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Journal Policies

Insight Urology is the official journal of the Thai Urological Association under Royal Patronage. We accept submissions on interesting urological topics from physicians and all medical providers. The topics must not have been previously published.

Objectives

1. To enhance medical research in urology
2. To instigate academic discussions in urology
3. To distribute dedicated works and research in urology

Our experts and native English speakers will review all chosen topics. All of the content and opinions in this journal belong solely to the authors, and do not express the opinions of the editors or the Thai Urological Association under the Royal Patronage.

Owner The Thai Urological Association under the Royal Patronage (TUA)

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Date of Issue Semi-annually (June and December)

Editorial

The third issue of Insight Urology (ISU) has now been proudly published. It is comprised of 11 original articles, 2 case reports, and 1 review article, and covers several fields of urology, namely oncologic urology, pediatric urology, endourology, functional urology, andrology, and general urology. Interestingly, 13 articles were conducted by urologists and 1 article was conducted by radiologists. Ten articles were submitted from training centers, 3 articles were submitted from government hospitals, and 1 article was submitted from a private hospital. There are 3 prospective randomized control studies, 1 prospective cross-sectional study, and 7 retrospective studies. All of them are of excellent quality. We are certain that you will enjoy reading and applying the articles' content for your current urological practice.

Why are citations essential to a journal? Citations are essential because the number of citations represents the relative scientific significance or quality of papers, and citation indicators are sometimes presented as measures of scientific quality. The methodologies used to assess journal quality include citation analysis; authors tend to first consider the reputation of the journal by using the impact factor. You can cite articles published in journals whether you are an author of a manuscript that has been submitted to that journal, another journal in the Thai Citation Index, or other journals in international databases, such as Scopus, Web of Science, and PubMed. When you cite articles, you are sharing important or interesting papers and, also, increasing the strength of the journals at the same time.

The COVID-19 pandemic is still a grave situation worldwide despite vaccinations. The infection rate in many countries is still high, while the mortality rate is decreasing. The virus mutates so that humans cannot protect themselves from it. It is still too soon to say whether the virus will shortly go away, so we must learn to live with it as the "new normal." The Editorial Board of ISU hopes that the white cover of this issue will symbolize our hope for peace for everyone in the world.

No reserve. No retreat. No regret.

Assoc. Prof. Phitsanu Mahawong, M.D.
Editor in Chief of Insight Urology

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Original Article

Impact on clinical outcome of segmental vs diffuse parenchymal thinning in infants with prenatal urinary tract dilation

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Keywords:
Urinary tract dilation, parenchymal thinning, differential renal function

Abstract

Objective: To determine the difference in renal function and rate of surgical intervention between neonates with diffuse and segmental parenchymal thinning.

Materials and Methods: First postnatal ultrasonography images of neonates with prenatal urinary tract dilation were evaluated and measurements taken. Neonates with parenchymal thinning were categorised into segmental and diffuse parenchymal thinning groups using the medullary to intermedullary ratio. A statistical correlation of differential renal function and rate of surgical intervention between the two groups was calculated and evaluated using an independent t-test and Kaplan-Meier curve with Log-rank test, respectively.

Results: Of the 20 neonates, 10 had segmental parenchymal thinning, while the other 10 had diffuse parenchymal thinning. Mean differential renal function was 49.3% in the segmental parenchymal thinning group compared to 45.8% in the diffuse group ($p = 0.400$). Five patients (50%) from the segmental parenchymal thinning group underwent pyeloplasty in comparison to seven patients (70%) from the diffuse group ($p = 0.430$)

Conclusion: There were no significant differences in renal function or rate of surgical intervention between neonates with segmental parenchymal thinning and diffuse parenchymal thinning. Neonates with segmental parenchymal thinning need to be monitored as closely as those with diffuse parenchymal thinning for early detection of renal deterioration and to identify potential need for surgical intervention.

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Introduction

Dilation of the fetal renal collecting system, prenatal urinary tract (UT) dilation, is one of the most common abnormalities detected in prenatal ultrasonography.[1-3] Diagnosis of UT dilation occurs in 1-5% of all pregnancies.1-3 In the postnatal period, ultrasonography is often the first imaging modality effective in the evaluation of these infants.[3]

In 2014, a multidisciplinary consensus on the classification of prenatal and postnatal urinary tract dilation was achieved, thus showing a level of reliability in the assessment of UT dilation.[4] This classification organised postnatal urinary tract dilation into three groups: low, intermediate, and high risk, by using six ultrasonography parameters including anterior-posterior renal pelvic diameter (APRPD), calyceal dilation, parenchymal thickness, and parenchymal, ureter, and bladder appearance.

Focusing on the parenchymal thickness, a patient with parenchymal thinning will be classified as high risk for uropathy, which requires different management to low and intermediate risk categories. However, there are no guidelines that define parenchymal thinning in terms of which part of the parenchyma should be measured.

While several studies have reported that patients with parenchymal thinning have a higher risk of uropathy,[5,6] few studies provide information about the impact on the outcomes of severity for parenchymal thinning.

A previous study by H. Sibai reported that diffuse parenchymal thinning has a higher risk of a significant decrease in renal function compared to segmental parenchymal thinning.[6] The results, however, show some conflict in terms of anatomy, segmental parenchymal thinning predominantly affecting the medullary region, which might cause pressure on more glomeruli. Thus, the pressure on the glomeruli may not be the main factor that affects the renal function.

The purposes of this study were to determine the difference in renal function and rate of surgical intervention between neonates with diffuse and segmental parenchymal thinning.

Materials and Methods

We conducted a retrospective cohort study of all neonates diagnosed with prenatal urinary tract dilation by ultrasonography at King Chulalongkorn Memorial Hospital based on electronic medical records dating from January 1st, 2010 to December 31st, 2016. The study protocol was approved by the institutional review board of the Faculty of Medicine, Chulalongkorn University, and informed consent was not required (IRB No. 334/62). We only included neonates who met the following criteria: (1) Neonates (≤ 1 month old); (2) diagnosed with hydronephrosis or urinary tract dilation as documented by a pediatric nephrologist or pediatric urologist, according to the medical records; (3) a report of parenchymal or cortical thinning by first postnatal ultrasonography (UTD P3, SFU grade IV or PCD grade IV). Patients were excluded from the study if they had: (1) contralateral significant urinary tract dilation (UTD P2 and P3), or (2) other congenital anomalies of the KUB system such as cystic kidney disease, duplication anomalies and ureteroceles, vesicoureteral reflux, ureterovesical obstruction, or urethral obstruction. Contralateral significant urinary tract dilation and congenital anomalies of the KUB system were excluded due to the possibility they could affect differential renal function. Patients were also excluded if (3) there was no renal function study or (4) there was loss to follow-up within 36 months, unless UT dilation had already resolved before then.

Ultrasonographic images from the Picture Archiving and Communication System (PACS) were used. Evaluation and measurement of the first postnatal ultrasonographic images were done in consensus by a pediatric radiologist and a radiology resident.

Predominate caliectasis at the medullary zone usually gives the appearance of segmental parenchymal thinning, while diffuse caliectasis at both the medullary and intermedullary zones usually gives the appearance of diffuse parenchymal thinning. Thus, the definitions of segmental and diffuse parenchymal thinning were categorised using the parenchymal thickness at the intermedullary and medullary zones.

From ultrasonographic images of the kidney longitudinal axis, the measurement of parenchymal thickness was done at the upper, mid, and lower poles of the kidney for each medullary and intermedullary zone (Figure 1). Subsequently, the average thickness of the medullary zone and intermedullary zone was calculated as a ratio.

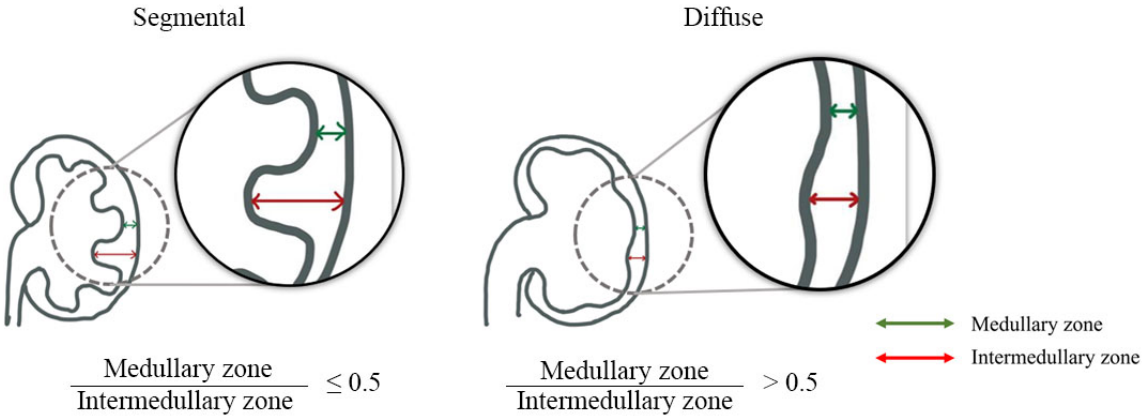

Figure 1. Measurement of parenchymal thickness in medullary zone and intermedullary zone

Based on appearance of segmental and diffuse caliectasis as mentioned above, we used a cut point ratio of 0.5. If the ratio of the medullary zone to intermedullary zone is equal to or less than 0.5, it was categorised as segmental parenchymal thinning. In contrast, it was categorised as diffuse parenchymal thinning if the ratio of the medullary zone to intermedullary zone was more than 0.5.

All neonates underwent diuretic renography using mercaptoacetyltriglycine (MAG3), which enables a calculation for differential renal function (DRF). The first differential renal function for each patient was collected. The differential renal function reflects the relative ability of the kidney to extract a radiotracer from the blood, a measurement ranging from 0 to 100 percent. A statistical correlation between the two groups of urinary tract dilation and differential renal function was performed using an independent t-test. SPSS version 22 was used for all statistical analyses.

We monitored the patients for up to 36 months to discover whether they underwent relevant surgery, specifically pyeloplasty. Indications for pyeloplasty were recorded. Difference in the rate of surgical intervention between the two groups was analysed using the Kaplan-Meier curve with Log rank test.

Results

A total of 47 neonates met the inclusion criteria, 27 were excluded. A total of 20 neonates were evaluated. Measurements were taken from their first postnatal ultrasonographic images and then individuals were classified into segmental and diffuse parenchymal thinning groups. Examples of cases of segmental and diffuse parenchymal thinning are shown in Figures 2 and 3.

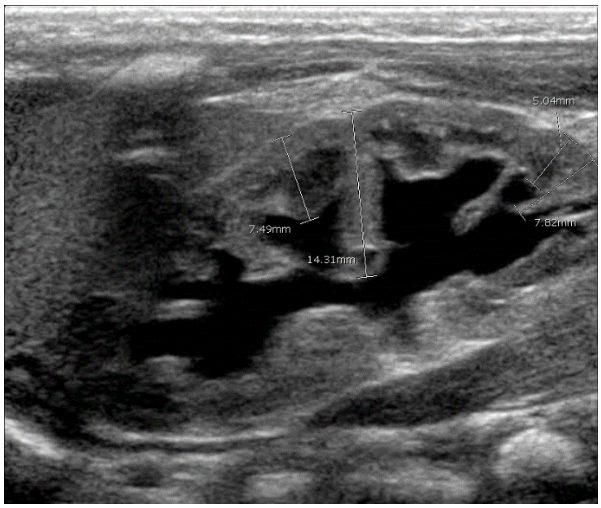

Figure 2. Segmental parenchymal thinning

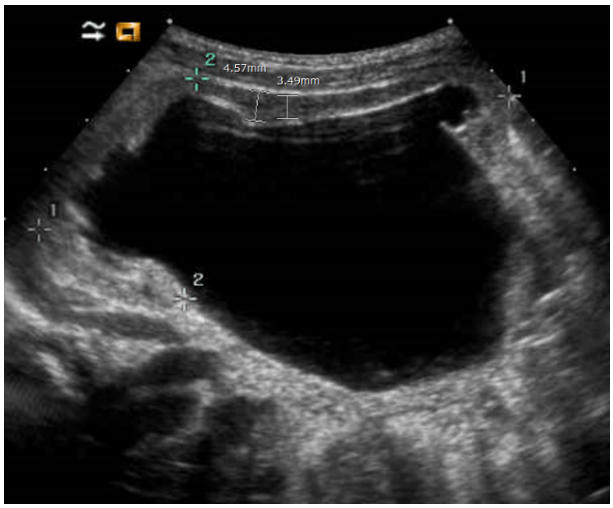

Figure 3. Diffuse parenchymal thinning

Demographic data and clinical characteristics are shown in Table 1.

Mean differential renal function was 49.3% in the segmental parenchymal thinning group and 45.8% in the diffuse group. Statistical analysis showed no significant differences in differential renal function between neonates with diffuse and segmental parenchymal thinning (p = 0.400).

There were 5 patients (50%) from the segmental parenchymal thinning group and 7 patients (70%) from the diffuse parenchymal thinning group who had undergone associated surgery, which was pyeloplasty. Every patient underwent surgery as advised by our institution including 9 patients with less than 40% differential renal function on the affected side, 2 patients with a higher than 5% decrease in differential renal function on serial renography and 1 patient with progressive urinary tract dilation on serial ultrasonography. As illustrated by the Kaplan-Meier curve (Figure 4) with Log rank test, there was no significant difference in the incidence of pyeloplasty between neonates with diffuse and segmental parenchymal thinning (p = 0.430).

Discussion

From our data, it is apparent that urinary tract dilation was more common in the left than the right kidney, findings similar to a study by Carlo C. Passerotti, who reported that hydronephrosis was more prevalent on the left side.[5]

Our results showed that there is no significant difference in differential renal function between segmental and diffuse parenchymal thinning. The results of our study differ from a prior study by Sibai H, which indicated that patients with diffuse parenchymal thinning experienced a significant decrease in differential renal function in comparison to segmental parenchymal thinning.[6]

There is no significant difference in the rate of surgical intervention between segmental and diffuse parenchymal thinning.

The results indicated that, even with parenchymal thinning only in the intermedullary zone, there might be cause for concern and the need for close follow-up due to a significant risk of renal deterioration and the need for surgical intervention, to the same extent as in diffuse parenchymal thinning.

Table 1. Demographic data and clinical characteristics

Demographic data	Segmental	Diffuse
Patients (n)	10	10
Sex		
- Male	9	5
- Female	1	5
Birth		
- Term	9	9
- Preterm	1	1
Average age of 1st ultrasound (days)	18	13
Average age of 1st diuretic renogram (days)	669	527
Laterality		
- Right	2	2
- Left	8	8

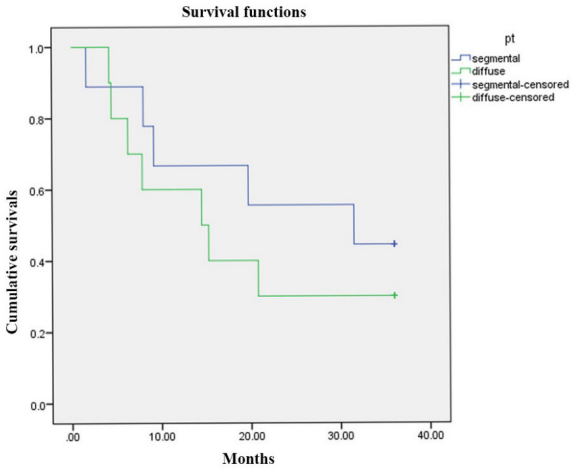

Figure 3. Kaplan-Meier curve showing time to pyeloplasty in segmental parenchymal thinning vs. diffuse parenchymal thinning group

There were some limitations to this study. Firstly, this is a retrospective study and data was extracted from medical records in which investigations had been carried out by a range of professionals leading to some variation. In addition, some images did not clearly focus on each part of the kidney leading to some difficulties in taking measurements. A future prospective study should be conducted with an increased sample size as in this study the numbers were restrictive as we excluded contralateral significant urinary tract dilation which may affect the differential renal function. A prospective study could focus on the measurements for each part of the kidney giving more consistent data. A future study using other cut point values for the medullary to

intermedullary ratio may also show significant differences between the two groups.

Conclusion

Neonates with segmental parenchymal thinning and diffuse parenchymal thinning tend to have no significant differences in renal function or rate of surgical intervention. However, as the sample size in this study was small, the results should not be construed as being precise. It is clear that neonates with segmental parenchymal thinning should be monitored as closely as those with diffuse parenchymal thinning for the early detection of renal deterioration and the need for surgical intervention.

Conflict of Interest

The authors declare no conflict of interest.

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Original Article

Experience of Maharaj Nakorn Chiang Mai Hospital in extravesical ureteral reimplantation for vesicoureteral reflux in pediatric patients

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Keywords:
Extravesical, ureteral, reimplantation, vesicoureteral reflux, pediatric

Abstract

Objective: The most commonly used technique for vesicoureteral reflux (VUR) treatment in pediatric patients in Maharaj Nakorn Chiang Mai Hospital is extravesical ureteral reimplantation (EUR). This report describes our experience of clinical outcomes of this technique.

Materials and Methods: A total of 30 children underwent EUR for unilateral and bilateral VUR between July 2007 and June 2015. We retrospectively reviewed their medical records. Patient characteristics, operative time, duration of catheter drainage, length of postoperative hospital stay, and perioperative complications were evaluated.

Results: Twenty-two boys and 8 girls with a mean age of 4.4 years (range, 0.5-14.6) were included in the study. Reflux was graded 1 to 5. Fourteen unilateral and 16 bilateral procedures were performed. A Pfannenstiel incision was implemented in the first 20 cases and inguinal incision in the last 10 cases. Mean operative time was 115.5 minutes. Mean duration of catheter insertion was 5.7 days. Mean length of postoperative hospital stay was 6.1 days and mean estimated blood loss was 28.7 ml. Overall success rate was 90%. One patient (3.3%), developed a postoperative urinary tract infection, while 3 cases had persistent VUR after surgery. Acute urinary retention occurred in 1 patient (3.3%) on postoperative day 4 but following catheterization the patient was able to urinate by day 7.

Conclusion: EUR for the treatment of VUR is a simple, safe, and effective procedure. The prevalence of postoperative urinary retention in bilateral reimplantation is low and transient. The inguinal approach is a viable option and as effective as classical procedures.

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Introduction

Vesicoureteral reflux (VUR) is one of the most significant risk factors for febrile urinary tract infection in pediatric patients. VUR occurs in approximately 30% of children who have had at least 1 urinary tract infection (UTI).[1] Nephropathy with associated renal scarring and subsequent hypertension leading to end-stage renal disease is still the most concerning issue in VUR.[2] There are many different treatment modalities for VUR including medical and surgical treatment.

Open ureteral reimplantation has been the gold standard for definitive treatment of primary VUR with a success rate of more than 90%.[3,4] The surgical procedure can be performed either intravesically or extravesically with similar success rates.[5] Extravesical ureteral reimplantation (EUR) is associated with lower morbidity compared to intravesical ureteral reimplantation.[6] The advantage of the EUR approach is that the bladder is not opened, therefore, there is a lower incidence of bladder spasm and post-operative hematuria.[7,8] Also to its advantage is this technique is simple and easy for clinicians to learn. The main concern with this technique has been the development of transient voiding inefficiency which is seen in up to 20% of children who undergo bilateral extravesical reimplants.[9,10]

The extravesical technique of ureteral reimplantation pioneered by Lich in America and Gregoir in Europe in the 1960s has proved to be an excellent alternative to intravesical techniques for VUR correction, with a success rate of 90-99%.[11-13] This technique is mainly used in our institution, Maharaj Nakorn Chiang Mai Hospital, for both unilateral and bilateral VUR patients. Traditionally, this technique has been performed through a standard Pfannenstiel incision. However, during the 2012, we gradually changed to the inguinal incision approach. This report describes our experience of the clinical outcomes of this technique. The objectives of this report are to retrospectively evaluate the clinical outcomes of EUR in our hospital and to compare outcomes between Pfannenstiel and inguinal incisions for EUR approaches.

Materials and Methods

Data pertinent to 40 children who underwent EUR for unilateral or bilateral VUR in Maharaj Nakorn Chiang Mai Hospital between July 2007 and June 2015 were reviewed. Ten cases with neurogenic bladder, posterior urethral valves, dysfunctional voiding, ureterocele, or concomitant ureterovesical junction obstruction (UVJO) were excluded. EUR was performed in 30 patients through Pfennensteil or inguinal incision. Indications for surgery were breakthrough febrile UTI, persistent high-grade reflux, renal function deterioration, new cortical renal scarring and preteen females (Figure 1).

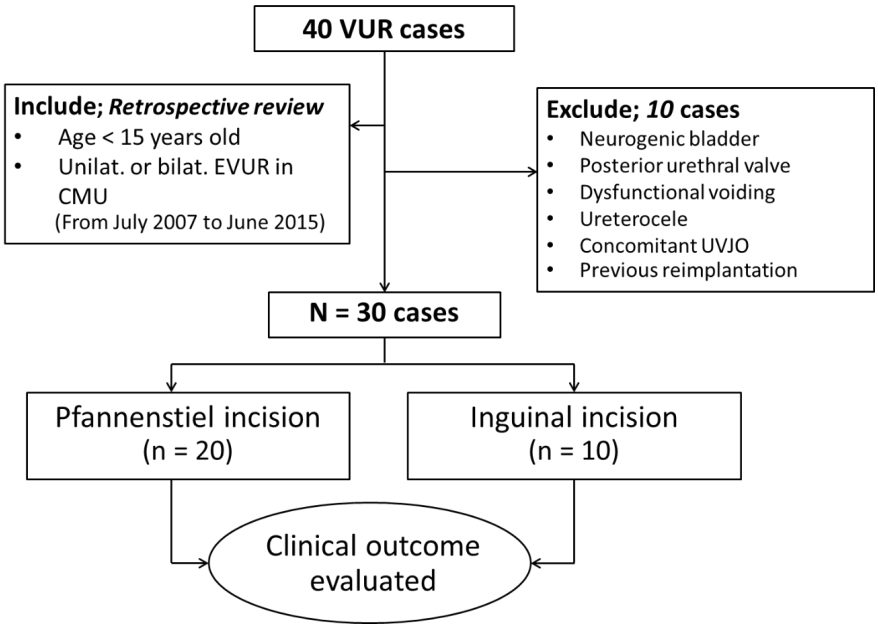

Figure 1. Study population and design

We retrospectively reviewed their medical records. Clinical outcomes of interest were studied, including patient characteristics (age, gender, reflux grade, underlying diseases and anomalies), indications for surgery, operative time, duration of catheter drainage, postoperative hospital stay, postoperative analgesic usage, estimated blood loss, intraoperative, and perioperative complications. After surgery all patients were followed up with urine examination and ultrasound kidneys for between 6 and 24 months. Some patients were re-evaluated using voiding cystourethrography (VCUG) or dimercaptosuccinic acid (DMSA) renal scan when clinically indicated. The success of the operative treatment was defined as no documented UTI and no hydronephrosis on ultrasound during the follow up. An oral prophylactic antibiotic was continued for 3 months postoperative. We compared the surgical outcomes between the two surgical incision groups, Pfannenstiel and inguinal incision, with the parameters listed above. The study protocol was approved by the Ethical Committee of Chiang Mai University (Research ID: 3535/ Study Code: SUR-2558-03535).

Results

Of the 30 cases who underwent EUR treatment 22 were boys and 8 girls. The mean age of the subjects was 4.43 years old. Mean ages of the Pfannenstiel and inguinal groups were 4.70 and 3.80, respectively. Reflux grades were grade I to V with no significant difference between the two incision groups. The indications for surgery were new cortical renal scarring, breakthrough febrile UTI, deterioration in renal function, persistent high-grade reflux, and preteen female in 20, 11, 9, 4, and 1 cases, respectively. Sixteen cases or 53.3% of all cases had bilateral EUR, whereas 14 cases or 46.7% had unilateral EUR. Mean follow up duration was 19.8 months (Table 1).

Table 2 shows the surgical outcomes of the study. Mean operative time was 115.5 (± 27.8) minutes. Mean duration of catheter was 5.7 (± 3.5) days. Mean Postoperative analgesic usage was 1.5 (± 1.5) doses. Mean length of postoperative hospital stay was 6.1 (± 3.5) days and mean estimated blood loss was 28.6 (± 14.3) ml.

There was no intraoperative complications during surgery. Postoperative complications developed in 5 patients, specifically 1 patient (3.3%) developed postoperative UTI, 3 cases (10%) with persistent VUR after surgical correction and 1 case (3.3%) with postoperative urinary retention. The retention case was a 6-month-old boy with bilateral reimplantation who was wean off the catheter one day after surgery. He developed AUR at postoperative day 4. After 7 days of catheterization, he could spontaneously urinate after catheter removal.

When comparing the surgical outcomes between the two EUR techniques we found that duration of catheterization and estimated blood loss were statistically significantly different. As regards success rate of surgery, we considered persistent VUR, abnormal urinalysis to be a failed case. Consequently, the overall success rate of EUR from this study was 90%. The success rate for the Pfannenstiel group was 85% and for inguinal group was 100%.

Discussion

There are several surgical techniques to correct VUR. Both extravesical and intravesical reimplantations are considered to be the gold standard for definitive treatment of VUR. The extravesical approach is generally accepted in Europe and Canada whereas the intravesical approach is more popular in United States for unilateral EUR.[14-16] At Maharaj Nakorn Chiang Mai Hospital EUR is usually selected for both unilateral and bilateral VUR cases. The reasoning behind this is that in general the extravesical approach is considered to be less invasive than the intravesical approach. The bladder is not opened resulting in reduced post-operative bladder spasm and hematuria as well as less postoperative pain.[7,8] In addition, no ureteral stent or perivesical drainage were needed in the extravesical approach. Other studies have shown that this technique requires shorter operative time and hospital stay than the intravesical approach.[9,17] Although there are several advantages to EUR, the main concern with this technique has been the development of transient postoperative urinary retention in children who undergo bilateral EUR. It is thought to be due to the bilateral disruption of the nerves to the bladder. The risk factors for this condition are bilateral procedure, male patients who are younger than 3 years old, and bilateral high grade reflux.[18]

Talbe 1. Patient characteristics and duration of postoperative follow up

	Total (N=30)	Pfannenstiel (n=20)	Inguinal (n=10)	P-value
Gender, n (%)				0.770
Male	22 (73.33)	15 (75.00)	7 (70.00)	
Female	8 (26.67)	5 (25.00)	3 (30.00)	
Age (years)				0.546
Median (25%, 75%)	3.58 (1.37,6.67)	4.25 (1.25,6.96)	2.79 (2,4.25)	
Mean (SD)	4.43 (3.56)	4.70 (3.79)	3.8 (3.14)	
Range	0.5-14.67	0.5-14.67	0.83-11.7	
Reflux Grade, n (%)				0.502
Grade I	2	2 (10.00)	0 (0.00)	
Grade II	1	0 (0.00)	1 (10.00)	
Grade III	2	2 (10.00)	0 (0.00)	
Grade IV	10	6 (30.00)	4 (40.00)	
Grade V	8	5 (25.00)	3 (30.00)	
Operation, n (%)				0.936
Bilateral EUR	16 (53.33)	11 (55.00)	5 (50.00)	
Unilateral EUR	14 (46.67)	9 (45.00)	5 (50.00)	
Underlying disease, n (%)	5 (16.67)	3 (15.00)	2 (20.00)	0.729
Previous surgery, n (%)	6 (20.00)	11 (25.00)	1 (10.00)	0.333
Associated anomaly	10 (33.33)	8 (40.00)	2 (20.00)	0.273
Indications for surgery (N=45)*				0.091
New renal cortical scarring	20 (44.44)	11 (40.74)	9 (50.00)	
Breakthrough febrile UTI	11 (24.44)	6 (22.22)	5 (27.78)	
Renal function deterioration	9 (20.00)	6 (22.22)	3 (16.67)	
Persistent high-grade reflux	4 (8.88)	4 (14.81)	0 (0)	
Preteen female	1 (2.22)	0 (0)	1 (5.56)	
Duration of follow up (months)				0.011
Median (25%,75%)	11 (6, 31)	16 (9,44.5)	6 (5,10)	
Mean	19.83 (19.74)	26.15 (21.57)	7.2 (2.78)	
Range	0-70	0-70	4-11	

EUR = extravesical ureteral reimplantation, UTI = urinary tract infection.
*15 cases presented with 2 indications for surgery and 15 cases presented with 1 indication for surgery.

