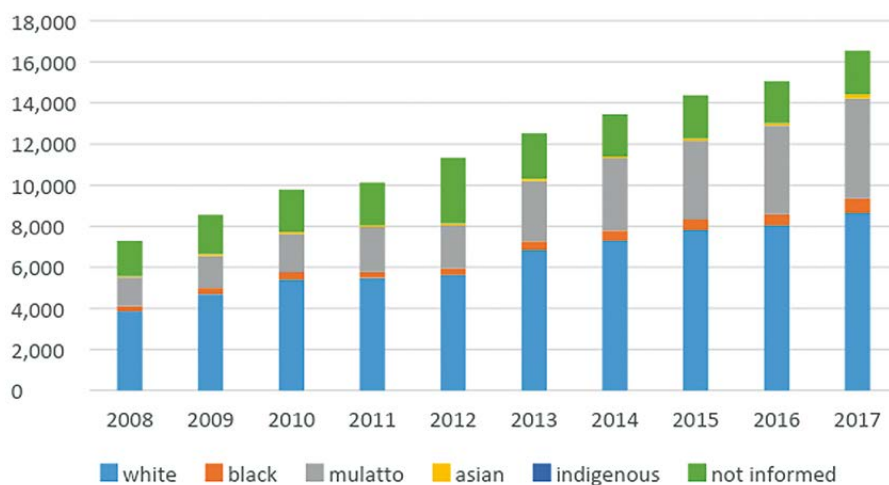
related to BC went from 7,277 in 2008 to 16,547 in 2017. Patients admitted with BC were mostly white males aged 60 to 79 years. Figures 1-4 demonstrates admission growth tendency during the time of the study (Figure-1) and the distributions of these patients according to gender (Figure-2), age group (Figure-3) and ethnicity (Figure-4). The death rate among patients admitted with BC remained quite stable, being 6.4% in 2008 and 6.6% in 2017. Table-1 summarizes BC admissions, deaths and mortality rate.

**Figure 1 - Bladder Cancer Admissions on Brazilian Public Health System (2008-2017).**



**Figure 2 - Bladder Cancer admissions according to gender (2008-2017).**



**Figure 3 - Bladder Cancer admissions according age group (2008-2017).****Figure 4 - Bladder Cancer admissions according to ethnicity (2008-2017).**

Across the studied years, among individuals who have undergone surgery, there was a 6.75% mortality rate, being 7.4% for women and 6.5% for men. Highest mortality rate occurred in 2008, when it reached 7.2% for all individuals and 7.7% for women along with 7.0% for men. BC mortality during hospitalization was higher among patients who were over 80 years-old (Figure-5).

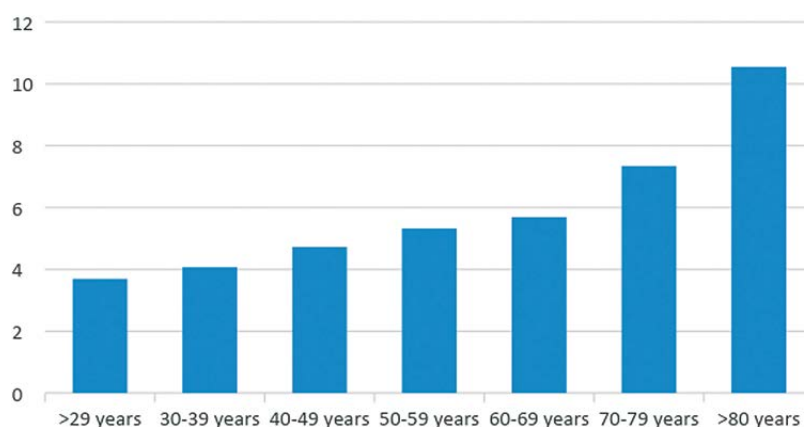
During procedure analysis, it was found 77.353 endoscopic procedures to treat BC with 915 deaths and 8.925 open procedures with 441 deaths performed during the decade evaluated, which

translates to a mortality rate of 1.2% and 5.0%, respectively, between 2008-2017 (Table-2). There were 54.759 elective transurethral bladder resections (TURb) during the studied period, with 326 documented deaths, while there were 589 deaths among the 22.595 urgent TURb, corresponding respectively, to a mortality rate of 0.6% and 2.6% (Table-3). Mortality rates for urgent radical cystectomies were about 50% higher than the rate for elective radical cystectomies (9.74 vs. 6.02).

The open procedures were mostly radical cystectomies, being 1.966 (22.0%) partial cystec-

**Table 1 - BC Admissions, Deaths and Mortality Rates from 2008-2017.**

Year	Population using Public Health System	BC cases (n=119.058)	BC rate (x10 <sup>-5</sup> )	BC deaths	Mortality rate (%)
2017	162.077,403	16,547	10.21	1,100	6.6%
2016	160.022,071	15,069	9.42	1,032	6.8%
2015	156.750,009	14,387	9.18	1,005	7.0%
2014	154.265,099	13,445	8.72	879	6.5%
2013	153.223,204	12,521	8.17	873	7.0%
2012	152.901,741	11,340	7.42	762	6.7%
2011	152.746,237	10,133	6.63	651	6.4%
2010	151.858,919	9,781	6.44	666	6.8%
2009	153.659,783	8,558	5.57	615	7.2%
2008	152.427,207	7,277	4.77	466	6.4%

**Figure 5 - Bladder Cancer Mortality during hospitalization according to age group.**

tomies. About 4.209 (47.2%) of the open procedures were performed in Brazilian Southeast Region, followed by South, Northeast, Midwest and North regions with 1.935 (21.7%), 1.403 (15.7%), 742 (8.3%) and 636 (7.1%) of these surgeries, respectively.

Mean length of hospital stay after was 6.9 days for partial cystectomies and 13.6 days for radical cystectomies. Patients who have undergone surgeries in North Region presented the lowest mean

hospital stay of 10.3 days followed by patients from South (11.11), Northeast (12.07), Midwest (12.82) and Southeast (13.27) regions, respectively. For TURb, mean length of hospital stay was of 4.3 days.

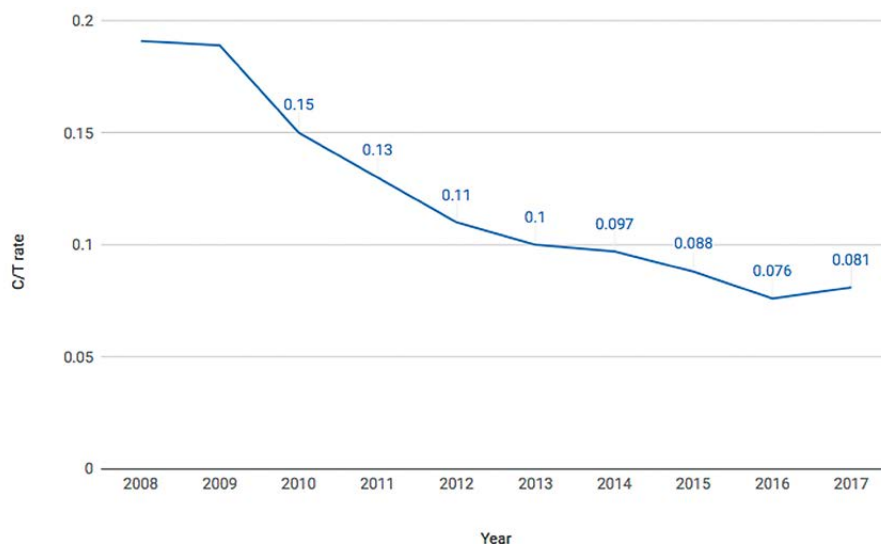
During the decade evaluated, the correlation between radical cystectomy and TURb (C/T ratio) presented a significant reduction. In 2008, the C/T ratio was 0.19, while in 2012 it reduced to 0.11 and then to 0.08 in 2017 (Figure-6).

**Table 2 - Endoscopic vs Open Procedures and related Death rates.**

Year	TURB			Radical Cystectomies		
	Cases	Deaths	Rate	Cases	Deaths	Rate
2008	5,495	72	1.31%	1,053	38	3.61%
2009	5,814	67	1.15%	1,099	52	4.73%
2010	6,313	62	0.98%	982	41	4.18%
2011	6,632	62	0.93%	875	42	4.80%
2012	7,053	96	1.36%	795	43	5.41%
2013	8,205	109	1.33%	883	47	5.32%
2014	8,836	117	1.32%	858	54	6.29%
2015	9,028	120	1.33%	800	37	4.63%
2016	9,496	99	1.04%	730	33	4.52%
2017	10,481	111	1.06%	850	54	6.35%
<b>Total</b>	<b>77,353</b>	<b>915</b>	<b>1.18%</b>	<b>8,925</b>	<b>441</b>	<b>4.98%</b>

**Table 3 - Deaths after TURb, elective vs. urgent.**

	Deaths after TURb (elective vs urgent)					
	Elective			Urgent		
	Surgeries	Deaths	Rate (%)	Surgeries	Deaths	Rate (%)
2008	3,627	29	0.8	1,868	43	2.3
2009	3,950	27	0.684	1,864	40	2.15
2010	4,416	22	0.498	1,897	40	2.1
2011	4,720	19	0.403	1,912	43	2.24
2012	5,026	29	0.577	2,027	67	3.3
2013	5,954	47	0.789	2,251	62	2.8
2014	6,309	43	0.682	2,527	74	2.9
2015	6,382	37	0.58	2,646	83	3.1
2016	6,850	32	0.467	2,646	67	2.5
2017	7,525	41	0.545	2,956	70	2.36
<b>Total</b>	<b>54,759</b>	<b>326</b>	<b>0.595</b>	<b>22,594</b>	<b>589</b>	<b>2.6</b>

**Figure 6 - Cystectomy over TURb Rate from 2008 – 2017.**

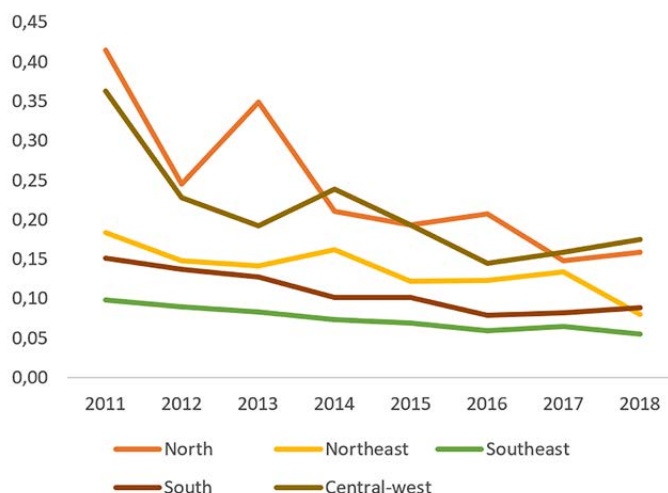
## DISCUSSION

Recent studies have reported that worldwide BC incidence trends towards stabilization or decline in men versus increase in women with an overall decrease in mortality. In Brazil there is paucity of data, but Antonini et al. demonstrated similar trends regarding incidence whilst there was a slightly increase in mortality (14). Our study has some important findings.

First, during the studied decade the number of hospital admissions related to BC has significantly increased. There were 7.277 admissions in 2008 and in 2017 16.547 were recorded. Even though this finding could be attributed to an increase in BC incidence, it is our belief that better access to health systems and better notification also explains this increment. There are some findings that reinforce the latter hypothesis. Although there was a large number of admissions, death rates among patients admitted with BC related diagnosis remained stable: 6.4% in 2008 vs. 6.6% in 2017. Additionally, the number of BC admissions more than doubled while the number of individuals that rely on Brazilian Public Health System has increased only 6.3%.

Second, it is important to highlight our findings regarding the C/T ratio for BC treatment. Across the years the C/T ratio has decreased from

0.19 in 2008 to 0.08 in 2017. It is our understanding that in an ideal scenario the vast majority of bladder tumors would be treated in early stages by endoscopic procedures. Thus, the C/T ratio decrease might point that early diagnosis might have been performed and more superficial BC cases were treated vis a vis invasive disease. Access to Public Health System might have improved since not only the number of individuals admitted to manage BC has significantly increased but also the proportion of cystectomies has decreased, which, as mentioned before, may reflect an improvement of BC treatment in early stages with TURb. The C/T ratio might also reflect regional disparities in Brazil. Over 68% of the cystectomies were performed in Southeast and South regions; those Brazilian regions present the highest Human Development Index (HDI) (15). In these southern regions, C/T ratio was lower than that presented in underdeveloped northern regions of the country (Figure-7). This finding might be related to better access to health care along with more equipped hospitals in these regions leading to higher diagnosis rates and adequate treatment. We acknowledge, however, that definite conclusions should not be made regarding the C/T ration as this is not a validated index and further studies encompassing different populations and in a more controlled scenario are

**Figure 7 - Cystectomy over TURb Rate from 2008 – 2017 according to geographic regions in Brazil.**

needed to evaluate the usability of the C/T ratio as a quality of care index. Figure-7 demonstrates the C/T ratio in the five geographic regions of Brazil during the last years.

Third, there were some factors associated with increased mortality following BC treatment. Mortality significantly increased with age (Figure-5), which, according to literature, may reflect late BC stages at diagnosis and poorer biologic response for both the disease and the morbidity of its treatment (16). This increment in mortality in the elderly population might become progressively more relevant, since we have also observed that population aging process can be translated into a progressively higher number of octogenarians being diagnosed and treated for BC. A large SEER database analysis of over 10.000 patients treated in the US with RC between 1984 and 2004 showed that at 90 days mortality is 1% for patients younger than 60 years of age, 6% between ages 69 and 83 and 14% for patients over age 89 (17).

Cumberbatch et al., at a recent systematic review, reported that mortality varies worldwide but trends to be higher in men than in women (18). According to SEER database, despite 30-day mortality after radical cystectomy was higher for men, 90-day mortality became higher for women (4.8% Vs. 3.2%) (17). In accordance, our data, shows higher BC mortality among women vs. men (7.38% Vs. 6.49%).

In addition, surgeries performed as an urgent basis burdened a significant higher mortality rate than elective procedures (2.1% vs. 0.4%,  $p < 0.0001$ ). Likewise, higher mortality relative rates occurred following radical cystectomies performed urgently vs. elective (9.74 vs. 6.02,  $p < 0.0001$ ). The reported rate of perioperative mortality after radical cystectomy ranges from 0.8% to 5.6% in foreign contemporary cystectomy series (17). Mortality rates in the current Brazilian series was somewhat higher than that. Several variables may affect this rate, including patient age, nutrition status, tumor characteristics/advanced stages at diagnosis and the lack of large volume centers. This elevated mortality rates after BC treatment in Brazil is still to be studied in detail as several factors might have influence on this finding: from the data acquisition method to problems related to health care access, especially for the poorer living in remote areas of Brazil.

Fourth, partial cystectomies rate was high, representing 22% of all open procedures. It has been previously demonstrated in the SEER database that while high volume centers perform partial cystectomies in 12% of patients, low volume centers tend to perform partial cystectomies in as much as 34% of all open procedures. These high rates might suggest that many patients are being inadequately treated for their diseases (19).

Our study has some limitations. As an epidemiologic study, definitive conclusions cannot be

made based exclusively on our findings. Like other neoplasms, BC might still be underreported as cause of hospitalization and death, especially in developing countries as Brazil. Additionally, admissions are not considered in an individual basis, and patients can be considered twice in data analysis. The C/T ratio is also not a validated tool and might be biased by several distinctive factors. However, mainly as a result of the difficulty to gather these data, there is a paucity of data of epidemiologic studies in BC in Brazil. Therefore, our study outlines BC trends in Brazilian population in the last decade and might bring insights to help establish public health policies.

## CONCLUSIONS

In Brazil, BC incidence seems to corroborate the current literature when it comes to gender and ethnicity. Furthermore, despite BC relatively low incidence, it still represents a significant social economic burden in Brazil, as it presents with recurrent episodes that might require multiple hospitalizations and surgical treatment. Present data might suggest that population access to health care and notification have improved between 2008-2017, with significant growth in the number of hospital admissions related to BC. Considering the impact of BC in Brazilian Public Health system, our data reinforces the importance of further studies and policies on BC risk factors and treatment.

## CONFLICT OF INTEREST

None declared.

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# Role of preoperative MR volumetry in patients with renal cell carcinoma for prediction of postoperative renal function after radical nephrectomy and nephron sparing surgery

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## ABSTRACT

**Purpose:** Preoperative computed tomography or magnetic resonance (MR) imaging are commonly used for radiological evaluation of renal cell carcinoma (RCC) before radical nephrectomy or nephron sparing surgery (NSS). This study aimed to assess the role of MRI for predicting postoperative renal function by preoperative estimation of renal parenchymal volume and correlation with glomerular filtration rate (GFR).

**Materials and Methods:** A prospective observational study was conducted from February 2015 to October 2016 at a tertiary care hospital in northern India. MR imaging was done on 3 Tesla MR scanner (Signa Hdxt General Electrics, Milwaukee, USA). MR volumetry was used to estimate the renal parenchymal volume. GFR was measured in all patients using Tc99m Diethyl-triamine-penta-acetic acid using Russell's algorithm. Such measurement was done preoperatively, and postoperatively 3 months after surgery.

**Results:** 30 patients with suspected RCC underwent NSS (n=10) and radical nephrectomy (n=20). Median tumour volume was 175.7cc (range: 4.8 to 631.8cc). The median volume of the residual parenchyma on the affected side was 84.25±41.97cc while that on the unaffected side was 112.25±26.35cc. There was good correlation among the unaffected kidney volume and postoperative GFR for the radical nephrectomy group (r=0.83) as well as unaffected kidney volume, total residual kidney volume and residual volume of affected kidney with postoperative GFR for the NSS group (r=0.71, r=0.73, r=0.79 respectively; P <0.05).

**Conclusion:** Preoperative residual parenchymal volume on MR renal volumetry correlates well with postoperative GFR in patients with RCC undergoing radical nephrectomy or NSS.

## ARTICLE INFO

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## INTRODUCTION

Renal cell carcinoma (RCC) is the most common renal malignant tumor in adults (1). Its incidence has constantly increased over the last decades and currently 150,000 new cases are

diagnosed every year (2). Once characterized by the classical triad of abdominal mass, flank pain and hematuria, the majority of cases are now diagnosed incidentally, these incidental masses are usually smaller compared to the historically large tumours (3). The surgical approach is direc-

ted towards removing the tumour in such a way that the maximum possible mass of the nephrons is salvaged. Consequently, nephron sparing surgery (NSS) has become the treatment of choice for small, localized RCC (4).