The surgical technique used was the classical EUR first described by Lich and Gregoir in 1961 and 1964. To prevent nerve injury in bilateral EUR we limit the extent of the ureteral dissection to not proceed distally to the ureterovesical junction and approach the anteromedial part of the bladder. We also limit ureteral mobilization, minimize cauterization and avoid bladder overdistention.[19-21] Traditionally, EUR in our institution had been performed through a standard Pfannenstiel incision. We changed to the inguinal incision approach in 2012. This technique was first described by Chen and colleagues in 2004.[22] The authors claimed that this technique uses a mini-inguinal incision so it may be considered as a less invasive surgical approach. The technique has been shown to be simple, safe and highly effective with lower morbidity.[22] Wiygul and Palmer[23] also supported the advantages of the inguinal approach for EUR and promoted this technique as a practical approach in pediatric patients as a minimally invasive ureteral reimplantation. We performed EUR via inguinal incision in unilateral EUR in early cases, then we progressed to bilateral EUR surgery. Although the bilateral EUR via inguinal incision may result in an equal length of incision as the Pfannenstiel, we continued to use the bilateral inguinal incision according to the informed preference of the surgeon.

Postoperative complications among the 30 cases numbered only 1 (3.3%), the complication being postoperative urinary retention due to early catheter removal. This patient maybe should not

Talbe 2. Perioperative and postoperative clinical outcomes

	Total (N=30)	Pfannenstiel (n=20)	Inguinal (n=10)	P-value
Operative time (minutes)				0.168
Mean (SD)	115.5 (27.83)	120.5 (30.68)	105.5 (18.47)	
Range	80-135	60-130	80-135	
Duration of catheter (days)				0.039
Mean (SD)	5.73 (3.49)	6.65 (3.78)	3.9 (1.85)	
Range	1-14	1-14	2-7	
Postoperative analgesic dosage, n (%)				0.108
Mean (SD)	1.53 (1.52)	1.89 (1.53)	0.9 (1.37)	
Range	0-6	0-6	0-4	
Length of hospital stay (days)				0.282
Mean (SD)	6.1(3.54)	6.6 (3.23)	5.1 (4.09)	
Range	1-16	1-14	2-16	
Estimated blood loss (ml)				0.002
Mean (SD)	28.67 (14.31)	34 (13.91)	18 (7.88)	
Range	1-2	1	2	
Postoperative complications, n (%)				0.392
Urinary retention	1 (5.0)	1 (5.0)	0 (0)	
Urinary tract infection	1 (5.0)	1 (5.0)	0 (0)	
Persistent VUR	1 (5.0)	3 (15.0)	0 (0)	
Overall success rate, n (%)	27	17 (85)	10 (100)	0.196

SD = standard deviation, VUR = vesicoureteral reflux.

have been considered as a good candidate for early removal of catheter because he had risk factors for postoperative urinary retention. Other than postoperative urinary retention, there was a single case (3.3%) who developed UTI and 3 cases (10.0%) that had persistent VUR. All 5 patients with postoperative complications had undergone surgery using the Pfannenstiel incision, the method used by the surgeons in the early cases before the department switched to using the inguinal approach. This higher number of complications, however, may be in cases in the Pfannenstiel group due to less surgical experience of the surgeons.

With regard to the bilateral VUR, the bilateral inguinal incisions may need more operative time than surgery involving the Pfinensteil incision. On the other hand, the bilateral inguinal incisions may result in less operative pain, better cosmetic outcomes, and less transient bladder dysfunction. However, the number of the patients in our study was too small for a statistically robust analysis comparing the treatment outcomes between these two types of incisions. Also, there is no comparative study investigating the advantages and disadvantages of Pfinensteil versus bilateral inguinal incisions for bilateral VUR in current literature. Interestingly, the case of postoperative transient bladder dysfunction in our study had undergone the Pfinensteil not the bilateral inguinal incision.

The rationale of the use of a postoperative prophylactic antibiotic after surgery is still controversial. A prophylactic antibiotic was given to all the patients in our study for 3 months. We believed that the use of a postoperative prophylactic antibiotic still has some benefits especially for the cases that have high grade reflux and/or a history of breakthrough UTI before the surgery. Since the success rate of ureteral reimplantation for primary VUR is very high we did not need to perform the VCUG in every case after surgery unless clinically indicated. We tried to perform a DMSA renal scan at least once in the 6-12-month period postoperative. The postoperative follow up schedule with periodic urine examination and ultrasound kidneys is universally acceptable. The period of follow up was 3-24 months depending on time after surgery and may stop when the patients become adult.

A retrospective study of pneumovesicoscopic Cohen's crosstrigonal ureteral reimplantation for primary VUR was reported by Semmard et al. in 2016. There were 50 pediatric patients

(20 girls and 30 boys) with an age range of 11-132 months. The total success rate was 78% and the mean blood loss was 22.8 (range 5-100) ml. The mean operative time was 184 (range 140-270) minutes for unilateral reimplantation and 222 (range 180-2,600) minutes for bilateral reimplantation. The urethral catheter duration and the length of stay in hospital were 9.5 and 11.3 days, respectively.[24] The results of this minimally invasive surgery study were not superior to our open surgery in terms of operative time, urethral catheter duration, postoperative hospital stay, and success rate.

There are some limitations to this study. First, this is a retrospective study so there are some cases with incomplete records which had to be excluded from the study. Second, the sample size is relatively small. Third, improved skills of a single surgeon during the study may result in better surgical outcomes in the later cases especially in the inguinal group. Fourth, low compliance of the patients and their parents in this study results in the short follow up period as reported.

Conclusion

EUR for treating VUR is a simple, safe, and effective procedure. The prevalence of postoperative urinary retention in bilateral reimplantation is low and transient. The inguinal approach is a viable option and as effective as the classical method used prior to 2012 in this institution.

Conflict of Interest

The authors declare no conflict of interest.

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Original Article

Gynecologic organ involvement and incidental gynecologic organ neoplasms in female patients with urothelial carcinoma of the bladder undergoing anterior pelvic exenteration in Rajavithi Hospital

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Keywords:
Female, urothelial carcinoma of bladder, anterior pelvic exenteration, gynecologic organ

Abstract

Objective: To evaluate the pathological data of the bladder and gynecologic organs obtained from anterior pelvic exenteration and review the incidence of gynecologic organ involvement and primary gynecologic tumor.

Materials and Methods: The clinicopathological data of 70 patients who were diagnosed with bladder transitional cell carcinoma and underwent anterior pelvic exenteration in Rajavithi Hospital between January 2008 and October 2020 were analyzed to examine and determine any correlations.

Results: Thirteen (18.5%) patients had gynecologic organ involvement. This consisted of 4 cases (5.7%) involving the uterus, 7 (10%) involving the vagina, 2 (2.8%) involving the ovaries, and 10 (14.2%) involving the cervix. Female patients with gynecologic organ invasion were more likely to have a high pathological T stage ($p < 0.001$), and have pre-operative hydronephrosis ($p = 0.002$). From multivariate logistic regression, pre-operative hydronephrosis was associated with increased risk of gynecologic organ invasion (odds ratio 9.57; 95% confidence interval, 1.86 - 49.18; $p = 0.007$). There were 23 (32%) female patients incidentally diagnosed with benign gynecologic tumors, specifically 16 (22%) cases of myoma uteri, 7 (10%) of adenomyosis and 4 (2.8%) with ovarian cysts. No patient was diagnosed as having primary gynecologic malignancy.

Conclusions: The incidence of gynecologic organ involvement in female patients who had undergone anterior pelvic exenteration for urothelial carcinoma of the bladder was 18.5%. Pre-operative hydronephrosis was a risk factor associated with increased risk of gynecologic organ involvement. Information from this study may allow better identification of candidates for gynecologic organ sparing surgery.

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Introduction

Bladder cancer is the ninth most common cancer worldwide.[1] More than 60% of all bladder cancer cases and half of all the bladder cancer deaths occur in the less developed regions of the world. Three-quarters of all bladder cancer cases occur in men.[1] Despite having a lower incidence of bladder cancer, females have more advanced tumors at the time of diagnosis.[2]

Anterior pelvic exenteration is the standard treatment for recurrent high grade or muscle-invasive bladder cancer. This operation in women involves en bloc removal of the bladder, entire urethra and adjacent vagina, uterus, distal ureters, and regional lymph nodes.[3] Despite good oncologic outcomes, anterior pelvic exenteration has a great impact on functional outcomes.[4] Even though the literature regarding involvement of the gynecologic organs in female patients with bladder cancer reported relatively low rates of gynecologic organ involvement, the data in the literature tends to be from small sample sized studies and information about risk factors for gynecologic organ involvement is limited.[5-8] Currently, there are no standard guidelines for preservation of the uterus or other gynecologic organs in anterior pelvic exenteration.[9] It is recognized and advisable that gynecologic organ preservation should be considered for younger women who desire to retain their fertility.[10]

In this study, we aimed to investigate the incidence of gynecologic organ involvement at the time of anterior pelvic exenteration, which may allow better identification of candidates for gynecologic organ sparing surgery.

Materials and Methods

We retrospectively reviewed the records of female patients diagnosed with bladder cancer who underwent anterior pelvic exenteration including removal of the bladder, bilateral pelvic lymph nodes, uterus, fallopian tubes and anterior vaginal wall from January 2008 to October 2020 at Rajavithi Hospital. The research was approved by the ethics committee of Rajavithi Hospital (Study Code: 63236).

The patients were excluded from further analysis if non-urothelial primary malignancy was found in the final pathology, there was a prior total abdominal hysterectomy with bilateral salpingo-oophorectomy and no gynecologic organs were present in the final cystectomy specimen, or data from hospital records was incomplete.

We collected the clinicopathological and radiological data from hospital charts. Tumor staging was performed according to the American Joint Commission on Cancer TNM classification, 8th edition.[11] All cystectomy specimens were examined by an experienced pathologist.

The baseline data of patients were analyzed. Descriptive statistics are reported as number, percentage, mean, median, standard deviation, minimum and maximum. In the case of inferential statistics, quantitative data which was normally distributed were analyzed by Student T-test and abnormally distributed by Mann-Whitney U test. Qualitative information comparisons were analyzed by Chi-square test or Fisher's Exact test. Binary logistic regression was performed to evaluate the association between each of the clinicopathologic variables and the risk of gynecologic organ involvement.

A p-value less than 0.05 was considered to indicate statistical significance. Statistical analyses were performed using SPSS version 22.0.

Results

In this study, 95 female patients underwent anterior pelvic exenteration between January 2008 and October 2020. 25 patients were excluded due to primary adenocarcinoma (6), squamous cell carcinoma (3) and sarcoma (1) of bladder, incomplete clinical data (11), previous gynecologic surgery (4).

Therefore 70 female patients remained for analysis. Their clinicopathologic data are reported in Table 1. Mean age was 64.80 years. Thirteen (18.5%) patients had any gynecologic organ involvement, including 4 (5.7%) involving the uterus, 7 (10%) involving the vagina, 2 (2.8%) involving the ovaries, and 10 (14.2%) involving the cervix.

Data of gynecologic organ involvement are reported in Table 2. There were 23(32%) female patients incidentally diagnosed as benign gynecologic tumor; this consisted of 16 (22%) myoma uteri, 7 (10%) adenomyosis, 4 (2.8%) ovarian cyst (Table 3). Between the non-gynecologic organ invasion and gynecologic organ invasion groups, there were no significant differences with regard to age, body mass index, hypertension and diabetes

history, neoadjuvant chemotherapy history, glomerular filtration rate, smoking history, pathological grade. There was a correlation between female patients with advanced pathological T stage ($p < 0.001$), and pre-operative hydronephrosis ($p = 0.002$) and gynecologic organ involvement (Table 4).

From the multivariate logistic regression, pre-operative hydronephrosis was associated with increased risk of gynecologic organ invasion (odds ratio 9.57; 95% confidence interval, 1.86 - 49.18; $p = 0.007$).

There were 6 patients with no gynecologic organ involvement diagnosed with pathologic stage T4. These included 3 cases involving the abdominal wall and 3 involving the adjacent colon. There were no incidental primary gynecologic malignancies in the patients.

Discussion

Approximately 75% to 85% of bladder cancer cases present with non-muscle invasive bladder tumors and 20 to 30% of bladder cancer cases present with muscle-invasive disease or beyond.[12,13] Anterior pelvic exenteration in female patients historically included resection of the bladder, urethra, anterior vagina, uterus, and cervix. This allows for adequate resection. It should also be noted that initial presentation in women is usually at a more advanced stage of disease in comparison to men.[14,15] Although bladder cancer is rarely diagnosed before the age of 40, female patients who undergo premenopausal oophorectomy may have cardiometabolic disease, bone resorption issues, sexual dysfunction, and cognitive disorders.[12,16] Furthermore prolonged hormone replacement therapy used to alleviate symptoms and minimize these risks has been associated with increased incidence of breast cancer, especially if used for more than 5 years.[17]

The rate of involvement of gynecologic organs is variable. Gregg et al. reported that 32 (23%) out of 139 patients with no prior history of hysterectomy had genital organ involvement.[18] Whereas Chen et al. reported 5.2% of 115 patients had gynecologic organ involvement.[8] In this study, the incidence of involvement of the gynecologic organs in association with bladder cancer was 13 (18.5%) (Table 5).

Some prior studies investigated the risks of gynecologic organ involvement to determine

Table 1. Demographic and clinical characteristics of the study patients

Data	Total (N = 70)
Characteristics	Mean ± SD (min-max)
Age (years)	64.80±10.53 (24-88)
Body mass index	23.31±4.16 (15.8-36.4)
Glomerular filtration rate	66.27±25.42 (7-110)
	Number (%)
Hypertension	29 (41.4)
Diabetes mellitus	16 (22.9)
Smoking	2 (2.9)
Neoadjuvant chemotherapy	6 (8.6)
Pre-operative hydronephrosis	32 (45.7)
Pathological data	**Number (%)**
Pathologic stage	
Ta	1 (1.4)
T1	11 (15.7)
T2	23 (32.9)
T3	16 (22.9)
T4	19 (27.1)
Pathologic grade	
Low	6 (8.6)
High	64 (91.4)
Pelvic lymph node involvement	17 (24.3)

Table 2. Gynecologic organ involvement at pathologic examination

	Total (N = 70) Number (%)
Gynecologic organ involvement	13 (18.5)
Vagina	7 (10)
Uterus	4 (5.7)
Ovaries	2 (2.8)
Cervix	10 (14.2)
Single organ involvement	5 (7.1)
Multiple organ involvement	8 (11.4)

Table 3. Primary gynecologic organ neoplasm at pathologic examination

	Total (N = 70) Number (%)
Primary gynecologic organ neoplasm	23 (3.3)
Myoma uteri	16 (2.3)
Adenomyosis	7 (10)
Ovarian cyst	4 (28)
Single gynecologic organ neoplasm	20 (28.6)
Multiple gynecologic organ neoplasm	3 (4.3)

Table 4. Correlation between patient characteristics

	Gynecologic organ involvement		
	Yes (n=13)	**No (n=57)**	**P-value**
	Mean ± SD		
Age (years)	66.23±8.19	64.47±11.02	0.591
BMI (kg/m^2)	22.44±4.59	23.51±4.07	0.405
GFR (ml/min)	61.92±26.14	67.26±25.37	0.498
	Number and percentage		
Hypertension	6 (20.7)	23 (79.3)	0.702
Diabetes mellitus	4 (25)	12 (75)	0.476
Smoking	1 (50)	1 (50)	0.339
Neoadjuvant chemotherapy	1 (16.7)	5 (83.3)	1.000
Pre-operative hydronephrosis	11 (65.6)	21 (34.4)	0.002
Pathologic stage			< 0.001
Ta	0 (0)	1 (100)	
T1	0 (0)	11 (100)	
T2	0 (0)	23 (100)	
T3	0 (0)	16 (100)	
T4	13 (68.4)	6 (31.6)	
Pathologic grade			1.000
Low	1 (16.7)	5 (83.3)	
High	52 (81.3)	12 (18.8)	
Pelvic lymph node involvement	6 (35.3)	11 (64.7)	0.069

Table 5. Gynecological organ involvement

References	Patient numbers N	Countries	Invasion n (%)
Chen et al. (1997)[8]	115	USA	6 (5.2)
Tran et al. (2004)[27]	221	USA	11 (5.0)
Varkarakis et al. (2007)[10]	54	Austria	3 (5.7)
Djaladat et al. (2012)[5]	267	USA	20 (7.5)
Gregg et al. (2016)[18]	139	USA	32 (23)
Choi et al. (2017)[19]	112	South Korea	11 (9.8)
Huang et al. (2019)[9]	49	China	5 (10.2)
This study	70	Thailand	13 (18.5)

which patients are likely candidates for gynecologic organ sparing cystectomy. Choi et al. reported that tumor location at the trigone or bladder neck at TUR-BT, maximum tumor size > 4.8 cm from CT, and hydronephrosis from CT were independent predictors of female organ involvement.[19] Gregg et al stated that lack of trigonal or bladder floor tumor, intraoperative palpable posterior mass, and clinical lymphadenopathy were associated with absence of female pelvic organ involvement. Taylor et al. reported that the presence of gynecologic organ involvement during anterior pelvic exenteration was associated with advanced pathologic T stage.[20] Djaladat et al. retrospectively reviewed 267 patients and found that palpable mass and hydronephrosis were among the preoperative clinical factors associated with reproductive organ involvement.[5] Chen et al. examined 115 patients and reported that vaginal and cervical invasion both showed a correlation with stages T3b and T4 of disease.[8] Varkarakis et al. retrospectively reviewed 54 women with clinical organ confined transitional cell bladder cancer and found that 3 (5.7%) patients had tumor invasion to gynecologic organs. There were no preoperative risk factors found

in their study.[10] In our retrospective study, we found that pre-operative hydronephrosis was associated with increasing risk of gynecologic organ invasion

In this study, one patient developed low grade transitional cell carcinoma with gynecologic organ involvement. Stage progression and tumor-related mortality of low grade bladder transitional cell carcinoma were approximately 10% and 5% respectively.[21] In muscle invasive bladder cancer there is usually a high incidence of high grade transitional cell carcinoma but application of histologic grade to the invasive component provided no additional prognostic information.[22,23] However, this is retrospective study and there were several pathologists involved in the interpretation of the specimens leading to some potential variation.

Gynecologic organ sparing surgery in female patients had been reported by few studies. Ali-El et al. reported 15 cases which had undergone gynecologic organ sparing surgery with good functional outcomes and with no recurrence developing in the retained gynecologic organs.[24] Moursy et al. reported 18 pre-menopausal women who underwent radical cystectomy and orthotopic urinary diversion with preservation of gynecologic organs and found 14 of these patients were able to void satisfactorily, while four patients needed clean intermittent catheterization. Sexual life remained unchanged in 15 cases, while three patients reported dyspareunia and there was no local recurrence.[25]

The overall incidence of gynecologic malignancies was reported as being very low in previous studies. Chang et al. reported 1 case (2.5%) of an incidental low-grade stromal sarcoma.[7] Ali-El-Dein et al. detected no primary gynecologic malignancies in 609 female patients in their study.[26] Tran et al identified clinically unexpected malignant or premalignant gynecologic lesions in 8 out of 221 patients (3.6%).[27] In our study, there was no incidental primary gynecologic malignancies found in the patients.

Benign gynecologic organs neoplasm reported by Tran et al. and Ali-El-Dein et al. were commonly recognized entities, uterine leiomyomas and simple serous cysts being respectively the most common.[25,26] Our study discovered 23 patients had benign ovarian neoplasms, of which myoma uteri were the most common.

The limitations of this study are that it was a single-center study with limited number of patients. It was also retrospective in nature which can result in some variation due to the number of different health professionals involved in the original examinations and procedures.

Conclusion

The incidence of gynecologic organ involvement in female patients who undergo anterior pelvic exenteration for urothelial carcinoma of the bladder in this study was 18.5%. Pre-operative hydronephrosis was a risk factor associated with increasing risk of gynecologic organ involvement. Information from this study may allow better identification of candidates for gynecologic organ sparing surgery. Further large multi-center studies are needed to appropriately define the criteria for gynecologic organ sparing surgery.

Conflict of interest

The authors declare no conflict of interest.

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Original Article

Incidental prostatic adenocarcinoma and transitional cell carcinoma involvement of the prostate gland in patients undergoing radical cystoprostatectomy for bladder cancer treatment in Rajavithi Hospital

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Keywords:
Incidental prostate cancer, radical cystoprostatectomy, transitional cell carcinoma involvement of the prostate gland

Abstract

Objective: To determine the incidence of incidental prostatic adenocarcinoma and transitional cell carcinoma (TCC) involvement of the prostate gland in patients undergoing radical cystoprostatectomy in Rajavithi Hospital, Secondly, to assess the possible influence of the patient factors and bladder cancer on the pathological findings of the prostate gland.

Materials and Methods: We retrospectively reviewed 169 male patients who had undergone radical cystoprostatectomy for bladder cancer between April 2013 and August 2019. Pathologic findings of the prostate gland and urothelial cancer in the prostate gland were catalogued. Information including age, body mass index (BMI), underlying disease, glomerular filtration rate (GFR), pathologic stage, and grade was collected and analyzed to determine any correlations.

Results: Incidental prostatic adenocarcinoma and TCC involvement of the prostate gland were found in 15 patients (8.9%) and 29 patients (17.2%), respectively. There were no correlations between patient demographics and pathological findings of the prostate gland.

Conclusion: Although the incidence of incidental prostatic adenocarcinoma and TCC involvement of the prostate gland in our research is low, the screening of every candidate for prostate sparing cystectomy with a digital rectal examination, prostate-specific antigen, and transurethral biopsy of the prostatic urethra and bladder neck prior to surgery are recommended.

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Introduction

According to the data in the GLOBOCAN 2020 database, bladder cancer ranked as the sixth most commonly found cancer in males while prostate cancer is the second-highest. Age standardized incidence rates in 2020 were 9.5 and 30.7 per 100,000 respectively.[1] The standard treatment for muscle-invasive bladder cancer and persistent non-muscle invasive bladder cancer is radical cystectomy.[2,3] In men, standard radical cystectomy includes resection of the bladder, regional lymph nodes, prostate gland and seminal vesicles. This surgery has a major impact on urinary continence and sexual function.[4,5]

There are some reports of prostate sparing radical cystectomy, which improves the patient's continence and sexual performance after surgery.[6,7] However, this method of surgery is risky for patients who are potential prostatic cancer sufferers or in whom there may be transitional cell carcinoma (TCC) involvement of the prostate gland.[7-9] As a consequence, candidates must be carefully scrutinized before selection and patients who are recommended for sparing radical cystectomy must be those in whom primary bladder cancer has not yet progressed into the prostate gland and not a prostate cancer.[8]

The purpose of this study is to investigate the incidence of prostatic adenocarcinoma and prostatic involvement by TCC in radical cystoprostatectomy specimens, and to determine the any correlation between patient demographics and the findings of the prostate gland.

Materials and Methods

Study design

We retrospectively reviewed 169 male patients who underwent radical cystoprostatectomy for bladder cancer at Rajavithi Hospital between April 2013 and August 2019. Institutional research ethics board approval was obtained prior to data collection (Study Code: 63013).

The exclusion criteria were: 1) Final pathology was not TCC, 2) Patient who received neoadjuvant chemotherapy before the procedure, 3) Patient diagnosed with prostate cancer before radical cystoprostatectomy, and 4) Missing data.

All data were collected and analyzed including patient age, body mass index (BMI), underlying disease, glomerular filtration rate (GFR), pathologic T stage and grade of bladder TCC. We also investigated any correlation between these factors and the findings of the prostate gland.

Statistical analysis

Statistical analysis was carried out using the Statistical Package for the Social Sciences v.17.0 (SPSS Inc, Chicago, IL, USA). Descriptive data are presented as percentage, mean, mode, and standard deviation (SD). Comparisons between the two groups were carried out using the Student T-test, Mann-Whitney U test, Chi-square test and Fisher Exact test. For all statistical tests, a p-value of less than 0.05 was considered to indicate statistical significance.

Results

A total of 224 patients had undergone radical cystoprostatectomy. Following a review of the pathological reports 55 patients were excluded. Reasons for exclusion were: adenocarcinoma (5 cases), squamous cell carcinoma (4 cases), sarcomatoid carcinoma (1 case), small cell carcinoma (1 case), had received neoadjuvant chemotherapy before the procedure (12 cases), and missing data (32 cases).

One hundred and sixty-nine patients met the inclusion criteria with a mean age of 65.1 years.

The most common final pathologic stage was pT2 (52 patients, 30.8%). Twenty seven patients (16%) had low grade and 142 patients (84%) had high grade TCC (Table 1).

Table 1. Patient demographics

Factors N=169	n	%
Age (years), mean±SD	65.1±9.9	
BMI (kg/m^2), mean±SD	22.8±4.2	
Diabetes mellitus, n (%)	33	19.5
Hypertension, n (%)	68	40.2
GFR (ml/min), Median (min-max)	51.4 (8-183)	
T stage, n (%)		
T0	6	3.6
Tis	2	1.2
T1	39	23.1
T2	52	30.8
T3	40	23.7
T4	30	17.8
Grade, n (%)		
Low	27	16
High	142	84

BMI = body mass index, GFR = glomerular filtration rate.

The number of patients with incidental prostatic adenocarcinoma was 15 (8.9%). There were no significant differences between the groups negative and positive for the carcinoma and age, BMI, diabetes, hypertension, GFR, and pathological grade (Table 2).

The numbers in the negative and positive groups showed statistically significant differences with regard to the T stages ($p < 0.001$). However, there was no correlation between the T stage of bladder cancer and incidental prostatic adenocarcinoma (Table 2).

The most common Gleason Score was 3 + 3 = 6, observed in 7 out of 15 patients (46.6%), and the others are described in Table 3.

Twenty-nine patients (17.2%) had TCC involvement of the prostate gland. In this patient group, 7 patients (31.8%) had prostatic urethra involvement and 22 patients (68.2%) had tumor involved prostatic parenchyma. There were two cases with both primary prostatic adenocarcinoma and TCC invasion of prostatic parenchyma (Table 4).

The comparisons between the negative and positive groups and age, BMI, diabetes, hypertension, GFR, and pathological grade did not show any statistically significant differences.

Although, the numbers in the negative and positive groups showed statistically significant differences among the T stage groups ($p < 0.001$), there was no correlation between T stage of bladder cancer and TCC involvement of the prostate gland (Table 4).

Table 2. Patient factors with incidental prostatic adenocarcinoma

Factors	Negative	Positive	P-value
Age (years), Mean±SD	65.0±10.1	65.8±8.2	0.774
BMI (kg/m^2), Mean±SD	22.7±4.1	23.8±5.5	0.353
Diabetes mellitus, n (%)	30 (90.9)	3 (9.1)	1.000
Hypertension, n (%)	62 (91.2)	6 (8.8)	0.984
GFR (ml/min), Median (min-max)	51.5 (8-183)	49.0 (18-119)	0.851
T stage, n (%)			< 0.001
T0	3 (50.0)	3 (50.0)	
Tis	0 (0.0)	2 (100.0)	
T1	36 (92.3)	3 (7.7)	
T2	48 (92.3)	4 (7.7)	
T3	40 (100.0)	0 (0.0)	
T4	27 (90.0)	3 (10.0)	
Grade, n (%)			0.470
Low	26 (96.3)	1 (3.7)	
High	128 (90.1)	14 (9.9)	

BMI = body mass index, GFR = glomerular filtration rate.

Table 3. Gleason Score of patients with prostatic adenocarcinoma

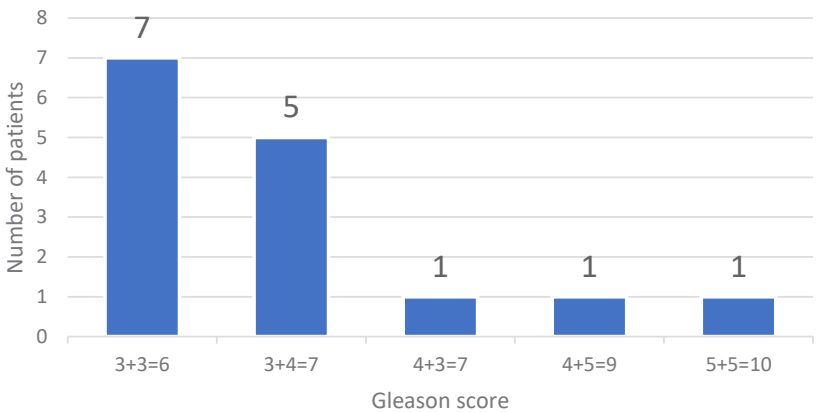

Table 4. Patient factors and transitional cell carcinoma involvement of the prostate gland

Factors	Transitional cell carcinoma involvement of the prostate gland		
	Negative	Positive	P-value
Age (years), Mean±SD	65.5±9.9	63.2±9.8	0.261
BMI (kg/m^2), Mean±SD	22.6±4.1	23.6±4.8	0.251
Diabetes mellitus, n (%)	25 (75.8)	8 (24.2)	0.229
Hypertension, n (%)	53 (77.9)	15 (22.1)	0.166
GFR (ml/min), Median (min-max)	52.8 (11-183)	39.0 (8-115)	0.057
T stage, n (%)			< 0.001
T0	6 (100.0)	0 (0.0)	
Tis	2 (100.0)	0 (0.0)	
T1	36 (92.3)	3 (7.7)	
T2	50 (96.2)	2 (3.8)	
T3	38 (95.0)	2 (5.0)	
T4	8 (26.7)	22 (73.3)	
Grade, n (%)			0.363
Low	24 (88.9)	3 (11.1)	
High	116 (81.7)	26 (18.3)	

BMI = body mass index, GFR = glomerular filtration rate.

Discussion

The GLOBOCAN 2020 data indicates that incidence rates of prostate cancer vary from 6.3 to 83.4 per 100,000 men across regions, with the highest rates found in Northern and Western Europe, the Caribbean, Australia/New Zealand, Northern America, and Southern Africa and the lowest rates in Asia and Northern Africa. The incidence rate of prostate cancer in Thailand is 14.6 per 100,000 of population and the number of new cases in 2020 was 8,630 patients (9.2%).[1]

In our study, the incidence of incidental prostatic adenocarcinoma was 8.9% (15 patients). This lower incidence of prostatic adenocarcinoma than those reported in other studies may be due to race and ethnicity. As can be seen in Table 5 there is a large variation in percentage, the USA being the highest and Thailand the lowest.[6]

Baade et al. reported that prostate cancer rates had increased in some Asian countries including Japan and China. Fourteen percent of all prostate cancer diagnosed worldwide in 2008 were within the Asia-Pacific region and approximately 60% of these prostate cancer cases were diagnosed in either Japan (32%) or China (28%).[11]

Pu et al. and Baade et al. reported that although some of the increases in incidence rates may be the consequence of enhanced screening, in actuality, westernization of lifestyle, reduced physical activity, and increased consumption of fat may be major contributors.[12,13]

Although there is currently no evidence to indicate factors related to differences in incidence, it seems likely that the cause is multifactorial. Dembowski et al. and Ram et al. reported that in their study in Poland the most common prostatic Gleason score found from cystoprostatectomy specimens was 3+3 = 6, the same as in our study.[17,22]

The incidence of prostatic TCC involvement was 17.2% (29 patients) which was less than in previous studies (Table 6). The reason for these being lower is unclear; however, it may be related to differences in patient populations, age at presentation, sample size, variance in pathological sampling techniques or even duration of each study.

We found no significant differences between the patients with coexistence of both types of neoplasms (TCC and prostatic adenocarcinoma) and isolated TCC of the bladder as regards BMI, diabetes, hypertension, GFR of patients, findings similar to a previous study by Ram et al.[22] The T stage and grade of bladder cancer did not show a correlation with incidental prostatic adenocarcinoma or TCC involvement of the prostate gland in our study.

Table 5. Published reports of incidental prostatic adenocarcinoma

References	Nations	Duration	Mean age	Samples	Prostatic adenocarcinoma n (%)
Romero et al.[14]	Brazil	1997-2003	66.7	60	17 (28.3)
Pettus et al.[15]	USA	2001-2004	69.0	235	113 (48.0)
Abdelhadey et al.[16]	Canada	1987-2003	67.0	217	58 (28.0)
Dembowski et al.[17]	Poland	2009-2014	68.9	116	17 (14.6)
Sanli et al.[18]	Turkey	2001-2004	66.9	97	21 (21.6)
Tanaka et al.[19]	Japan	1994-2016	66.0	431	43 (18.1)
Yang et al.[20]	China	2004-2014	66.0	340	95 (28.0)
Tang et al.[21]	China	1994-2012	63.5	762	132 (17.3)
Ram et al.[22]	India	2013-2014	65.0	175	38 (21.0)
Our study	Thailand	2013-2019	65.0	169	15 (8.9)

Table 6. Published reports of prostatic involvement by transitional cell carcinoma (TCC)

References	Nations	Duration	Mean age	Samples	Prostatic involvement by TCC
Ayyathurai et al.[23]	USA	1992-2006	68.0	320	78 (24.0)
Pettus et al.[15]	USA	2001-2004	69.0	235	77 (33.0)
Revelo et al.[24]	USA	2000-2002	67.4	121	58 (48.0)
Richards et al.[25]	USA	2014-2016	67.0	96	24 (25.0)
Tabibi et al.[26]	Iran	2003-2007	62.6	100	21 (75.0)
Our study	Thailand	2013-2019	65.0	169	29 (17.2)

Finally, the majority of reports are limited to small retrospective cohorts and need to be analyzed within the context of such limitations therefore it is also important for the surgeon to weigh the oncologic risk of organ preservation against cancer recurrence. If prostatic preservation is a potential option, digital rectal examination, prostate-specific antigen, and transurethral sampling of the prostatic urethra and bladder neck are all advisable to maximize the procedure most appropriate for the patient.[27]

There are some limitations in our study. First, more than one pathologist was involved in the examination of the specimens resulting in some potential bias as regards interpretation. Second, the study comprised only a small sample size reducing the statistical power of the study. Third, it is retrospective in nature resulting in limitations with regard to variations in technique in recording of the data.

Conclusion

The incidental prostatic adenocarcinoma and TCC involvement of the prostate gland from our study were found to be lower than in previous studies. However, there are significant factors which need to be considered to indicate the possible coexistence of primary prostate cancer and TCC involvement in the patient diagnosed with primary bladder cancer. The screening of every candidate for prostate sparing cystectomy with a digital rectal examination, prostate-specific antigen, and transurethral biopsy of the prostatic urethra and bladder neck prior to surgery are recommended.

Conflict of interest

The authors declare no conflict of interest.

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Original Article

A correlation of PI-RADS score and pathological grading outcome post radical prostatectomy: A retrospective review

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Keywords:
Correlation, PI-RADS score, pathological grading, outcome, radical prostatectomy

Abstract

Objective: To investigate the correlation between the PI-RADS score and the pathologic Gleason score in the final pathological grading and to detect risk factors associated with the outcomes.

Materials and Methods: Data from January 2017 to September 2019 were reviewed. Inclusion criteria included patients who had undergone standard protocol prostate magnetic resonance imaging (MRI) in King Chulalongkorn Memorial Hospital and underwent radical prostatectomy during the period. Data collected were age, PI-RADS score, Gleason score (GS), prostate-specific antigen (PSA), prostate size, PSA density, lesion size, and extraprostatic extension (EPE) evident in MRI.

Results: One hundred and eight patients were included. PI-RADS was significantly associated with GS (Chi-Square p = 0.039). The percentage of significant tumors found in PI-RADS 3, 4, 5 were 66%, 86% 90% respectively. Analysis of independent risk factors only found PI-RADS 5 to have a statistically significant association with GS ≥ 7 (OR6.67 (1.24-35.71) p = 0.03). The cut-off value of lesion size ≥ 15 vs < 15 and PI-RADS 4 had a higher odds ratio than other parameters (OR 3.89 (0.82-18.41) p = 0.09, OR 3.29 (0.79-13.86) p = 0.11 respectively).

Conclusion: The PI-RADS scoring system was found to be highly associated with Gleason's grading score. No association was found between any significant risk factor and significant prostate cancer. Lesion size could be used to combine with the PI-RADS scoring system in the detection of significant tumors. A high percentage of significant tumors were found with a PI-RADS 3 score and it may be worth taking a biopsy in the case of a PI-RADS 3 lesion.

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Introduction

Prostate cancer is the 4th most common cancer in Thai males with a prevalence of 7.1:10000.[1] The presentation of the disease varies extensively, ranging from indolent cancer to aggressive metastatic-potential disease, the range being defined in categories from very low-risk to very high-risk disease.[2] Studies have shown that the majority of prostate cancer patients do not die from the cancer itself.[3,4] The modern practice is to not only diagnose the condition but to differentiate between a significant tumor from one that is non-significant to maximize the benefit of definitive treatment and minimize the complications of overtreatment.

The pathology is defined using the Gleason Score, non-significant prostate cancers being given a score of 6, while significant cancers have a Gleason score ≥ 7.[5] In 2014 the International Society for Urological Pathology (ISUP) proposed a grading system which stratified the Gleason Score into grades 1-5.[6]

Multiparametric Magnetic Resonance Imaging (mpMRI) consisting of T2-weighted imaging (T2WI), diffusion-weighted imaging (DWI), and dynamic contrast-enhanced imaging (DCEI), have had an increasing role in prostate cancer diagnosis and staging.[7] Prostate Imaging Reporting and Data System (PI-RADS) version 2 was proposed in 2015 to improve the accuracy and consistency in the use of imaging for the diagnosis for prostate cancer.[8]

The use of MRI for diagnosis of prostate cancer is an accepted diagnostic method with increasing evidence of a correlation between PI-RADS and Gleason score (GS)[9-12] A recent meta-analysis showed a correlation between ISUP grade ≥ 2 (GS ≥ 7) lesion and PI-RADS 3, 4 and 5 in PPV of 12%, 48%, 72% respectively.[13] The correlation between MRI and final pathological diagnosis is gradually receiving more attention but most of the studies reviewed the relationship between MRI and pathological specimen from the MRI fusion biopsy. A study by Radtke et al.[14] into mpMRI showed a promising result of 92% successful detection of a lesion when correlated to radical prostatectomy (RP) specimens while a study by Lashay et al. which also studied correlation between mpMRI and final pathology, showed an accuracy in detection of significant prostate cancer of 76.3%.[15] A greater understanding of the correlation between these 2 methods is important and would be beneficial for improving the diagnostic accuracy of screening and treatment regimes for of prostate cancer. The primary objective of the study was to examine the correlation of the PI-RADS score to the pathologic Gleason score in the final pathological grading and the secondary objective was to detect risk factors affecting the outcomes.

Materials and Methods

Study design and population

Data from patients who underwent radical prostatectomy regardless of operation method from January 2017 to September 2019 were enrolled onto the study. Inclusion criteria included patients with standard protocol prostate MRI, officially reported in PI-RADS version 2 system by radiologists at King Chulalongkorn Memorial Hospital (KCMH) and who later underwent radical prostatectomy during the period. One hundred and sixty nine patients were included initially. The patients who had multiple lesions with multiple PI-RADS scores on the MRI were excluded from the study due to the lack of whole-mount pathologic sections, which precluded the ability to relate multiple different lesions from MRI to the pathological specimen. After exclusion, there were 108 patients eligible for the study. Data on age, PI-RADS score, Gleason score (GS), prostate-specific antigen (PSA), prostate size, PSA density, lesion size, and extraprostatic extension (EPE) on MRI were collected

Study endpoint

The primary outcome was to investigate the correlation between the PI-RADS score and the pathologic Gleason score in the final pathological specimen. The secondary outcome was to determine the risk factors associated with significant cancer. Significant cancer was defined as Gleason score ≥ 7. PSA level, prostate size, PSA density, lesion size, and EPE on MRI were investigated as potential risk factors.

Imaging

Multiparametric MRI (mpMRI) was performed in all patients using a 3 Tesla machine without an endorectal coil. The imaging protocol consisted of T1 and T2-weighted imaging, diffusion-weighted imaging (DWI), and dynamic

contrast-enhanced imaging (DCEI). The lesions on the MRI were reported using the PI-RADS scoring system version 2 and 2.1 by radiologists at KCMH. Two radiologists reported the findings from the initial imaging results in this study.

Surgery

Radical prostatectomy was performed by experienced urologists at KCMH. The recruited data regardless of the type of procedure, including open radical prostatectomy, laparoscopic radical prostatectomy, and Robotic-assisted laparoscopic radical prostatectomy. Six urologists performed the surgery.

Histology

The final pathological specimens from the radical prostatectomy were analyzed by 3 pathologists at KCMH. Gleason scores were evaluated using ISUP 2014 (modified) definitions.

Statistical analysis

Descriptive data are presented as percentage, and mean values with standard deviation. Median and inter-quartile range were used if the data were not normally distributed. A Chi-square test was used to evaluate the association between PI-RADS and Gleason score. Independent factors affecting Gleason score ≥ 7 were calculated using binary logistic regression. Statistical analysis was performed using STATA version 15.1.

Results

Demographic data

Data from 108 patients with a mean age of 66 ± 5.2 years was included in the study. The characteristics of patients and general demographic data are shown in Table 1. The mean PSA was 12.9 ± 16.8 ng/ml and lesion size was 1.4 ± 0.6 cm. Nearly all patients were treated with laparoscopic surgery, only 2 patients were treated with open surgery. Mean time of patients who underwent MRI before biopsy was 86 ± 52.8 days and the MRI after biopsy was 100.9 ± 67.4 days. No patients underwent MRI within 3 weeks of the biopsy but 8 patients had an MRI in the fourth week after the biopsy.

Table 1. Demographic data

Data	Median (IQR)	Mean (SD)
Age (years)	66 (62-70)	66 (5.2)
Prostate size (ml)	36.2 (27-48)	41.7 (22.4)
PSA (ng/ml)	9.3 (7.3-13.5)	12.9 (16.8)
PSA density (ng/ml^2)	0.27 (0.19- 0.42)	0.36 (0.41)
Days of MRI before Bx	72 (48-117)	86 (52.8)
Days of MRI after Bx	90 (48-159)	100.9 (67.4)
Lesion size (cm)	1.4 (1-1.7)	1.4 (0.6)
Method of surgery	n (%)	
LRP	22 (20.2)	
RALRP	84 (78)	
Open radical prostatectomy	2 (1.8)	

PSA = prostate-specific antigen, MRI = magnetic resonace imaging, Bx = biopsy, LRP = laparoscopic radical prostatectomy, RALRP = robot-assisted laparoscopic radical prostatectomy.

The pathological outcomes defined by the ISUP grade group were categorized in accordance with PI-RADS and are shown in Table 2. The grade was statistically significantly correlated with the PI-RADS score (p = 0.039). Significant

Table 2. Pathological outcomes categorized by PI-RADS

Characteristics	PI-RADS 3	PI-RADS 4	PI-RADS 5	Total (%)
Number, n (%)	12 (11.1)	53 (49.1)	43 (39.8)	108 (100)
Grade group*				
Grade 1	4	7	4	15 (13.8)
Grade 2	7	37	22	66 (61.5)
Grade 3	1	6	6	13 (11.9)
Grade 4	0	3	6	9 (8.4)
Grade 5	0	0	5	5 (4.6)
% of significant tumors	66.6	86.7	90.6	86.1

*Grade group had statistical significant correlation with PI-RADS group at p = 0.039 by Chi-square test.

tumors were found in 66.6% with PI-RADS 3, 86.7% with PI-RADS 4, 90.6% with PI-RADS 5, giving an overall total of 86.1%. Most patients were in PI-RADS 4 (49.1%), reducing to PI-RADS 5 (39.8%), and PI-RADS 3 (11.1%).

Independent risk factor analysis

Analysis of independent risk factors found no statistically significant results as regards age, prostate size, EPE on MRI, range of PSA, PSA density, and lesion size, as shown in Table 3. PI-RADS 5 showed a significant association with GS ≥ 7 with the highest odds ratio (6.67, 1.24-35.71, p = 0.03). The lesion size ≥ 15 vs < 15 mm (OR 3.89 (0.82-18.41) p = 0.09) and PI-RADS 4 (OR 3.29 (0.79-13.86) p = 0.11) showed high OR but no statistical significance.

A subgroup analysis was carried out in relation to PI-RADS lesions as shown in Table 4. It was found that PI-RADS 5 had the highest density of PSA (0.52 ± 0.57 ng/ml^2) and the largest size of the lesion (18.88 ± 5.97 mm), significantly more than any other PI-RADS score (p < 0.05).

Data relationship

From the previous analysis, the most significant-tumor-related data were further analyzed by each grade group, specifically lesion size and PI-RADS score. From the PI-RADS to grade group aspect, high PI-RADS score was reported in all grade groups. PI-RADS 3 was reported only in grade group 1-3 with only 1 case of PI-RADS 3 in grade group 3, PI-RADS 3 was not reported at all in grade group 4 and 5. In grade groups 4 and 5 only PI-RADS 4 and PI-RADS 5 were reported from the MRI. The data are shown in Figure 1.

From lesion size to grade group aspect, relationships of lesion size of 15 cm and 20 cm cut

Table 3. Risk factors associated with Gleason score ≥ 7

	OR (95%CI)	P-value
Age	1.04 (0.92-1.16)	0.51
Prostate size	0.98 (0.96-1.01)	0.14
PSA ≥ 10 vs < 10 ng/ml	0.63 (0.20-1.796)	0.43
PSA ≥ 20 vs < 20 ng/ml	0.89 (0.10-7.96)	0.91
PSA density ≥ 0.15 vs < 0.15 ng/ml^2	1.56 (0.39-6.30)	0.53
Lesion size ≥ 15 vs < 15 mm	3.89 (0.82-18.41)	0.09
Lesion size ≥ 20 vs < 20 mm	2.28 (0.28-18.80)	0.45
PI-RADS score		
3	Ref	
4	3.29 (0.79-13.86)	
5	6.67 (1.24-35.71)	
EPE on MRI	1.72 (0.36-8.32)	

PSA = prostate-specific antigen, EPE = extraprostatic extension, MRI = magnetic resonace imaging.

Table 4. Distribution of baseline data in subgroup analysis of PI-RADS lesion, showing data as mean and SD.

PI-RADS lesion	PI-RADS 3	PI-RADS 4	PI-RADS 5
Age (years)	65±4.1	66±5.2	66±5.6
Prostate size (ml)	56.9±29.65	42.73±20.93	34.34±16.10
PSA (ng/ml)	10.50±5.25	10.22±5.9	16.93±25.54
PSA density (ng/ml^2)	0.22±0.16	0.28±0.17	0.52±0.57*
Lesion size (mm)	10.50±3.28	11.42±3.55	18.88±5.97*

*Statistically significant from other groups at p-value < 0.05 by oneway analysis of variance and Dunnett T3 post hoc test.

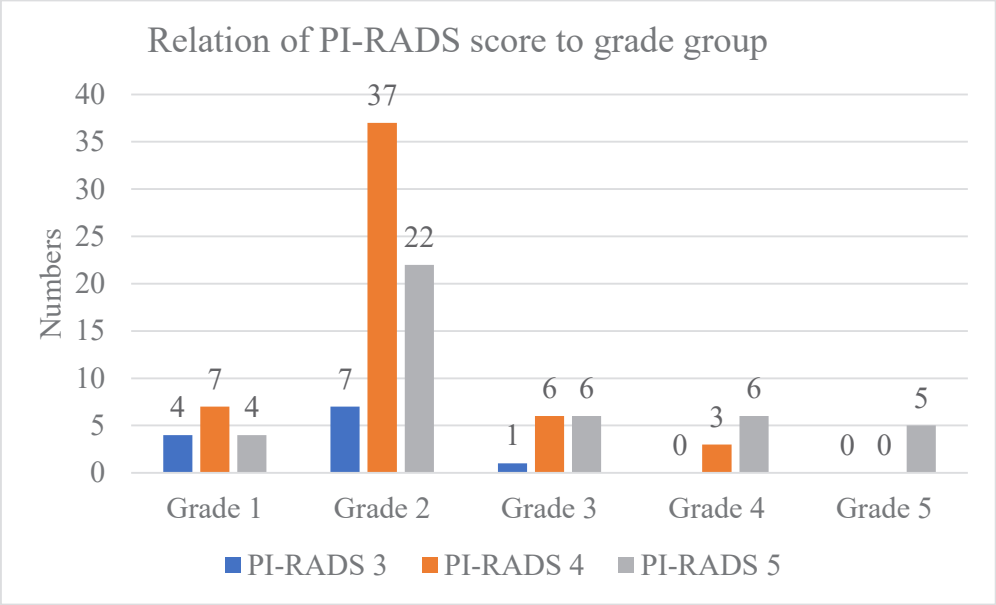

Figure 1. The relationship of PI-RADS score to Gleason grade group (ISUP)

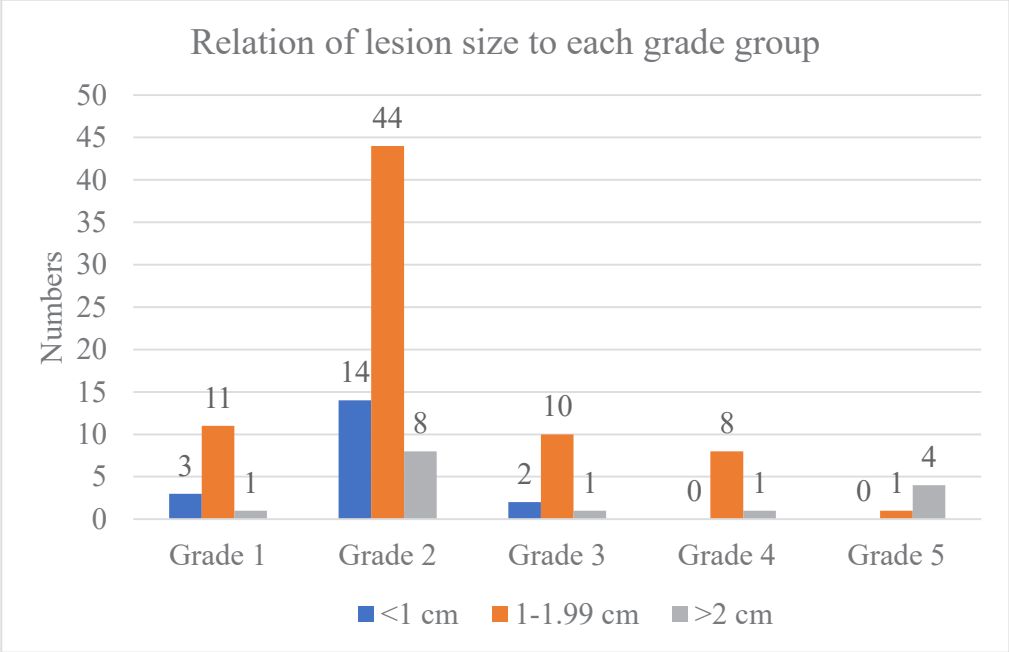

Figure 2. The relationship of lesion size in a range of <1, 1-1.99, ≥ 2 cm to each Gleason grade group (ISUP)

off points to grade group were analyzed but did not produce any significant or notable results so a further segmentation was performed using a range of < 1, 1-1.99 and ≥ 2 cm comparing them to each grade group. It was shown that small lesion size was correlated with lower grade groups. Lesions smaller than 1 cm were not found in grade group 4 and 5. These data are shown in Figure 2.

Discussion

This study primarily aimed to investigate the presence of a correlation between the PI-RADS score and the pathologic Gleason score in the final pathological specimens. A significant correlation between PI-RADS 5 and Gleason score ≥ 7 was found. Regarding the independent risk factor analysis, PI-RADS 5 was significantly associated with GS ≥ 7 with the highest odds ratio (6.67, CI1.24-35.71), PI-RADS 4 also showed a high

OR (3.29, CI 0.79-13.86) but without statistical significance. It was found that tumor grade groups 4 and 5 were observable by MRI only as PI-RADS 4 and 5.

For the secondary objective in the independent factor analysis, lesion size at cut-off point ≥ 15 mm versus < 15 mm showed a high odds ratio (3.89, CI 0.82-18.41) but statistical significance could not be demonstrated. The cut-off was elevated to ≥ 20 mm versus < 20 mm as an endeavor to evaluate significance but this also had a negative result. The relation between lesion size and each grade group showed that there was only lesion larger than 1 cm in Grade groups 4 and 5.

A high percentage of significant tumors were found in PI-RADS 3 (66.6%) reaching 90.6% in PI-RADS 5. These data suggested that it may well be worth carrying out a biopsy on PI-RADS 3 lesion.

The PRECISION study16 reported the detection rate of significant tumors in PI-RADS 3 was 12%, PI-RADS 4 60%, and PI-RADS 5 83%. These findings suggested the correlation between PI-RADS and Gleason score was especially strong with PI-RADS 4 and 5. However, the findings from our study can not be transferred to the detection rate of significant cancer in the general population due to the study design only including prostate cancer cases.

Many studies stated that the size of the lesion and PSA density were the risk factors for significant cancer.[17-19] Bratan et al.[17] studied the influence of lesion size from MRI images on histological RP specimens in 2013 and reported that the detection rates for Gleason 6 tumor size < 0.5 cc, 0.5-2 cc, and > 2 cc were 29%, 54%, 75%, for Gleason 7 were 63 %, 88%, and 97% and for Gleason ≥ 8 were 80%, 93%, and 100% respectively. In their study, the whole mount sections were used for the reading of the pathology so it could provide a false positive result. They also used a detection rate from the MRI which our retrospective study did not include. Nevertheless, the potential weakness of their study was that the MRI results were reported in a 5-point subjective suspicion score, the measurement scale used before the PI-RADS era.