Preoperative radiological evaluation and staging of RCC has the following aims: (a) to evaluate the tumor for involvement of adjacent organs, lymph nodes and/or tumor thrombus, and (b) to assess the vascularity of the tumor in terms of number of arteries/veins and parasitic vessels. Using these parameters, it is possible to plan a surgical approach, however, these parameters do not help to know how much actual renal parenchyma is salvageable. Magnetic resonance imaging (MRI) is a non-invasive diagnostic tool which has the additional benefit of lack of ionizing radiation and need for iodinated contrast agent compared to computed tomography (CT), and it can be used to estimate the renal parenchymal volume (RPV) preoperatively. It is imperative that with such advantages, MRI could be a potential tool for studying the anatomy of kidneys in patients with RCC and the RPV thus calculated could quantify the nephron function in terms of glomerular filtration rate (GFR). Hence, the objective of this study was to assess the role of MRI in preoperative estimation of RPV in patients with RCC and correlate RPV with GFR to predict postoperative renal function.

## MATERIALS AND METHODS

This prospective observational study was conducted at a tertiary care hospital in northern India from February 2015 to October 2016. The study was approved by the Institution's Ethics Committee (IEC code: 2015-26-MD-EXP) and all patients signed the consent before enrolment. Inclusion criterion was patients aged 18 years and older who were diagnosed with renal mass on ultrasonography and were planned for NSS or radical nephrectomy. Exclusion criteria were: (a) patients with claustrophobia, (b) presence of allergy to intravenous gadolinium contrast medium, (c) medical contraindications to MRI (such as orthopaedics in patients with congestive heart failure), (d) presence of MRI incompatible cardiac pacemaker,

and (e) patients who were found to have tumors other than RCC on histopathological examination. The sample size was estimated assuming type one error of 0.05, a type two error of 0.02 and an expected correlation coefficient of 0.50, which yielded a value of 29 (5).

MR imaging was done on a 3 Tesla MR scanner (Signa Hdxt General Electrics, Milwaukee, USA). The coil used was phased array Torso PA (Body Coil) with patient in supine position. Sequences were entirely breath-held with field coverage of area of interest and imaging protocol included pre and post contrast sequences in axial, coronal and sagittal planes. The contrast used was Gadobenate dimeglumine (Multihance®) and the dose was 0.1mmol/kg.

GFR was measured in all patients by plasma clearance method. GFR estimation was done once before surgery and then 3 months after surgery. Plasma clearance of Tc99m Diethyl-triamine-penta-acetic acid (Tc99m-DTPA) was calculated using two venous blood samples at 60 and 180 minutes after injection of 1mCi Tc99m-DTPA. Russell's algorithm was used to calculate the GFR and plasma was made protein free prior to measurement of radioactivity (6).

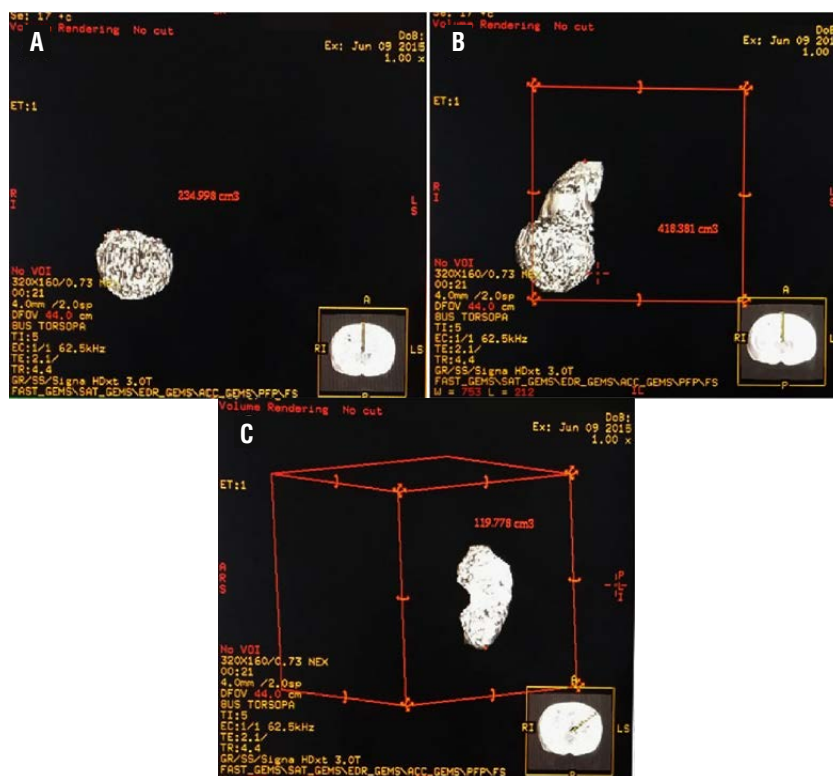
## MR Volumetry

MRI based RPV was estimated using advanced GE workstation (Figure-1). The nonfunctional renal tissues (such as renal sinus) were excluded from these measurements. Patients were divided into two groups: one who underwent NSS and other who underwent radical nephrectomy. In NSS patients, parenchymal volume of both affected and normal kidneys correlated with postoperative GFR calculated using Tc99m-DTPA. Similarly, in radical nephrectomy patients, parenchymal volume of normal kidney correlated with postoperative GFR calculated using Tc99m-DTPA.

## Statistical analysis

MRI based preoperative RPV correlated with postoperative renal function (i.e. GFR) using Pearson's correlation coefficient (0.0-0.2, poor; 0.2-0.4, fair, 0.4-0.6, moderate, 0.6-0.8, good, 0.8-1.0,

**Figure 1 - MR 3D volume reconstructed images showing (A) tumour volume, (B) affected kidney volume with tumour, and (C) unaffected kidney volume, in a patient planned for radical nephrectomy.**



excellent) using SPSS. A p-value of 0.05 or less was considered as statistically significant.

## RESULTS

During the study period, 30 patients with suspected RCC underwent MR volumetry and GFR estimation as per protocol described earlier. Out of these, 10 patients underwent NSS while 20 patients underwent radical nephrectomy. The mean age at diagnosis was  $51.56 \pm 14.74$  years. There were 22 males and 8 females.

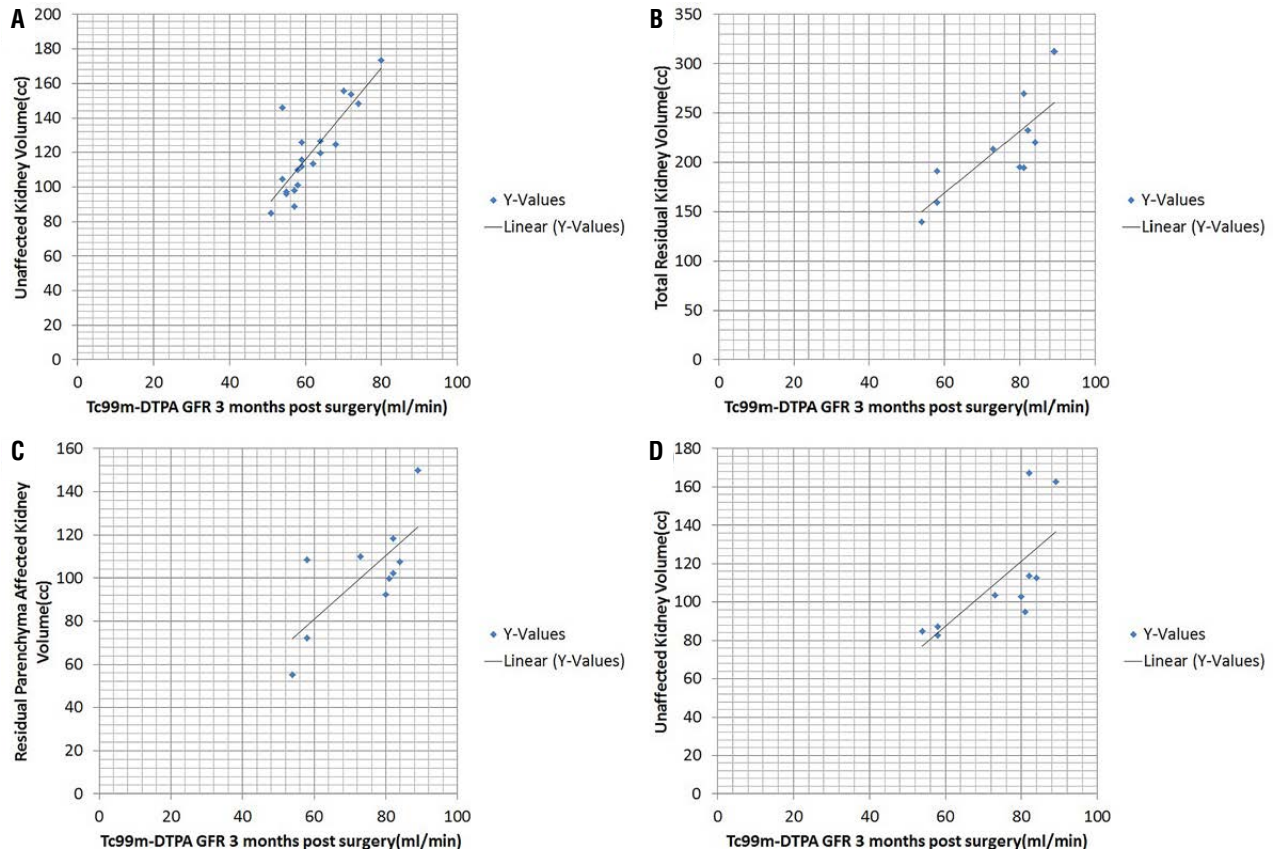
The median tumour volume in these patients was  $175.70 \pm 178.72$ cc (range: 4.80 to 631.80cc) while the median residual parenchyma of the affected kidney was  $84.25 \pm 41.97$ cc (range: 23.20 to 183.40cc). The median residual parenchyma of the unaffected kidney was  $112.25 \pm 26.35$ cc (range: 82.8 to 173.4cc). The mean serum creatinine was  $1.2 \pm 0.4$ mg/dL before surgery and  $1.1 \pm 0.3$ mg/dL at 3 months after surgery ( $P=0.721$ ).

The mean preoperative GFR as estimated using Tc99m-DTPA was  $74.60 \pm 17.18$ mL/min/ $1.73$ m<sup>2</sup> while the mean GFR at 3 months after surgery was  $65.70 \pm 11.19$ mL/min/ $1.73$ m<sup>2</sup> ( $P=0.253$ ). The correlation of the GFR with kidney volume is presented in Figure-2. Table-1 shows the correlation between the estimated radiological volume and Tc99m-DTPA GFR ( $P<0.05$ ).

## DISCUSSION

The only curative treatment for RCC is its complete surgical excision. Traditionally, radical nephrectomy has been the gold standard but recently, as more tumors are diagnosed earlier when they are still smaller, nephron sparing surgery (NSS) has become very popular. NSS is considered the standard surgical treatment of small renal tumors (7). Preoperative cross-sectional imaging with either CT or MRI is paramount in determining the feasibility of NSS. Other than detailing the

**Figure 2 - Correlation analysis of (A) GFR and unaffected kidney volume on imaging 3 months after radical nephrectomy surgery, (B) GFR and total residual kidney volume (affected+unaffected kidney) on imaging 3 months after Nephron sparing surgery, (C) GFR and residual parenchyma affected kidney volume on imaging 3 months after Nephron sparing surgery, and (D) GFR and unaffected kidney volume on imaging 3 months after nephron sparing surgery.**



**Table 1 - Correlation between estimated radiological volume on MRI and Tc99m-DTPA Glomerular filtration rate (GFR).**

Surgical Procedure	Estimated Radiological Volume	Pearson's Correlation Coefficient (vs. Tc99m-DTPA GFR)
Partial Nephrectomy	Total Residual Kidney Volume (Affected+Unaffected kidney)	0.79
	Affected Kidney Volume	0.73
	Unaffected Kidney Volume	0.71
Radical Nephrectomy	Unaffected Kidney Volume	0.83

tumor size, location and relationship with the collecting system, MRI also detects the pseudo-capsule, its thickness and integrity which is particularly associated with small renal tumors and serves as a good indication for partial nephrectomy (8).

The volume of solid visceral organs can be accurately measured with CT and MRI with error less than 3% (9). With newer software programs, nonfunctional renal tissues such as renal sinus and tumor can be excluded from these measurements, thus providing a more accurate determination of functional parenchyma. This software technology is available with most MRI imaging systems and can be learned and executed easily, as was done in the present study.

The correlation between CT renal volume measurements and renal function has been studied previously. Morrisroe et al. evaluated the utility of CT based RPV measurements as a surrogate marker for differential renal function (10). In their study, CT determined renal volume measurement strongly correlated with differential renal function measured on nuclear renal scans in normal and chronically obstructed kidneys. These volume measurements were calculated in non-contrast as well as contrast images. Ng et al. demonstrated a correlation between differential renal volume calculated on non-contrast CT imaging and differential creatinine clearance measured in 24-hour urine sample in obstructed kidney (11). Johnson et al. found that in potential transplant donors, RPV determined on contrast enhanced CT scans, correlated strongly with GFR ( $r=0.62$ ) (12). On MRI, Di et al. demonstrated measurement of renal volume using respiratory-gated MRI in subjects without known kidney disease and concluded that renal volume measurement by MR imaging is highly reproducible (13). Coulam et al. studied measurement of renal volumes with contrast-enhanced MRI and an excellent correlation was found between MRI measurement of total renal parenchymal volume and autopsy volume ( $R^2=0.86$ ) and weight ( $R^2=0.90$ ) (14).

The utility of CT and MRI based RPV measurements in predicting postoperative renal function following radical nephrectomy and NSS has been scantily studied. There is an increasing

body of evidence suggesting that preserved RPV and other non-modifiable factors are the primary determinants of long term postoperative renal function (15). Sorberlini et al. found that the percentage change in renal volume was associated with postoperative renal insufficiency (16). When we correlated the preoperative residual renal volume with postoperative Tc99m-DTPA GFR three months after surgery, we found an excellent correlation among volume of the unaffected kidney and postoperative GFR ( $r=0.83$ ) for the radical nephrectomy group. For the partial nephrectomy group, we correlated the volume of unaffected kidney, the residual volume of the affected kidney and total volume of unaffected kidney plus residual volume of affected kidney separately with the postoperative GFR and found good correlation ( $r=0.71$ ,  $r=0.73$ ,  $r=0.79$  respectively,  $P < 0.05$ ). Kuru et al. evaluated role of volumetry in prediction of early renal function after nephron sparing surgery in 35 patients with a solitary kidney (17). Tumor volumetry was performed on CT or MRI with the Medical Imaging Interaction Toolkit. Follow-up data included renal function for 3 years. Mean tumor volume on imaging was  $27.5 \pm 48.6$ cc which was substantially lower than the tumor volume in the present study. They found a correlation between renal function estimated by Modification of Diet in Renal Disease (MDRD) equation and residual kidney volume on imaging 1-week post-surgery while mid- and long-term renal function did not have such correlation. They concluded that renal volumetry may predict early renal function after NSS. Jeon et al. performed CT based volumetry for patients with radical and partial nephrectomy and correlated the residual renal volume with GFR estimated using modified Cockcroft-Gault formula. They found that residual renal volume and GFR correlated, although not as strongly as reported by Kuru et al. ( $r=0.53$  for radical nephrectomy and  $r=0.42$  for partial nephrectomy) (18). In the present study, we have correlated the RPV with Tc99m-DTPA based GFR which is more accurate than MDRD equation or modified Cockcroft-Gault formula. Liu et al. too correlated the RPV determined via CT with Tc99m-DTPA based GFR and found that the two correlated well (5). Kunzel et al. performed CT based volumetry in patients

with renal mass who were planned for nephrectomy (19). In these patients, preoperative CT based RPV measurements were found to be independently associated with the development of CKD after surgery. Isotani et al. reported similar results in their cohort of 60 patients undergoing radical nephrectomy who underwent renal volumetry using CT and GFR measurement by MDRD equation ( $r=0.54$ ) (20). Besides Kuru et al., only three more studies have correlated MRI renal volumetry with renal function/GFR for patients undergoing nephrectomy (Table-2) (21-23). However, in one of these studies, patients other than those with renal mass were also included. Further, in these studies, it is unclear as to how many patients in these studies actually had volumetry done on MRI and not CT. Nevertheless, a significant correlation was reported between the predicted and actual function renal volume and renal function after surgery. In contrast, the present study focuses on patients with renal mass only, CT volumetry has not been done because the objective of the study was to assess the role of MR volumetry and the method used for GFR estimation is most accurate unlike previous studies. Hence, although the sample size in the present study may appear small, it includes only MR volumetry.

The present study is limited by the small number of patients. The decision of radical nephrectomy versus NSS was primarily guided by the appearance of the tumor on MRI and its relation with the collecting system, main vessels, etc. rather than the volumetry data. The ideal application of the outcomes of such a study would be as a tool to guide the decision of NSS in a patient with borderline renal function where preservation of renal parenchyma is not only desirable but essential. The strength of this study is that this is a unique study which has correlated the residual renal volume with postoperative renal function using MRI, while most of the existing literature has such correlation performed on CT which has radiation concerns, especially for NSS where frequent imaging is needed in follow-up. Secondly, while most of the studies have used creatinine based estimates for GFR, we have used Tc99m-DTPA increasing the accuracy of GFR estimation.

In conclusion, the preoperative residual renal parenchymal volume on MR renal volumetry correlates well with the postoperative renal function. These measurements will enhance the surgeon's ability to provide the benefit of nephron preservation without compromising the surgical outcomes.