Washino et al.[18] reported that patients with PI-RADS ≥ 4 with a PSA density ≥ 0.15 and PI-RADS 3 with PSA density ≥ 0.3 were highly associated with clinically significant prostate cancer. Distler et al.[19] showed a 79-89% negative predictive value (NPV) of significant prostate cancer when the PSA density ≤ 0.15. Despite trying many different cut-off points to find significant independent risk factors in our study (showed in table only for PSA density ≥ 0.15 vs < 0.15 ng/ml^2), there was only lesion size ≥ 15 vs < 15 mm that showed a high odds ratio and a trend of association with significant cancer.

The limitation of this study was mainly the selection bias due to the retrospective nature hence there may have been data errors. Also the lack of a whole mount section which may have shown other lesions. The patient with multiple lesions and different PI-RADS were excluded from the study to reduce complexity in the analysis, therefore the study consisted of only single lesion or multiple but homogeneous lesion prostate cancer patients. The sensitivity, specificity and detection rate could not be demonstrated due to this reason. Secondly, a small sample size makes a large difference in the number between a patient in the non-significant and significant cancer groups making the statistical analysis less robust. A larger sample size could improve the statistical value of both parameters and the outcomes.

Conclusion

The PI-RADS scoring system was found to be closely associated with Gleason's grading score. In this study no significant risk factor showed a correlation with significant prostate cancer. Lesion size showed the highest odds ratio with significant cancer therefore could be combined with the PI-RADS scoring system in the detection of significant tumors and a high percentage of significant tumors were still found in PI-RADS 3 therefore it may be worth carrying out a biopsy on the PI-RADS 3 lesion. A larger prospective study is encouraged to identify potential risk factors for significant tumors and improve the diagnosis of prostate cancer enabling more effective outcomes for the patient.

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Desmopressin melt therapy in children with non-monosymptomatic nocturnal enuresis: a prospective study

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Keywords:
Desmopressin, melt, children, non-monosymptomatic, nocturnal enuresis

Abstract

Objective: The negative consequences of enuresis in children can be far reaching and an understanding of the impact of these is essential for effective treatment by the clinician. Enuresis can be categorized into monosymptomatic nocturnal enuresis (MNE) and non-monosymptomatic nocturnal enuresis (NMNE). There have been several studies in treatment of MNE with lyophilizate desmopressin melt but very limited research into the efficacy of desmopressin melt in treating NMME. The objectives of this study were to measure the efficacy and side effects of desmopressin melt in treating children with NMNE.

Materials and Methods: Children aged 6 to 18 years with NMNE who visited the outpatient department of pediatric urology were included in this prospective study. Any underlying diseases and lower urinary tract symptoms were corrected then their enuresis was treated with 120-240 mcg of desmopressin melt for 6-8 weeks. Outcomes were defined as complete response, partial response, and no-response as defined by the International Children's Continence Society guidelines.

Results: A total of 25 children with NMNE were included in the study. The results showed 44% complete response, 20% partial response, and 36% no-response. The mean volume of nocturnal enuresis decreased from 159.96 to 115.30 ml in the pre and post treatment periods, respectively ($p = 0.012$). The mean frequency of enuresis decreased from 4.36 to 2.84 days per week in pre and post treatment periods, respectively ($p < 0.001$). The mean whole night urine volume decreased from 373.39 to 292.37 ml in pre and post treatment periods ($p = 0.061$). There were no major side effects in the study.

Conclusion: Desmopressin melt is effective and safe in treating NMNE in children. However, to add weight to the findings of this study further research with a larger number of patients should be considered in the near future.

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Introduction

Nocturnal enuresis (NE) is defined as discrete episodes of urinary incontinence during sleep in children older than 5 years of age.[1] In a study of almost 3,500 children in Thailand, the prevalence of enuresis declined with increasing age from 10%, 5.3%, 3%, 1.2% at ages 5, 7, 10 and 12 years, respectively.[2] In two other studies in New Zealand and Belgium, the same pattern was seen, prevalence also declined with increasing age from 15%, 13%, 10%, 7%, 5%, 2-3%, 1-2% at ages 5, 6, 7, 8, 10, 12-14 and 15 years, respectively.[3,4] Enuresis in children frequently has a negative impact on the self-esteem, socializing capacity, [5,6] and intellectual quotient of the children,[7] also impacting on their parents sleep and well-being. The sleep deprivation can seriously affect family life, causing a reduction in patience when dealing with the children, having impact on the working hours of parents,[8] increase household costs of laundry for clothes and sheets[9] and may lead to child abuse or abandonment.[10,11] A previous study reported that the successful treatment of enuresis will improve the personality, behavior and emotions of both children and parents.[12]

NE is categorized into monosymptomatic nocturnal enuresis (MNE) or non-monosymptomatic nocturnal enuresis (NMNE). NE with any daytime lower urinary tract symptoms (LUTS) is defined as NMNE.[13,14] In treatment of primary MNE, there is level 1 evidence to support the use of an enuresis alarm and desmopressin,[15] however, in treatment of NMNE, there are various options available to deal with LUTS. These include clean intermittent catheterization (CIC), anti-muscarinic agents, alpha-blocker agents, behavioral treatment and bowel bladder training. However, no standard approach has been established for these treatments[13]. In our department, there are many underlying diseases associated with NMNE, specifically spina bifida, anorectal malformation, posterior urethral valves, dysfunctional voiding, attention deficit hyperactivity disorder, and obstructive sleep apnea. The most common underlying cause in our outpatient department was found to be spina bifida, which a previous study in our center also had a measurable negative impact on the quality of life.[16]

Anti-diuretic hormone (ADH) is released by the posterior pituitary gland and reduces urine production by increasing water reabsorption in the collecting tubules and ducts. Desmopressin is a synthetic analogue of ADH.[17] There are several forms of this medication, specifically tablet, melt and intranasal spray formulations. It has been shown that the melt formulation of desmopressin demonstrates the same levels of efficacy and safety as the tablet form but at lower dosing levels its bioavailability being almost 60% greater.[18] Several studies have investigated the efficacy of the tablet and intranasal spray formulations of this medication in the treatment of enuresis,[19] but there is limited work into the treatment of NMNE with melt form desmopressin. The aim of this study was to measure the efficacy of melt form of desmopressin in the treatment of NMNE in our center.

Materials and Methods

A prospective study was performed in children enrolled in the outpatient treatment program for NMNE in our pediatric urology center between 2018 and 2020. Criteria for enrollment on the study were assent of parents and children of ages 6 to 18 years with adequate treatment for other LUTS, for example anti-muscarinic agent, and CIC with continued treatment of previous use. Twenty-six children were enrolled onto the study and underlying causes of enuresis and severity of symptoms were varied (Figure 1). One child was subsequently excluded. The exclusion criteria were hyponatremia (defined as serum sodium < 135 mEq/L), chronic kidney stage III to V (defined as estimated glomerular filtration rate [eGFR] < 60 ml/min/1.73m^2) (eGFR was calculated as 0.413 x height [cm] / serum creatinine [mg/dl]), psychiatric underlying disease, symptomatic urinary tract infection at time of enrollment, and moderate to severe mental retardation or encephalopathy. Before inclusion all children were assessed by their medical history, physical examination, evaluation of serum blood urea nitrogen (BUN), serum creatinine and serum electrolytes. If required, urological imaging and/or urodynamic studies were performed to evaluate anatomical and/or neurological abnormalities.

After enrollment, child and parent were requested to record a urine chart for 7 days without the use of desmopressin and directed to not drink water 1 hour before sleep. Details of the urine chart included presence or absence of enuresis each day for 7 days, volume of morning void or

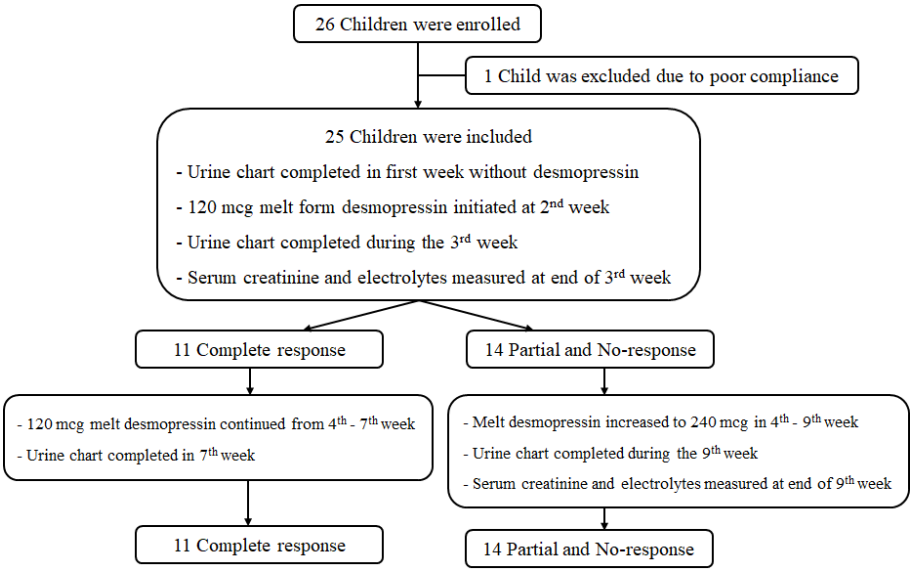

Figure 1. Flow chart of our study.

catheterization, volume of night void, volume of enuresis, and volume of night catheterization during sleep for 3 nights. We used a plastic tumbler with volume scale from Ferring Pharmaceuticals for the measurement of the volume of urine and scales from the same marque to measure the weight of enuresis of each child. After the first 7 days, desmopressin melt form 120 mcg 1 tablet was prescribed to be taken sublingually 1 hour before sleep. The urine chart was completed again on the second week after the start of this medication. After the second week each child was given an appointment to evaluate the incidence of any side effects such as nausea, vomiting, abdominal distension, alteration of consciousness, and seizure and also evaluate serum BUN/creatinine and electrolytes. If there were severe symptom or hyponatremia or the eGFR decreased below 60 the medication was discontinued.

The urine charts were analyzed in accordance with the International Children's Continence Society (ICCS) guidelines: No-response showed a decreased frequency of enuresis < 50%; Partial response showed a decreased frequency of enuresis of 50-99% and Complete response showed a decreased frequency of enuresis 100%.[1] In the complete response group, the child was prescribed 120 mcg desmopressin melt to be taken sublingually 1 hour before sleep for an additional 28 days and asked to complete a urine chart for the last 7 days on this medication. In the no-response and partial response groups, the child was given an increased dose of desmopressin to 240 mcg sublingually 1 hour before sleep for an additional 42 days and was directed to record a urine chart for the last 7 days on this medication and evaluations of serum BUN/creatinine and electrolytes were carried out at the final appointment. The final urine charts were used to analyze the outcome.

A dosage of 120-240 mcg of the melt form of desmopressin was selection following the findings published in a previous study which reported that this melt form dosage of desmopressin can be effective for a period of sleep at night of 7-11 hours.[20]

The Primary outcome was to describe the Complete response. The secondary outcome was to compare the before and after treatment data of average whole night urine volume, average nocturnal enuresis volume and frequency of enuresis.

Statistical analysis

Fisher's exact test and a paired t-test were used to analyze the data using the STATA program. A significance level of $p < 0.05$ was chosen and data were reported as mean ± standard deviation. The study protocol was approved by the Ethical Committee of Chiang Mai University (Research ID: 5323/ Study Code: SUR-2561-05323).

Results

Twenty-six children were enrolled onto the study. One child was excluded because she was unable to keep the appointments. Of the remaining 25, the most frequent underlying disease was

Table 1. Baseline characteristics of the NMNE patients in the study.

Parameters	Patients, n (%)
Gender	
Male	15 (60)
Female	10 (40)
Age, mean (SD)	9.04 (3.22)
Underlying disease	
Spina bifida	11 (44)
Obstructive sleep apnea	3 (12)
Anorectal malformation	2 (8)
Behavioral problem	2 (8)
Brain tumor	1 (4)
Autism	1 (4)
Legg-Clav-Perthes disease	1 (4)
No underlying disease	4 (16)
Other treatment	
Alarm therapy	4 (16)
Clean-intermittent catheterization	4 (16)
Bladder augmentation	1 (4)
Bladder capacity, mean (SD)	277.92 (126.59)

spina bifida (44%) followed by obstructive sleep apnea, anorectal malformation and behavioral problems (12%, 8%, 8%, respectively) (Table 1). The response rate was complete response 44%, partial response 20% and no-response 36% (Table 2). The average volume of nocturnal enuresis decreased significantly from 159.96 to 115.30 ml ($p = 0.012$). The frequency of nocturnal enuresis also decreased significantly from 4.36 to 2.84 days ($p < 0.001$). The average whole night urine did decrease but not significantly from 373.39 to 292.37 ml ($p = 0.061$) (Table 3).

Three children had adverse events leading to discontinuation of the medication, 1 child had allergic symptoms of urticaria to the medication, 1 child had asymptomatic hyponatremia (serum sodium was 134 mEq/L at dose 120 mcg) and 1 child had decreased eGFR from 103.25 to 50.36 ml/min/1.73 m^2 from inadequate CIC. Two children had adverse events, 1 with mild dyspepsia and 1 with mild nausea and dry mouth but following discussion it was decided not to discontinue the medication.

Table 2. Primary outcome in the NMNE patients taking desmopressin melt.

Response of nocturnal enuresis	n (%)
Complete response	11 (44)
Partial response	5 (20)
No-response	9 (36)

Discussion

NE is a common problem in Thailand.[2] It has significant impact on the self-esteem and psychosocial development of children and is also a serious burden for their parents.[5-11] Treatment of enuresis therefore, will patently improve these conditions. Enuresis has been categorized as MNE and NMNE. There are several studies investigating the efficacy of desmopressin in treating MNE with reports of significantly improved symptoms[21], but there are limited studies on the ability of desmopressin to treat NMNE. In the first instance some facets of NMNE which may have impact were addressed including constipation, LUTS, and obvious underlying causes. If the enuresis remained after these were addressed we set out to ascertain if desmopressin melt therapy could help these children.

At our hospital most patients with NE meet the pediatricians first. If NMNE was diagnosed with other underlying causes, the child will then meet our urologist. The most common underlying cause of NMNE in our study is spina bifida. From a previous study it was demonstrated that NMNE was more prevalent in children with spina bifida occulta and had a lower response to behavioral treatment.[22] Therefore these initial treatments may not improve the NMNE.

Table 3. Secondary outcomes in the NMNE patients to desmopressin melt.

Outcomes	Before treatment mean (SD)	After treatment mean (SD)	P-value
Volume of nocturnal enuresis (ml)	159.96 (171.30)	115.30 (244.83)	0.012*
Volume of nocturnal urine (ml)	373.39 (222.06)	292.37 (279.00)	0.061
Nocturnal enuresis (days)	4.36 (2.45)	2.84 (3.20)	< 0.001*

* Denotes statistical significance

In our study there was a complete response rate of 44% with a statistically significant improvement in frequency of enuresis and enuresis urine volume. There was improved whole night urine volume but the data did not reach statistical significance. From a previous study, response of enuresis to melt form 120 mcg desmopressin is lower in spina bifida occulta patients with severe LUTS.[23] That study also treated LUTS daytime with oxybutynin similarly to the treatment given our study. Response of enuresis in children with spina bifida tended to be lower in our study, and also in children with severe enuresis frequency and volume.

Another study demonstrated that the combination of antimuscarinics and desmopressin was more effective than antimuscarinics alone in children with an overactive bladder and enuresis.[24] Similar to our study, after treating daytime LUTS with antimuscarinics, if enuresis persisted we also used desmopressin to control enuresis.

There is an earlier study into children with enuresis. In that study, 82.8% who had NMNE used desmopressin melt form 120 mcg with propiverine 7.5 mg twice per day. The complete response of this study was 87%.[25] This may be higher than our study because they included MNE children in this study.

Our study demonstrated an initial positive response to desmopressin in the treatment of NMNE, but there was limited data for the impact of long-term use. Another study demonstrated that a tapering dose to result in a complete response had a low rate of relapse.[25] It was not possible in our study to continue the medication long term to assess the impact and also to observe the outcome of progressive discontinuation of the drug as the majority of our children could not continue on desmopressin because of financial implications.

There were several limitations to our study. Firstly, the number of the children enrolled onto the study were lower than the population that was required to ensure robust statistical conclusions. Since there were a limited number of previous studies, the minimum population required was 82 children, but only 25 were available because of restrictions of attendance at clinic due to COVID-19. Also, in the Thai culture parents underestimate the problem of enuresis and as a result the whole night urine parameter was not statistically significant. With a higher population this statistic may have reached significance.

Secondly, our study included only a treatment group with no control. This limited our calculation for statistical significance in primary outcome of complete response to bring results for use in treatment. However, as the parameters of enuresis volume and enuresis frequency improved statistically significantly the next randomized controlled trial should to planned to reach statistical significance for this primary outcome. Thirdly, our protocol is only initial short-term outcome, the next study may look for the long-term treatment of NMNE in children. Another limitation might be the method of use of the oral lyophilisate formulation of desmopressin (melt form) which could be ineffective if it was taken the wrong way such as eating or chewing this medication, or drinking a lot of water after taking the medication. The children and parents were advised as to how to use the melt at the time of enrollment but there may have been deviations from the method requested. Lastly, our urine chart only recorded data of urine volume for 3 days and presence or absence of enuresis for 7 days. To calculate a more accurate percentage of volume and frequency, in a future study it may be better to have a longer duration of recorded data. The latter two limitations are a consequence of the culture in our country as in many patients there is a lack of compliance.

Conclusion

Desmopressin melt is effective and safe in treating NMNE in children. A future study with a larger sample size should be considered to further substantiate the findings of this study and add weight to the accumulating body of evidence surrounding the efficacy of this treatment.

Acknowledgement

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Conflict of Interest

The authors declare no conflict of interest.

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Original Article

Comparison of open and laparoscopic radical cystectomy as regards long-term oncological outcomes for bladder cancer

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Keywords:
Radical cystectomy, laparoscopic, open, bladder cancer, long-term, oncological outcome

Abstract

Objective: Recently, the laparoscopic technique has become widely accepted as a minimally invasive modality which reduces morbidity and provides similar oncological outcomes to open surgery. However, the number of clinical trials comparing laparoscopic and open radical cystectomy are limited. The objectives of this study are to compare the long-term oncological outcomes between open radical cystectomy (ORC) and laparoscopic radical cystectomy (LRC) for bladder cancer.

Materials and Methods: Out of 144 radical cystectomy patients admitted to our institute from January 2006 to December 2016, 87 patients were categorized as being in the LRC group, and 57 patients in the ORC group. Baseline characteristics, perioperative variables, and pathology results were collected retrospectively. Oncological outcomes including overall survival (OS), recurrence-free survival (RFS) and cancer-specific survival (CSS) were analyzed and compared between the two groups.

Results: The mean age of the patients was 64.19 ± 9.89 years in the ORC group and 61.90 ± 10.47 years in the LRC group. The most frequent urinary diversion procedure in both groups was ileal conduit. All pathology results between the LRC group and the ORC group showed no statistical significance. The median follow-up duration was 57.18 ± 44.68 months in the ORC group and 53.96 ± 34.97 months in the LRC group. There was no statistically significant difference in overall survival (OS), recurrence-free survival (RFS) and cancer-specific survival (CSS) between the groups (p = 0.322, 0.946, and 0.528, respectively).

Conclusion: Our study demonstrated that the long-term oncological outcome of LRC is comparable to ORC in the management of bladder cancer. LRC is an alternative option to open radical cystectomy and is safe, effective, and feasible. However, further large comparative studies with adequate long-term follow-up are recommended to support our results.

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Introduction

Bladder cancer is one of the top ten most common adult malignancies worldwide.[1] The incidence and prevalence rates show a correlation with age, male gender, and smoking behavior, but varies across geographic regions or countries.[2,3] In Thailand, bladder cancer is the ninth most common malignancy in men. In Chiang Mai, Northern Thailand, this is particularly the case with bladder cancer being the sixth most common malignancy in men, the estimated incidence being 5.7 per 100,000 population.[4]

Invasive bladder cancer is represented in almost 20-40% of bladder cancer patients worldwide. Furthermore, more than 85% die within 2 years if not treated.[5] There are around 80 patients treated for bladder cancer at Maharaj Nakorn Chiang Mai Hospital every year and each year about 16 cases (20%) have an invasive form of the disease which requires radical surgery.[4]

There are many surgical approaches, including open radical cystectomy (ORC), laparoscopic radical cystectomy (LRC), or other minimally invasive radical cystectomy. Open radical cystectomy with pelvic lymphadenectomy has long been the treatment of choice for management of bladder cancer.[6-8] However, de Badajoz et al. performed the first LRC in 1993,[8] and more recently, laparoscopic surgery has been accepted as a minimally invasive treatment reducing morbidity in comparison to open surgery. Several studies have shown that LRC is technically achievable and oncologically safe.[7-9]

The advantages of laparoscopic surgery include lower estimated blood loss, lower need for transfusion, less pain killer requirements, fewer post-operative complications, a shorter postoperative convalescence period, and less surgical scarring.[5,7,10,11] Importantly, the oncologic outcomes of laparoscopic surgery are comparable to conventional surgery.[12-14]

However, comparative studies that compare LRC with ORC as regards long-term oncologic outcomes are limited. In addition, robot-assisted laparoscopic radical cystectomy (RALRC) may not be a viable option for most Thai people because of financial concerns. Thus, LRC is an additional choice for the management of bladder cancer.[8,12-18]

The objective of our study was to compare open and laparoscopic radical cystectomy as regards long-term oncological outcomes of bladder cancer at Maharaj Nakorn Chiang Mai Hospital.

Materials and Methods

This study was retrospective in nature, medical records from January 2006 to December 2016 were reviewed and included patients aged more than 18 years old, who underwent open or laparoscopic radical cystectomy for bladder cancer at Maharaj Nakorn Chiang Mai Hospital. Exclusion criteria were palliative cystectomy, intra-operative unresectable tumor, simultaneous nephrectomy, and non-urothelial histologic subtype. The study protocol was approved by the Ethical Committee of Chiang Mai University (Research ID: 6454/ Study Code: SUR-2562-06454). Data pertaining to 144 patients fulfilled the inclusion criteria and were analyzed. Of the 144 patients, 57 patients had undergone ORC, and 87 patients LRC. The follow-up data were collected by either chart review or telephone contact. Survival status of all patients was last updated in December 2020.

The operative procedures were similar in both groups with the exception of approach. The technique for LRC, the same as was reported by Lin et al.[7] and Haber et al.[19], has been previously described. Standard pelvic lymphadenectomies were performed in our center, and the most common extracorporeal urinary diversion was ileal conduit.

Postoperatively, patients were admitted for at least 7-14 days. Clear liquid diets were started at postoperative day 5 progressing to a full diet within 7 to 10 days, depending on clinical response.

Patient baseline characteristics, intra-operative data, pathological findings and postoperative complications were assessed. Mean and standard deviation (SD) were used to express quantitative data and comparisons between the two groups were made using a Mann Whitney U test. Count and percentage were used for qualitative data and comparisons between the two groups were made using Fisher's exact test. Primary outcomes, including overall survival (OS), recurrence-free survival (RFS), and cancer-specific survival (CSS) were analyzed by Kaplan-Meier survival analysis and the two groups were compared using the log-rank test. A p value less than 0.05 was considered statistically significant. SPSS version 21 was used to analyze statistical data.

Results

Patient demographics

The baseline characteristics of all 144 patients, divided into the ORC group and the LRC group, are shown in Table 1. The mean age was 64.19 ± 9.89 years in the ORC group and 61.90 ± 10.47 years in the LRC group. The ratio of male to female in the ORC group was lower than the LRC group; the difference between the two genders was statistically significant (p = 0.006).

The majority of ASA scores in both groups were class 2. An ASA score of 3 was given to 8 (14.04%) patients in the ORC group and 3 (3.45%) patients in the LRC group. The comparisons between the ASA scores of the LRC group and the ORC group were statistically different (p = 0.041). The other preoperative data, including body mass index (BMI), clinical T stage, clinical N stage and clinical M stage showed no difference between the LRC group and the ORC group (p = 0.993, 0.041, 0.089, and 0.665, respectively).

Perioperative data and complications

Perioperative data are shown in Table 2.

Type of urinary diversion was similar between the ORC group and the LRC group (p = 0.236). Ileal conduit was the most frequent urinary diversion. A colonic conduit was the outcome in two patients in the ORC group (3.51%) because they had previously received radiation.

The mean values of anesthetic pain control (total morphine) were 17.65 ± 17.55 mg in the ORC group and 23.13 ± 16.83 mg in the LRC group (p = 0.062). Patients in the LRC group received fewer epidural blocks than patients in the ORC group (p < 0.001)

The mean length of hospital stay was 14.47 ± 6.38 days in the ORC group and 15.13 ± 7.88 days in the LRC group (p = 0.602)

Operative time was significantly shorter in the ORC group compared with the LRC group (p < 0.001). However, estimated blood loss and blood transfusion rates were significantly higher in the ORC than in the LRC group (p < 0.001 and < 0.001, respectively).

There was a statistically significant difference in the incidence of perioperative complications (Clavian-Dindo classification) between the two

Table 1. Baseline characteristics of patients who underwent open radical cystectomy (ORC) and laparoscopic radical cystectomy (LRC) at Maharaj Nakorn Chiang Mai Hospital between January 2006 and December 2016.

Characteristics	ORC n = 57	LRC n = 87	P-value
Age, Mean (SD)	64.19 (9.89)	61.90 (10.47)	0.191
Gender, n (%)			0.006
Male	43 (75.44)	81 (93.10)	
Female	14 (24.56)	6 (6.90)	
Body mass index (kg/m2), Mean (SD)	22.16 (3.53)	22.15 (3.50)	0.993
ASA score, n (%)			0.041
1	8 (14.04)	20 (22.99)	
2	41 (71.93)	64 (73.56)	
3	8 (14.04)	3 (3.45)	
Clinical T stage, n (%)			0.089
< T2	1 (1.75)	0	
T2	26 (45.61)	53 (60.92)	
T3	22 (38.60)	29 (33.33)	
T4a	8 (14.04)	5 (5.75)	
Clinical N stage, n (%)			0.665
N0	53 (92.98)	76 (87.36)	
N1	2 (3.51)	4 (4.60)	
N2	2 (3.51)	4 (4.60)	
N3	0	3 (3.45)	
Clinical M stage, n (%)			0.396
M0	56 (98.25)	87 (100)	
M1	1 (1.75)	0	

Table 3. Pathological outcomes for open radical cystectomy (ORC) and laparoscopic radical cystectomy (LRC) at Maharaj Nakorn Chiang Mai Hospital.

Pathologic Outcomes	ORC	LRC	P-value
Grade, n (%)			1.000
LG	7 (12.28)	10 (11.49)	
HG	50 (87.72)	77 (88.51)	
Concomitant CA prostate, n (%)			0.648
Yes	1 (1.75)	4 (4.60)	
No	56 (98.25)	83 (95.40)	
Concomitant CIS, n (%)			0.246
Yes	3 (5.26)	10 (11.49)	
No	54 (94.74)	77 (88.51)	
Pathologic T stage, n (%)			0.945
< T2	18 (31.58)	28 (32.18)	
T2	21 (36.84)	31 (35.63)	
T3	10 (17.54)	13 (14.94)	
T4	8 (14.04)	15 (17.24)	
Pathologic N stage, n (%)			0.075
LN positive	18 (31.58)	16 (18.39)	
LN negative	39 (68.42)	71 (81.61)	
LN count, Mean (SD)	15.07 (9.45)	12.78 (7.60)	0.112
Number of LN Positive, Mean (SD)	2.5 (1.95)	2.56 (2.06)	0.194
Surgical margin, n (%)			1.000
Positive	7 (12.28)	12 (13.79)	
Negative	50 (87.72)	75 (86.21)	
LVI, n (%)			0.865
Positive	26 (45.61)	38 (43.68)	
Negative	31 (54.39)	49 (56.32)	

LG = low grade, HG = high grade, CIS = carcinoma in situ, LN = lymph node, LVI = lymphovascular invasion.

groups (p = 0.028). Severe complications (Clavian-Dindo class 4 to 5) were 9 in the ORC group and 3 in the LRC group.

Pathology results

Pathology results for each group are shown in Table 3.

There was not statistical difference between the ORC group and the LRC group in pathologic grade, concomitant prostate cancer, concomitant CIS, pathological T stage, pathological N stage, lymph node count, positive lymph node number, surgical margin, or LVI (p = 1.000, 0.648, 0.246, 0.945, 0.068, 0.112, 0.194, 1.000, and 0.865, respectively).

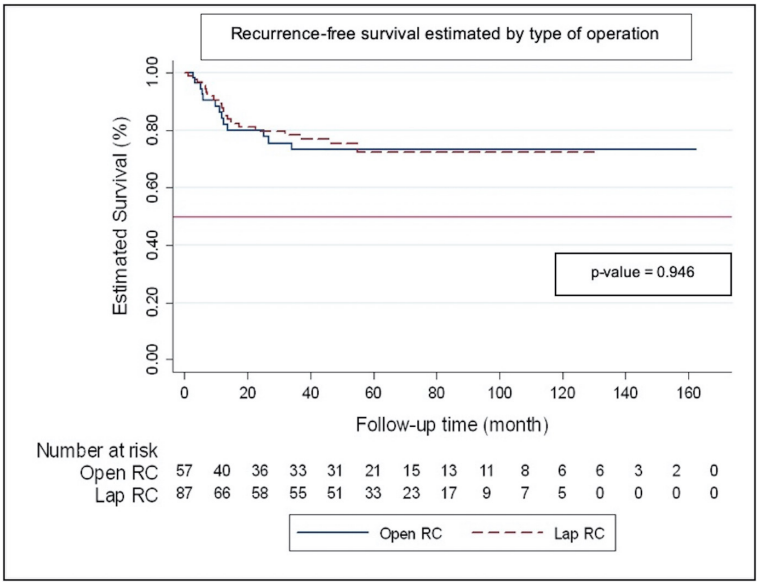
Oncological outcomes

The median follow-up time was 57.18 ± 44.68 months in the ORC group and 53.96 ± 34.97 months in the LRC group; 31 patients (21.53%) were followed for more than 10 years. Overall, patient deaths at the time of analysis were 35 (61.40%) in the ORC group and 57 (65.52%) in the LRC group.

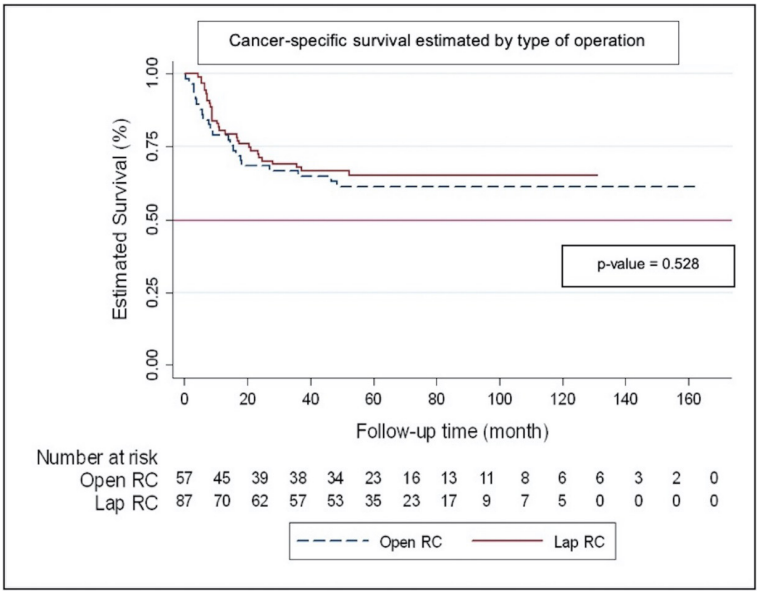
Recurrent bladder cancer was found in 13 patients in the ORC group and in 21 patients in the LRC group. Patients who died from bladder cancer numbered 23 (40.35%) and 29 (33.33%) in the ORC group and the LRC group, respectively.

There was no statistical difference in overall survival (OS), recurrence-free survival (RFS), and cancer-specific survival (CSS) between the ORC group and the LRC group (p = 0.322, 0.946, and 0.528, respectively, Figure 1).

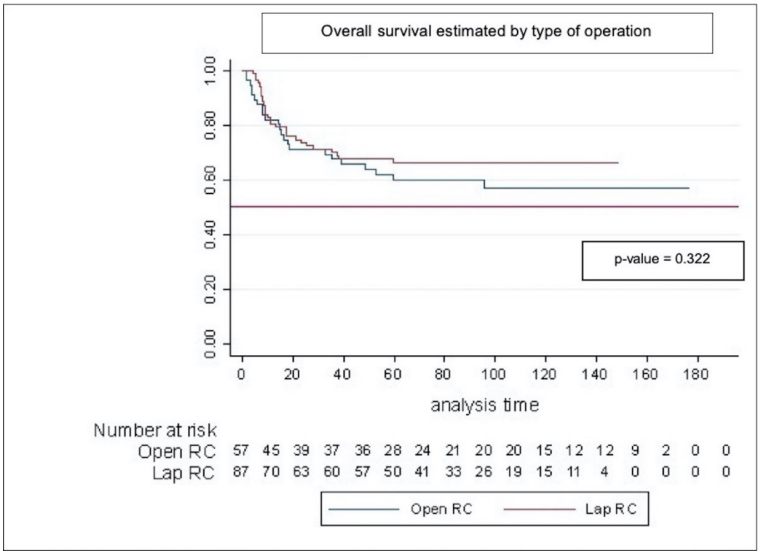
A subgroup analysis of our study demonstrated that there was no statistically significant difference between cancer-specific survival in the ORC group and the LRC group, in terms of organ confined cancer (≤ T2), extravesical involvement by cancer (≥ T3), no LN metastasis (N0), and



(A) Recurrence-free survival (RFS)



(B) Cancer-specific survival (CSS)



(C) Overall survival (OS)

Figure 1. Comparison of: (A) recurrence-free survival (RFS) between the LRC group and the ORC group, (B) cancer-specific survival (CSS) between the LRC group and the ORC group, (C) overall survival (OS) between the LRC group and the ORC group by Kaplan-Meier survival analysis and log-rank test

LN metastasis (N+) (p = 0.075, 0.235, 0.602, and 0.345, respectively).

Discussion

The world today has an ageing society. Because of the developments in health care and medical technology, the proportion of the elderly has become progressively larger in the majority of countries. In correlation with the increase in age the incidence and prevalence rates of bladder cancer increase.[18]

Advanced age is associate with multiple medical conditions, increasing the need and therefore the risk involved in surgical procedures. Minimally invasive modalities such as laparoscopic techniques, are of increasing interest for the management of bladder cancer because LRC has lower associated morbidity than ORC.[7,8,10,18] However, the gold standard treatment remains ORC.[6]

The perioperative variables of our study demonstrated that estimated blood loss and transfusion rates were significantly higher in the ORC group, but the operative time was significantly shorter in comparison to the LRC group. The analgesic requirement was comparable between the two groups because the ORC group received more epidural analgesic blocks than the LRC group but the LRC group had a higher morphine intake. Omar et al.[5] showed that during LRC intraoperative blood loss, transfusion rate, and postoperative opioid consumption was significantly lower, recovery time was significantly more rapid, and hospital stay was significantly shorter than in ORC, but operative time was significantly longer. Lin et al.,[7] Tae et al.,[9] and Guillotreau et al.10 report findings similar to Omar et al.[5] Our study showed that the duration of hospital stay of the two groups was similar. Due to policies of our institution, the most frequent urinary diversion procedure was ileal conduit; duration of admission was about 14 days.

The severe complications identified in our study were lower in the LRC group than in the ORC group. Omar et al.[5] observed 155 patients in a single center who underwent radical cystectomy and followed up for a mean of 53 months. Results showed that the LRC group had significantly more intraoperative complications than the ORC group. However, severe complications were significantly more frequent in the ORC group but no statistical differences were shown as regards individual complications between the ORC and LRC groups. Zeng et al.[18] found that the ORC group experienced more complications than the LRC group. Lin et al.[7] and Omar et al.[8] found the same results. However, no differences were found in mild and severe complications in a study by Hemal et al.[13]

Comparison between the oncological outcomes from LRC with ORC for bladder cancer remains limited, in terms of the number of patients and long-term follow-up duration. Several comparative studies from many centers have demonstrated similar oncological results in 3 to 5 year follow-up. Ha et al.[12] reported comparable oncological outcomes between LRC and ORC in a 3-year follow up. They included 70 patients (34 patients who underwent ORC and 36 patients LRC) in 1996 to 2003, and the median follow-up was 21 months (3-56 months). The other studies by Tae et al.,[9] Hemal et al.,[13] Gillion et al.,[14] and Zeng et al.[18] reported similar oncological results in mid-term duration. Interestingly, Tae et al.[9] concluded that the oncological outcomes were not dependent on the surgical approach. In Thailand, Nisaworn et al.16 reported comparable results from the different types of surgical approach as regards 5-year survival outcomes. In a longer term study, Snow-Lisy et al.[15] compared minimally invasive surgery with ORC. The median follow-up was 5.5 years. The data showed comparable outcomes in both groups. In addition, their study had 9 patients (7%) who were followed for more than 10 years.

T Lin et al.[7] conducted a RCT that compared oncological outcomes of LRC with ORC. However, the study pool was too small to be conclusive.

Our study demonstrated that the oncological outcomes in the long term were comparable between the ORC group and the LRC group with a median follow-up time of more than 50 months, 31 patients (21.53%) having a longer than 10 year follow-up.

Several factors impacted the oncological outcomes, specifically, lymph node count and surgical margin[9]. The high quality of radical cystectomy, an adequate lymph node yield of more than 10 lymph nodes, and the positive surgical margin (PSM) rate varied from 0% to 13%.[9,12] Furthermore, a greater number of lymph nodes dissected proved to be beneficial and improved

the survival outcome[12]. Recently, extended pelvic lymphadenectomies have been recommended.[14] In this study, median lymph node counts were comparable in both groups (p = 0.112), and both gave adequate yields, although we performed standard lymphadenectomies. Rates of positive surgical margins were no different between the groups and ranged from 0% to 13.79%. This was comparable to the standard for radical cystectomy.

Limitations

There were several limitations to this study, the main ones being the retrospective nature which always gives variability in determination of data and also there were selection biases. The surgical approach was mainly chosen by the surgeon in conjunction with patient preference. The economic status of the patient also had an impact. This study was heterogeneous as different surgeons performed radical cystectomies, there was a difference in the ratio of male to female in each group, and a wide variation in patient comorbidities. Looking to the future the ERAS protocol is becoming increasing popular and we would look to incorporating this in our approach. In addition, perioperative chemotherapy (neoadjuvant and adjuvant), which may impact survival outcomes, would be incorporated into a future study.

Conclusions

Our study demonstrated that LRC is comparable to ORC for management of bladder cancer as regards long-term oncological outcomes with no measurable negative impact. LRC is therefore an alternative option for muscle invasive bladder cancer treatment. It is safe, effective, and feasible. However, further large and long-term comparative studies are recommended to support our results.

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Conflict of Interest

The authors declare no conflict of interest.

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Original Article

Oncological outcomes of metastatic castration resistant prostate cancer (mCRPC) treated with different therapies sequences after completion of docetaxel: a retrospective study in Songklanagarind Hospital

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Keywords:
Metastatic castration-resistant prostate cancer, abiraterone acetate, enzalutamide, cabazetaxel, ketoconazole, overall survival

Abstract

Objective: Many treatment options of metastatic castration-resistant prostate cancer (mCRPC) after docetaxel chemotherapy have proved efficacious in clinical trials but, to date, knowledge regarding oncological outcomes is limited.

Materials and Methods: We assessed the oncological outcome of 4 drugs (abiraterone acetate, cabazetaxel, enzalutamide and ketoconazole) in a normal clinical setting in a university-based hospital. Our cohort consisted of 69 patients with post-docetaxel mCRPC. The primary endpoint was overall survival (OS). The secondary endpoint was predicted factor associated overall survival with all second-line mCRPC treatment outcomes according to the Cox proportional hazards regression model.

Results: This cohort consisted of 69 patients with progressive mCRPC after docetaxel chemotherapy. Median overall survival following treatment with abiraterone acetate and ketoconazole was 25.92 and 9.59 months respectively ($p < 0.05$). Overall survival rates at 1-year following abiraterone acetate, cabazetaxel, enzalutamide and ketoconazole therapy were 76.3%, 83.3%, 100% and 41.9%, respectively. Multivariable analysis found that abiraterone acetate, cabazitaxel and enzalutamide significantly improved survival in comparison to ketoconazole ($p < 0.001$).

Conclusion: Analysis of overall survival following second-line treatment of mCRPC post docetaxel in our study statistically significantly confirmed that abiraterone acetate, cabazitaxel and enzalutamide improve overall survival in comparison to ketoconazole. The study also found that enzalutamide treatment resulted in better outcomes in comparison to the other drugs.

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Introduction

Approximately 8630 new cases of prostate cancer were diagnosed in Thailand in 2020, representing about 9.2% of all new cancer diagnoses in Thai men[1] and age-standardized (World) incidence and mortality rate are 14.5 and 6.9 per 100,000 respectively. Prostate cancer with a high risk of advancement usually progresses quickly. Despite accounting for less than 15% of diagnoses, high-risk prostate cancer patients have a cancer-specific death rate of 15% after ten years and are more likely to acquire advanced prostate cancer. The development of drugs to target these pathways or therapeutic interventions for disease prevention has been sparked by a better knowledge of the mechanisms that lead to the establishment of advanced metastatic disease .[2] If prostate cancer progresses to metastatic castration- resistant prostate cancer (mCRPC) a positive clinical outcome is uncertain despite the discovery of novel therapeutic agents.[3,4] However, many drugs have been approved in Thailand for alternative treatment of mCRPC which are associated with survival improvement. These include the androgen receptor (AR)-targeted agents: abiraterone acetate, enzalutamide, cabazitaxel and ketoconazole.[5] The lack of evidence from prospective studies regarding second-line mCRPC post docetaxel treatment and its association with the best possible patient outcomes, also remains limited.[6]

Most patients with mCRPC have received docetaxel as part of their long-term treatment regimen as it is a standard treatment for patients with symptomatic metastases. In patients with mCRPC who have progressed after docetaxel, there is no strong evidence or direct comparison between a second-line option of chemotherapy (cabazitaxel), second-line AR-targeted therapy (abiraterone acetate or enzalutamide) or ketoconazole. Understanding the treatment outcome of each drug will be useful in informing health professionals and hence be beneficial for patients.[7,8]

The objective of this study was to evaluate the clinical outcomes of mCRPC post-docetaxel treatment in a real-world setting in a university-based hospital. We have retrospectively evaluated and analyzed the outcomes of second-line treatments post-docetaxel and their association with overall survival. Currently, little is known about these treatment outcomes in Thailand.

Materials and Methods

Study design

This study was retrospective in design. Overall survival was defined as a period from the start of the second-line therapy to either the end of data availability, the data cut-off date or death, depending on which event came first. The study protocol was approved by the Ethical Committee of Prince of Songkhla University (Study Code: REC.63-068-10-4).

Eligibility criteria

Inclusion criteria were a confirmed diagnosis of prostate cancer, an age of 18 years or over at the time of the diagnosis of prostate cancer, had received docetaxel as a first-line therapy and had received an mCRPC treatment of interest (abiraterone acetate, cabazitaxel, enzalutamide or ketoconazole).

Endpoints of the study

The primary endpoint was overall survival (OS), which was defined as the time from the start of the second-line therapy to death from any cause.

Study population

Medical records from the electronic database of post-docetaxel mCRPC patients who were treated in Songklanagarind Hospital from April, 2015 to March, 2019 were reviewed. All mCRPC patients who had had 6 cycles of docetaxel and then had been treated with second-line treatment were included. We defined high volume as ≥ 4 lesions of bone metastasis or visceral metastasis. Patients were excluded if the diagnosis was accidental or staging was incomplete or had there had been a switch to other treatment. Demographic data including patient age at diagnosis, initial prostate specific antigen, diagnosis date, Gleason score, volume of metastasis, nadir of the prostate specific antigen, PSA at the start of the second line treatment, the date treatment was started and the end point of the study were recorded.

Statistical analysis

The median OS was assessed using the Kaplan-Meier method. The primary statistical method of comparison for the time-to-event endpoints was log-rank test stratified by potential factors. The Cox proportional hazards model

was used to estimate the hazard ratio (HR) and its associated CI. Disease factors including the initial Prostate specific antigen, ECOG status, volume of disease, Gleason score, PSA at the start of the second-line treatment were recorded and their correlations with the overall survival were calculated by univariable regression analyses. Statistical significance for each correlation were estimated with a 95% confidence interval and a $p < 0.05$. Multivariable analysis for overall survival was performed to evaluate potential prognostic factors take as those registering as $p < 0.05$ from the univariable analysis (ECOG status, volume of disease, Gleason score, PSA at the second-line start of treatment). These were analyzed using Cox proportional hazards regression.

Descriptive statistics were used to summarize patient demographic and clinical characteristics at the start of second-line therapy. Demographic data was tabulated as mean (SD), and median (IQR). Comparisons between cohorts were carried out using Chi-squared tests for categorical variables and Wilcoxon rank-sum tests for continuous variables.

The data was amassed using a spreadsheet template in Microsoft Excel and all statistical analysis was performed using R program version 3.6.1.

Results

Out of all mCRPC patients treated with docetaxel in Songklanagarind Hospital, a total of 69 patients were treated with second-line therapy and all were included in the study. The proportions of patients undergoing each form of treatment, linked to survival status after treatment are shown in Figure 1.

Demographic data

A total of 69 cases of metastatic castration resistant prostate cancer (mCRPC) patients were treated with second-line treatment, post-docetaxel, at Songklanagarind Hospital between 2015 and 2019. Patient characteristics are presented in Table 1. The initiation of post-docetaxel therapy, and the characteristics of patients in each group were generally similar. The mean age of the patients was 71.9 years old (± 9.7), Gleason score in the high risk category (GS ≥ 8) had an incidence of 40 out of 69 patients (58%), and the volume of metastases was high in 55 out of 69 patients (79.7%). The median PSA at the date of the start second-line treatment was 130 ng/ml (IQR 53-330).

Median overall survival and 1-year overall survival

Out of 69 patients with progressive mCRPC after 6-cycles of docetaxel the median OS was 16.6 months [95% CI; 13.1-NA] as shown in Figure 2.

The median overall survival of each treatment arm showed that the OS of patients treated with abiraterone acetate was 25.92 months, and those with ketoconazole was 9.59 months. The difference in median OS for patients receiving abiraterone acetate in comparison to ketoconazole was statistically significant (25.92 vs. 9.59 months; $p < 0.05$). However, cabazitaxel and enzalutamide did not have median overall survival due to less event occurred to calculated, but appeared higher than ketoconazole. The 1-year OS for abiraterone acetate, cabazitaxel, enzalutamide

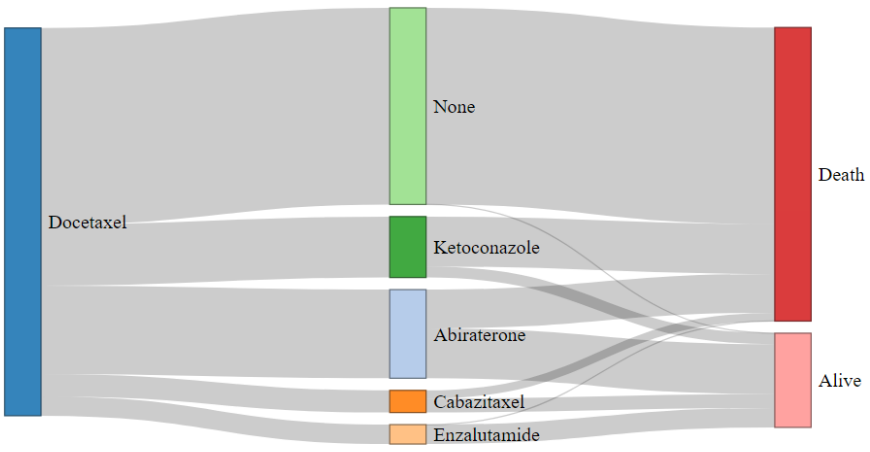

Figure 1. Sankey diagram: proportion of second-line treatment of mCRPC patients associated to survival status.

Table 1. Characteristics of mCRPC patients receiving second-line treatment in post-docetaxel setting.

Characteristics	Second-line therapy received					
	Abiraterone (n=32)	Cabazitaxel (n=8)	Enzalutamide (n=7)	Ketoconazole (n=22)	Total	P-value
Total	32	8	7	22	69	
Age (years)						0.488
Mean (SD)	73.3 (10.2)	67.8 (6.6)	69.9 (7.5)	71.9 (10.3)	71.9 (9.7)	
PSA at diagnosis (ng/mL)						0.783
Median (IQR)	300 (175,766.2)	681.5 (244,1061.8)	347 (227.5,601)	275 (142.8,750)	300 (172,780)	
ECOG						1
0-1	31 (96.9)	8 (100)	7 (100)	22 (100)	68 (98.6)	
2	1 (3.1)	0 (0)	0 (0)	0 (0)	1 (1.4)	
Gleason score						0.557
≤ 7	15 (46.9)	2 (25)	4 (57.1)	8 (36.4)	29 (42)	
≥ 8-10	17 (53.1)	6 (75)	3 (42.9)	14 (63.6)	40 (58)	
Volume of metastasis						0.6
High	24 (75)	6 (75)	7 (100)	18 (81.8)	55 (79.7)	
Low	8 (25)	2 (25)	0 (0)	4 (18.2)	14 (20.3)	
PSA at start of second line treatment						0.057
Median (IQR)	69 (35.8,225.5)	130 (80,319.5)	120 (98,143.5)	294 (69,1051.2)	130 (54,330)	
Anemia						0.018
No	16 (50)	4 (50)	4 (57.1)	3 (13.6)	27 (39.1)	
Yes	16 (50)	4 (50)	3 (42.9)	19 (86.4)	42 (60.9)	

PSA = prostate specific antigen, ECOG = Eastern Cooperative Oncology Group scale.

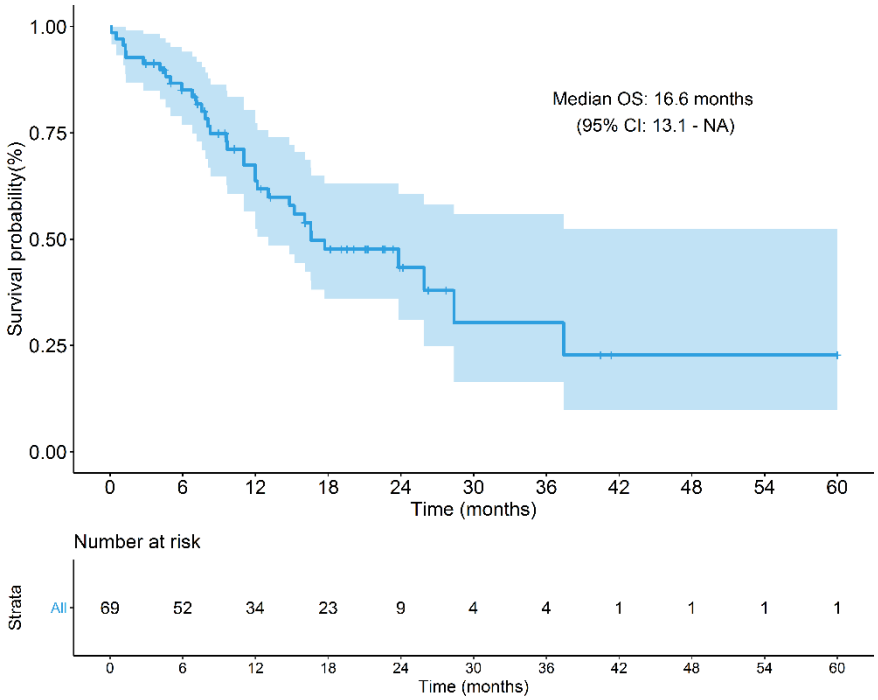

Figure 2. Kaplan Meier overall survival curve of all mCRPC patients treated with second-line treatment.

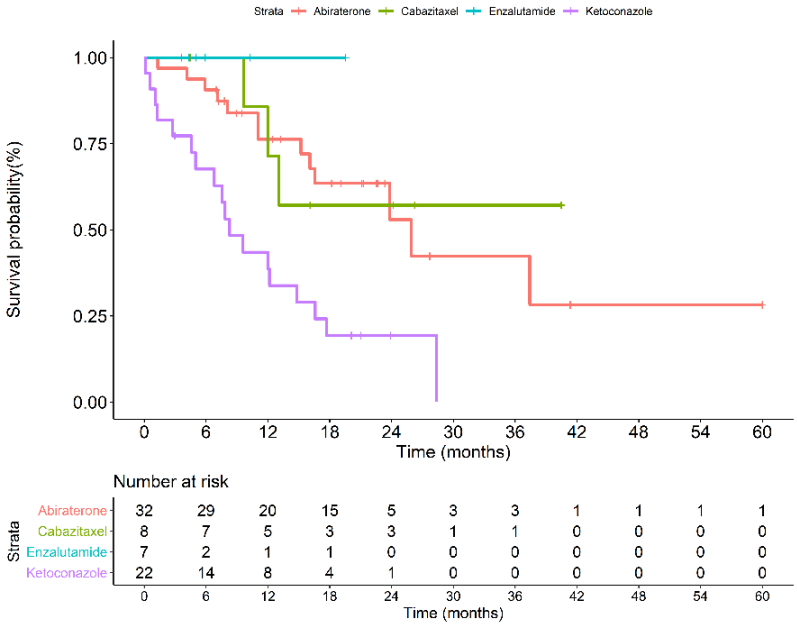

Figure 3. Kaplan Meier's survival curve demonstrating overall survival of post-docetaxel mCRPC patients treated with abiraterone acetate, cabazitaxel, enzalutamide and ketoconazole.

Table 2. Univariable and multivariable analysis of each affected factors associated to overall survival.

Factor	Univariable analysis		Multivariable analysis	
	Crude HR (95%CI)	P-value	HR (95%CI)	P-value
Ketoconazole		0.034*		0.001*
Abiraterone	0.3 (0.14, 0.62)		0.32 (0.15, 0.66)	
Cabazitaxel	0.25 (0.07, 0.87)		0.22 (0.06, 0.77)	
Enzalutamide	0 (0, Inf)		0 (0, Inf)	
Age group > 75 vs ≤ 75	1.39 (0.71, 2.74)	0.849		
ECOG 2 vs 0-1	1.66 (0.23, 12.3)	0.491		
GS 8-10 vs ≤ 7	2.06 (0.98, 4.31	0.034*	2.1 (0.99, 4.47)	0.046*
Volume metastasis low vs high	1.32 (0.62, 2.83)	0.832		
Median PSA at started second-line treatment > 130 vs ≤ 130 ng/ml	1.69 (0.83, 3.44)	0.377		
Anemia: Yes vs No	2.8 (1.3, 6.05)	0.199		

*Statistical significance < 0.05

and ketoconazole were 76.3%, 83.3%, 100% and 41.9% respectively, as shown in Figure 3.