**Table 2 - Previous studies correlating MRI based renal volumetry with renal function.**

Authors	Year	No. of patients	Imaging modality	GFR measurement method	Correlation coefficient (r)
Tanaka N (21)	2004	102	CT, MRI#	Cockcroft-Gault formula	0.86 (RN), 0.98 (NSS)
Kuru TH (17)	2014	35	CT, MRI#	MDRD equation & CKD-EPI formula	0.75
Hosokawa Y (22)	2014	83*	CT, MRI#	MDRD equation	0.46
Mibu H (23)	2015	139	CT, MRI#	MDRD equation	0.79 (RN), 0.79 (NSS)
Present study	2019	30	Only MRI	Tc 99m-DTPA renography	0.83 (RN), 0.79 (NSS)

**RN** = Radical Nephrectomy; **NSS** = Nephron Sparing Surgery; **MDRD** = Modification of Diet in Renal Disease Study; **CKD-EPI** = Chronic Kidney Disease Epidemiology Collaboration; **DTPA** = Diethyl-triamine-penta-acetic acid

\*also includes patients other than those with renal mass

#all patients did not undergo MRI

## ABBREVIATIONS

RCC = Renal cell carcinoma  
 NSS = Nephron sparing surgery  
 MRI = Magnetic resonance imaging  
 CT = Computed tomography  
 RPV = Renal parenchymal volume  
 GFR = Glomerular filtration rate  
 DTPA = Diethyl-triamine-penta-acetic acid  
 CKD-EPI = Chronic Kidney Disease Epidemiology  
 Collaboration

## CONFLICT OF INTEREST

None declared.

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## Editorial Comment: Role of preoperative MR volumetry in patients with renal cell carcinoma for prediction of postoperative renal function after radical nephrectomy and nephron sparing surgery

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Lal and Colleagues from India (1) in a interesting study shows the role of MRI for predicting postoperative renal function by preoperative estimation of renal parenchymal volume and correlation with glomerular filtration rate (GFR) in a prospective observational study in 30 patients with renal cancer. The MRI volumetry was used to estimate the renal parenchymal volume and shows that preoperative residual parenchymal volume on MRI renal volumetry correlates well with postoperative GFR in patients with RCC undergoing radical nephrectomy or nephron sparing surgery. Partial nephrectomy (open, laparoscopic or robotic) is considered the gold standard for treating localized renal tumors (2-6). Renal parenchymal preservation is the great objective of the partial nephrectomy. Methods that assist in programming the surgical preservation are very well coming. Recently interesting papers about the 3D printed technology shows a lot of applications in kidney surgery (7-9). Papers using the preoperative estimation of renal parenchymal volume with MRI can help a lot in planning the partial nephrectomy.

### CONFLICT OF INTEREST

None declared.

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# Can natural killer cell activity help screen patients requiring a biopsy for the diagnosis of prostate cancer?

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## ABSTRACT

**Purpose:** To evaluate the usefulness of natural killer cell activity (NKA) in diagnosing prostate cancer (PC).

**Materials and Methods:** The medical records of patients who underwent transrectal prostate biopsy (TRBx) at Korea University Ansan Hospital between May 2017 and December 2017 were retrospectively reviewed. NKA levels were measured using NK Vue® Tubes (ATgen, Sungnam, Korea). All blood samples were obtained at 8 AM on the day of biopsy. Patients with other malignancies, chronic inflammatory conditions, high prostate-specific antigen (PSA) level (>20ng/mL), or history of taking 5-alpha-reductase inhibitor or testosterone replacement therapy were excluded.

**Results:** A total of 102 patients who underwent TRBx for PC diagnosis were enrolled. Among them, 50 were diagnosed with PC. Significant differences in age and NKA level were observed between the PC and no-PC groups. Receiver operating characteristic (ROC) curve analysis showed that the optimal cut-off of NKA level for the prediction of PC was 500pg/dL, with a sensitivity of 68.0% and a specificity of 73.1%. In addition, NKA level (0.630) had the greatest area under the ROC curve compared to those for the ratio of total PSA to free PSA (0.597) and PSA density (0.578).

**Conclusions:** The results of this pilot study revealed that low NKA and high PSA levels were likely to be associated with a positive TRBx outcome. NKA detection was easy and improved the diagnostic accuracy of PC.

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## INTRODUCTION

Prostate cancer (PC) is one of the most common malignancies in Korean men (1). The prostate-specific antigen (PSA) level is widely used in the diagnosis and follow-up of PC, and the increase in the incidence of PC has been attributed to the widespread testing of PSA level in daily clinical practice (2). Depending on each clinician, patients with PSA levels >3.5-4.0ng/mL may be recommended to undergo prostate biopsy. However, although PSA is an useful biomarker for the diagnosis of PC,

its specificity is low and significantly high-risk PC cases cannot be detected based on PSA levels (3). In addition, the American Cancer Society reported that the sensitivity of PSA for PC detection is only 21%, whereas the specificity is 91% when the normal PSA level is defined as <4.0ng/mL (4). Although transrectal prostate biopsy (TRBx) is the most widely used method to diagnose PC, it may lead to various complications; therefore, patients should be carefully selected (5, 6).

To overcome the current limitations, various biomarkers have been evaluated to improve the

diagnostic accuracy of PC (7-9). However, most of these novel markers had limitations of difficulty in assessment, expense, and additional intervention. However, increasing attention has been focused on natural killer (NK) cells in cancer settings as they are involved in innate immunity and play a major role in anticancer mechanisms (10, 11). Previous studies reported a correlation between low NK cell level and PC stage, prognosis, and treatment response (12, 13). However, some conflicting issues exist regarding the use of NK cell activity (NKA) as a marker for PC detection and screening. In their pilot study, Barkin et al. first reported that patients with low NKA levels (<200pg/mL) were more likely to have a positive outcome at prostate biopsy (14). However, Song et al. reported that NKA was not very useful for the detection of PC and prediction of Gleason grade (15). To address this issue, we measured the NKA levels of patients with suspected PC who underwent transrectal ultrasonography-guided prostate biopsy and evaluated the clinical usefulness of NKA in diagnosing this cancer.

## MATERIALS AND METHODS

The institutional review board of Korea University Ansan Hospital approved this study's protocol (IRB No. 2019AS0060). This study was conducted in accordance with the guidelines of the Declaration of Helsinki. Data collected from patients who visited the Department of Urology between May 2017 and May 2018 were retrospectively evaluated. Men aged  $\geq 18$  years with elevated PSA levels (>2.5ng/mL) and/or abnormal findings on digital rectal examination were enrolled in our analysis. The exclusion criteria were as follows: (1) chronic inflammatory condition requiring anti-inflammatory treatment, (2) other medical conditions that might affect immune response (e.g., ulcerative colitis, Crohn's disease, lupus, or other connective tissue diseases), (3) medical history of 5-alpha reductase inhibitor use, (4) history of testosterone replacement treatment, and (5) history of other cancers.

### NKA measurement

NKA levels were measured as described by Song et al. (15). One milliliter of whole blood was

collected using NK Vue® Tubes (ATgen, Sungnam, Korea). All blood samples were obtained at 8 AM on the day of biopsy. The collected samples were incubated at 37°C for 24h under 5% CO<sub>2</sub> with the indicated dose of Promoca™ (ATGen, Seongnam-si, Korea) and 1mL of RPMI 1640 medium (Cellgro/Mediatech, Manassas, VA, USA). The supernatant was then collected, centrifuged at 11,500 x g for 5min., collected in another conical 1.5mL Eppendorf tube, and immediately loaded onto the enzyme-linked immunosorbent assay (ELISA) plates. During the 24h incubation at 37°C, cytokine (Promoca) stimulated the NKA and levels of interferon (IFN)- $\gamma$  secreted into the plasma was quantitated by ELISA. IFN- $\gamma$  was measured in pg/mL and the detection/sensitivity range of the ELISA was 40-2,000pg/mL.

### Statistical Analysis

The patients were divided into two groups according to the presence or absence of PC, and NKA levels between the two groups were compared by non-parametric Wilcoxon-Mann-Whitney tests. The diagnostic test performance of NKA was evaluated by receiver operating characteristic (ROC) curve analysis. Youden's index was calculated to quote the concentration at which the sum of sensitivity and specificity is maximized. In addition, ROC curves were compared for the diagnostic performance of NKA, ratio of total PSA to free PSA (FTR), and PSA density (PSAD). The sensitivity, specificity, and positive and negative values of the PC marker confirmed by prostate biopsy were calculated at a cut-off value of 500pg/dL. The cut-off points for the calculated biomarker coefficients (NKA, FTR, and PSAD) were determined using MedCalc® (MedCalc Software, Mariakerke, Belgium). Data were analyzed using IBM SPSS Statistics for Windows, version 21.0 (Armonk, NY, USA). P-value <0.05 were considered statistically significant.

## RESULTS

A total of 102 patients who underwent prostate biopsy for suspected PC were included. Among them, 50 were diagnosed with PC. The baseline characteristics of all patients are listed

in Table-1. Significant differences in age (mean  $61.30 \pm 10.49$  vs.  $65.52 \pm 7.35$  years,  $p=0.03$ ) and NKA level ( $p < 0.01$ ) were observed between the PC and no-PC groups. However, there were no significant differences in PSA levels (mean  $7.19 \pm 3.86$  vs.  $7.96 \pm 4.24$  ng/mL,  $p=0.54$ ), prostate volume (mean,  $45.97 \pm 28.58$  vs.  $39.82 \pm 14.58$  mL,  $p=0.06$ ), or free PSA levels (mean  $0.98 \pm 0.73$  vs.  $1.27 \pm 1.02$ ,  $p=0.397$ ).

The baseline characteristics according to NKA level are described in Table-2. Significant differences in free PSA and prostate volumes were observed according to NKA level. The NKA  $<200$  and NKA  $<500$  groups had higher positive rates for PC (60% vs. 88.9% vs. 20.0% vs. 35.3%, respectively;  $p < 0.001$ ). However, no significant differences in age, proportion of positive digital rectal exam (DRE), and serum PSA level were observed among the four groups.

**Table 1 - Baseline characteristics of the studied population (n = 102).**

	Total	No tumor group	Tumor Group	P value
<b>No. of patients (%)</b>	102	52	50	
<b>Age (year, SD)</b>	$63.37 \pm 9.29$	$61.30 \pm 10.49$	$65.52 \pm 7.35$	0.032
<b>Prostate volume (mL)</b>	$42.96 \pm 22.92$	$45.97 \pm 28.58$	$39.82 \pm 14.58$	0.058
<b>Positive DRE</b>	27 (26.5%)	4 (7.7%)	23 (46.0%)	0.001
<b>Serum PSA (ng/mL)</b>				
Mean, SD	$7.57 \pm 4.05$	$7.19 \pm 3.86$	$7.96 \pm 4.24$	0.539
<4 ng/mL [no. (%)]	16 (15.7%)	6 (11.5%)	10 (20.0%)	0.463
$\geq 4$ ng/mL [no. (%)]	62 (60.8%)	34 (65.4%)	28 (56.0%)	
$\geq 10$ ng/mL [no. (%)]	24 (23.5%)	12 (23.1%)	12 (24.0%)	
<b>PSA density (ng/mL/mL)</b>				<b>0.357</b>
<0.15 [no. (%)]	42 (41.2%)	20 (38.5%)	22 (44.0%)	
$\geq 0.15$ [no. (%)]	60 (58.8%)	32 (61.5%)	28 (56.0%)	
Free PSA	$1.12 \pm 0.89$	$0.98 \pm 0.73$	$1.27 \pm 1.02$	0.397
<b>NKA</b>				<b>0.001</b>
<200	30 (29.4%)	12 (23.1%)	18 (36.0%)	
200-500	18 (17.6%)	2 (3.8%)	16 (32.0%)	
>500	54 (52.9%)	38 (73.1%)	16 (32.0%)	
<b>Gleason sum at biopsy</b>				
6 [no. (%)]	24 (23.5%)	-	24 (48.0%)	
7 [no. (%)]	8 (7.8%)	-	8 (16.0%)	
$\geq 8$ [no. (%)]	18 (17.6%)	-	18 (36.0%)	

**DRE** = digital rectal exam; **PSA** = prostate specific antigen, **SD**: standard deviation

**Table 2 - Baseline characteristics according to NKA (n = 102).**

	NKA<200	200≤NKA<500	500≤NKA<1000	1000≤NKA	P value
<b>No. of patients (%)</b>	30	18	20	34	
<b>Age (year, SD)</b>	62.93±7.62	66.11±8.49	60.50±10.42	64.06±10.17	0.478
<b>Prostate volume (mL)</b>	42.35±15.43	35.80±9.92	45.05±17.62	46.06±33.58	0.041
<b>Positive DRE</b>	8 (26.7%)	7 (38.9%)	2 (10.0%)	10 (29.4%)	0.183
<b>Serum PSA (ng/mL)</b>					
<b>Mean, SD</b>	7.96±4.19	8.10±4.62	6.99±2.86	7.28±4.29	0.335
<b>Serum PSA (ng/mL)</b>					<b>0.429</b>
<4 ng/mL [no. (%)]	4 (13.3%)	4 (22.2%)	2 (10.0%)	6 (17.6%)	
≥4 ng/mL [no. (%)]	22 (73.3%)	8 (44.4%)	14 (70.0%)	18 (52.9%)	
≥10 ng/mL [no. (%)]	4 (13.3%)	6 (33.3%)	4 (20.0%)	10 (29.4%)	
<b>PSA density (ng/mL/mL)</b>					<b>0.437</b>
<0.15 [no. (%)]	16 (53.3%)	8 (44.4%)	14 (70.0%)	18 (52.9%)	
≥0.15 [no. (%)]	14 (46.7%)	10 (55.6%)	6 (30.0%)	16 (47.1%)	
Free PSA	1.23±0.88	1.24±1.38	0.92±0.43	1.09±0.78	0.036
<b>Prostate cancer [no. (%)]</b>	18 (60.0%)	16 (88.9%)	4 (20.0%)	12 (35.3%)	<0.001
<b>Gleason sum at biopsy</b>					<b>&lt;0.001</b>
No tumor	14 (46.7%)	4 (22.2%)	16 (80.0%)	22 (64.7%)	
6 [no. (%)]	6 (20.0%)	4 (22.2%)	4 (20.0%)	6 (17.6%)	
7 [no. (%)]	4 (13.3%)	0 (0%)	0 (0%)	4 (11.8%)	
≥8 [no. (%)]	6 (20.0%)	10 (55.6%)	0 (0%)	2 (5.9%)	

The absolute risk of diagnosing PC at different NKA levels was calculated and shown in Table-3. Among the 48 patients biopsied with NKA levels below the 500pg/mL cut-off, 70.8% (34/48) were diagnosed with PC with 68.0% sensitivity, 73.1% specificity, and 70.4% negative predictive value. However, among the 30 patients with NKA levels below the 200pg/mL cut-off, 60.0% (18/30) were diagnosed with PC, with a sensitivity of 12.0%, specificity of 76.9%, and negative pre-

dictive value of 55.6%. The risks of PC in patients with PSA levels between 2.5 and 10.0ng/mL or between 10.0 and 20.0ng/mL at different cut-off NKA values are also summarized in Table-3.

Univariate analysis revealed that FTR (odds ratio [OR] 2.437, p=0.031), positive DRE (OR 10.222, p=0.001), and NKA (<500, OR 5.768, p=0.001) were significant predictive determinants of PC Table-4. However, PSAD was not an independent prognostic factor of PC in logistic regres-

**Table 3 - Sensitivity and specificity for the NK cell-cutoff.**

		Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value	Negative predictive value
All patients	NKA <200	12.0% (4.5-24.3)	76.9% (63.2-87.5)	60.0%	55.6%
	NKA <500	68.0% (53.3-80.5)	73.1% (59.0-84.4)	70.8%	70.4%
	NKA <1000	76.0% (61.8-86.9)	46.2% (32.2-60.5)	55.9%	64.7%
PSA<10	NKA <200	15.8% (6.0-31.3)	75.0% (58.8-87.3)	61.5%	57.7%
	NKA <500	68.4% (51.3-82.5)	70.0% (53.5-83.4)	68.4%	70.0%
	NKA <1000	79.0% (62.7-90.4)	40.0% (24.9-56.7)	55.6%	66.7%
PSA≥10	NKA <200	16.7% (2.1-48.4)	83.3% (51.6-97.9)	50.0%	50.0%
	NKA <500	66.7% (34.9-90.1)	83.3% (51.6-97.9)	80.0%	71.4%
	NKA <1000	66.7% (34.9-97.9)	33.3% (9.9-65.1)	57.1%	60.0%

**NKA** = Natural killer cell activity

**Table 4 - Univariate and multivariate analyses of parameter for predicting prostate cancer.**

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
PSAD >0.15	0.795 (0.361-1.753)	0.570	1.215 (0.419-3.525)	0.582
FTR <0.10	2.437 (1.085-5.474)	0.031	3.269 (1.058-10.264)	0.040
DRE	10.222 (3.199-32.666)	0.001	12.626 (3.452-46.177)	0.001
NKA <500	5.768 (2.457-13.543)	0.010	7.547 (2.717-20.964)	0.001

**PSAD** = PSA density (value 0.15<); **FTR** = ratio of total PSA to free PSA (<0.10); **NKA** = Natural killer cell activity

sion analysis. Positive DRE (OR 28.437, p=0.001), NKA (<500, OR 8.400, p=0.001), and FTR (OR 3.269, p=0.040) remained significant predictors of PC in the multivariate analysis.

Univariate analysis revealed that FTR (OR 3.600.031), PSAD (OR 2.941, p=0.049), and NKA (<500, OR 13.000, p=0.001) were significant predictive determinants of a high risk of PC Table-5. However, positive DRE was not an independent prognostic factor of PC in the logistic regression analysis. PSAD (OR 8.433, p=0.013), NKA (<500, OR 10.275, p=0.004), and FTR (OR 11.659, p=0.004) remained significant predictors of a high risk of PC in multivariate analysis.

The estimated area under the ROC curve of NKA was 63.0% (95 confidence interval [CI]: 52.9-72.4%) Figure-1. However, this area was not significantly higher than that obtained for PSAD (p=0.520) (57.8%, 95% CI: 47.7-67.6%). Moreover, NKA was not significantly superior to FTR (p=0.679), with an area under the ROC curve of 59.7% (95% CI: 49.5-69.3%) for PC diagnosis. Finally, the Youden's index for NKA in this cohort was 500pg/dL.

**DISCUSSION**

PSA is the most commonly used serologic marker for PC screening. Patients with PSA levels ≥3.5 are recommended to undergo prostate biopsy, although criteria differ depending on the clinician.

However, PSA is not a perfect marker; therefore, many patients undergo unnecessary prostate biopsy (16). To overcome this limitation, researchers have developed various models using PSA, including FTR:PSA velocity and doubling time or PSAD (17, 18).