The univariable analysis by drug as a second line treatment of mCRPC indicated that abiraterone acetate, cabazitaxel, and enzalutamide have statistically significant better survival outcomes in comparison to ketoconazole (p = 0.034). The analysis also shows that a high Gleason score has significantly higher risk of mortality than a lower Gleason score (p = 0.034). However, there was no statistically significant association between age, ECOG, volume of metastasis, median PSA level at the date of the start of second line treatment at a cutoff of 130 ng/ml and anemia before treatment and overall survival.

The multivariable Cox regression showed significantly better overall survival following abiraterone acetate, cabazitaxel and enzalutamide therapy in comparison to ketoconazole (hazard ratio: 0.29, 0.19 and 0, respectively; 95% Confidence Interval [CI] 0.13–0.61, p = 0.001) as shown in Table 3.

Discussion

Findings from this retrospective study provide an insight into the efficacy of post-docetaxel treatment in mCRPC patients. It also describes the characteristics of patients who received either abiraterone acetate, cabazitaxel, enzalutamide or ketoconazole as second-line treatments in a real-world setting. Our study assessed the OS following a novel phase of treatment in a post-docetaxel setting in Songklanagarind Hospital. Therapies used included AR-targeted therapy (abiraterone acetate and enzalutamide), cabazitaxel, and ketoconazole. The majority of patients received abiraterone acetate post-docetaxel for many reasons, including the clinical condition of patients, reimbursement and the drug registry period.

In the post-docetaxel setting, recent studies have suggested that there may be a survival benefit when the patient receives abiraterone acetate, cabazitaxel and enzalutamide.[9-11] In our study we found that abiraterone acetate, cabazitaxel and enzalutamide improved overall survival in comparison to ketoconazole. Interestingly, we did find that the subgroup of patients with a worse disease prognosis at the initiation of second-line therapy benefitted from receiving second-line abiraterone acetate, cabazitaxel, or enzalutamide when compared with ketoconazole.

Interestingly, we did not find any differences in terms of OS in patients in head-to-head comparison between cabazitaxel versus AR-targeted (abiraterone acetate or enzalutamide) therapies. This may have been due to some results not reaching the median OS of the entire cohort and the small numbers of the 4 treatment populations, but it seems likely that enzalutamide had the greatest potential benefit to survival as all cases were still alive after the 18 month follow up. This is a limitation of this investigation and longer term studies need to be carried out to confirm these findings. Several studies reported that enzalutamide therapy results in a better PSA response rate and PFS in treating mCRPC patients. A meta-analysis, showed that OS was 8.3 months higher in the pre-docetaxel setting, and 2.2 months in the post-docetaxel setting, in enzalutamide-treated mCRPC patients in comparison to the abiraterone acetate group. However, these differences did not reach statistical significance.

In another network meta-analysis, the findings suggested that enzalutamide was the most effective agent in improving OS (HR = 0.71) and abiraterone acetate was less effective in comparison to enzalutamide (HR = 0.78).[12] However, based on a pooled data analysis, differences between the pre- and post-chemotherapy settings were neglected. A pooled data analysis of major phase III clinical trials including PREVAIL, AFFIRM COU-AA-301 and COU-AA-302, yielded similar but contradictory findings between the different regimens in mCRPC have been observed in literature indicating that sensitivity to one compound is impaired by another with a similar or overlapping mechanism of action.[12]

Therefore, a more confident clinical application of our results requires further randomized control studies with larger sample sizes. A second limitation is that patient numbers differ between groups, limiting the power of the statistical analysis. Prospective randomized trials are warranted to validate these results. Future research should also consider other approved therapies, as well as adverse events or the impact on health-related quality of life.

Conclusion

Our findings confirm that in this study all the second line treatments of mCRPC tested prolong overall survival in a post-docetaxel setting. Abiraterone acetate, cabazitaxel and enzalutamide therapy were statistically significantly associated with better overall survival in comparison to ketoconazole. Enzalutamide showed the most benefit with regard to prolonging survival.

Acknowledgment

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Conflict of Interest

The authors declare no conflict of interest.

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Original Article

A comparison of stone free rate between a diuretic and a control group of patients undergoing extracorporeal shock wave lithotripsy: a prospective, randomized, double-blind, placebo-controlled trial

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Keywords:
Extracorporeal shock wave lithotripsy, diuretic, stone free rate

Abstract

Objectives: To compare the stone free rate and treatment success rate between a diuretic group of patients undergoing extracorporeal shock wave lithotripsy (ESWL) and a control placebo group (normal saline solution).

Materials and Methods: One hundred and ninety-four patients with solitary renal calculi or ureteric calculi size of 5 mm or over were prospectively randomized into 2 groups. Ninety-seven patients in the first group (diuretic group) underwent ESWL after intravenous injection of furosemide 40 mg, and 97 patients in the second (control) group received normal saline solution 4 ml instead of furosemide prior to ESWL. The treatment protocol included 3,000 shockwaves per patient in each session with the energy beginning at 8 and progressing up to 15 kilovolts. A maximum of 3 ESWL sessions were permitted per patient. The primary outcome was stone free rate, and the secondary outcome was treatment success rate at 3 months after the first ESWL treatment.

Results: The stone free rate was 48.5% compared to 50.5% for diuretic group and control group respectively and the treatment success rate was 81.4% compared to 64.9%. The difference in stone free rate was not statistically significantly different ($p = 0.87$), however the treatment success was, $p = 0.01$.

Conclusion: A combination of diuretic therapy followed by ESWL improves the treatment success rate compared with standard ESWL therapy alone.

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Introduction

Extracorporeal shock wave lithotripsy (ESWL) has been used as a treatment of urolithiasis since 1980.[1] As a minimally invasive procedure, the efficacy of ESWL[2] is accepted worldwide especially in the treatment of small renal or ureteric calculi. However, some patients require repeat ESWL treatment due to the failure or limitation of stone fragmentation. The success of ESWL treatment depends on several factors including stone size, stone number, stone composition, and renal function.

Diuretics increase urine flow around the stone during ESWL,[3,4] therefore, improving stone fragmentation[5] and removal. The main mechanism employed is the cavitation phenomenon. When a shock wave generated by an extracorporeal shock wave lithotripter interacts with a solid, it can produce cavitation bubbles at the interface between the solid and the surrounding liquid. The implosion of the cavitation bubbles plays an important role in the disintegration of the stone.

The aim of this study was to compare stone free rate[6,7] and treatment success rate between a diuretic with ESWL and placebo (normal saline solution) with ESWL. The hypothesis is that the diuretic combined with ESWL improves the stone free rate and the treatment success rate when compared with standard ESWL therapy alone.

Materials and Methods

A prospective, randomized, double blinded, placebo-controlled trial was conducted between December 2020 and May 2021 at Chaophraya Yommarat Hospital. This study was approved by the Ethics Committee of Human Research (ECID: YM 033/2563) and approved by the Thai Clinical Trials Registry (TCTR) committee on 1st June 2021. The TCTR identification number is TCTR 20210601002.

From the original cohort of 200 patients, 6 patients were excluded due to loss of follow up, the remaining 194 patients were enrolled in the study. All patients had solitary radiopaque renal or ureteric calculi, written consent was given by all participants.

Demographic data including age, sex, body mass index (BMI), stone size, and stone location were collected. As shown in Table 1, the patients were randomly divided into 2 groups using computer-generated numbers. In the first group (diuretic group), the patients received 40 mg of furosemide intravenous injection 30 minutes before each ESWL session. In the second (control group), the patients received 4 ml of normal saline solution as placebo instead of furosemide 30 minutes before each ESWL session. All patients in both groups received hydration with normal saline 500 ml intravenously during the procedure at the rate of 60 ml/hour. Blood pressure, and oxygen saturation were monitored during the procedure. For ESWL, all patients were treated as outpatients under intravenous analgesia; pethidine 25 mg.

A Dornier Delta III (Dornier Medtech, Munich, Germany) machine was used for the ESWL, with 3,000 shock waves given at the rate of 60-90 shockwaves/minute with the energy beginning at 8 and progressing up to 15 kilovolts. Patients were followed up at the outpatient department every 3 weeks after ESWL for 3 months with a plain film kidney ureter bladder (KUB) x-ray.

ESWL was repeated if no stone fragmentation occurred or residual stone fragments were larger or equal to 5 mm. Patients were permitted a maximum of 3 sessions of ESWL, 3 weeks apart.

The primary outcome was stone free rate at 3 months after ESWL. Stone free rate was defined as the complete clearance of stone or no visible stone seen on plain film KUB. Clinically insignificant residual fragments (CIRF) was defined as residual fragments of stone smaller 4 mm or less on plain film KUB.

The secondary outcome was the treatment success rate, defined as the complete clearance of stone (stone free) or CIRF, and treatment failure was defined as having residual stone fragments over 5 mm on plain film KUB after 3 ESWL sessions.

Inclusion criteria were patients above 18 years old, with a single radiopaque renal or ureteric calculi size over or equal to 5 mm. The exclusion criteria were patients who were pregnant, suffered from uncontrolled coagulopathy, or urinary tract infection, and those with multiple or bilateral stones.

Statistical analysis was done using a statistical package for the social sciences (SPSS version 16; SPSS Inc: IBM corp., Armonk, NY, USA). Categorial variables were compared using the Chi-square test. Continuous data are presented as mean and standard deviation (SD), which were compared using a student's T test.

Results

A total of 194 patients were enrolled onto the study and randomly divided into two groups, 97 patients being allocated into each arm. There were no differences between the 2 groups with regard to age, sex, BMI, stone size and stone location (Table 1). The mean ages of the diuretic group and the control group were 54.23 years (SD 11.4) and 54.35 years (SD 13.5) respectively, p-value 0.95. The mean BMI of the diuretic group and the control group were 25.53 kg/m^2 (SD 4.93) and 25.23kg/m^2 (SD 3.83) respectively, p = 0.64. The mean size of the stones of the diuretic group and the control group were 9.63 mm (SD 4.65) and 10.27 mm (SD 4.59) respectively, p = 0.67. 108 patients (55.7%) had a renal stone and 86 patients (44.3%) had a ureteric stone. Patients with renal stones in the diuretic group and control group numbered 53 patients (49.1%) and 55 patients (50.9%) respectively. Patients with ureteric stone in the diuretic group and the control group totaled 44 patients (51.2%) and 42 patients (48.8%) respectively.

There was no statistical difference in the stone free rate of the diuretic group and the control group (48.5% vs 50.5%, p = 0.87). However, the CIRF incidence in the diuretic group was statistically significantly higher than in the control group (33% vs 15.5%, p < 0.01). In addition, the overall treatment success rate in the diuretic group was significantly higher than in the control group. (81.4% vs 64.9%, p = 0.01) Table 2.

There were 9 patients (9.3%) in the diuretic group and 11 patients (11.3%) in the control group respectively who received double-J stent placement due to steinstrasse and severe pain after ESWL. Three patients (3.1%) from both the diuretic group and the control group were treated

Table 1. Demographic data

Characteristics	Diuretic group (N=97) n (%)	Control group (N=97) n (%)	P-value
Sex			0.67
Male	51 (52.6)	48 (49.5)	
Female	46 (47.4)	49 (50.5)	
Age (years)			0.81
< 40	11 (11.3)	14 (14.4)	
41-60	55 (56.7)	53 (54.6)	
> 60	31 (32)	30 (30.9)	
Mean (SD)	54.2 (11.4)	54.4 (13.5)	0.95
BMI (kg/m^2)			0.35
< 18.5	4 (4.1)	5 (5.2)	
18.5-22.9	24 (24.7)	20 (20.6)	
23-24.9	24 (24.7)	16 (16.5)	
> 25	45 (46.4)	56 (57.7)	
Mean (SD)	25.5 (4.9)	25.2 (3.8)	0.64
Stone size (cm)			0.25
< 1	66 (68)	55 (56.7)	
1.1-2.0	28 (28.9)	39 (40.2)	
> 2.0	3 (3.1)	3 (3.1)	
Mean (SD)	9.6 (4.7)	10.3 (4.6)	0.67
Stone location			
Renal calculi (n=108)	53 (54.6)	55 (56.7)	0.73
Upper calyx	13 (13.4)	9 (9.3)	
Middle calyx	17 (17.5)	18 (18.6)	
Lower calyx	23 (23.7)	28 (28.9)	
Ureteric calculi (n=86)	44 (45.4)	42 (43.3)	0.47
Upper	24 (24.7)	25 (25.8)	
Middle	2 (2.1)	5 (5.2)	
Distal	18 (18.6)	12 (12.4)	

BMI = body mass index, SD = standard deviation

Table 2. Results of the ESWL treatment

Characteristics	Diuretic group n (%)	Control group n (%)	P-value
Stone free	47 (48.5)	48 (50.5)	0.87
CIRF[a]	32 (33.0)	15 (15.5)	< 0.01
Treatment success[b]	79 (81.4)	63 (64.9)	0.01

[a]Clinically Insignificant Residual Fragment, residual stone fragment less than or equal to 4 mm after 3 sessions of ESWL

[b]Treatment success; defined as stone free including CIRF

with Ureterorenoscopy to remove residual stones, 1 patient (1.03%) in the diuretic group and 3 patients (3.1%) in the control group required open stone surgery after failed ESWL treatment (Table 3). None of the auxiliary treatments showed any significant difference.

Discussion

ESWL is the treatment of choice for urolithiasis with small size stone, due to the minimally invasive nature of the procedure. The mechanisms involved[8,9] in ESWL treatment for stone disintegration are compressive fracture, spallation, acoustic cavitation, and dynamic fatigue, of which cavitation is the most important. Diuretics can increase urine flow around the stone and form a fluid film interface between the stone and renal or ureteric wall which improves the possibility for cavitation and enhances stone fragmentation. The use of diuretics followed by ESWL allows the outer shell of the stone to be cracked then the center of the stone becomes more exposed to the subsequent shockwaves allowing entry of urine through the broken surface. Therefore, the diuretic increases the surface area of the stone on which the shock wave can act.[10,11]

The success of the ESWL treatment depends on several factors such as stone size, stone number, and stone composition[12]. From previous studies, diuretics were also used to enhance the efficacy and outcome of ESWL treatment. Dong et al.[13] conducted a meta-analysis which indicated that the use of diuretics during ESWL treatment significantly increased the stone clearance rate (odds ratio, 1.73; 95% confidence interval (CI), 1.35-2.22, $p < 0.0001$) and the stone fragmentation rate (odds ratio, 2.83; 95% CI; 1.30-6.16, $p = 0.009$).

Table 3. Auxiliary treatment post ESWL

Characteristics	Diuretic group n (%)	Control group n (%)	P-value
Double J stent placement	9 (9.3)	11 (11.3)	0.64
Ureterorenoscopy	3 (3.1)	3 (3.1)	1.00
Open stone surgery	1 (1.1)	3 (3.1)	0.31

Furthermore, Azm et al.[14] showed that the use of diuretics with ESWL improved stone clearance rate with the diuretic and ESWL clearance rate being 92.3% compared to 87% ESWL alone without diuretics in 106 ureteric calculi patients. A study by Sohu et al.[15] in 714 patients reported a higher stone free rate in the diuretic group compared to the standard ESWL, 77% compared to 65% respectively ($p < 0.001$).

Zomorrodi et al.[16] investigated 86 patients, divided into 2 equal comparative groups and reported stone fragmentation rates of 81% and 93% and stone clearance rates of 68.2% and 88.4% in the diuretic group and the control group respectively.

In our study ,there was no statistical significant different in overall stone free rate between the diuretic group and control group ($p = 0.886$), but the results did show that CIRF in the diuretic group was significantly higher than in the control group ($p = 0.004$). As mentioned above the reason that CIRF in the diuretic group was significant higher than the control group was because the diuretic increases urine flow around the stone during ESWL which together with cavitation bubbles from the shockwave increases the pieces of fragmented stone shell resulting in more residual stone fragments in the diuretic group. The treatment success rate (stone free rate and CIRF) was significantly higher in the diuretic group than in the control group (81.4%: 64.9%, $p = 0.001$). These results substantiated our hypothesis. It is reasonable to assume that if the period of follow up were longer, some CIRF may be passed and incidence of the stone free rate may increase over time.

Our survey of other literature found that the definition of stone free varied from study to study. Some authors defined stone free as complete clearance of stone but some authors defined stone free as complete clearance of stone

and CIRF. Ahmed et al.[17] defined stone free as no visible stone or residual fragment < 4 mm on x-ray film KUB or ultrasound, and Elkholy et al.[18] defined stone free status as the complete clearance of stone, the treatment success being defined as the stone free state or CIRF < 4 mm These results were in accordance with the findings of our study.

There were several factors found which could interfere with the success of ESWL treatment, for example, stone size, stone number, stone composition, patient related factors such as intrarenal anatomy[19], or stone location especially in the case of lower caliceal stones. Therefore, the choice of treatment which is the minimally invasive, while treating the condition effectively in each patient is an important issue that urologists should consider.

In the future, many factors that enhance the efficacy of ESWL treatment will be developed. The findings of many studies currently being carried out will improve ESWL outcomes and promote a higher success rate of treatment for the maximum benefit for urolithiasis patients[20]. This will ultimately mean that in more and more cases invasive surgery can be avoided. The benefits of this are legion, improving patient experience and the need for hospitalization, reducing costs to the hospital and particularly in this Corona Virus Disease 19 (COVID -19) era where surgery could increase infection rate, a minimally invasive procedure is invaluable.

Conclusions

Diuretics did not improve the stone free rate after ESWL in this study but diuretics improved treatment success rate of ESWL treatment in comparison with standard ESWL.

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Conflicts of Interest

The author declares no conflict of interest.

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Original Article

Nocturia and effect on the quality of life. A study at Ramathibodi Hospital

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Keywords:
Nocturia, quality of life, lower urinary tract symptoms, impact, sleep quality

Abstract

Objective: To investigate the impact and the incidence of nocturia on the quality of life of patients in Ramathibodi Hospital.

Materials and Methods: This study was a hospital-based cross-sectional study to measure the QoL of nocturia patients using a Nocturia Quality-of-Life questionnaire (N-QoL). Cronbach's alpha coefficient was used to explore internal consistency. Pearson's correlation coefficient (r) was used to determine the strength of the relationship between the scores for each item. Uni- and Multivariate analyses were used to explore the significant parameters.

Results: One hundred and fifty-five nocturia patient were included in the study analysis. Most of the questionnaire respondents were male (80.65%) and the vast majority had at least 1 underlying disease requiring long-term follow-up by a physician (86.45%) with a median urination of 3 times per night and a 3 hour median first urination after retiring to bed. From our study questionnaire, most patients responded that they had moderate to good quality of life with a minor inconvenience from nocturia, requiring them to nap during the day on some days. An increasing frequency of urination per night and a first urination of less than 2 hours after retiring is significantly related to low levels of energy the next day, sleep deprivation, worry over treatment options, overall inconvenience and a reduction in quality of life.

Conclusion: Our study demonstrated nocturia patients experience a significant reduction in quality of life, and a decrease in quality of sleep. The incidence of urination in the night and the timing of the first urination after bed had more impact on overall quality of life.

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Introduction

Nocturia, as defined by The International Continence Society (ICS), is waking up to urinate at night after falling asleep and after urinating the patients returns to bed.[1] This is a common condition, especially in patients with lower urinary tract disease such as benign prostatic hyperplasia (BPH). The prevalence of nighttime urination has been recorded as 25.2% in men and 31.3% in women,[2,3] with an increase in incidence with older age[4]. The prevalence of nocturia in women attending the menopause clinic in Ramathibodi was 40.3%.[5] Many elderly patients have to wake up and urinate every hour after going to bed, resulting in insufficient rest and an inability to work efficiently the next day.[6] Some patients also have a risk of falling while waking up to urinate.[7] Some studies have shown that patients who wake up to urinate at night have more depression problems than those who sleep well throughout the night.[8] It has also been found that people without nocturia had a longer survival rate than those who needed to wake up to urinate at night.[9]

Nocturia has been classified into four main categories including nocturnal polyuria, diminished nocturnal and/or global bladder capacity, global polyuria and mixed nocturnal polyuria and diminished nocturnal and/or global bladder capacity. However, in individual cases, more than one of these etiologies might be involved.[10] If the patient is diagnosed, investigated for the underlying cause and receives the correct treatment a decrease in the frequency of night urination is possible. The aim of this study is to assess the effects of nocturia and the frequency of nocturia on the quality of life in Thai patients.

Materials and Methods

Study design

This study was a cross-sectional and questionnaire-based survey conducted among nocturia patients at the outpatient unit of Department of Surgery, Ramathibodi Hospital. The study was approved by the Ethical Clearance Committee on Human Rights Related to Research Involving Human Subjects of the hospital (Study Code: ID 02-60-23).

Participants

The recruitment criteria were: patients with nocturia, of either gender, aged between 25 and 75, and had the capacity to answer the questionnaires. Nocturia was defined as waking to void at least once in the night over the past month. Written informed consent was obtained from all patients who met the eligibility criteria.

Study questionnaire

The effect of nocturia on quality of life (QoL) was studied using the Nocturia Quality-of-Life questionnaire (N-QoL) developed by Abraham et al.[11] The questionnaire was translated into Thai language by a proficient in English translator and verified by two independent urologists. We sought and received permission by email from the original team who constructed the ICIQ, N-QOL questionnaire. The N-QoL questionnaire consists of 13 questions, 12 questions (Q1-Q12) being directly related to nocturia and 1 a global QoL item. Questions 1-12 were divided into two subscales a sleep/energy domain (Q1-Q7, with the exception of Q6) and a bother/concern domain (Q6-Q12). Each question has 5 answers. The scores for each question range from 0-4 (5-point scale), reflecting most impact to no impact. The score with higher values indicating increased impact on quality of life.

The N-QoL overall score is the total of the scores from Q1-Q12. Total subscale scores are calculated from the scores of the questions in the specific domain.

Statistical analysis

Descriptive statistics were used to describe the characteristics of the respondents and summarized the quality of life of the patients. The internal consistency reliability of the translated N-QoL questionnaires was calculated and presented using Cronbach's alpha coefficient. A Cronbach's alpha coefficient greater than 0.7 was used to show internal inconsistency between the overall NQoL and its subscale scores.[12] Pearson correlation coefficients (r) were used to determine the strength of the relationship between each item and the scores. The absolute values of correlation coefficients were interpreted as 0.90 to 1.00, 0.70 to 0.90, 0.50 to 0.70, 0.30 to 0.50, and 0.00 to 0.30 as the following correlations: very high, high, moderate, low and negligible respectively.[13]

Univariate analysis by exact test for categorical variables and linear regression/median tests for continuous variables were used to explore the

existence of relationships between each question and urinating at night (frequency of urination, first urination time, urinary incontinence) and patient characteristics (gender, having at least one chronic disease, and prostatic hyperplasia or prostate cancer). Multivariate linear regression with backward selection was carried out using univariate variables that had a $p < 0.10$ to explore the significant variables for each question and a NQoL overall score. $p < 0.05$ were considered as statistically significant unless otherwise specified.

Results

Respondent characteristics

The estimated size necessary for this study is 370 calculated from the prevalence of nocturia patients from the menopause clinic mentioned earlier. One hundred and sixty-seven volunteers with a diagnosis of nocturia signed the consent form and were included in analysis. Twelve volunteers were excluded because they did not respond to any questions on the questionnaires. Therefore, 155 respondents were included in the analysis. The majority of the questionnaire respondents were male (80.65%) and at least 1 had an underlying disease requiring long-term follow-up by a physician (86.45%). The median urination at night was 3 time per night and the median first urination after retiring to bed was 3 hours. A summary of patient characteristics are shown in Table 1.

Reliability

Cronbach's alpha coefficient for the N-QOL (Q1-Q12) and two subscale scores showed good reliability for internal consistency (greater than 0.7) and overall NQoL and sleep/energy and bother/concern subscale scores, (0.884, 0.797, and 0.857 respectively). The correlation coefficients between overall NQoL and two subscale scores for sleep/energy showed a high correlation for sleep/energy and bother/concern subscale scores (r: 0.894 and 0.931 respectively). Supplementary Table 16 shows the correlation coefficient between each item and each total score)

Impact of nocturia on quality of life (QoL)

(Responses to the study questionnaire are summarized in Table 2.)

Table 1. Patient characteristics (N=155).

Variable	n (%)
Male gender	125 (80.65)
At least one chronic underlying disease	134 (86.45)
Benign prostatic hyperplasia or prostate cancer	65 (41.94)
Urination at night	
Mean n (SD)	2.99 ±1.39
Median n (IQR)	3 (2, 4)
Average frequency of urination per night	
1	21 (13.55)
2	36 (23.23)
3	50 (32.26)
4	30 (19.35)
5 or more	18 (11.61)
Urinary incontinence	20 (12.90)
The first urination after bed (n=153)[a]	
Mean (SD)	178.43± 97.62
Median (IQR)	180 (120, 240)
Min-Max	0, 10
First urination after bed (n=153) a	
Within 1 hr	20 (13.07)
More than 1 hour but within 2 hours	41 (26.80)
More than 2 hours but within 3 hours	42 (27.45)
More than 3 hours but within 4 hours	30 (19.61)
More than 4 hours but within 5 hours	9 (5.88)
More than 6 hours	11 (7.19)

[a]Two volunteers did not answer the question.