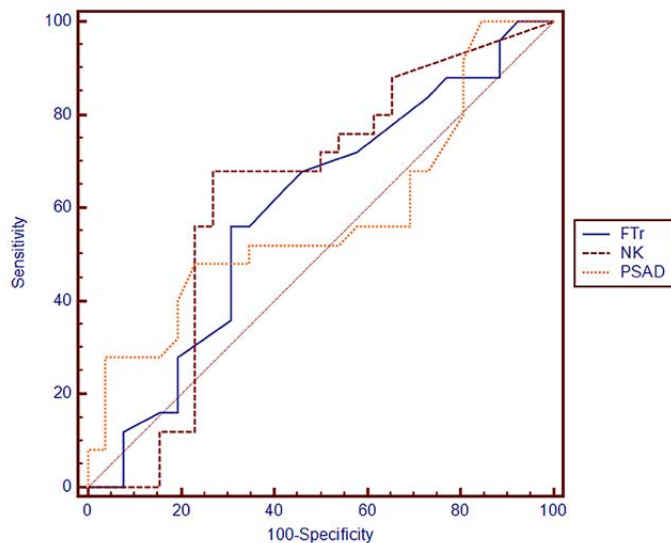
NK cells play an important role in tumor immunosurveillance because they activate both the innate and adaptive immune responses in reaction to tumor cells, even without surface antigens (19). Furthermore, various activating and inhibitory receptors on the cell surface regulate NKA, thereby initiating cytolytic processes in tumor cells and avoiding tissue damage (10). Thus, the role of NK cells in suppressing the progression of various tumors is becoming increasingly apparent (20, 21). Their roles in patients with metastatic PC have also been extensively evaluated (22, 23). However, only two studies to date have investigated the efficacy of NKA as a screening tool for PC, with conflicting results (14, 15).

Among the 102 patients enrolled in the present study, 50 (49.0%) were diagnosed with PC. When the patients were divided into two groups according to the presence of PC, no significant difference was observed in the NKA value (P=0.001). Among the 50 patients with PC, the NKA value did not differ significantly according to the Gleason grade (data not shown). These results are inconsistent with those of Song et al. (15). In addition, this study showed that NKA had the highest odds

**Table 5 - Univariate and multivariate analyses for the association of covariates with high risk of prostate cancer.**

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
PSAD >0.15	2.941 (1.006-8.596)	0.049	8.433 (1.574-45.187)	0.013
FTR <0.10	3.600 (1.226-10.567)	0.020	11.659 (2.214-61.393)	0.004
DRE	0.667 (0.222-1.998)	0.469	(-)	(-)
NKA <500	13.000 (2.802-60.308)	0.001	10.275 (2.076-50.852)	0.004

PSAD = PSA density (value 0.15-); FTR = ratio of total PSA to free PSA (<0.10); NKA = Natural killer cell activity.

**Figure 1 - Diagnostic criteria of the receiver operating characteristic (ROC) curve for the tested parameters.**

**NK** = Natural killer cell activity; **FTr** = ratio of total PSA to free PSA; **PSAD** = PSA density.

ratio for PC using a cut-off of 500pg/mL. These findings are consistent with those of Barkin et al., however, unlike the previous study that reported NKA values of <200pg/mL, this study presented a higher cut-off value. The reason for the different results among previous studies may be that NKA values differ depending on the measurement time and environment (24). The previous two studies did not mention the blood sampling time of NKA measurements. To reduce bias in the present study, blood sampling was performed between 7 and 8 AM on the day of prostate biopsy.

Several studies have been conducted to assess methods for avoiding unnecessary prostate biopsy. The European Association of Urology (EAU) guidelines indicate the potential prognostic role of serum testing or parameters using PSA in detecting PC (6). Among them, PSAD and FTR are representative and may be clinically helpful. In the present study, NKA differed significantly between the established parameters and showed higher diagnostic accuracy for PC in the ROC curve comparison.

Our results suggest that NKA value can be useful for PC screening in patients who underwent prostate biopsy. However, several limitations must be overcome for NKA to have a diagnostic role in PC screening. First, NK cells are phenotypically

and functionally heterogeneous; thus, the reference intervals of NKA values may vary in different populations (25). The patients selected in this study were from a single institution, therefore, further multinational or multicenter investigations with large sample sizes are required. Second, the biological activity of the NK cells is dependent on the integration of signal transducer and activator of transcription signals following stimulation by cytokines such as interleukin (IL)-12 and IL-18, whereas the signal transducer and activator of transcription (STAT) expression within the NK cells may differ among individuals based on various parameters (26). Therefore, the responsiveness of NKA may vary under cytokine stimulation due to differences in various intracellular STAT concentrations (25).

Song et al. showed that prostatic tissues are not properly infiltrated by NK cells and observed a low frequency of NK cells in both normal prostate and PC tissues (27). In addition, CD56<sup>dim</sup> cells are often dominant in the peripheral blood, whereas CD56<sup>bright</sup> cells are significantly abundant in tissues, regardless of PC invasion (15). Therefore, Song et al. assumed that the NKA values in patients with localized PC did not differ significantly from those in healthy persons.

Despite these limitations, the strengths of the present study include corroboration of the finding by Barkin et al. that previously-assessed NKA is valuable in PC screening, although our study was conducted in a different race. Second, in contrast to those of Song et al., our findings suggested that NKA may be helpful in screening Korean patients requiring prostate biopsy. Finally, to minimize variations in daytime NKA levels, sampling was performed at the same time for all patients.

## CONCLUSIONS

The results of this pilot study revealed the association between low NKA and high PSA levels and positive outcome of TRBx. NKA was easily detected and improved the diagnostic accuracy of PC. Large multi-institutional prospective studies are required to validate the role of NKA in PC diagnosis.

## ABBREVIATIONS

DRE = digital rectal exam;  
EAU = European Association of Urology;  
PC = Prostate cancer;  
PSA = prostate-specific antigen;  
NK = natural killer;  
NKA = natural killer cell activity,  
TRBx = transrectal prostate biopsy;  
ELISA = enzyme-linked immunosorbent assay;  
ROC = receiver operating characteristic;  
FTR = ratio of total PSA to free PSA;  
PSAD = PSA density.

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the manuscript. All authors approved the final version to be published.

## CONFLICT OF INTEREST

None declared.

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# The outcomes of mini-laparoscopic pyeloplasty in children - brazilian experience

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## ABSTRACT

**Objective:** Pelvicureteric junction (PUJ) obstruction is the main cause of hydronephrosis in childhood. Open pyeloplasty has been the gold standard treatment of this condition with success rate above 90%. The role of laparoscopic pyeloplasty (LP) in children is less well defined and has slowly emerged as an alternative procedure. We report outcomes of our initial experience with LP in 38 children from 2 months of age.

**Materials and Methods:** From June 2015 to December 2017 38 children aged 2-60 months (mean age 1.7 years) underwent LP for correction of PUJ obstruction. The mean pre operative anteroposterior diameter of the renal pelvis (APD) was 43,5mm and all patients had hydronephrosis (APD 21.4-76 mm) and obstructed curve on diuretic renogram. Anderson-Hynes pyeloplasty was the performed technique. Results are reported.

**Results:** Mean operative time was 107 minutes (70-180) with no conversion to open procedure. Pain control was needed mainly in the first 12hs. Mean hospitalization was 2 days (1-5). There were complications in 5 children not affecting the final outcome. Two patients had a re-obstruction requiring a second procedure with good result. The mean follow up was 18 months (13-36). The mean reduction on the postoperative APD was 41% -  $p < 0,001$  (end APD 5 to 41mm). Overall success rate was 94,7%. All children had good cosmetic results.

**Conclusions:** This is a small series limited by short follow up, however its data suggest that LP has good functional and cosmetic results, not compromising the success of the open procedure, regardless patient age.

## ARTICLE INFO

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## INTRODUCTION

Pelvic-ureteric junction (PUJ) obstruction is a common problem and the main cause of hydronephrosis in childhood. The advent of pre-natal ultrasound (US) has brought the diagnosis even earlier, before symptoms occur. Thus, treatment has been proposed at younger ages.

Open pyeloplasty has long been the gold standard treatment of PUJ obstruction in children. The open approach was described by Anderson-Hynes in 1949 with success rates over 90% (1). Laparoscopic pyeloplasty (LP) was first performed in adults in 1993 (2). The approach results are already well established, and it has been the first choice where such technology is available, with

advantages of a minimally invasive procedure. The proposed benefits are shorter hospitalization, reduced postoperative pain, early return to daily activities and improved cosmetic appearance, while providing good functional results in a reasonable operative time (3, 4).

The first LP in children was performed in 1995 (5). It has gained popularity for older children. The role of LP in youngers and mainly in infants is less well defined. It has just slowly emerged as safe and an alternative to the open procedure (6).

From the end of 2014 on we started a multidisciplinary program to develop minimally invasive pediatric urology. Since June 2015, all children with PUJ obstruction have been submitted to LP in our institution.

The results of our initial experience with LP in children from 2 months to 5 years old are reported here, addressing pre and postoperative data.

## MATERIALS AND METHODS

From June 2015 to December 2017 38 children undergoing LP due to PUJ obstruction and aged 5 years old or younger were enrolled to this study.

Inclusion criteria were: follow-up of at least 6 months after double J (DJ) stent removal and US after this period of time.

Indications for surgery were worsening hydronephrosis and anteroposterior diameter of the renal pelvis (APD) above 20mm on US, plus obstructed pattern on diuretic renogram (DR)-Tc 99m diethylenetriamine penta-acetic acid (DTPA).

The surgical technique performed was Anderson-Hynes dismembered pyeloplasty.

LP is performed positioning the child in a 60-degree lateral decubitus with the side to be treated up. Four ports are used: 3 to 3mm instruments (20cm long) and 15mm to the telescope. The telescope is positioned lateral to the umbilicus on the side of the affected kidney. The next 2-3mm ports are placed mid clavicular and anterior axillary lines in a triangular fashion to the telescope port. The last 3mm port is placed in the lower abdomen, also in the mid clavicular line.

Warmed pneumoperitoneum is maintained at a mean pressure of 8mmHG. Most of the time, the renal pelvis is easily seen. When necessary, the colon is reflected medially or it is approached trans-mesocolon on the left side. A hitch stitch is placed through the abdominal wall to stabilize the renal pelvis. The PUJ is dismembered and the healthy ureter is spatulated on its lateral aspect. 6.0 (until 2 years old) or 5.0 polyglactin threads (>2 years old) are used in a running suture fashion for pelvi-ureteric anastomosis. Except in a very large APD (>50mm), no attempt is made to trim the dilated pelvis. The anastomosis is performed anterior to anomalous lower pole vessel, when it is present. The DJ stent is placed toward the bladder in an antegrade fashion. A drain is introduced through the lower port. Local bupivacaine is used in all trocar ports. A bladder catheter is left in place during hospitalization (Figures 1 and 2).

Oral intake is started as soon as the patient is recovered from anesthesia.

Pain control is available on patient and or parents demand. Intravenous dipyrone and oral paracetamol are available to usual pain. Morphine is available to non-regular pain.

All patients have been followed by US at 1, 3 and 6 month after DJ removal and thereafter at every 6 months. DR was repeated when renal dilatation persisted on US.

Statistical analysis was performed by statistical software. Data were expressed in mean and range for continuous variables. Students t-test was used to compare pre and postoperative parameters. A p value of <0.05 was considered significant.

## RESULTS

From June 2015 to December 2017 thirty eight children aged 2-60 months (mean 1, 7 years old) underwent LP and were included in this study. All patients were operated on by the same team-2 surgeons (CRL and RSQS).

There were 28 boys and 10 girls. Twenty patients were younger than 1 year old, 6 were between 13 and 24 months and 12 between 25 months to 5 years old. The mean weight was 8.2Kg (4 to 22Kg).

**Figure 1 - Trocars position - lateral decubitus.**

Child positioned to left pyeloplasty in a 60-degree lateral decubitus. One 5mm trocar to the telescope placed lateral to the umbilicus on the side of the affected kidney and two 3mm ports placed in a triangular fashion to the telescope port. The last 3mm port is placed in the lower abdomen on the mid clavicular line.

**Figure 2 - Trocars position - postoperative period.**

Position of the trocars - right pyeloplasty, one 5mm port to the telescope placed above and lateral to the umbilicus on the side of the affected kidney and three 3mm trocars to the instruments.

PUJ obstruction was diagnosed by antenatal hydronephrosis in 27 patients, urinary tract infection (ITU) in 6 and abdominal pain in 5 patients.

Comorbidities were present in 6 children: 1 vesicoureteric reflux, 1 horse shoe kidney, 2 chromosome disease, 1 multicystic dysplastic kidney, 1 renal stones. Two patients had previous pyelostomy.

Obstruction was on the left renal pelvis in 20 children (52%).

The mean pre-operative APD was 43.5mm (21.4 to 76mm) on US. Loss of renal cortex was found in 17 patients (68%).

All patients had an obstructed pattern on DR and post furosemide  $T1/2 > 20$ min. Of them, 9 presented split renal function  $< 40\%$  on the affected side Table-1 shows details of the procedure.

Mean surgical time was 107 minutes (70-180min) from port insertion to port closure. There was no conversion to open procedure. Eleven patients had a lower pole vessel obstructing the PUJ (29%).

Oral intake was started from 40 to 240 min (mean 120min) after the end of the procedure.

Mean time of analgesia requirement was 12hs (0-24hs). Dipyron was used. No opioid was necessary.

Mean hospitalization was 2 days (1-5 days).

DJ stent was removed in mean after 45 days after the procedure (15-62 days). There were complications in 6 children (15.7%) with no effect on the final outcome. Three children had UTI, one of them needing hospitalization. Two had dislodgement of the DJ stent. One had omental fat exteriorization during drain removal.

Two patients had worsening hydronephrosis and re-obstruction after DJ removal, requiring a second intervention. The second procedure was performed by laparoscopic approach with very good results. The first one had chromosomal disease and abnormal renal vessels. The second one had previous infective stones which were removed at the LP.

Median follow-up was 18 months (from 13 to 36 months).

Mean reduction on the postoperative APD was 41.8% (end APD 5 to 41mm)  $p < 0.001$ . Three patients had improved, but maintained postoperative hydronephrosis. All of them showed a good washout curve on DTPA. All children are symptoms free. All children had good cosmetic results. Overall success rate was 94.7%, Table-2 shows results according to age.

All parents of the children signed the informed consent for LP.

**Table 1 - Laparoscopic Pyeloplasty - surgical details.**

<b>Pelvis approach</b>	
Colon mobilization	27 (71%)
Transmesocolon	11 (29%)
<b>Anastomotic thread</b>	
Vicryl 5.0	12 (32%)
Vicryl 6.0 (<2 years old)	26 (68%)
<b>Drain</b>	
Penrose	4
Suction	33
No one	1
Bladder catheter + Double J	38
<b>Surgical time (min.)</b>	
Mean	107 min.
Range	70-180 min.
Conversion to open procedure	0

**Table 2 - Laparoscopic Pyeloplasty - results by age.**

N (38)	Age	APD reduction	Surgical time min	Success Rate
20	< 1 year	44,6%	82-180	20/20
6	1-2 years	43%	70-160	6/6
12	3-5 years	38%	98-170	10/12

**N** = number of patients; **APD** = anteroposterior pelvic diameter

## DISCUSSION

PUJ obstruction is a common problem in children. The open dismembered pyeloplasty described by Anderson--Hynes has long been the gold standard treatment with success rate above 90%. Although LP has been widely performed in adults, its benefits in infants have been less clear. The minimally invasive approach has slowly emerged as safe and effective alternative to treat PUJ obstruction in children.

By the end of 2014 we started a multidisciplinary program in pediatric urology which comprised adult videourology and pediatric urology teams. Adult experience was already established and after experience was obtained with older children we were able to start operating the younger ones. Since June 2015 all children with PUJ

obstruction have been submitted to LP in our institution. We report here the outcomes and details of 38 LP in children aged 2 months to 5 years old.

Minimally invasive surgery has gained the world and its benefits are well known: image magnification, decreased blood loss, lower analgesia requirement, faster recovery, better cosmetic outcome. LP also has another reported benefit. Through laparoscopic view, the PUJ is seen in its real position, in contrast to the open or video assisted procedure which brings the PUJ outside, disrupting its normal anatomy. LP is thought to provide better identification to anomalous vessels and avoid twisting or bad positioning of the ureter (3, 7).

The dismembered LP for treatment of PUJ obstruction in children was first described in 1995 (5). Since then, a few pediatric large se-

ries are available in the literature. Many reference centers do not have programs to perform LP in young children-less than 2-3 years old (8). However, while early series had reported anastomotic stenosis in babies (9, 10), subsequent studies demonstrated feasibility irrespective of patient age and weight (6, 7, 11-13).

LP has been thought to be a technically challenging procedure in children. In fact it requires suture training and an experienced laparoscopist (3, 8). There is a learning curve to LP with is far more difficult to pediatric surgeons. Since the beginning of training, pediatric surgeons have smaller and more delicate structures to work with, compared to adult surgeons who find larger structures in their patients. Therefore, limited laparoscopic working space and small ureteral caliber make anastomosis challenging. Also, even in reference centers, the number of pediatric cases in general suitable for laparoscopic procedures in the same period of time is lower to pediatric urology when compared to the adult urology, slowing the learning curve further. Despite this, virtual labs and multidisciplinary practice may be useful to speed the learning curve.

In our institution after having established a pre and postoperative protocol, all patients were operated by the same team (2 surgeons CRL and RSQS). Therefore, the surgical steps were redrawn as needed.

Robotic surgery certainly will add technical facilities in pyeloplasty (14, 15). However, the need of larger incisions for larger port placement and no availability of 3mm instruments makes its role in younger children questionable at moment.

Concerning technical details, we use three ports. The third port helps on exposure. Not placing the telescope into umbilical scar brings all the instruments near the target PUJ. This may avoid organs injuries in small spaces as reported even by expert laparoscopists (3, 6).

While operating on babies it is important a full integration of the anesthetic team to laparoscopic procedures at younger ages.

Although most series report longer operative time in LP, (mean 155-240min) (3, 8, 11,

16) we had spent a mean of 107min., which may be near the open procedures time. Previous adult experience, same team, routine and focusing on simplifying every step certainly play a role in the operative time.

DJ stent is inserted by laparoscopic view. A guide wire is placed through a 3mm aspirating tube in an antegrade fashion, saving the cystoscopy time. Those who favor cystoscopy insertion affirm that retrograde DJ insertion avoids stent dislodgement and related complications (8). However, a study of 15 academic European institutions showed that the antegrade fashion provided the lowest complication rate compared with retrograde stent insertion (17).