Table 2. Response to the study questionnaire

Question	Answer (score given)	n (%)	Median (IQR)	Correlation coefficient between row/column variables				
				Overall QoL(Q13)	NQoL overall score	Total Q1-11	Subscale scores	
							Sleep/ energy	Bother/ concern
Q1: Has made it difficult for me to concentrate the next day	every day (4) most day (3) some days (2) rarely (1) never (0)	4 (2.63) 7 (4.61) 20 (13.16) 36 (23.68) 85 (55.92)	0 (0, 1)					
Q2: Has made me feel generally low in energy the next day	every day (4) most day (3) some days (2) rarely (1) never (0)	3 (1.96) 4 (2.61) 43 (28.10) 34 (22.22) 69 (45.10)	1 (0, 2)					
Q3: Has required me to nap during the day	every day (4) most day (3) some days (2) rarely (1) never (0)	21 (13.64) 17 (11.04) 48 (31.17) 25 (16.23) 43 (27.92)	2 (0, 2)					
Q4: Has made me less productive the next day	Every day (4) Most day (3) Some days (2) Rarely (1) Never (0)	2 (1.30) 3 (1.95) 18 (11.69) 50 (32.47) 81 (52.60)	0 (0, 1)					
Q5: Has caused me to participate less in activities I enjoy	Extremely (4) Quite a bit (3) Moderately (2) a Little bit (1) Not at all (0)	2 (1.32) 4 (2.63) 11 (7.24) 56 (36.84) 79 (51.97)	0 (0, 1)					
Q6: Has caused me to be careful about when or how much I drink	All the time (4) Most of the time (3) Some of the time (2) Rarely (1) Never (0)	1 (0.67) 2 (1.33) 8 (5.33) 9 (6.00) 130 (86.67)	0 (0, 0)					
Q7: Has made it difficult for me to get enough sleep at night	Every night (4) Most nights (3) Some nights (2) Rarely (1) Never (0)	1 (0.67) 2 (1.33) 8 (5.33) 9 (6.00) 130 (86.67)	0 (0, 2)					

Table 2. Response to the study questionnaire

Question	Answer (score given)	n (%)	Median (IQR)	Correlation coefficient between row/column variables				
				Overall QoL(Q13)	NQoL overall score	Total Q1-11	Subscale scores	
							Sleep/ energy	Bother/ concern
Q8: Concerned that I am disturbing others in the house because of having to get up at night to urinate	Extremely (4) Quite a bit (3) Moderately (2) A little bit (1) Not at all (0)	3 (1.96) 5 (3.27) 6 (3.92) 37 (24.18) 102 (66.67)	0 (0, 1)					
Q9: Preoccupied about having to get up at night to urinate.	All the time (4) Most of the time (3) Some of the time (2) Rarely (1) Never (0)	3 (1.94) 12 (7.74) 17 (10.97) 43 (27.74) 80 (51.61)	0 (0, 1)					
Q10: Worried that this condition will get worse in the future	Extremely (4) Quite a bit (3) Moderately (2) A little bit (1) Not at all (0)	5 (3.23) 15 (9.68) 18 (11.61) 51 (32.90) 66 (42.58)	0 (0, 1)					
Q11: Worried that there is no effective treatment for this condition (having to get up at night to urinate)	Extremely (4) Quite a bit (3) Moderately (2) A little bit (1) Not at all (0)	5 (3.23) 9 (5.81) 15 (9.68) 44 (28.39) 82 (52.90)	0 (0, 1)					
Q12: Overall, how inconvenient having to get up at night to urinate has been during the past two weeks?	Extremely (4) Quite a bit (3) Moderately (2) A little bit (1) Not at all (0) very well (0)	6 (3.92) 11 (7.19) 18 (11.76) 72 (47.06) 46 (30.07) 7 (4.58)	0 (0, 1) 2 (1,2)	NA				
Q13: Overall, how is your overall quality of life?	Well (1) Moderately well (2) Fair (3) Poor (4)	61 (39.87) 76 (49.67) 8 (5.23) 1 (0.65)						
NQoL overall score Q1-Q12a	Min, Max: 0, 44	9.99±7.72	9 (4, 14)	0.452	NA			
Total score of Q1-11a		8.93 ±7.05	8 (4, 12)	0.445	0.995	NA		
Subscale scores for Sleep/Energya		5.70± 4.19	6 (2, 9)	0.416	0.894	0.910	NA	
Subscale scores for Bother/Concerna		5.52±5.08	4 (1, 8)	0.423	0.931	0.913	0.684	NA

[a]143 patients who completed all 13 questions were included in analysis

1. Concentration the next day

Around half of the patients answered that getting up at night to urinate had never made it difficult to concentrate (55.92%). An impact of nocturia on concentration the next day on some days was reported by approximately a quarter of the patients (23.68%). Only 4 of the patients (2.63%) reported that the nocturia had impact on their concentration every day. There was no significant relationship between the frequency of urination per night, urinary incontinence, or the first urination after retiring to bed or patient characteristics and the level of impact on concentration the next day.

2. Low in energy the following day

The response from nearly half (45.10%) the patients with nocturia was that nocturia had never made them feel generally low in energy the next day around a quarter of the patients reported that having to get up at night to urinate rarely had any impact (22.22%) on energy levels and on some days (28.10%). Only 2% of patients reported that nocturia made them low energy every day. The univariate analysis showed a statistically significant relationship between low energy levels the next day and the frequency of urination per night ($p < 0.001$), urinary incontinence at night ($p = 0.045$), and the first urination within 2 hours of retiring ($p = 0.001$). The multivariate analysis found that higher frequency of urination per night (multivariate $p = 0.004$, β Coefficient 0.183) and first urination within 2 hours of retiring (multivariate $p = 0.036$, β coefficient 0.501) were significant parameters in relation to greater impact on low energy the next day.

3. Sleep during the day

Nearly one third of patients (31.17%) required a nap during the day on some days due to nocturia, followed numerically by never required, rarely required, required every day and most days, respectively. Increasing frequency of urination per night has a significant relationship to a greater napping requirement according to both the univariate and multivariate analysis (multivariate $p = 0.001$, β coefficient 0.267). However, there was no relationship between urinary incontinence at night, the time to first urination of retiring and patient characteristics.

4. Productiveness

Approximately half patients (52.60%) answered that nocturia had never made them less productive the next day, followed by rarely (32.47%) and some days (11.69%). A few patients reported that nocturia impacted on productiveness every day (1.30%) or most days (1.95%). Both the univariate and multivariate analysis showed that earlier first urination after retirement was the only significant parameter predicting a level of impact on productiveness the next day (multivariate $p = 0.030$ and β coefficient -0.015). It was found that one third (33.33%) of the patients reporting a first urination within 2 hours of retiring reported that the nocturia had never had any impact on their productiveness the next day while just over half of patients (56.25%) reporting first urination within 2 hours of retiring or later answered that the nocturia had never impacted on their productiveness the next day.

5. Physical activities

Around half of patients (51.97%) reported that the nocturia had never caused them to participate less in activities they enjoy, followed by a small impact (36.84%). Less than 10% of patients reported that nocturia had caused them to participate less in activities they enjoy moderately (7.24%), quite a bit (2.63%), and extremely (1.32%). There was no significant relationship found between frequency of urination per night, urinary incontinence, or the first urination after retiring for the night or patient characteristics and levels of participation in activities they enjoy the following day.

6. Fluid restriction

Most of the patients (86.67%) reported that the nocturia had never caused them to be careful about when or how much they drank. Very few patients reported that nocturia caused them to restrict fluid intake some of the time (5.33%) or most of the time (1.33%). There was no significant relationship found between frequency of urination per night, urinary incontinence, or the first urination after retiring to bed or the patient characteristics and impact on level of fluid restriction.

7. Inadequate sleep at night

Most of the patients (86.67%) reported that the nocturia had never resulted in insufficient

sleep. Very few patients reported that nocturia caused them to have inadequate sleep at night some of the time (5.33%) or most of the time (1.33%). The univariate analysis showed that a statistically significant relationship exists between the frequency of urination per night ($p < 0.001$), urinary incontinence at night ($p = 0.007$), and the first urination within 2 hours of retiring ($p = 0.003$) and sleep disturbance. The multivariate analysis found that a higher frequency of urination per night (multivariate $p < 0.001$, β Coefficient 0.272) was a significant parameter in related to more impact on inadequate sleep at night.

8. Disturbance of others

Two thirds of the nocturia patients (66.67%) answered that nocturia had never caused disturbance to others. Around a quarter of the patients reported that having to get up at night to urinate caused little disturbance to others (24.18%). Only 2% of patients reported that nocturia had caused extreme disturbance to others. The univariate analysis showed a statistically significant relationship exists between frequency of urination per night ($p = 0.006$), urinary incontinence at night ($p = 0.042$), and the first urination within 2 hours of retiring ($p = 0.027$) and disturbance of others. The multivariate analysis found that urinary incontinence (multivariate $p = 0.034$, β Coefficient 0.453) and first urination within 2 hours of retiring (multivariate $p = 0.009$, β coefficient 0.509) was a significant parameter in relation to more impact on the disturbance of others.

9. Worrying about the effective treatment

Approximately half patients (52.90%) answered that nocturia had never made them worry about the efficacy of treatment, followed by a little bit (28.39%) and moderately (9.68%). Less than 10% of patients reported that nocturia had caused them to worry about the efficacy of treatment quite a bit (5.81%), and extremely (3.23%). The univariate analysis showed that a statistically significant relationship exists between the frequency of urination per night ($p < 0.001$), urinary incontinence at night ($p = 0.005$), and the first urination within 2 hours of retiring ($p = 0.002$) and level of worrying over treatment options. The multivariate analysis found that higher frequency of urination per night (multivariate $p = 0.004$, β coefficient 0.135), urinary incontinence (multivariate $p = 0.016$, β coefficient 0.590) and first urination within 2 hours of retiring (multivariate $p = 0.027$, β coefficient 0.541) was a significant parameter related to a greater impact of worrying about effective treatment.

10. Inconvenience of getting up at night to urinate

Around half of the nocturia patients (47.06%) experience a minor level of inconvenience due to nocturia, followed by never inconvenient (30.07%). About 10% of patients reported that nocturia had inconvenienced them, quite a bit (7.19%), and extremely (3.92%). The univariate analysis showed a statistically significant relationship exists between frequency of urination per night ($p < 0.001$), and urinary incontinence ($p = 0.001$) and overall inconvenience. The multivariate analysis found that higher frequency of urination per night (multivariate $p = 0.001$, β Coefficient 0.188) and urinary incontinence (multivariate $p < 0.001$, β coefficient 0.891) were significant as regards relationship to greater inconvenience to get up from nocturia while there was no relationship between the first urination after retiring and the patient characteristics.

11. Overall quality of life (Q13)

Approximately half of the patients (49.67%) answered that despite the nocturia they had a moderately good quality of life, followed numerically by good (28.39%), fair (5.23), very good (4.58%). Only one patient (0.65%) reported that the nocturia impacted poorly on their quality of life. Increasing frequency of urination per night has a significant relationship with overall quality of life as shown by both the univariate and multivariate analysis (multivariate $p = 0.002$, β coefficient 0.120) while there was no relationship between having urinary incontinence at night, the time of first urination after bed and the patient characteristics.

12. N-QoL overall score and total score of Q1-Q11

One hundred and forty-three patients who completed all 13 questions were included in the analysis. Mean N-QoL overall score (Q1-Q12) was 9.99, with an SD of 7.72., and the highest score was 44. Mean N-QoL overall score was 9.99, with an SD of 7.72., and the highest score was 44.

Table 3. Linear relationship between NQoL overall scores (Q1-Q12)/total scores of Q1-Q11 and overall QoL (Q13).

Variable	n	NQoL score (%)					Univariate linear regression p-value	Beta Coef.
		Very poor (4)	Poor (3)	Fair (2)	Good (1)	Very good (0)		
NQoL overall score	143						< 0.001	0.041
Mean (SD)		44	16.85 (8.89)	11.35 (7.17)	7.68 (6.07)	2.86 (2.85)		
Median (IQR)		44 (44, 44)	17 (5, 26)	10.5 (6, 16)	7 (3 ,10)	2 (0, 6)		
Total score of Q1-11	143						< 0.001	0.044
Mean (SD)		40	14.86 (7.82)	10.13 (6.51)	6.98 (5.66)	2 (2.77)		
Median (IQR)		40 (40, 40)	16 (4, 22)	9.5 (5, 14.5)	7 (2.5, 9)	0 (0, 4)		

Alike total score of Q1-11, mean total score of Q1-11 was 8.93, with an SD of 7.05. Univariate liner regression found that NQoL overall score (univariate linear regression $p < 0.001$, β coefficient 0.041) and total score of Q1-11 ((univariate linear regression $p < 0.001$, β coefficient 0.044) showed that a significant linear relationship exists between NQoL overall score (Q1-Q12)/ total scores of Q1-11 and overall QoL (Q13). The linear relationships between NQoL overall scores (Q1-Q12)/total scores of Q1-Q11 and overall QoL (Q13) are shown in Table 3.

Increasing frequency of urination per night has a significant relationship with the NQOL overall score (Q1-Q12) including total score of Q1-11) in both the univariate and multivariate analysis (Multivariate $p = 0.002$, β coefficient 1.54 and 1.527, respectively). The univariate analysis shows a statistically significant relationship exists between the first urination within 2 hours of retiring ($p = 0.002$) and the NQoL overall score (Q1-Q12) including total score of Q1-11. There was no significant relationship found between urinary incontinence or patient characteristics and the NQoL overall score (Q1-Q12) including total score from Q1-11.

Discussion

Nocturia is defined as the need to void ≥1 time during the sleeping period of the night. Clinically relevant nocturia (≥ 2 voids per night) affects 28-62% for those aged 70-80 years.[14] Choi et al. found that sleep quality mediated the association between nocturia and health-related quality of life (HRQOL).[15]

Nocturia is associated with multiple comorbidities.[16] Increased nocturia severity is related to decreased quality of life, higher age, urinary tract symptom scores, nocturnal urine volume, evening fluid consumption and beta-blocker medication rates. Furthermore, increased nocturia severity has also been found to be associated with higher nocturnal polyuria, global polyuria and reduced bladder capacity rates.[17] Worryingly, Pesonen et al. found that nocturia is potentially associated with an approximately 1.3-fold increased risk of death.[18]

Torimoto et al. reported nocturia has close relationships with the first uninterrupted sleep period (FUSP) and the number of wake-ups and can result in decreased daytime quality of life in young Japanese people.[19] Zeng et al. reported that nocturia patients presented as having a significantly reduced quality of life, reduced work productivity and increased utilization of healthcare resources when compared with OAB and/or BPH.[20]

Theerawirojana et al. reported a correlation between bladder capacity and lower urinary tract symptoms after renal transplantation and concluded that nocturia and nocturnal polyuria are characteristics of lower urinary tract function after renal transplantation, and are probably associated with long term anuria during hemodialysis and small bladder capacity. Quality of life was not impacted by lower urinary tract symptoms evidenced by a low symptom score for most patients.[21]

From our study, most patients had moderate to good quality of life with some inconvenience from nocturia, and the impact required them to nap during the day on some days. Increasing frequency of urination per nights was significantly related to low energy levels the next day, greater napping requirements during the day, inadequate sleep at night, worry over treatment options, overall inconvenience, and overall quality of life as shown by the NQoL overall score (Q1-Q12)

and total score of Q1-11.

Our analysis shows a statistically significant relationship exists between urinary incontinence and disturbance of others, preoccupation with waking at night, and worry over the condition worsening. Furthermore, we also found that a time to first urination after bed of less than 2 hours was significantly related to low energy levels and lower productivity the next day, disturbing others in the house, and worry that there is no effective treatment for nocturia. These were significantly related to NQoL overall score (Q1-Q12) and total score of Q1-11.

On the other hand, there was no significant relationship found between the frequency of urination per night, urinary incontinence, the first urination after retiring for the night, patient characteristics, fluid restriction, levels of concentration or participation in activities they enjoy the next day.

Our study demonstrated that nocturia patients report a significant reduction in quality of life, and decreased sleep quality. Nocturia was reported as negatively affecting patient concentration and activity, and there is clear impact on the reduction in energy levels necessitating a greater need for napping during the day from sleep deprivation and worry about treatment options including overall quality of life.

Conclusion

We found that nocturia patients experienced a significant reduction as regards quality of life and a decrease in sleep quality due to their nocturia. To improve the overall quality of life of these patients, clinicians need to focus on reducing the frequency of nighttime urination and delaying the time of first urination after retiring to bed.

Conflict of Interest

The authors declare no conflict of interest.

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Original Article

One-shot dilation versus metallic dilation technique for access in percutaneous nephrolithotomy: comparison of efficacy, access time and fluoroscopic time

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Keywords: Percutaneous nephrolithotomy, one-shot dilation, telescopic metal dilatation, efficacy, access time, fluoroscopic time

Abstract

Objective: The aim of this study was to compare the efficacy, access tract dilation time and fluoroscopic time between the one-shot dilation technique and telescopic metal dilatation technique in patients undergoing percutaneous nephrolithotomy in Nakornping Hospital.

Materials and Methods: Sixty-six patients who underwent percutaneous nephrolithotomy from January 2020 to July 2021 were included in the study and they were randomly divided into two groups. In group 1 (32 patients), telescopic metal dilation was used, in group 2 (33 patients), the one-shot technique was used. Success rates of dilation, access tract dilation time and fluoroscopic time were evaluated.

Results: The success rate of dilation was 100% in both groups. The access tract dilation time was 835.63 ± 309.68 seconds in group 1 and 569.42 ± 314.75 seconds in group 2 ($p = 0.001$). The fluoroscopic time was 48.16 ± 22.16 seconds in group 1 and 41.97 ± 23.99 seconds in group 2 ($p = 0.29$). The access tract dilation time of the one-shot dilation technique was statistically significantly shorter than that in the telescopic metal dilatation group. The mean fluoroscopic time of the one-shot dilation technique was shorter than in telescopic metal dilatation but was not statistically significant.

Conclusion: One-shot dilation technique is as effective as telescopic metal dilatation, with a significant reduction in access tract dilation time.

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Introduction

Percutaneous nephrolithotomy (PCNL) is an effective and safe method of management of large renal calculi.[1,2] One of the most important steps in PCNL is access tract creation. Currently, access tract creation can occur by three techniques: Alken telescopic metal dilation, Amplatz serial fascial dilation and high-pressure balloon dilation. Telescopic metal dilation, and Amplatz fascial dilation are serial dilation methods. The disadvantages of these methods are that they are more time-consuming and involve longer exposure time to x-ray.[3,4] Balloon dilation is the most accepted option and perceived as being the safest method but its high cost limits its routine use.[5,6] The recognized link between exposure to x-rays and some risk of cancer necessitates limitation of exposure during the procedures.[7] To reduce the x-ray exposure time the one-shot dilation technique was introduced. This technique consists of single tract dilation of the access tract with a 25-30 Fr Amplatz dilator.[8]

In Nakornping Hospital, urologists have usually used the telescopic metal dilation technique with fluoroscopic guidance for access tract creation in PCNL. Many studies have shown that the one-shot dilation technique is as effective as telescopic metal dilatation and also significantly reduces x-ray exposure during access tract dilation. However, this technique has not been studied in the patients in our hospital. The aim of this study was to evaluate and compare the efficacy between one-shot dilation and telescopic metal dilation techniques in terms of success rate, access time and fluoroscopic time.

Materials and Methods

This randomized controlled trial was approved by the Institutional Ethics Committee of Nakornping Hospital (IRB Number 067/63). The study was conducted at Nakornping Hospital from January 2020 to July 2021. Inclusion criteria included all patients aged over 18 years with renal calculi who had indications for PCNL surgery. Exclusion criteria were patients who were contraindicated for PCNL, patients who refused to participate in the study and patients who required more than one tract access. The sample size was calculated using the n4Studies application to test non-inferiority of two independent means. Sixty-six patients were enrolled onto this study. A single urologist carried out all operations. Patients were divided by permuted-block randomization into two groups; group 1 telescopic metal dilation (33 patients) and group 2 one-shot dilation (33 patients). After randomization, information concerning the study was explained to the patients and informed consent forms were signed.

Under general anesthesia the patients were put in the lithotomy position. A 6 Fr ureteral catheter was placed via a cystoscope then patient was turned into the prone position and the puncture was performed using fluoroscopic guidance. A guidewire was inserted into the collecting system. In group 1 the telescopic metal dilation technique was used by insertion of the Alken guide followed by a telescopic dilator between 10 Fr to 30 Fr, then an Amplatz sheath 30 Fr was advanced over the dilator which was then removed, leaving the Amplatz sheath in the collecting system (Figure 1). A nephroscope was inserted and the stone was disintegrated by ultrasonic and pneumatic lithotripsy. A nephrostomy tube was inserted at at the end of operation in all cases. In group 2 the one-shot dilation technique was used by insertion of an 8 Fr fascial dilator first, then a 30 Fr Amplatz dilator was advanced overriding the 8 Fr fascial dilator and an Amplatz sheath 30 Fr was advanced over the dilator (Figure 2). The next steps of the procedure were followed as in group 1.

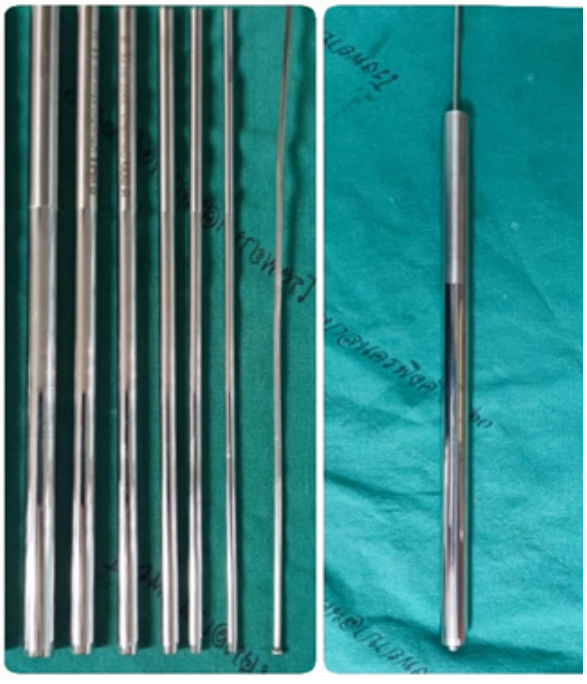

Figure 1. Telescopic metal dilator

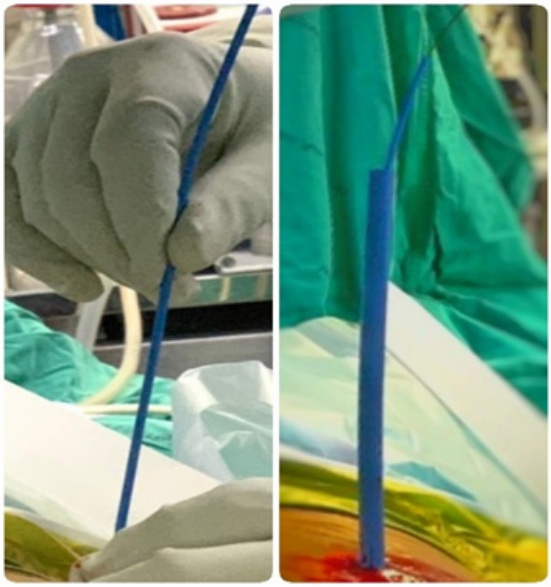

Figure 2. 8 Fr Fascial dilator and 30 Fr Amplatz dilator

Statistical analysis

Results are reported as mean ± standard deviation for quantitative variables. To compare the outcome of telescopic metal dilation and one-shot dilation technique, the data were analyzed statistically using Fisher's exact probability test for categorized data and Student-T test for numerical data. All data were analyzed with software STATA version 14.1. The access time in this study was defined as the duration recorded in seconds captured from renal puncture to successful placing of the nephroscope in the collecting system. The fluoroscopic time was total fluoroscopic time, defined by the number of seconds of radiation exposure that had elapsed, based on the dose summary of the fluoroscopy machine at the end of each procedure. The rate of stone-free status was defined by no stone fragments larger than 5 mm from being found from examination of plain film KUB in the period 48-72 hours postoperative. A p-value of less than 0.05 was considered statistically significant.

Results

A total of 66 patients underwent PCNL and were randomly divided into two groups according to the technique of dilation: group 1 telescopic metal dilation (33 patients) and group 2 one-shot dilation (33 patients). One patient in group 1 (telescopic metal dilation) was excluded due to requiring more than one tract access leaving 32 patients in this group. There were no significant differences in demographic data between the groups as shown in Table 1. Mean age of patients was 57.13 ± 7.15 years in group 1 (telescopic metal dilation) and 58.21 ±10.89 years in group 2 (one-shot dilation). The imaging modality used to define stone characteristics was intravenous pyelography in normal kidney function and retrograde pyelography in renal insufficiency. Stones were graded into grade 1 to 4 according to the Guy stone score system.[9] Mean stone size was 39.97 ± 14.41 mm in group 1 (telescopic metal dilation) and 46.21 ± 17.22 mm in group 2 (one-shot dilation). No mortality occurred in this study. Complications were reported as grades 1-5 in accordance with the modified Clavien Classification.[10] One patient in group 1 (3.13%) had hydrothorax requiring intercostal drainage in the post-operative period. In group 2 one patient had hydrothorax requiring intercostal drainage (3.03%) and another had respiratory failure (3.03%) requiring ventilation in the post-operative period due to heart failure.

The success rate was 100% in both groups. The mean access time in group 1 was 835.63 ± 309.68 seconds and 569.42 ± 314.75 seconds in group 2 (p = 0.001). The fluoroscopic time was 48.16 ± 22.16 seconds in group 1 and 41.97 ± 23.99 seconds in group 2 (p = 0.29). The access tract dilation time of the one-shot dilation technique was significantly shorter than telescopic metal dilatation. The mean fluoroscopic time of the one-shot dilation technique was shorter than in telescopic metal dilatation but did not reach statistical significance. The others clinical outcomes are shown in Table 2. There was no significant difference in operative time, decrease in hemoglobin, transfusion rate, complication and stone clearance.

Discussion

Several studies have been conducted to compare one-shot dilation and telescopic metal dilation technique in PCNL. The majority have reported that one-shot dilation technique is effective and can significantly reduce the access time and x-ray exposure time.[11-17] A recent systematic review and meta-analysis of one-shot dilation versus serial dilation technique for access in PCNL has reported a shorter access time in the one-shot dilation group than in the serial dilation group. Seven randomized controlled trials showed that one-shot dilation significantly decreased fluoroscopic time compared with serial dilation

Table 1. Baseline characteristics of the one-shot dilation and the telescopic metal dilation groups

Variable	Telescopic metal dilation n=32	One shot dilation n=33	P-value
Sex			0.21
Male	17 (53.12%)	23 (69.7%)	
Female	15 (46.88%)	10 (30.3%)	
Age (years), mean±SD	57.13 ± 7.15	58.21 ± 10.89	0.64
BMI (kg/m^2), mean±SD	22.78 ± 4.03	23.52 ± 3.30	0.41
Side			0.14
Left	14 (43.75%)	21 (63.64%)	
Right	18 (56.25%)	12 (36.36%)	
Stone size (mm), mean±SD	39.97 ± 14.41	46.21 ± 17.22	0.12
Guy stone score*			0.25
Grade 1	11 (34.38%)	8 (24.24%)	
Grade 2	3 (9.38%)	0 (0%)	
Grade 3	3 (9.38%)	4 (12.12%)	
Grade 4	15 (46.88%)	21 (63.64%)	
History of previous surgery			1.0
Yes	4 (12.5%)	5 (15.15%)	
No	28 (87.5%)	28 (84.84%)	
Puncture site			0.10
Upper pole, supracostal	13 (40.62%)	8 (24.24%)	
Upper pole, subcostal	17 (53.12%)	17 (51.52%)	
Lower pole	1 (3.12%)	7 (21.21%)	
Middle pole	1 (3.12%)	1 (3.03%)	

*Guy stone score comprises 4 grades: grade1, solitary stone in mid/lower pole or solitary stone in the pelvis with simple anatomy; grade 2, solitary stone in upper pole or multiple stones in a patient with simple anatomy or a solitary stone in a patient with abnormal anatomy; grade 3, multiple stones in a patient with abnormal anatomy or stones in a caliceal diverticulum or partial staghorn calculus; grade 4, staghorn calculus[9]

Table 2. Baseline characteristics of the one-shot dilation and the telescopic metal dilation groups

Variable	**Telescopic metal dilation n=32**	**One shot dilation n=33**	**P-value**
Success rate (%)	100	100	1.0
Access time (seconds), mean±SD	835.63 ± 309.68	569.42 ± 314.75	0.001
Fluoroscopic time (seconds), mean±SD	48.16 ± 22.16	41.97 ± 23.99	0.29
Operative time (minutes), mean±SD	59.59 ± 27.0	58.36 ± 28.91	0.86
Decrease in Hb (g/dL), mean±SD	1.45 ± 1.19	1.35 ± 0.87	0.71
Transfusion rate, n (%)	3 (9.38)	0 (0)	0.11
Complications*, n (%)			0.12
Grade 0	17 (53.12)	25 (75.76%)	
Grade 1	2 (6.25)	2 (6.06%)	
Grade 2	12 (37.5)	4 (12.12%)	
Grade 3	1 (3.12)	1 (3.03%)	
Grade 4	0 (0)	1 (3.03%)	
Grade 5	0 (0)	0 (0%)	
Stone free, n (%)	18 (56.25)	16 (48.48)	0.62

*In accordance with the modified Clavien classification: grade 1, any deviation from the normal postoperative course without the need for pharmacological treatment or surgical intervention also includes wound infections opened at the bedside; grade 2, complications requiring pharmacological treatment with drugs, blood transfusions and total parenteral nutrition; grade 3, complications requiring surgical, endoscopic or radiological intervention; grade 4, life-threatening complications requiring ICU management; grade 5, death[10]

and none of the six randomized controlled trials found significant differences in success rate and stone-free rate between one-shot dilation and serial dilation techniques.[18]

In this study, we evaluated the success rate of access tract dilation as the primary outcome and the access time, fluoroscopic time as the secondary outcome. The success rate of dilation was 100% in both groups and the access time of the one-shot dilation group was significantly shorter than in the telescopic metal dilatation group. The mean fluoroscopic time of the one-shot dilation technique was shorter than in telescopic metal dilatation but not statistically significant. Our results showed the same trends in success rate and access time as reported by other studies.