We had one child whose DJ didn't reach the bladder. Since then, we focus on urine drops reflowing from the stent as it reaches the bladder. The bladder catheter is inserted at the end of the procedure or otherwise kept closed in the bladder until there.

Surgical site drainage may be a matter of discussion since the postoperative leakage is usually little. Perinephric drain offers the advantage of warning about complications. Postoperative ileus is described by series where drains are avoided (3, 6). We started using a Penrose drain, but moved on to suction drain. Although we had a small omental prolapse, it wasn't necessary any surgical procedure to deal with. Adequate size Blake® drains may reduce the reported risk (8).

Our children had oral intake soon after anesthetic recovery with very good tolerance. After local bupivacaine injection at the end of the procedure, pain control was on patient and parents demand. It was used in mean during the first 12hs which is a short time when compared with open procedures. No opioids were necessary. Two patients didn't require any postoperative analgesia.

Hospitalization was in average 2 days. Although a subjective data, patients were noticed to be with more mobility when compared to our experience in open procedures. In a comparative prospective study of open versus laparoscopic pyeloplasty in children, Piaggio et al. observed fewer narcotic need and shorter hospitalization for LP as others (16, 18).

Our study showed very good functional results in 33 children with significant reduction of the hydronephrosis - mean reduction on the postoperative APD was 41.8% (preoperative APD-21 to 76mm and final APD-5 to 41mm)  $p < 0.001$ . We don't regularly trim the renal pelvis and the APD reduction found is associated with success rate according to the literature (19).

Four patients underwent DR as they had maintained postoperative hydronephrosis. Despite persistent dilatation, all of them showed a good washout curve on DTPA with no obstructed pattern, ensuring a good result after LP. Two children needed reoperation due to worsening hydronephrosis post operatively. One patient had abnormal chromosomes and disrupted anatomy with intra-renal pelvis and anomalous vessels to the kidney. The fail was due to the fact that the pelvic-ureteric anastomosis had been performed above the first anomalous vessels, which seemed to be usual for cases of pyeloplasty. In the second procedure it seemed clear that the anastomosis was again obstructed and needed to be higher and proximal to other anomalous vessels, on a small space available of the abnormal renal pelvis. The other patient had infective stones removed during the first LP. A second laparoscopic procedure was performed in both patients with success, as described in literature (20).

As reported in literature, our study showed no different outcomes related to children's age or weight (17, 21-23). The overall success rate was 100% in the 20 infants and operative time was compared to laparoscopic procedure for older children.

The overall success rate of 94.7% in this study is similar to open procedure and others reported LP series (24-26).

The cosmetic outcome was very satisfactory, with the 3mm scars barely apparent. In spite of that, the argument of open procedure through small incisions has been still supported by some, who do not consider that even small scars grow with patients development and may cause dissatisfaction later. Concerning pain related to open small incision, it may be underestimated in small children (2, 6, 8, 16).

This study demonstrated functional results as reported to open surgery and benefits of a minimally invasive procedure as described by other series in literature (12, 13 17, 22, 27, 28).

## CONCLUSIONS

Our study is limited by short follow-up and small number of patients, however its data suggests that LP has acceptable percentage of complications, good functional and cosmetic results, not compromising the success of the open procedure, regardless patient age.

## CONFLICT OF INTEREST

None declared.

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## Editorial Comment: The outcomes of mini-laparoscopic pyeloplasty in children – brazilian experience

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The advantages of laparoscopic pyeloplasty (LP) in the treatment of Pediatric obstructive hydro-nephrosis (less pain, early dismissal from hospital and less scarring/better cosmesis) are already established for school-aged children and adolescents. A preferential role for LP in small children, however, is not yet recognized, and most comparative trials attest on non-inferiority of laparoscopic techniques, mostly because in this age group lumbar or posterior incisions are usually small and frequently there is no need of muscular incision, even in open techniques. This paper reports the results of LP in severe cases of congenital hydronephrosis (2/3 SFU grade 4 cases), with a 18.4% complication rate, including 2 reoperations for reobstruction, two dislocations of the double J stent (one patient with an intra-ureteral stent) and one omental evisceration in the post-operative period (follow up: minimal 13 months, mean 18 months) (1). All children were  $\leq 5$  years-old and a third of the cohort were children in their first year of life, including a horse-shoe kidney and two patients previously submitted to a pyelostomy. Surprisingly, considering the ages on the cohort, 29% of the cases showed an obstructive polar vessel.

We congratulate the authors for their efforts to progress to minimally invasive techniques, whose advantages are well pointed in the discussion.

LP in small children is certainly feasible (2, 3). This Brazilian group confirms in this observational study that the results are non-inferior to the traditional open access techniques, but, still, proof for advantages over the open procedures are needed in this age group.

Adding to the authors' remarks about the specific difficulties to establish minimally invasive surgery to treat babies, I would say that in small children the quality of the equipment is fundamental to get the best results, including acceptable duration of anesthesia: sub-optimal laparoscopic equipment implies prolongation of surgery, as well as increased tiredness, technical difficulties and frustration to the operating surgeon.

Concerning public health services, the managers must be aware of the imperative technical needs and also of the need of institutionally organized and financed training to health professionals, in order to allow progress towards the new minimally invasive techniques that are on the horizon. At the end of the day, however expensive an initial investment on minimally invasive surgery may seem to be, the final results are largely compensatory, including from an economical point of view, appearing as shorter hospital stays and less usage of pain medications, with the same good results exhibited by the open techniques.

There are certainly many ways to skin a cat, but some of them may be quicker and the cat might suffer less.

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## Primary Vesicoureteral reflux and chronic kidney disease in pediatric population. What we have learnt?

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### INTRODUCTION

Vesicoureteral reflux (VUR) can be defined in a simplistic way as a retrograde flow of urine from the bladder to the upper urinary tract, affecting approximately 30% for children with urinary tract infection (UTI) and 17% without infection (1). However, when including only children that presented with UTI in the first year of life, this percentage now represents up to 70% (2).

It is worth to mention that, asymptomatic infants followed post-natal for pre natal hydronephrosis who had resolved or downgraded the renal dilatation previously identified, a prevalence of 15% of VUR still can be found (3).

The medical interest of VUR contemplates famous public figures from the past as Galeno and DaVinci, however, was only in the 1970's with Ransley and Risdon (4) that the relationship amongst urinary tract infection, vesicoureteric reflux, and renal scar were determined.

Interesting, the classification following grades based on voiding cystourethrography (VCUG) was only established in 1985 (5). Since the very beginning, special attention was turned to dilated grade VUR (Grades 3 to 5), mainly in males.

Back in 1965, Bialestock (6) postulated an evident relation between pyelonephritis and VUR.

Marra et al. (1994) (7) and later Swerkersson S. et al. (2007) (8) showed a direct relationship between males, high-grade VUR and renal dysplasia. Their findings were reinforced in 2010 by Craig and Rushton (9).

With the advance of antenatal images and consequently early suspicion of renal / ureteric abnormalities and hydronephrosis, newborns are deeply investigated following well-established protocols (10) and, when indicated, promptly initiated on antibiotic prophylaxis or even, surgical intervention.

In terms of intervention for VUR patients, which will be better revised later in this article, we changed from invasive to conservative management mainly after 1997 following Yeung and colleague's publication (11).

Curiously, in terms of high-grade primary VUR, the early diagnosis, and precocious intervention seem not to be capable to prevent children from developing renal scars and even worse, chronic kidney disease (CKD) including renal failure.

Numbers obtained in 2006 from The North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) (12) and The Italian Kid Project (2004) (13) showed that, amongst pediatric population, respectively 5.2% and 25% of patients on renal replacement therapy (peritoneal or hemodialy-

sis and/ or renal transplantation) were due to reflux nephropathy or past medical history of VUR.

Then, VUR is not only back-flow urine. At least, it does not seem to be in patients with reflux nephropathy, term established in 1973 by Bailey (14). In this cohort, besides VUR follow-up, special attention should be taken to the patient's somatic growth, hypertension, UTIs as well as kidney's aspect on imagens, including signs of dysplasia, grade of hydronephrosis and ureteric dilatation. All these characterizes must be seen as a single component added to genetic predisposition and socioeconomic condition, among others (15).

In this article, we intend to review the most significant literature in terms of primary VUR and CKD.

We will also explore some definitions and imaging resources that might help physicians to better understand this particular group of VUR patients.

## HISTOLOGICAL ASPECTS

First of all, it is important to understand some concepts and definitions regarding the kidney's histological aspect, and primordially determine differences between an acquired scar from a dysplastic/ hypoplastic kidney.

The term renal dysplasia reports to an anomalous differentiation of the renal parenchyma which is a consequence of abnormal interaction of the ureteric bud. One mechanism that can possibly interfere on the ureteric vesical junction (UVJ) balance may be an ongoing mechanical high-pressure of sterile fetal VUR, and can be associated to a temporarily abnormal bladder behavior with hypertonicity and uncoordinated voiding happening during gestation (mainly in male patients) (6). These changes seem to drive to a peculiar and definitive renal parenchyma tissue of rudimentary nephronic structures (16, 17).

Craig and Rushton (9), considered that "Congenital renal impairment" would be a better term to describe these antenatal compromised kidneys.

On the other hand, a hypoplastic kidney is the one that has a reduction of the total mass of glomerulus and tends to be a globally smaller kidney (17).

On the opposite, renal scar is acquired post-natal following an acute inflammatory reaction from bacterial infection (8). In this condition, females with dilated reflux had a greater chance to develop acute pyelonephritis and, consequently, renal scarring. Here, different from boys with congenital changes, low doses of prophylactic antibiotics seem to reduce the risk of renal scarring (18).

Long term consequences for patients with renal scars are well known and include hypertension, proteinuria, compromising somatic growth and renal failure.

## WHAT SHOULD WE LOOK ON IMAGES?

Urinary tract dilatation is the first clue of VUR seen in the Ultra sound (US) , which is a non-invasive, without exposure to ionizing radiation and available at the majority of the centers. It provides high-resolution anatomical images of renal parenchyma, calyx, pelvis, and bladder. Ureters and urethra are only partially visualized.

First of all, imaging methods can be categorized into those that provide anatomical detail (US, VCUg and urography magnetic resonance imaging (MRI-urography) , those that provide functional information (DMSA nuclear scintigraphy, or both (Functional-MRI (fMRI) and contrast-enhanced US (CE-US) ) (19).

In terms of US, other than evaluating the urine collection system, it can provide anatomical details of renal parenchyma that are critically important for the diagnosis and follow-up of vesical reflux nephropathy. Progression to chronicity can be noted in US in kidneys followed longitudinally. We can identify in follow up images reduction of the parenchyma thickening associated to an increase on cortical echogenicity.

The kidneys may present at US irregular characteristics as renal asymmetry, distorted papillae with caliectasis, pseudo nodular areas due to segmental hypertrophy, corticalization with parenchymal loss, cystic dysplasia and parenchymal scars. These last ones can be suspected in kidneys previously affected by pyelonephritis episodes.

It is worth to mention the important difference between a multicystic dysplastic kidney (MCDK) and a kidney with cystic dysplasia. Mercado-Deane et al (2002) describes this difference as: "A dysplastic kidneys usually retain a reniform shape and have more abundant parenchyma than classic MCDK. The kidneys are normal to small in size with highly echogenic cortex, loss of corticomedullary differentiation, and scattered cysts that are smaller than those commonly seen with MCDK" (20).

Another interesting finding is a radial and regular arrangement of vessels on Doppler US done on top of areas of pseudo nodularization (21-23). Doppler tracing may also show a reduction of the wave profile amplitude due to glomerular atrophy secondary to renal mass loss (fibrotic replacement), leading to transmural renal pressure with reduction of vascular capacitance (24).

DMSA scintigraphy is the gold standard for quantification of the renal parenchyma functioning (25), and, can be done in an acute episode of pyelonephritis or later to confirm established scars, although the imaging findings can be similar, it is necessary to evaluate images in comparisons from different times for definition. DMSA replaced the intravenous urogram (IVP) reducing significantly the time and radiation exposure, however, it does not provide anatomical details.

MRI-urography (26-28) is a method capable of providing high-resolution anatomical details of the entire urinary system. Its main indication includes complex genitourinary malformations, in which the detailed anatomy of the entire collecting system in three-dimensional or panoramic images is desired, being the best method for characterizing the ureters (especially useful in the evaluation of ectopic ureter).

MR urography is able to distinguish areas of acute infection from initial scarring by the different enhancement patterns of these two processes, which is an advantage over DMSA scanning in the evaluation of pyelonephritis and renal scarring at any time.

Although MRI does not use ionizing radiation, its main downside that broadly limits its use are examination time (on average 40 minutes) and the need for general anesthesia in children under

5 years. For this reason, the initial investigation with US and VCUG remains the most appropriate.

MRI also allows adding functional assessment using applicable programs and protocols (fMRI). With this, it is possible to indirectly obtain glomerular filtration rates of each kidney, renal parenchyma perfusion curves, and collection system excretion curves. It is especially useful in cases of ureteric hydronephrosis where scintigraphy is inconclusive and in postoperative cases where large residual system dilatation still remains.

Regards iMRVC for evaluation of VUR it is similar to a conventional VCUG, using instead, gadolinium into the urinary bladder, with the advantage of providing greater anatomical details and continuous surveillance for VUR during the entire filling, waiting, and voiding phases of the study.

Unfortunately, given the limitations of MRI in young children, this technique presents itself only as a possible alternative when other tests cannot be performed or are not conclusive.

### **WHAT IS THE PERCENTAGE OF CHILDREN WITH END STAGE RENAL DISEASE RELATED TO PRIMARY VUR?**

Define an accurate incidence of VUR is difficult. We already saw that it can be underestimated, mainly for these patients that never had a febrile UTI, or even for the ones that could have a past history of VUR, however, when presented with complications including renal scars could have it spontaneously resolved (11, 29).

Numbers from ANZDATA (The Australia and New Zealand Dialysis and Transplant Registry) from a retrospective study from 1971 to 1991 showed that 6.1% of men and 9.1% of women that were listed on renal transplant program had a reported past history of nephropathy VUR. This percentage goes up to 21% and 25% of boys and girls, respectively when looking only for patients younger than 16 years of age (30).

When accessing data from North America, numbers from the NAPRTCS (North American Pediatric Renal Trials and Collaborative Studies) there is an estimative of 3.5% to 5.2%

of the children in renal replacement therapy because of VUR nephropathy (12).

A Canadian report from 1995 describes that approximately 20-25% of the children younger than 15 years had a history of pyelonephritis and VUR. Around 5% of all ages listed had CKD due to reflux nephropathy (31). A similar number was found in Europe (32).

Most recent numbers from Canada from Canadian Organ Replacement Register Annual Report (33) now showed in a restricted population from 11 to 17 years, a total of 12 teenagers (3.7%) listed for renal transplant due to VUR.

Interestingly to mention is the high number of patients with CKD in Italy secondary to VUR insults. Numbers from the ITALKID project and reported on Marra's, et al. paper from 2004, described that 25.7% of patients with end stage renal failure were secondary to primary high grade VUR (grades 4 and 5). Of these, 77.5% were male (34).

In a Brazilian study from 2006, Silva et al. had accessed 735 children charts with primary VUR. Of the 684 patients followed longitudinally, 21 had CKD. A total of 10 patients progressed end stage CKF. However, their most interesting finding was the fact that before 1990 an amount of 5% of the patients had CKD after 10 years follow up, but, after 1990, only 2% advanced to renal replacement therapy (35).

### **CAN WE PREDICT WHICH GROUP OF CHILDREN WITH PRIMARY VUR ARE IN RISK FOR CKD?**

Bailey's paper earlier mentioned (14) and reinforced in Ishikura et al. (36) publication's, conclude that VUR alone might not be responsible for kidneys' deterioration. Their reports showed that the presence of hypoplasia/ dysplasia in refluxing units has a stronger association with the reduction of the glomerular filtration rate (GFR) other than VUR alone. Ishikura's paper includes as risk factors to progression to end-stage renal insufficiency: puberty, stages 4 and 5 of CKD (GFR of 15-30 mL/min. and <15 mL/min. for CKD stage 4 and 5 respectively) and heavy proteinuria, here defined as urinary protein/ creatinine ratio >2.

Different from others here mentioned, Ishikura includes also patients with secondary VUR, for example males with posterior urethral valve.

Another author that demonstrated the straight relation between urinary protein, VUR and CKD was S epibus et al. in 2017 (37), showing a downgrade on GFR in patients with high-grade VUR and high volume of urinary albumin excretion. This is reinforced by previously published literature (38, 39) and can be probably due to induced tubular atrophy and progressive renal failure.

In a prospective evaluation, an Italian report from 2004 from Caione et al. found that a creatinine level higher than 0.6mg/L obtained before one year of age and bilateral high-grade VUR were the most significant risk factors for worsening on renal function. Boys with these characteristics were at 125x risk of developing CKD in the first 6.3 years of life (40).

Sj ostr om et al. (41) in 2009 conducted a research by observing high-grade VUR patients that deteriorated renal function over the years. Curiously, there was no difference found between genders, however, patients with antenatal diagnosis and bilateral renal involvement at birth were the ones with a worse prognosis. This was similar to Silva et al. (35) findings.

Sj ostr om et al. also declared that worsening on patients' renal function was a rare event, however, there was a tendency to deterioration with the increasing degree of VUR and bladder dysfunction. This last one is highly associated with breakthroughs UTIs.

### **DOES SURGICAL INTERVENTION CHANGE THE FUTURE OF THESE CHILDREN?**

We are living in an era in which observation over intervention is preferred. This is a truth since 1992 after Koff and Campbell (42) showed that was safety observe kids with antenatal unilateral hydronephrosis.

In terms of VUR active intervention regarding renal protection, only few years after Koff's publication, Bayley et al. (30) described that proteinuria and hypertension could be per-

sistent or appear despite a successful surgical intervention for VUR patients.

Craig et al. in 2000 (43-45) in a before-after study observed what happened in terms of renal function protection after the introduction of active treatment for VUR (surgical intervention and/ or antibiotic prophylaxis). The authors observed that there was no reduction in numbers of patients that were listed for renal transplantation due to high-grade VUR nephropathy over the years despite any therapy. Patients that had significant deterioration on GFR were that one that already had an abnormal DMSA scan at the very begin. This led them to conclude that surgical intervention is not indicated with the intention of preventing long-term renal damage.

Wheeler et al. (46) in a meta-analysis of randomized controlled trials also did not find significant benefit of any interventional treatment over antibiotics on the prevention of UTI or renal damage. Their most impressive result was that to prevent one single episode of febrile UTI in VUR patients under prophylaxis would be necessary nine reimplantations. And, even more interesting was the fact that there was no reduction in the number of children that developed renal damage and post-operative UTI.

Also, the most recent Cochrane review on interventions for primary VUR (47) showed that antibiotic prophylaxis had insignificant difference to the risk of new/ continuous renal damage in patients followed with DMSA scans.

## CONCLUSIONS

High-grade VUR must be considered a chronic disease and patients should be followed closely.

Unfortunately, patients with antenatal changes confirmed post-natal to have dysplastic kidneys, mainly males with bilateral involvement and high grade VUR tend to have a worst prognosis in terms of CKD.

Surgery and antibiotic prophylaxis seem not to protect against this evolution to renal failure, however, avoiding new onset scars preventing recurrent febrile UTI and treating aggressively urinary protein loss and comorbidities confer some protection to the urinary tract function.

## CONFLICT OF INTEREST

None declared.

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# Editorial Comment: Efficacy and Safety of Complete Intraureteral Stent Placement versus Conventional Stent Placement in Relieving Ureteral Stent Related Symptoms: A Randomized, Prospective, Single Blind, Multicenter Clinical Trial

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## COMMENT

Ureteral stent related symptoms are among the most troublesome problems for the attending urologist. Stent design, positioning, material and size of the stent have been extensively studied (1).

This is a high quality study coming from Japan to investigate a novel concept in ureteral stent positioning to relieve stent related symptoms. The authors randomized patients who required ureteral stent after ureteroscopy into complete intraureteral or conventional stent placement group. Symptoms scores and total amount of analgesics administered were significantly lower in the intraureteral group. There was no difference in the complication rate between groups.

This innovative and ready to use stent placement technique should be tested with different populations with a larger long-term URI trend in view of the popularity of the technique. There is a need for specific cancer survival studies among the different techniques.

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# Editorial Comment: Renal Stone Features Are More Important Than Renal Anatomy to Predict Shock Wave Lithotripsy Outcomes: Results from a Prospective Study with CT Follow-Up

Toricelli FCM<sup>1</sup>, Monga M<sup>2</sup>, Yamauchi FI<sup>1</sup>, Marchini GS<sup>1</sup>, Danilovic A<sup>1</sup>, Vicentini FC<sup>1</sup>, Batagello CA<sup>1</sup>, Srougi M<sup>1</sup>, Nahas WC<sup>1</sup>, Mazzucchi E<sup>1</sup>

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## COMMENT

Predictors of shock wave lithotripsy (SWL) outcomes have been widely studied. Both renal stone features and collecting system anatomy are considered to play a major role to predict stone free rate of SWL. To date, EAU guideline recommends avoid SWL in lower pole kidney stone with an infundibulopelvic angle < 70°, an infundibular length > 30°, and an infundibular width ≤ 5 mm (1). However, those anatomical features were evaluated using intravenous pyelography, rarely used nowadays.

In this study, the authors used computerized tomography (CT) to challenge the concept of the importance of the lower pole location to the outcomes of SWL. In this prospective clinical study, the authors demonstrated the major predictors of SWL success were stone size, stone density and stone-skin distance but not stone location.

Interestingly, collecting system anatomy evaluated by CT seems to play a major role in flexible ureteroscopy (2) but not in SWL. In order to promote stone fragmentation, Holmium laser success depends more on collecting system anatomy but SWL depends more on stone features.

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## Editorial Comment: Role of pelvicalyceal anatomy in the outcomes of retrograde intrarenal surgery (RIRS) for lower pole stones: outcomes with a systematic review of literature

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### COMMENT

During the last decade, retrograde intrarenal surgery (RIRS) has been widely used to treat most kidney stones. Sometimes, indications of RIRS exceed the stone size limit of the guidelines and often neglect the collecting system anatomy. RIRS is currently recommended for treatment of kidney stones up to 20 mm and there is no established parameter of the collecting system for the indication of RIRS in the guidelines (1).

In this study, the authors reviewed previously published papers and themselves investigated the role of pelvicalyceal anatomy in the outcomes of RIRS for lower pole stones. They found steep infundibular pelvic angle (IPA) less than 30°, operative time and larger stone size were significant predictors of residual stone fragments. Moreover, IPA was the most important predictor for being stone free in the lower pole.

Other authors also demonstrated a critical role of IPA for outcomes of RIRS. Using computerized tomography (CT), they demonstrated a steep IPA less than 41° was a predictor for residual fragments after RIRS (2). Therefore, it is crucial to evaluate IPA in the preoperative CT to better predict the stone free rate of RIRS up to 20 mm.

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## Editorial Comment: A modified clinicopathological tumor staging system for survival prediction of patients with penile cancer

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## COMMENT

In this interesting paper, Drs. Zai-Shang Li, Antonio Augusto Ornellas and colleagues, test the prognostic validity of the The 8th American Joint Committee on Cancer tumor-node-metastasis (AJCC-TNM) staging system and to determine whether a modified clinicopathological tumor staging system that includes lymphovascular embolization could increase the accuracy of prognostic prediction for patients with stage T2–3 penile cancer.

The presence of lymphovascular embolization, perineural invasion, and the degree of differentiation are all considered prognostic indicators of survival for penile cancer patients (1, 2)

They analyzed 411 patients who were treated at 2 centers (China and Brazil) between 2000 and 2015. They were staged according to the 8th AJCC-TNM staging system. The internal validation was analyzed by bootstrap-corrected C-indexes and to external validation, where used the data from 436 patients treated at 15 centers over four continents.

The authors found a survivorship overlap was observed between T2 and T3 patients classi-

fied according to the 8th AJCC-TNM staging system. The T2 and T3 patients with lymphovascular embolization showed significantly shorter CSS than did those without lymphovascular embolization ( $P < 0.001$ ).

The authors proposed a modifications to the 8th AJCC-TNM staging system with the T2 and T3 categories should be subdivided into two new categories as follows: t2 tumors invade the corpus spongiosum and/or corpora cavernosa and/or urethra without lymphovascular invasion, and t3 tumors invade the corpus spongiosum and/or corpora cavernosa and/or urethra with lymphovascular invasion.

With this modifications they suggest that the new staging system which the involving lymphovascular embolization showed improved prognostic stratification with significant differences in CSS among all categories (all  $P < 0.005$ ) and exhibited higher accuracy in predicting patient prognoses than did the 8th AJCC-TNM staging system (C-index, 0.739 vs. 0.696). And they show that these results were confirmed in the external validation cohort.

Further studies with other patient cohorts should be performed to validate these findings.

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## Editorial Comment: New Insights on the Mechanisms Affecting Fertility in Men with Non-Seminoma Testicular Cancer before Cancer Therapy

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### COMMENT

In this paper, Tania Dias and colleagues, try to compare the sperm proteome of patients with NSTC, who cryopreserved their sperm before starting cancer treatment, with that from healthy fertile men.

Because patients with non-seminoma testicular cancer (NSTC) cancer can be subfertile or infertile, and present reduced sperm quality and the underlying mechanisms are unknown, this paper may help to identify the underlie causes involved with this condition.

The authors collected Semen samples after 2 to 3 days of abstinence and evaluated Volume, sperm motility, and sperm concentration according to World Health Organization (WHO) 2010 guidelines. Semen samples were then cryopreserved in TEST-yolk buffer and stored in liquid nitrogen at -196°C.

The identification of the differentially expressed proteins (DEPs) between the control and NSTC groups was con- ducted via Scaffold software. (Proteome Software Inc., Portland, OR, USA)

The criteria for the selection of DEPs for validation by Western blot (WB) included: 1) proteins involved in reproductive system development and function; 2) proteins involved in the top canonical pathways; 3) proteins with a higher difference of abundance between the experimental groups; 4) proteins with a well-described function in the literature

The authos identified 189 differentially expressed proteins (DEPs) in the dataset, from which five DEPs related to sperm function and fertilization were selected for validation by Western blot.

And they identified that underexpression of the mitochondrial complex subunits NADH:Ubiquinone Oxidoreductase Core Subunit S1 (NDUFS1) and ubiquinol-cytochrome C reductase core protein 2 (UQCRC2), as well as the underexpression of the testis-specific sodium/potassium-transporting ATPase subunit alpha-4 (ATP1A4) in the NSTC group.


The results indicate that sperm mitochondrial dysfunction may explain the observed decrease in sperm concentration, total sperm count and total motile count in NSTC patients. The identified DEPs may serve as potential biomarkers for the pathophysiology of subfertility/infertility in patients with NSTC.

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**Int Braz J Urol. 2020; 46: 277-8**



## Editorial Comment: Does YouTube include high-quality resources for training on laparoscopic and robotic radical prostatectomy?

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### COMMENT

In this interesting paper Dr. Arslan from Turkey showed the increasing use of online resources to seek visual information for both patients and health care providers. The YouTube has become the second largest search engine with more than one billion users and six billion hours of video watched for each month (1). The authors assessed the quality of the YouTube video content related to conventional laparoscopic radical prostatectomy (LRP) and Robotic-assisted radical prostatectomy (RARP). Of the 1,688 videos collected from YouTube content, 226 videos were analyzed (were excluded duration less than 3 min, duplicate and/or irrelevant videos). They were evaluated regarding a scoring tool, named as Prostatectomy Assessment and Competency Evaluation (PACE) score, which was developed and validated by Hussein et al. (2). They evaluated critical steps using a 5-point scale. The median of video length and median of views were 10 minutes and 586 views for LRP, and 22 minutes and 742 views for RARP. The majority of the videos (70.3%) were uploaded by a medical professional. The open access nature of YouTube allows great interaction for upload and views. They showed that longer video might predict the high-quality scores because there is more time to present all steps of the operation systematically. They concluded YouTube website includes high-quality videos for both laparoscopic and robot-assisted radical prostatectomy, and can help in future the development of training programs.

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**Int Braz J Urol. 2020; 46: 279-80**



## Editorial Comment: Best practices in near-infrared fluorescence imaging with indocyanine green (NIRF/ICG)-guided robotic urologic surgery: a systematic review-based expert consensus

Cacciamani GE <sup>1</sup>, Shakir A <sup>2</sup>, Tafuri A <sup>2,3</sup>, Gill K <sup>2</sup>, Han J <sup>2</sup>, Ahmadi N <sup>2,4</sup>, Hueber PA <sup>2</sup>, Gallucci M <sup>5</sup>, Simone G <sup>5</sup>, Campi R <sup>6,7</sup>, Vignolini G <sup>6,7</sup>, Huang WC <sup>8</sup>, Taylor J <sup>8</sup>, Becher E <sup>8</sup>, Van Leeuwen FWB <sup>9,10,11</sup>, Van Der Poel HG <sup>9</sup>, Velet LP <sup>12</sup>, Hemal AK <sup>12</sup>, Breda A <sup>13</sup>, Autorino R <sup>14</sup>, Sotelo R <sup>2</sup>, Aron M <sup>2</sup>, Desai MM <sup>2</sup>, De Castro Abreu AL <sup>2</sup>

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### COMMENT

In this very nice paper Dr Cacciamani e other experts explained about use of indocyanine green (ICG) to allow visualization of both the vasculature and contours of anatomic structures (1). The use of near-infrared fluorescence (NIRF) technology with ICG has been explored in several surgical specialties (2). It is able to provide an enhanced anatomical view of the surgical field with potentially improved perioperative surgical outcomes (3, 4). They highlight the potential uses of NIRF with ICG for robotic urologic surgery integrating with Firefly® technology in the Da Vinci Surgical platform and systema-

tically (guidelines set out by PRISMA) investigated the impact of this technology in robotic urologic surgery (5). Interestingly they generated several QRcodes to link a video-clip to readers. They reported in a review that NIRF/ICG technology has emerged as an interesting tool improving the identification of anatomical landmarks for oncological and nononcological procedures. This approach facilitates challenging reconstructive and oncologic robotic procedures. The NIRF with ICG can be used in robotic partial nephrectomy (RPN) mainly to localize small branches and perform selective clamping. This approach is useful to discern between pathological and normal renal tissue (6). In robotic-assisted radical prostatectomy (RARP) it can be used for to visualize the arteries of neurovascular bundle or helping identification of regional lymph nodules. It can

better-assist in understanding lymphatic drainage improving diagnostic findings (7, 8). Furthermore, they described the use of this technology during robotic surgery for different types of adrenal pathologies helping in adrenal-sparing surgery (9). They showed also encouraging studies for use in robotic inguinal lymphadenectomy (10). In robotic radical cystectomy, the use of NIRF/ICG-guided can be helpful in identification of sentinel nodes and assessing the vascularity of bowel avoiding mesenteric arcades during intracorporeal deviation. The authors also cited the use during robotic ureteral re-implantation/reconstruction in the evaluation of the vascularity of the ureteral margins and during kidney transplant. However the paper described despite NIRF in urology are promising, the level of evidence is low. Further investigations are needed to improve the understanding on the technology.

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**Int Braz J Urol. 2020; 46: 281-2**



## Editorial Comment: Anticholinergic Drug Exposure and the Risk of Dementia: A Nested Case-Control

Coupland CAC<sup>1</sup>, Hill T<sup>1</sup>, Denning T<sup>2</sup>, Morriss R<sup>2</sup>, Moore M<sup>3</sup>, Hippisley-Cox J<sup>1,4</sup>

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### COMMENT

There is increasing evidence for a possible causal association between the chronic use of anticholinergics and the risk of developing dementia. The inherent limitation for establishing such causal nexus is precisely the fact that the prevalence of overactive bladder (OAB) symptoms and the prescription of antimuscarinics tends to increase in older individuals, exactly in the same age groups in which the incidence of dementia is higher (1).

Coupland et al. carried out a nested case-control study based on the QResearch primary care database from England, including 58 769 patients with a diagnosis of dementia and 225 574 controls 55 years or older matched by age, sex, general practice, and calendar time. Primary exposure was defined as the total standardized daily doses (TSDDs) of anticholinergic drugs prescribed in the 1 to 11 years prior to the date of diagnosis of dementia. There were significant increases in dementia risk for the anticholinergic antidepressants (adjusted OR [AOR], 1.29; 95%CI, 1.24-1.34), antiparkinson drugs (AOR, 1.52; 95%CI, 1.16-2.00), antipsychotics (AOR, 1.70; 95% CI, 1.53-1.90), bladder antimuscarinic drugs (AOR, 1.65; 95%CI, 1.56-1.75), and antiepileptic drugs (AOR, 1.39; 95%CI, 1.22-1.57) all for more than 1095 TSDDs. Associations were stronger in cases diagnosed before the age of 80 years.

Despite attempts to control for confounding variables, the results of case-control studies should be viewed with caution. Even so, this is not the first study to suggest an association between the chronic use of anticholinergics and the development of dementia. Physicians should be aware of new evidences and attempt to reduce exposure to anticholinergic drugs in middle-aged and older people. One question still needs to be answered: are all antimuscarinics alike?

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**Int Braz J Urol. 2020; 46: 283-4**



## Editorial Comment: Robotic versus other nephroureterectomy techniques: a systematic review and meta-analysis of over 87,000 cases

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### COMMENT

This is a meta-analysis of the latest publications on robotic nephro ureterectomy (RNU) comparing it with other techniques. Through research of publications over the last 20 years until April 2019. The authors were able to filter 80 studies as eligible for research. They performed a historical review that adopted nephro ureterectomy with bladder cuff removal as the gold standard for curable resectability in high-grade upper urinary tract urothelial carcinoma.

Over the years, open techniques have been replaced by laparoscopic and laparoscopic robotic assisted. However, robust data are lacking comparing the different techniques regarding intra and postoperative results. Thus, these variables were evaluated in the most different studies: age, gender, body mass index (BMI), race (Caucasian), Charlson Comorbidity Index (CCI)  $\geq 2$ , American Society of Anesthesiologist (ASA) score  $\geq 3$ , tumor location (pelvicalyceal, ureteral, multifocal), and surgery performed in an academic hospital; – surgical outcomes: estimated blood loss (EBL), operative time (OT), intraoperative complications, transfusions, overall complications, major complications (Clavien  $\geq 3$ ), and length of stay; – pathological outcomes: pT  $\geq 3$ , high-grade tumor, pN+, nodes removed, and positive surgical margins (PSM); – survival outcomes: recurrence, metastasis, death, 2- and 5-years recurrence free survival (RFS), 2- and 5-years cancer specific survival (CSS), and correlation between surgical technique and RFS and CSS.

The authors then compared the open nephroureterectomy (ONU), pure laparoscopic (LNU), laparoscopic hand assisted (HALNU), laparoscopic assisted robot (RNU).

The authors mention that over the last 19 years (2000–2019) there has been an increase of up to 36% with series for the procedure performed by (RNU) including the 80 selected articles.

There was no difference between the initial criteria adopted in the different studies. Bladder cuff extraction was performed intracorporeally in all series with RNU, and in 50% of the LNU. Lower bleeding rate in the RNU and higher in the open. Less surgical time at the ONU and no difference between the other techniques. RNU with a lower rate of intraoperative complications and no difference in blood transfusion between RNU and LNU. RNU was more frequently performed in patients with high-risk cancer, but without pathological differences between specimens, but HALNU documented the lowest rate of positive margins as well as the lowest recurrence rate and metastasis. The ONU had the lowest cancer-specific survival rate in 05 years. Intracorporeal Bladder CUFF extraction documented the lowest local recurrence rate.

Another series report with 78 patients who underwent RNU in high volume centers, from 2008 to 2017, on the Si and Xi platforms. It presented similar results in cancer control and progression-free survival. However, as documented in this study, no

comparisons were made between the different techniques (1).

The authors cite that this was the largest published meta-analysis of 87,000 patients, with no differences between studies in their baseline criteria or tumor location. Robotic bladder cuff extraction has lower transfusion rates when compared to other techniques. No difference in transfusions between RNU and LNU, no time difference in RNU when compared to other techniques. Much of the decrease in surgical time in the RNU has been attributed to improved platforms. Long-term complications were equivalent for all techniques and shorter hospital stay.

However, this data may be biased, considering the routine of different services at the time of hospitalization. The RNU also showed a higher number of dissected lymph nodes compared to other techniques. The different techniques did not present statistically significant differences for local recurrences, with a lower intra-bladder recurrence rate for RNU. Although there was a tendency for a higher rate of metastasis to the RNU, however, these patients had a higher risk disease.

Finally, the authors argue that all techniques have similar long-term oncological outcomes with a larger long-term URI trend in view of the popularity of the technique. There is a need for specific cancer survival studies among the different techniques.

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**Int Braz J Urol. 2020; 46: 285-6**



# Synchronous and multiple renal cell carcinoma, clear cell and papillary: An approach to clinically significant genetic abnormalities

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## INTRODUCTION

Renal Cell Cancer (RCC) is a heterogeneous disease that is characterized by distinct pathological phenotypes due to the differences in genetic alterations and signaling pathways affected (1). Bilateral renal tumors are often thought to be familial, however, they are only found in 14% of RCC cases and 4% of von Hippel-Lindau disease (VHL) cases. Therefore, most people with bilateral kidney tumors might have sporadic tumors caused by somatic mutations (2). These figures suggest that a deep genomic study is fundamental for understanding the cause of this disease.

The objective of this report was to describe a clinical case of a patient with bilateral kidney tumors of different subtypes, and how the genetic abnormalities found in this patient relate to the clinical phenotype.

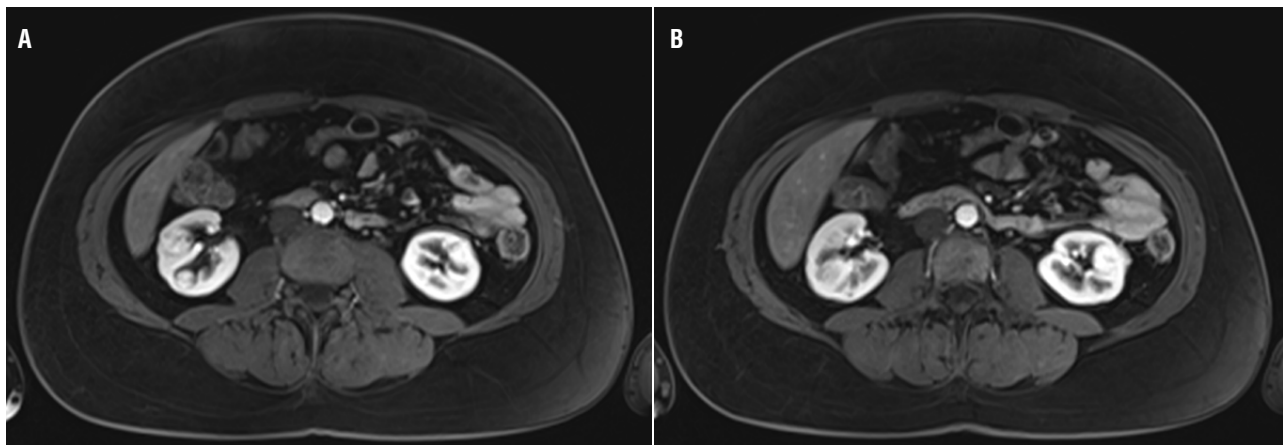
## CASE REPORT

We report the case of a 43 years old female patient with gross hematuria and renal colic who was evaluated by a community urologist. An abdominal non-contrast CT showed small kidney stones without obstruction and a left 14mm renal mass. She underwent abdominal magnetic resonance imaging (MRI), which revealed two right hyper-intense masses (9×7mm and 6×5mm) and

one left mass (16×9mm), which was associated with one unspecific left pulmonary node (Figures 1a and 1b). These findings were evaluated at the uro-oncology clinic in March 2013. Initially, surgery was not recommended considering the young age of the patient and the small size of the tumors (less than 3cm). Furthermore, since this was a case of bilateral renal cell carcinoma (RCC), preserving renal function was important for future treatments. An active surveillance protocol with strict follow-up instructions was established according to the recommendations set by the National Cancer Institute. In September 2013, the MRI revealed that the left mass had grown to a volume of 21×15mm, but other tumors did not grow according to the imaging results.

A genetic test was performed in June 2013. This test specifically genotyped single nucleotide polymorphisms (SNPs) that were relevant to: (a) pharmaceutical drug response (b) genetic diseases and (c) complex diseases. In the latter group, colorectal, lung and breast cancer were included. Results from this genotyping test are presented in Table-1.

In January 2014, we asked for a genetic sequence specific for renal cancer. We carried out a very extensive genomic sequencing study to identify polymorphisms associated with renal cancer and Birt-Hogg-Dubé (BHD) syndrome. This study sequenced a panel of five genes: the VHL gene, which has been associated with von Hippel-Lindau

**Figure 1 - Abdominal Magnetic resonance.****a)** Right renal mass. **b.** Left renal mass.

disease (3, 4), the MET gene, which is associated with papillary carcinoma of kidney cells (5, 6), genes SDHB and SDHD, which are associated with hereditary paraganglioma-pheochromocytoma (7, 6), and the FLCN gene, which is associated with BHD syndrome (8, 9). Predictive studies in silico of variants with unknown significance were performed using Alamut software V.2.11 (Interactive Biosoftware, <http://www.interactive-biosoftware.com>). Results from this sequencing are shown in Table-2.

As shown in Table-2, a total of twelve variants were found in the patient. These variants were already reported in the literature. Out of these twelve, four are localized to the coding region of the analyzed genes. However, they are silent mutations since they do not change the sequence of the encoded protein. The remaining eight mutations were intron-located variants. Six of the eight were deep intronic variants, which are generally considered innocuous. The other two (rs8065832 y rs2018781) are located near splicing sites, which makes them clinically relevant but still unknown. These variants were analyzed using an in silico splicing analysis tool to predict whether they cause splicing defects (Table-3).

Five different splice site prediction algorithms were used: (a) Splice Site Finder - SSF (<http://www.interactive-biosoftware.com>), (b) Gene Splicer -GS (<http://www.tigr.org/tdb/>

GeneSplicer/gene\_spl.html), (c) Splice site prediction by Neural Network - NNS ([http://www.fruitfly.org/seq\\_tools/splice.html](http://www.fruitfly.org/seq_tools/splice.html)), (d) MaxEntScan-MES ([http://genes.mit.edu/burgelab/maxent/Xmaxentscan\\_scoreseq.html](http://genes.mit.edu/burgelab/maxent/Xmaxentscan_scoreseq.html)), and (e) Human Splicing Finder - HSF (<http://www.umd.be/HSF3/>). SSF, MES, GS, and NNS were run simultaneously using the Alamut V.2.11. Default thresholds were used for all the analyses. The results of these in silico analyzes are shown in Table-3.

The in silico analyses (Table-3) predicted that the variant rs2018781 most likely has probably no impact on splicing. However, for the variant rs8065832, two of the algorithms predicted a higher score than the natural splicing site score (> 10%). According to the criteria by They et al., this result indicates that this variant may generate a novel splice site (10). In addition, variant rs8065832, was referenced in the Clinvar database (<https://preview.ncbi.nlm.nih.gov/clinvar/>) and Leiden Open Variation Database-LOVD (<http://www.lovd.nl/3.0/home>); In Clinvar, six reports were found for this variant, all of which categorize it as a benign mutation. However, LOVD yielded nine reports, which all categorized it as having an unknown effect.

The follow-up abdominal MRI scans performed in April 2014 and November 2014 showed no significant changes compared to the previous scans. When the February 2015 MRI scan showed a tumor greater than 3cm, she

**Table 1 - SNP genotyping results associated with some cancer types.**

	Gen/Locus	Marker	Genotype
Colorectal Cancer	BMP4	rs4444235	T/C
	CDH1	rs9929218	G/G
	CRAC1	rs4779584	T/C
	EIF3H	rs16892766	A/A
	Intergenic_10p14	rs10795668	G/G
	Intergenic_20p12	rs961253	C/C
	Intergenic_8q24 region3	rs6983267	G/G
	LOC120376	rs3802842	A/C
	RHPN2	rs10411210	C/C
	SMAD7	rs4939827	T/T
Lung Cancer	BAT3	rs3117582	A/A
	CHRNA3	rs1051730	T/C
	TERT	rs2736100	C/C
	AKAP9	rs6964587	T/G
	CASP8	rs1045485	G/G
Breast Cancer	CHEK2 1100delC		C/C
	ESR1	rs2046210	G/G
	FGFR2	rs1219648	A/A
	Intergenic_2q35	rs13387042	G/G
	Intergenic_8q24	rs13281615	A/G
	LSP1	rs3817198	T/T
	MAP3K1	rs889312	A/A
	MRPS30	rs10941679	A/G
	PALB2 1592delT		T/T
	TNRC9	rs3803662	C/C

underwent three right partial nephrectomies. In February 2015, the pathology report revealed that this tumor was multiple (#3) clear cell carcinoma, Fuhrman grade 2, one of them with positive margins (Figure-2a). In August 2015, she underwent two partial nephrectomies on the left kidney, which pathology reported as being two papillary-type renal carcinomas with

negative margins (Figure-2b). The patient was classified as having right clear cell carcinoma (T1aN0M0) and left papillary-type renal carcinoma (T1aN0M0). In June 2017, the new MRI revealed a hypervascular solid lesion of 10mm in the posterior middle-third portion of the left kidney, which suggests the formation of a new tumor under actual surveillance.

**Table 2 - Sequence variants found in VHL, MET, FLCN, SDHB, and SDHD gene sequencing.**

Gene	IDs.	HGVS	Patient	Functional consequence	Clinical Significance
SDHB	rs10887990	c.286+169A>G <sup>1</sup>	C	Intron variant	Likely benign
SDHB	rs732679	c.73-302G>A <sup>1</sup>	A	Intron variant	Likely benign
SDHB	rs2746462	c.18C>A <sup>1</sup>	A	Synonymous codon	Benign
VHL	rs779806	c.340+384G>A <sup>2</sup>	A	Intron variant	Likely benign
MET	rs34822187	c.1201-6898delA <sup>3</sup>	C	Intron variant	Likely benign
MET	rs41736, COSM150377	c.3912C>T <sup>3</sup> p.D1304D	T	Synonymous codon	Benign
MET	rs2023748, COSM150378	c.4071G>A <sup>3</sup> p.A1357A	A	Synonymous codon	Benign
MET	rs41737, COSM150379	c.4146G>A <sup>3</sup> p.P1382P	A	Synonymous codon	Benign
FLCN	rs8065832	c.1062+6C>T <sup>4</sup>	T	Intron variant	Unknown
FLCN	rs2018781	c.872-610C>G <sup>4</sup>	G	Intron variant	Unknown
FLCN	rs1736219	c.397-14C>T <sup>4</sup>	T	Intron variant	Benign
FLCN	rs1736212	c.-25+100C>G <sup>4</sup>	G	Intron variant	Benign

Transcript of reference BIOBASE:(1) NM\_003000.2, (2) NM\_000551.3, (3) NM\_001127500.1, (4) NM\_144997.5

**Table 3 - In silico splicing analysis of the intronic variants of unknown clinical relevance.**

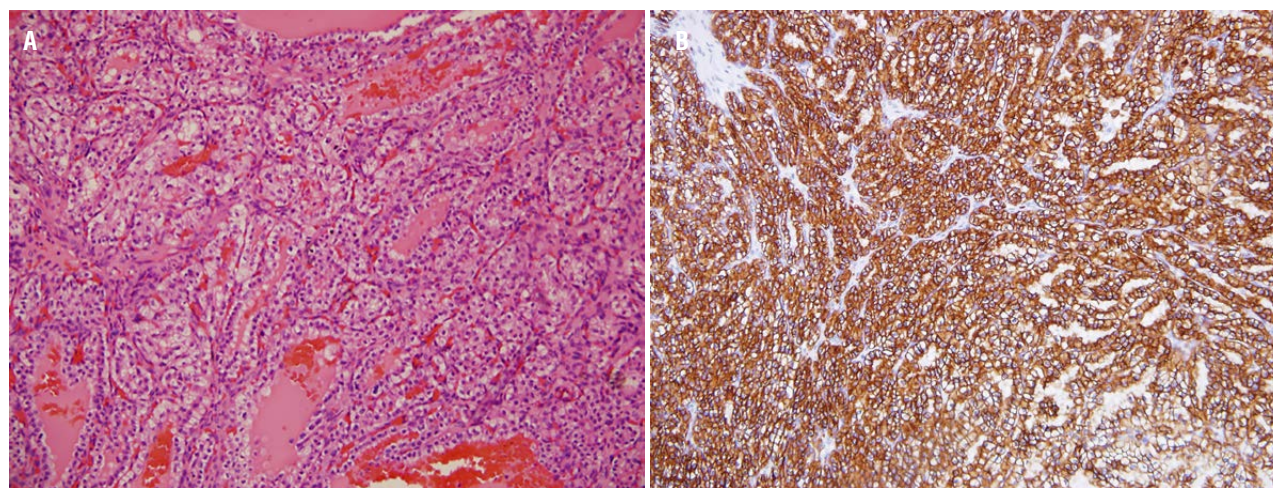
Variant	SpliceSiteFinder [0-100]	MaxEntScan [0-12]	NNSplice [0-1]	GeneSplicer [0-15]	Human Splicing Finder [0-100]
rs8065832 (c.1062+6C>T)	SD: 84.14-89.92 (+6.9%)	SD: 9.88-10.28 (+4.1%)	SD: 0.88-0.90 (+2.1%)	SD: 9.40-11.20 <b>(+19.2%)</b>	SD: 47.34-74.17 <b>(+56.68%)</b>
rs2018781 (c.397-14C>T)	SA: 84.42-87.19 (+3.3%)	SA: 10.50-9.56 (-8.9%)	SA: 0.89-0.90 (+0.6%)	SA: 5.59-5.51 (-1.4%)	No difference between mutant and reference sequence was found.

## DISCUSSION

We reported the case of a patient without a familial background who presented with synchronous bilateral kidney tumors of different subtypes (ccRCC and pRCC). After genomic analyses of five genes that are relevant to renal cancer

(VHL, MET, FLCN, SDHB, and SDHD), several polymorphisms were found, but most of them were not clinically relevant. The only exception was a variant in the FLCN gene, c.1062+6C>T (rs8065832). According to our in silico analyses, this mutation could affect the splicing process and function of the protein folliculin.

**Figure 2 - Light micrograph of a histologic specimen of human kidney.**



**a)** Hematoxylin and eosin of Clear cell carcinoma. **b)** Immunohistochemistry CK7 positive of Papillary-type renal carcinoma.

RCC is the most frequently diagnosed type of kidney cancer (2.4%) among all adult cancers and 90% of kidney tumors (11, 12). 75% of RCC cases are the clear cell subtype (ccRCC), followed by papillary subtype (pRCC), which is found in 15% of cases (13). Both tumor types originate in the proximal tubule. The patient reported in this study had one tumor of each subtype localized to each kidney (ccRCC in the right kidney and pRCC in the left one). According with Wiklund et al., (1) based on the Swedish Cancer Registry, the risk of having a bilateral synchronous renal tumor is 0.3% among the general population and 0.2% among women. However, this study did not report the risk related to the histologic subtype of renal tumor.

In our case, it is important to consider the presence of two different histological subtypes without a family history of RCC. In some patients, bilateral tumors could be considered metastasis. In this case, two different tumors were found (clear cell and papillary), which suggests that they arose independently. This symptom might also occur in a number of inherited forms of renal tumors such as von Hippel-Lindau and BHD syndrome (14). Additionally, it might occur in cases of non-familial bilateral and multifocal kidney disease, where the tumors arise independently, which might be the case for this patient.

Wiklund et al. (1), also reported the risk factors for bilateral metachronous tumors, which include being female and being under the age of 40 years old (RR 4.5, 95% CI 3.4 to 5.9 and RR 18, 95% CI 9.4 to 37.5 respectively). Although there was no report found for synchronous bilateral tumors like this case, but by extrapolating this information, we might consider that our patient fits both of these criteria.

Genome-wide association studies and next-generation sequencing methods have allowed for comprehensive molecular characterization of different cancers, including RCC. As previously mentioned, mutations in VHL, MET, FH, and FLCN genes have been associated with von Hippel-Lindau (VHL)-mediated ccRCC, hereditary type I pRCC, hereditary leiomyomatosis, type II pRCC and BHD. The most common form of sporadic ccRCC showed that VHL is affected by loss of heterozygosity at chromosome 3p in 90% of cases. However, somatic mutations or epigenetic silencing have been reported in >80% of these tumors, which is not surprising considering that this gene is a major driver of ccRCC pathogenesis (15, 16).

Pavlovich et al. (17) reported that among patients with BHD, 34% have chromophobic and 50% have oncocyctic tumors. However, clear cell and papillary tumors were also present, thus suggesting a general carcinogenic risk for the kidney. In our patient, we have found an intronic variant

(rs8065832) that potentially affects the splicing of the FLCN gene, which has been associated with BHD syndrome (11, 12). No studies have been performed to determine the relevance of this variant in regard to susceptibility to RCC. According to da Silva et al. (18) this variant was a low-penetrance susceptibility cancer allele in sporadic RCC and colorectal cancer (CRC). They also found this variant had a higher frequency among CRC cases compared to control patients ( $p=0.055$ ), which suggests that this variant is in linkage disequilibrium with other pathogenic variants.

In this patient, the FLCN gene variant was not associated with other clinical symptoms usually related with FLCN mutation and BHD syndrome. These symptoms included benign skin tumors (fibrofolliculomas), pulmonary cysts, and/or recurrent pneumothorax. Bartram et al. have investigated the mutation in the tumor suppressor gene FLCN that is associated with renal cancer, but additional functional and biochemical validation are required to guide further research regarding the role of FLCN in RCC development (19).

Since we already performed a previous genomic study for this patient, we decided to cross-check these results for breast, lung, and colorectal cancer and determine if there were any associations with RCC. We found that variant rs6983267 and the G/G genotype found in the patient is associated with higher risk of not only colorectal cancer, but an increased risk of thyroid, prostate, lung (20) and renal cancer (21).

We focused our attention on this case since this was a young patient with synchronous bilateral kidney tumor with two different histological subtypes. The patient was screened for germline mutations associated with renal cancer development. Our bioinformatics analyses identified a potentially relevant clinical variant. Since variant has a high frequency in some populations, it is possible that this variant might be a low-penetrance cancer susceptibility allele. The patient has the G/G genotype for rs6983267, which has been associated with a higher risk for developing CRC and renal cancer.

To our knowledge, these polymorphisms (rs8065832 and rs6983267) have not been described previously in the context of ccRCC or pRCC.

They might have pathogenic significance for a sporadic case of synchronous bilateral kidney tumors with different histological subtypes.

## CONCLUSION

Although these results are promising, future research is necessary to establish the role of FLCN variants rs8065832, and rs6983267 in regard to increasing susceptibility to renal cancer. It is important to remember that some genomic disturbances might be associated with synchronous bilateral kidney tumors with different histological subtypes, and it is important to perform a thorough genomic study. Furthermore, it is important that experts in urology, oncology, genomic, and other biomedical sciences work together as an interdisciplinary team to pursue future studies.

## Compliance with Ethical Standards

### Ethical approval

We accomplished all international ethical standards. This is a case report and the information was taken only from the clinical records, additionally there was a computational analysis.

### Informed consent

Informed consent was obtained from the participant.

## ACKNOWLEDGMENT

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## CONFLICT OF INTEREST

None declared.

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# Extraperitoneal Laparoscopic Radical Prostatectomy and Simultaneously Inguinal Hernia Repair with 3 Trocars

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## ABSTRACT

**Objectives:** Extraperitoneal laparoscopic radical prostatectomy (eLRP) is one of minimally invasive surgical treatment modalities of prostate cancer (PCa). We here evaluated our clinical data on eLRP with 3 trocars.

**Materials and Methods:** All consecutive patients undergoing eLRP in similar surgical procedures by two different surgeons (Y.A. & R.L.M.) between 2017 and 2018 at two different centres were included. Various clinical data including patients' demographics, intraoperative and postoperative data, complications, and follow-up were recorded and analysed. We are presenting a video of one such case of eLRP with simultaneously right inguinal hernia repair with using 3 trocars. Surgeons in different clinics performed similar modified surgical technique (Heilbronn technique) (1) for eLRP with 3 trocars.

**Results:** There were 28 cases in total (10 cases in Clinic 1 and 18 cases in Clinic 2). Mean follow-up was 8±0.4 months. Mean age was 69±3.2 years old. Mean prostate specific antigen was 8.8±1.2ng/dl. Mean operating time was 128±20.2 min. Mean estimated blood loss was 195±87.5 ml. Mean hospitalization day was 2.8±1 days. Mean catheter removal day was 8.8±3.6 days. Surgical margin was negative for all cases with 3 complications (Clavien 2) without major complications.

**Conclusions:** The first advantage of this technique is using just one assistant holding laparoscopic optic. Second one is to have similar results with traditional eLRP with fewer trocars. Indirectly, more cosmesis is third one, as our approach seems more minimally invasive than traditional eLRP.

eLRP with simultaneously hernia repair is feasible, safe, and effective with using just 3 trocars in selected cases.

## CONFLICT OF INTEREST

None declared.

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# Transabdominal and transvesical laparoscopic correction of vesico-vaginal fistula: 42 cases experience

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## ABSTRACT

**Introduction and Objective:** Several methods and techniques have been described for the treatment of vesicovaginal fistula (VVF) including abdominal, vaginal and endoscopic approaches. The development of laparoscopic surgery minimizes the morbidity associated with laparotomy, reducing the period of convalescence, being increasingly used in the management of VVF. This aim of this study is to present 42 cases of laparoscopic vesicovaginal fistula repair and to evaluate their results.

**Materials and Methods:** Forty-two patients with a diagnosis of VVF between 1998 and 2016 were included, with precise indications of abdominal surgical approach as recommended by Lee et al. (1) Cystoscopy, Retrograde urethrocytography and excretory urography confirmed the presence of VVF and ruled out ureteral lesions in all patients.

**Results:** Forty-two patients with VVF, mean age of 40.35 years (19-75 years), were treated. The most frequent cause of VVF was abdominal hysterectomy (80.95%) 34 patients (80.95%) had never been treated, while 7 patients (16.66%) had undergone unsuccessful abdominal surgical treatment. One patient (2.38%) underwent three attempts of correction, one vaginally and two abdominal without success. The average time of hospitalization was 3 days. The average duration of the vesical catheter was 12 days. Complications occurred in 4 patients (9.52%). Only 2 patients (4.76%) had recurrence at 40 and 90 days after their first surgery, both of them were previously submitted to radiotherapy.

**Conclusion:** The laparoscopic approach of VVF is an excellent alternative to the traditional abdominal approach. Therefore, it is a feasible, effective and minimally invasive method that can treat this entity.

## CONFLICT OF INTEREST

None declared.

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# Surgical excision of paraurethral cyst

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## ABSTRACT

**Purpose:** Patients with paraurethral cyst may be asymptomatic or bothered by sensation of a mass, pain, distorted urinary outflow, dyspareunia, and dysuria (1). Differential diagnosis includes ectopic ureterocele, pelvic organ prolapse, and urethral diverticulum. At present, the management of paraurethral cysts is unclear, but surgical excision appears as the best treatment option (1-3). Alternative methods include waiting for spontaneous rupture, needle aspiration and marsupialization (4). The aim of the video-tutorial is to provide anatomic views and surgical steps necessary to achieve a successful complete excision of a paraurethral cyst.

**Materials and methods:** A 54-year-old woman with a 2cm paraurethral cyst bothered by intermittent sensation of an introital mass, dyspareunia, and dysuria was admitted to surgical excision according to the described technique. Urethroscopy and ultrasonography were preoperatively performed to confirm the diagnosis and rule out an urethral diverticulum. Surgical steps included: cyst exposure; vaginal mucosa incision; adequate dissection (needle injection of saline solution inside the cyst can be performed to inflate the cyst) with scissors and swab, isolation and excision of paraurethral cyst, layered reconstruction with avoidance of suture layers overlapping.

**Results:** Surgical procedure was successfully achieved without complications. The postoperative course was uneventful. No recurrence was observed and the patient reported complete resolution of her symptoms.

**Conclusions:** The featured video showed complete excision of a paraurethral cyst successfully achieved without complications. Surgical excision represents a safe and effective procedure to manage paraurethral cysts. This step-by-step video-tutorial may represent an important tool to improve surgical know-how.

## CONFLICT OF INTEREST

None declared.

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# Robot-assisted transvesical partial cystectomy for leiomyoma of bladder trigone

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## ABSTRACT

**Introduction and objective:** Leiomyomas of the urinary bladder are very rare neoplasms and are the most common benign mesenchymal tumors of the bladder, accounting for 35% of these. Treatment of leiomyomas is mainly surgical and approaches range from transurethral resection to open segmental resection or laparoscopic partial cystectomy. We sought to present the surgical technique of robot-assisted transvesical partial cystectomy for bladder leiomyoma.

**Materials and methods:** A 25-year-old man presented to urology department with urinary frequency and urgency. Ultrasound and MRI examinations revealed a 30x20mm oval mass in the posterolateral aspect of bladder wall suggestive of bladder leiomyoma. Patient was submitted to cystoscopy with placement of a right ureteral stent and lesion demarcation, and then a robot-assisted partial cystectomy with the following steps was performed: opening of peritoneum over bladder dome and dissection of perivesical fat, opening of bladder wall, incision of bladder mucosa, sharp and blunt dissection of lesion, closure of bladder layers with a knotless closure device.

**Results:** Procedure was performed in 2 hours and there were no complications. Blood loss was minimal (50ml), patient was discharged after 24 hours and bladder catheter was removed after 5 days. Histopathological evaluation revealed a bladder leiomyoma with negative surgical margins.

**Conclusion:** Robot-assisted partial cystectomy is a feasible modality for treatment of intravesical bladder leiomyomas, facilitating transvesical resection and reconstruction.

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## CONFLICT OF INTEREST

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# Re: Association between enuresis and obesity in children with primary monosymptomatic nocturnal enuresis

Rujittika Mungmunpantipantip<sup>1</sup>, Viroj Wiwanitkit<sup>2</sup>

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To the editor,

We read the publication on “Association between enuresis and obesity in children with primary monosymptomatic nocturnal enuresis” with a great interest. Ma et al. concluded that “Obesity is associated with severe enuresis and low efficacy of behavioral therapy in children with nocturnal enuresis (1).” This report is concordant with a recent report from China (2) and Denmark (3). Nevertheless, the association between enuresis and obesity might be affected by some confounding personal illnesses. For example, the children with underlying hemoglobin disorder, such as thalassemia and sickle cell, has a chance for developing enuresis regardless of obesity (4). Indeed, those children with underlying hemoglobin disorder usually have malnutrition problem, not obesity (5).

## CONFLICT OF INTEREST

None declared.

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# Cardiac toxicity after intraurethral instillation of lidocaine: A case report and review of literature

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## INTRODUCTION

Local anesthetics are used in a wide range of clinical situations to prevent acute pain and to stop or ameliorate pain produced by cancer and chronic conditions. Local anesthetics may have similar chemical structures, but different pharmacokinetic properties (1). Outpatient flexible cystoscopy is a common procedure done in outpatient clinics and is usually associated with some discomfort. In current clinical practice, 2% lidocaine gel is widely used as a local anesthetic lubricant before various forms of transurethral instrumentation (urethral catheterization, flexible or rigid cystoscopy, urethral dilatation) (2). Systemic local anesthetic toxicity is infrequent, it can lead to neurological and cardiac complications. The estimate of clinically important local anesthetic toxicity is 7.5 to 20 occurrences per 10.000 peripheral nerve blocks and approximately four occurrences per 10.000 epidurals (3).

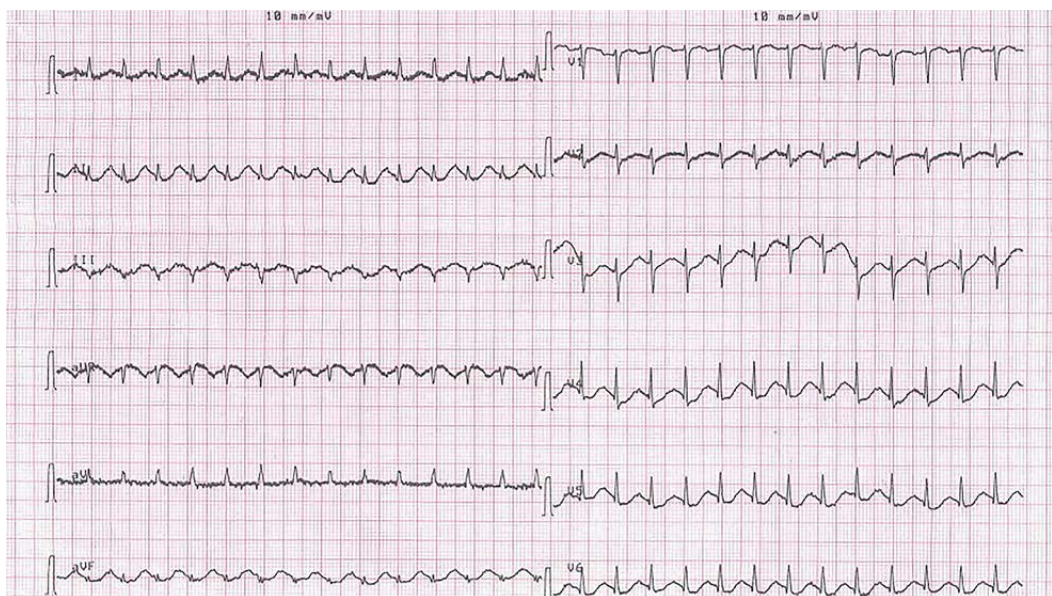
## CASE REPORT

A 65- year-old male known to have T1G3 transitional papillary carcinoma of the bladder diagnosed three months ago treated by transurethral resection of the tumor followed by intravesical Bacillus Calmette-Guérin (BCG) therapy of 6 doses, presented for flexible cystoscopy for control in the outpatient clinic of the hospital. He has a negative past medical history. He has no known

food or drug allergies. On pre-procedure assessment, his blood pressure was 110/80mmHg, heart rate 72 beats per minute (bpm), respiratory rate 13 per minute and temperature 37.1°C.

In the supine position, prepping and draping in the usual sterile manner were done. Twenty mL of 2% lidocaine gel was applied intraurethrally followed by application of a penile clamp across the distal penis. After 5 minutes, the patient started to experience difficulty breathing and palpitations. Upon suspicion of local anesthetic toxicity, the rapid response team was informed promptly about the case. When arrived at the clinic, the patient was attached to the monitor and two IV lines were inserted. Adequate oxygenation by a face mask was initiated. Examination revealed a heart rate of 160bpm, blood pressure of 180/100mmhg and respiratory rate of 22 per minute. ECG showed supraventricular tachycardia with a rate of 167/min (Figure-1). The patient was given immediately a 100mL bolus of 20% intravenous lipid emulsion (intralipids) over 3 minutes followed by 200mL infusion over 15min. Restoration of normal sinus rhythm was observed within 5 minutes of injection. Vital signs returned within the normal limits: blood pressure 120/90mmhg, heart rate 78bpm, respiratory rate 16per minute. The patient was admitted to CCU for monitoring. Blood examinations showed a normal troponin T level, CPK, CPK-MB, metabolic panel. Two days later, the patient was discharged and his clinical status was stable on follow-up.

**Figure 1 - A 12-lead electrocardiogram (EKG) showing a regular narrow complex supraventricular tachycardia at 167 beats per minute (bpm) that occurred after intraurethral lidocaine injection.**



## DISCUSSION

Cardiovascular collapse from accidental local anesthetic toxicity is infrequent. Cardiac toxicity of local anesthetics follows a biphasic pathway, at lower concentrations, sympathetic nervous system activation during the CNS excitatory phase can lead to hypertension and tachycardia. Then, a myocardial depression, conduction block and decreased autonomic flow occur (3, 4).

In a review of systemic toxicity cases from 1979 to 2009, Di Gregorio et al. studied the clinical presentation of local anesthetic systemic toxicity. They concluded that 60% of the patients follow the classic pattern that includes progressive worsening neurologic symptoms occurring shortly after the injection of local anesthetic and paralleling progressive increases in blood local anesthetic concentration then seizures and coma and in extreme cases cardiovascular collapse. In other cases, delayed symptoms can develop or only signs of cardiovascular toxicity without nervous system toxicity. Cardiovascular toxicity characteristics were bradycardia/asystole, tachycardia, hypotension, wide complex, ST-segment changes, ventricular tachycardia and ventricular fibrillation (5).

The risk factors for local anesthetic systemic toxicity are: extremes of age, hepatic dysfunction, low cardiac output states, cardiac pathology, pregnancy, use of  $\beta$ -blocker, digoxin, calcium antagonists (6).

The pathophysiology of local anesthesia systemic toxicity is difficult to discern with the lack randomized trials assessing this point. Most theories are based upon which binding site, ion channel, signaling pathway, are involved in CNS and cardiac toxicity (7). The principal mechanism of cardiac toxicity relates to the blockade of myocardial voltage-dependent sodium channels, which leads to an increase in the PR interval and QRS duration, while persistent sodium channel blockade predisposes to re-entrant arrhythmias (3). De La Coussaye demonstrated that bupivacaine, more potently than ropivacaine alters ventricular conduction via the His-bundle (8).

The diagnosis of lidocaine toxicity is usually clinical as serum levels are not readily available, old studies suggests plasma concentrations above  $5\mu\text{g mL}^{-1}$  were associated with neurological symptoms and levels above  $10\mu\text{g mL}^{-1}$  with cardiovascular instability (9).

Chang et al. reported a case of cardiac arrest immediately following intraurethral administration of lidocaine for cystourethroscopy in an 87-year-old man with intraurethral mucosa lesions from previous attempts of Foley catheter insertion (10). Clapp et al. reported a case of a 2.5-year-old-girl who suffered of a generalized tonic-clonic seizure secondary to the intravesical instillation of lidocaine for the symptomatic relief of postoperative bladder spasm (11).

Initial management of local anesthesia cardiac toxicity should be focused on airway management and circulatory support. The management is symptomatic to prevent hypoxia, acidosis, and hyperkalemia, which may increase the risk of cardiac toxicity (12). Management of local anesthetic-induced cardiac arrest is focused on restoring cardiac output with standard ACLS guidelines with a few adjustments such as small doses of epinephrine (less than 1 microgram/kg) (13).

Intravenous infusion of a lipid emulsion has become part of the treatment for systemic toxicity from local anesthesia, it can be used to treat cardiovascular and central nervous system failure (14). American Society of Regional Anesthesia and Pain Medicine recommends for patients who weigh less than 70kg an initial bolus of 1.5mg/kg of 20% intravenous lipids over 2-3 minutes followed by a continuous infusion of 0.25mL/kg/minute. If hemodynamic stability is not achieved, repeating the bolus dose (up to a total of 3 boluses, 3 to 5 min. apart), followed by increasing the infusion (to 0.5mL/kg/min) is recommended. Infusion should be continued for at least 10 min. after circulatory stability is attained (15).

The exact mechanism of action of lipid emulsions in the treatment of local anesthesia systemic toxicity is not completely known. Several theories are proposed, among which the "lipid sink theory". This theory postulates that the administration of a lipid emulsion provides an alternative binding surface and therefore acts as a "sink" for the fraction of local anesthesia molecules rendering them ineffective (16). Other studies suggested that lipid emulsions can contribute to the enhanced redistribution and delivery of local anesthetics into lesser occupied or

perfused sites of deposition/metabolism (adipose tissue, muscle, liver) which has been described as a lipid shuttle theory. In addition to the "lipid sink and shuttle" theories, other mechanisms involved in lipid emulsion resuscitation are mainly: fatty acid supply, a reversal of mitochondrial dysfunction, inotropic effect, GSK-3 $\beta$  (Glycogen synthase kinase-3 $\beta$ ) phosphorylation inhibition of nitric oxide release and reversal of cardiac sodium channel blockade (17).

In our case, the patient had no history of heart disease and was not taking any medications that increase the risk of local anesthesia toxicity. He has no evident urethral injury that could increase the absorption of lidocaine beside transurethral resection of bladder tumor and BCG (*Bacillus Calmette-Guérin*) instillation of 6 times. The lesson learned is the need for the availability of lipid emulsion therapy in every emergency settings whenever local anesthesia is used. This therapy led to successful management of the arrhythmia. The cardiac toxicity after intraurethral administration of lidocaine is documented in only one case in the literature (10). It can occur as isolated toxicity as described in a recent review of published cases where one-fifth of LAST episodes presented with isolated cardiovascular system disturbances (18). Further investigations are needed to clarify the risks and etiologies.

## CONCLUSION

Systemic toxic effects after local lidocaine application are infrequent and could be life-threatening. The rapid identification of clinical symptoms is key to prevent mortality. The majority of data in the literature suggest that intravenous lipid emulsion is effective for reversing cardiovascular toxicity. Further basic and clinical studies seem to be indispensable to establish more effective treatment guidelines of cardiac arrhythmia induced by local anesthesia.

## CONFLICT OF INTEREST

None declared.

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