Trisakul Y reported a fluoroscopic time ranging from 60-130 seconds (mean 90 seconds) in 60 patients with standard PCNL with fascial dilation technique, obviously longer than our results.[19] Amirhassani et al. reported a mean fluoroscopic time in telescopic metal dilation of 48.4 ± 15 seconds and 41.2 ± 17 seconds in one-shot dilation, timings very close to our results. However, their study had a larger sample size and there was a significant difference in the mean fluoroscopic time between two groups ($p = 0.03$).[14] These findings warrant further investigation with a larger sample size to examine this correlation further. The overall stone free rate in this study was 52.3%. Comparing this with other studies in Thailand, a 67% stone free rate was reported in 2020 by Trisakul Y in standard PCNL with fascial dilation technique.[19] In standard PCNL with metallic dilation, Amornratananont et al. reported a 54.8% stone free rate in 2019[20] and another study was reported by Ahmadmusa N in 2020 with a 74.6% stone free rate.[21]

In our experience the one-shot dilation technique is simple, easy to carry out and does not require any extraordinary equipment. It can decrease access time and fluoroscopic time thus decreasing the risk of x-ray exposure to both the surgical team and patient. Minimizing x-ray exposure during percutaneous renal access is challenging. To date many techniques other than the one-shot dilation technique have been developed to decrease x-ray exposure[22]. Some techniques, such as a specific protocol for fluoroscope use and ultrasound guided access, could potentially be initiated in our hospital in the future.

There are some limitations in this study. The first is the limited number of patients due to it being conducted in a single-center. A large multicenter randomized controlled trial will definitely increase the information with regard to these initially very promising findings. Second, from the peer review there are some variations in the carrying out of the one-shot dilation technique in some studies. A standardization of approach could be a useful recommendation in the future. Finally, the definitions of access time and fluoroscopic or x-ray exposure time varied in the different studies which may affect the results.

Conclusion

The results of this study show that the one-shot dilation technique is as safe and effective as the telescopic metal dilatation method with a significant reduction in access tract dilation time. The one-shot dilation technique may be beneficial in reducing fluoroscopic time.

Conflict of Interest

The author declares no conflict of interest.

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Review Article

Innovation and new technology in ureteral stents

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Keywords:
Ureteral stent, stent-related symptoms, innovation

Abstract

Ureteral stent insertion is a procedure performed extensively by all urologists. Nevertheless, stent-related symptoms and stent encrustation are still common complications pushing the innovation and development of novel ureteral stents. Developments are focussing on three significant aspects: material, design, and removal technique. Various materials including silicone, polymers, and metals are frequently utilized, with or without an additional coating. The use of biodegradable materials is looking promising but these is a lack of proven clinical trials in association with this in humans. The new designs focus on the reduction of stent-related symptoms through the modification of the bladder end. The new stent removal techniques with extraction strings or novel magnetic end may exclude subsequent cystoscopic procedures. Finally, utilization of a ureteral stent tracker application helps in reminding both physicians and patients to remove the stent at the appropriate time.

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Introduction

Ureteral stent insertion is one of the most commonly performed endourological procedures. Its indication includes ureteral obstruction, the promotion of healing of ureteral anastomosis, and placement following stone management.[1] Even though its benefits are well-established, there are some drawbacks associated with its use. Stent-related symptoms, stent encrustation, and urinary tract infection significantly impact on patient quality of life, leading to the need to explore the development of a new ideal ureteral stent with optimal effectiveness but minimal side effects.

History of the Ureteral Stent

The endoscopic technique of ureter cannulation was initiated by Brown J in 1893. Using the Brenner-Leiter cystoscope with a working channel, he cannulated both ureters to enable the separate drainage and collection of urine.[2] For the earliest experiments with ureteral stent development, polythene tubes were used in an animal study but the results were not promising. The successful breakthrough came in 1952 when Tulloch S inserted a polythene tube into the right ureter and a T-tube into the left ureter of a patient with bilateral ureteral injury after a hysterectomy.[3] In 1967, Zimskind PD was the

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first to report a cystoscopic insertion of a silicone ureteral stent in 13 patients. In 1976, Gibbons et al. redesigned the ureteral stent by adding wings and flanges to prevent stent migration. They also added a radiopaque tip to enable the checking of the position of the stent under fluoroscopy (Figure 1).[5] Finally, in 1978, Finney et al. published their work describing the original double J stent design (Figure 2). Construction of both ends into a J-shape coil prevents stent migra-tion without compromising the overall shape and diameter.[6] However, this original stent design was not suitable for some specific situations for example extrinsic malignant ureteral obstruction. However, in 1992, Wallstent, a self-expandable metallic stent, was developed to overcome this issue.[7] The double J design has been a milestone in the development of the modern ureteral stent but even so innovation and technology are constantly being incorporated to improve the stent function, along with utilization of various synthetic polymers and metallic materials.

Ideal Stent

According to Finney RP,[6] the ideal ureteral stent should have the following properties:

1. A primary composition of silicone due to its softness, flexibility, and resistance to encrustation properties
2. Radio-opaque
3. Uniformed diameter without barb or flanges
4. Easy insertion from either antegrade or retrograde approach
5. Prevention of migration
6. Reusable ability by autoclaving

Although some of these ideal properties are invalid nowadays, they still may be summarized into three aspects: stent materials, stent design, and stent removal, on which this review aims to focus.

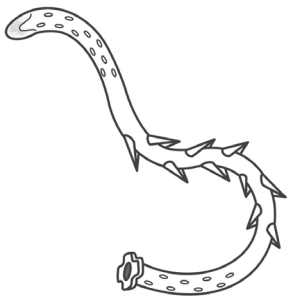

Figure 1. Gibbons ureteral stent by Gibbons RP (Illustration by Pea Poppan, MD)

Stent-related Symptoms

Unrelated to any medical indications, the use of the ureteral stent inevitably leads to stent-related symptoms (SRS). Researchers have raised several hypotheses to explain the etiology of SRS. They include: 1) irritation of the bladder mucosa by the stent's distal end; 2) stent migration during daily activities; and 3) urine reflux into the kidney resulting in increased intrarenal pressure.[8] To evaluate SRS objectively, Joshi et al. have proposed the Ureteral Stent Symptom Questionnaire (USSQ) which consists of six aspects: urinary symptoms, body pain, general health, work performance, sexual matters, and additional problems.[9] A later study on SRS revealed that stent placement affected patient daily life in 80% of cases, increased analgesic usage in 70% due to pain in the flank, suprapubic, or penis, and caused sexual dysfunction in 32% of patients.[10] Another study from the same group reported that 80% of patients with a ureteral stent had at least one lower urinary tract symptom according to the International Prostate Symptom Score (IPSS).[11]

To minimize SRS, innovation of ideal stent and medical treatment by either alpha-1 blockers or antimuscarinic agents have been explored.[12] The American Urological Association and Endourological Society Guidelines 2016 recommended alpha-1 blockers and antimuscarinic agents for reducing SRS.[13] According to a randomized controlled study, a daily dosage of 0.4 mg tamsulosin significantly reduced IPSS irritative and obstructive symptom scores.[14] A meta-analysis by Chen et al. reported that tamsulosin significantly decreased Urinary Symptoms ($p = 0.0001$) and Body Pain ($p = 0.0002$) USSQ

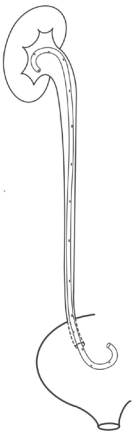

Figure 2. The original double J stent by Finney RP (Illustration by Pea Poppan, MD)

subscores.[15] Another meta-analysis by Wang et al. demonstrated that solifenacin significantly reduced the total USSQ score in comparison to controls (p = 0.005).[16] Moreover, a combination of alpha-1 blocker and antimuscarinic agent could improve an outcome.[17] Recently, more studies have shown that mirabegron and pregabalin may be effective in treating SRS.[18,19]

As a foreign body, the ureteral stent interacts with local tissue and induces inflammation. Bacteria may colonize on the ureteral stent and produce a biofilm, which precipitates stent encrustation.[20,21] Kawahara et al. demonstrated that the degree of encrustation was associated with indwelling time. Indwelling of a stent for less than 6 weeks, 6 to 12 weeks, and more than 12 weeks had encrustation rates of 26.8%, 56.9%, and 75.9%, respectively.[22] Stent encrustation may be associated with difficulty of stent removal. Sometimes, a more advanced endourological technique is necessary, which results in patient morbidities such as pain, ureteral injury, or even urosepsis.

1. Stent Material

The original double J stent designed by Finney RP was made from silicone, which is flexible and has a low order of tissue response. However, silicone has a high frictional coefficient, thus creating difficulty in stent insertion.[6] Later, several materials were explored, including polyethylene, polyurethane, metal, and co-polymers.[23] The development of effective stent materials is still an ongoing process. By integrating different polymers into one stent, better properties are created, and now there are a large variety of polymeric stents available on the market (Table 1).

Additional coatings play an important role in improving the properties of ureteral stents. Hydrogel, a hydrophilic polymer, becomes more slippery when in contact with water. Coating a ureteral stent with hydrogel helps pass a stent through the narrow path of the urinary tract. Coating a stent with ketorolac may reduce pain after stent insertion[24] and coating with antibiotic or metal compounds may reduce bacterial colonization (Table 2).[25,26]

Table 1. Advantages and disadvantages of different polymeric ureteral stent materials

Stent material	Advantages	Disadvantages
Silicone	• Biocompatibility • Encrustation resistance	• High frictional coefficient
Polyurethane	• Good urinary drainage	• High tissue reaction
Ethylene-Vinyl acetate (PercuflexTM, Boston Scientific, Marlborough, MA, United States)	• Coil retention to prevent stent migration • Large internal diameter • Softer at body temperature	• Easy compression
Ethylene/Butylene-Styrene copolymer with added polysiloxane (C-Flex®, Cook Medical, Bloomington, IN, United States)	• Low frictional coefficient • Resistance to biofilm formation and encrustation	
Polyester (Silitek®, Surgitek, Medical Engineering Corporation, Racine, WI, United States)	• Softer bladder end of the stent	• High bacteria adhesion

Table 2. Ureteral stent coatings and their properties

Coating	Properties
Hydrogel	Hydrophilic properties facilitating stent insertion and preventing biofilm formation
Ketorolac	Reduction of pain after stent insertion[24]
Heparin	Prevention of biofilm formation and stent encrustation[27]
Diamond-like carbon	Prevention of biofilm formation and stent encrustation[28]
Silver	Reduction of bacterial colonization[29]
Triclosan	Reduction of bacterial colonization[25]

Figure 3. Resonance® metallic stent (Cook Medical, Bloomington, IN, United States)

Metal is another material used for the construction of a ureteral stent. Compared to other materials, metallic ureteral stents are more rigid and durable, thus more preferable in the setting of malignant ureteral obstruction.[7] Chow et al. compared the Resonance® metallic stent (Cook Medical, Bloomington, IN, United States) (Figure 3) to polymeric stents in 42 patients with malignant ureteral obstruction. They found there was a longer functional duration at 4 months in the Resonance® stent.[30] Another study compared the UVENTA metallic stent (Instrumed Surgical, Mississauga, ON, Canada) with the polymeric stent. The metallic stent demonstrated a better patency and a lower technical failure (Table 3)[31].

Table 3. Advantages and disadvantages of various metallic ureteral stents

Metallic stent	Material	Advantages and disadvantages
Resonance® (Cook Medical, Bloomington, IN, United States)	Cobalt-chromium-nickel-molybdenum alloy (MP35N)	• Resistance to external compression[32] • Longer functional duration in cases of malignant ureteral obstruction[33] • Urine flow either through or around the stent • Lower cost compared to changing polymeric stent every 3 months[34]
UVENTA (Instrumed Surgical, Mississauga, ON, Canada)	Expanded polytetrafluoroethylene (PTFE) between two Niti-D stents (nitinol wire)	• Prevention of stent migration by Niti-D wire • Prevention of urothelial tissue ingrowth by PTFE layer • Fewer side effects due to the segmental stent design • Ability to be left in place for up to two years[31] • Ureteroenteric fistula and ureteroarterial fistula have been reported[35]
Allium URS (Allium Medical, Israel)	Super-Elastic nickel-titanium alloy (Nitinol) covered with co-polymer	• Larger diameter • Prevention of tissue ingrowth and encrustation by the co-polymer layer[36] • Facilitation of stent removal by the intra-vesical anchor
EGIS Urexel (S&G Biotech, Gyeonggi-do, Korea)	Silicone covered metallic stent	• Prevention of urothelial tissue ingrowth by the silicone layer[37]
MemokathTM 051 (Pnn Medical, Kvistgaard, Denmark)	Thermo-expandable nickle-titanium alloy spiral stent	• Themo-expandable capability • Higher stent migration rate compared to UVENTA[38]

Biodegradable ureteral stent (BUS)

The biodegradable ureteral stent (BUS) is a promising development in exploring an ideal stent since it does not necessitate another appointment for stent removal. Thus, BUS theoretically reduced the treatment time burden for all patients, saves medical expense, and avoids the painful experience of stent removal. Initial research demonstrated that gelatin, alginate, and gellan gum BUSs degraded at between 14 and 60 days in artificial urine.[39] In 2014, Zhang et al. invented a BUS made from polyglycolic acid and polyglycolic acid/ polylactic acid coated with barium sulfate. They compared this BUS to

polyurethane stents in 24 beagles and found no difference in inflammatory reaction. The BUS lost its mass by 44.8% at one week, 70.8% at two weeks, 99.1% at three weeks, and 100% at four weeks.[40] Chew et al. developed multiple generations of BUS from uriprene, which dissolved completely within 4 to 10 weeks.[41,42] Publications regarding BUS investigations in humans are still unavailable; however, one multi-center clinical trial began in December 2020.[43] It is envisioned that BUSs will be available in the foreseeable future for all patients, with clarified properties of stable degradable time and minimal tissue reaction.

In addition, a BUS integrated with supercritical CO_2 impregnation has been tested. This technology allows us to impregnate the material used to construct the BUS with chemotherapeutic agents such as paclitaxel, epirubicin, doxorubicin, and gemcitabine. Initial experiments in artificial urine showed a 50% release of the chemotherapeutic agent in the first 4 hours, a rate which stabilized until completion at 72 hours. The release level of the chemotherapeutic agent could inhibit the cell growth of T24 cells, a representative cancer cell line.[44] Implementation of 3D printing for constructing BUS is also under investigation. This method permits us to customize the most suitable stent for each individual in terms of anatomy.[45,46]

2. Stent Design

Design of the ureteral stent plays an important role in SRSs. The bladder end of the stent may irritate the bladder mucosa causing irritative symptoms and local tissue reaction.[8] In addition the larger diameter of the stent may intensify SRSs.[47] Lee et al. compared three ureteral stents with different firmness levels; Endo-Sof® Radiance® (rigid polyurethane with hydrophilic coating, Cook Medical, Bloomington, IN, United States), PolarisTM Loop (thermal polyurethane with hydrophilic coating; Boston Scientific, Marlborough, MA, United States), and PolarisTM Ultra (firm Percuflex plus in the renal pelvis, soft Percuflex in the bladder, Boston Scientific, Marlborough, MA, United States). International Prostate Symptom Score and Visual Analogue Pain Scale (VAS) were statistically significant lower in the PolarisTM Ultra group in comparison to the other two groups ($p = 0.016$ and < 0.001, respectively).[48]

Apart from the conventional J-shape of the bladder end, several new designs have been implemented. The loop-tailed ureteral stent (PolarisTM Loop) replaces the J-end with a smaller loop-tail made from a softer material (Figure 4). Lingeman et al. compared this loop-tail stent to other stents with the original double-J design. They found no difference in the total USSQ scores four days after insertion. Side effects were lower in the loop-tailed stent group but did not reach statistical significance.[49] Yoshida et al. modified the insertion technique of the loop-tailed stent by completely advancing it into the ureter and leaving only a string down into the bladder. When comparing this so-called complete intra-ureteral stent placement (CIU-SP) technique to conventional stent placement, the authors found significantly lower VAS scores at postoperative day 3 and 14 (4.85 versus 9.78, $p = 0.003$, and 3.15 versus 6.20, $p = 0.014$, respectively). In addition, the total analgesic use was also lower in the CIU-SP group (19.23 mg versus 88.54 mg, $p < 0.001$).[50] Finally, Vogt et al. customized their own stent by cutting the bladder end perpendicularly and replacing with a silicone end piece. They found significantly better Urinary Symptoms USSQ subscores at 15 days after insertion compared to the baseline (23.0 ± 7.0 versus 34.4 ± 3.6, $p = 0.0004$). Good urine drainage without dislodgement or calcification was observed during a 6-month period.[51]

Another promising stent design is the suture stent, created by cutting the bladder end perpendicularly and tying the edge with a polypropylene suture. The suture serves as a string in the bladder to facilitate stent removal. The later commercialized versions are known as JFil® and MiniJFil®

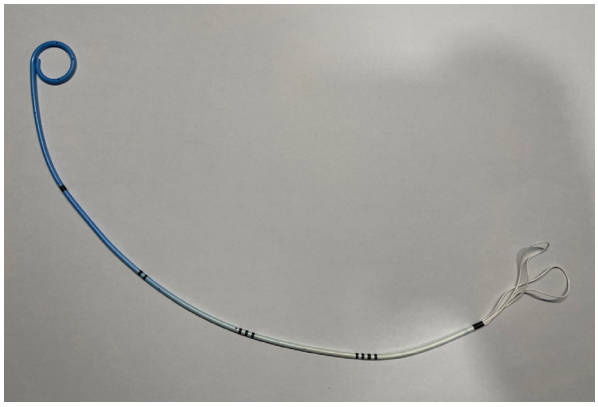

Figure 4. Polaris™ Loop loop-tailed ureteral stent (Boston Scientific, Marlborough, MA, United States)

(Rocamed, Signes, France) (Figure 5). Vogt et al. compared the suture stent to conventional stents and found a reduction in Urinary Symptoms (23.6 ± 5.4 versus 35.2 ± 7.5, $p < 0.001$) and less Body Pain (4.9 ± 3.1 versus 11.0 ± 3.9, $p < 0.001$) USSQ subscores. In addition, the ureteral diameter was found to be enlarged at one month after suture stent insertion, which may, in turn, facilitate ureteral access sheath insertion and stone clearance.[52] A later clinical study in 2016 demonstrated that inserting a MiniJFil® stent a few weeks before extracorporeal shock wave lithotripsy resulted in a stone clearance rate as high as 96.4%.[53]

3. Stent Removal

Modification of the stent removal technique may reduce treatment time, medical expense, and patient discomfort resulting from the removal procedure. Stents with an extraction string and magnetic ureteral stents are the available alternatives.

1. Stents with an extraction string (Figure 6) have a string attached to the bladder end.[54] The string continues to pass out through the urethra meatus for approximately 10 cm and is secured to the surrounding skin to prevent inward migration into the urethra. A systematic review by Sun et al. revealed a lower VAS following the removal of the stent with the extraction string in comparison to the traditional cystoscopic method (mean difference -0.14, $p < 0.00001$). However, the extraction string group encountered a higher incidence of stent dislodgement.[55] This finding showed a strong correlation with another study which also found that dislodgement may occur four times more frequently in females.[56]

2. Magnetic ureteral stent (Magnetic BlackStar, UROTECH GmbH Germany) is a polyurethane stent equipped with a magnet attached to the bladder end. Stent removal requires blind insertion of a Tiemann catheter with a magnetic tip via the urethra into the bladder. After the two magnets connect, the removal then carefully procedes. Rassweiler et al. carried out a study comparing the magnetic ureteral stent to the conventional stent and found a statistically lower VAS during removal (3 versus 4, $p = 0.019$). The subsequent cost analysis also showed a lower stent removal cost of 100 euro per case for the magnetic ureteral stent.[57]

Forgotten ureteral stent

Sometimes patients fail to present for stent removal. The longer the ureteral stent is left inside, the more potentially complicated the removal of the stent. The degree of stent encrustation is directly related to the indwelling time. When severe encrustation occurs, there is the potential for other complications to increase, such as ureteral obstruction, renal failure, urinary tract infection, and stent removal difficulty. Additional procedures, including extracorporeal shockwave lithotripsy, ureteroscopy, or percutaneous nephrolithotomy, may be necessary in such cases. In particular cases, stent fragmentation occurs, thus making stent removal more complicated.[58]

Notification via e-mail or text message is usually employed with limited success. Recently, a reminder through a smartphone-based tracking application has been a new approach. Ulker

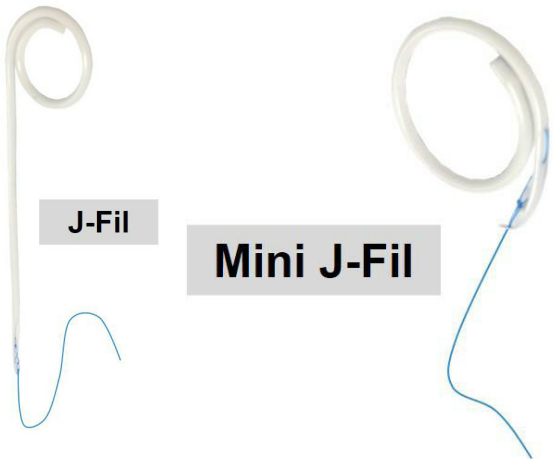

Figure 5. JFil® and MiniJFil® suture stents (Rocamed, Signes, France)

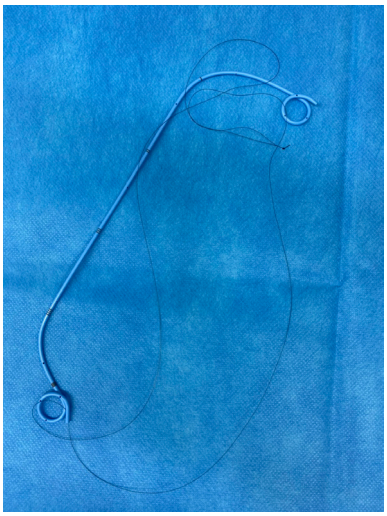

Figure 6. Stent with extraction string

et al. prospectively compared the Ureteral Stent Tracker application (Boston Scientific, Marlborough, MA, United States) to appointment cards. The application resulted in significantly shorter mean overdue times (2.5 ± 0.9 days versus 16.3 ± 5.0 days, p = 0.001) and helped track the stent patients more effectively.[59]

Conclusion

Ureteral stent insertion is fundamental for all urologists. The procedural skills and the knowledge of the equipment are crucial for the best treatment outcomes. The development of new ureteral stents continues enthusiastically, especially in the field of biodegradable ureteral stents. The predictability of degradation and the reliability of the manipulation of the stent are crucial factors in the breakthrough of new forms of this device. Integration of nanotechnology for stent coating and impregnation is another promising way to improve stent properties. Finally, 3-D stent printing, combined with computed tomography, may assist in the creation of a personalized stent for each patient.

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Case Report

A Brunn's cyst as a cause of bladder outlet obstruction: a case report

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Keywords:
Bladder neck obstruction, Brunn's cyst

Abstract

A Brunn's cyst in the proximity of the bladder neck is a rare cause of bladder outlet obstruction. This case study concerns a 45-year-old male presenting with bladder outlet obstruction secondary to a Brunn's cyst. A provisional diagnosis of Brunn's cyst was based on ultrasonography, CT scan and cystoscopic examination which indicated a cystic lesion at the bladder neck. Transurethral resection of the cyst was performed with successful resolution of the obstructive voiding symptoms. The final diagnosis of this case based on the pathology is a Brunn's cyst.

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Introduction

Bladder outlet obstruction in the elderly is frequently a result of enlargement of the prostate gland, but in younger men is usually caused by urethral stricture. Bladder outlet obstruction secondary to a Brunn's cyst is rare and was first described by Israel Franco in 1988.[1] Our objective in this study is to describe the clinical presentation, diagnosis, treatment and outcome of this rare case of bladder outlet obstruction secondary to a Brunn's cyst.

Case Report

A healthy 45-year-old presented with progression of obstructive voiding symptoms over a 3-month period. Symptoms included weakness of the urinary stream, hesitancy, abdominal straining, intermittency and sensation of incomplete emptying. He had not experienced gross hematuria, urinary incontinence, nocturia, urinary tract infection or trauma at the perineum or pelvic organ. He went to a private clinic for an ultrasound of the KUB system which showed a cystic lesion at the bladder neck approximately 1.6 x 1.7 x 2.0 cm with bladder outlet obstruction (Figure 1), a Brunn's cyst was considered a possible diagnosis.

He went to hospital and cystoscopic examination was performed, which showed a normal anterior and prostatic urethra. There was a smooth mucosal bladder neck mass at 7 o'clock adjacent to the prostate gland (Figure 2). Both ureteric orifices presented as normal. Contrast-enhanced computed tomography (CT) of the lower abdomen showed a smoothly thin-walled cystic lesion at the right-side of the bladder neck separating from the ureterovesical junction that was only seen

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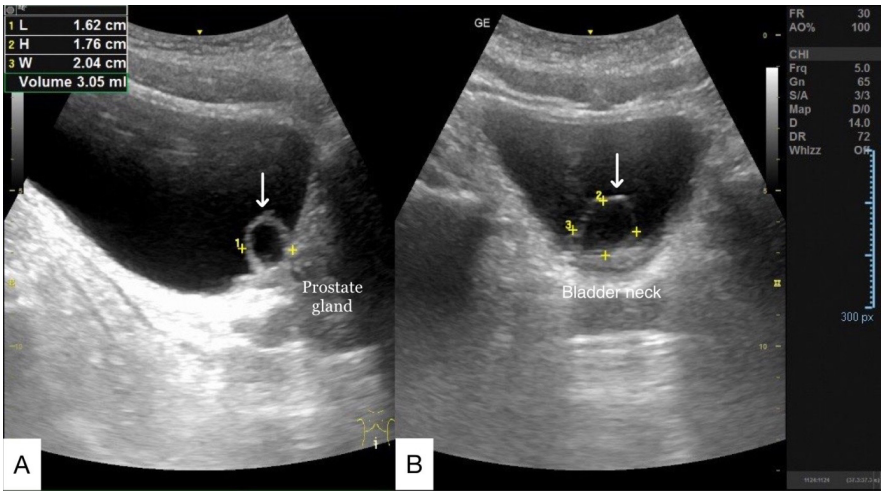

Figure 1. Bladder ultrasound showing cystic lesion at the bladder neck, size 1.62x1.76x2.04 cm (arrows). (A) Longitudinal view. (B) Transverse view.

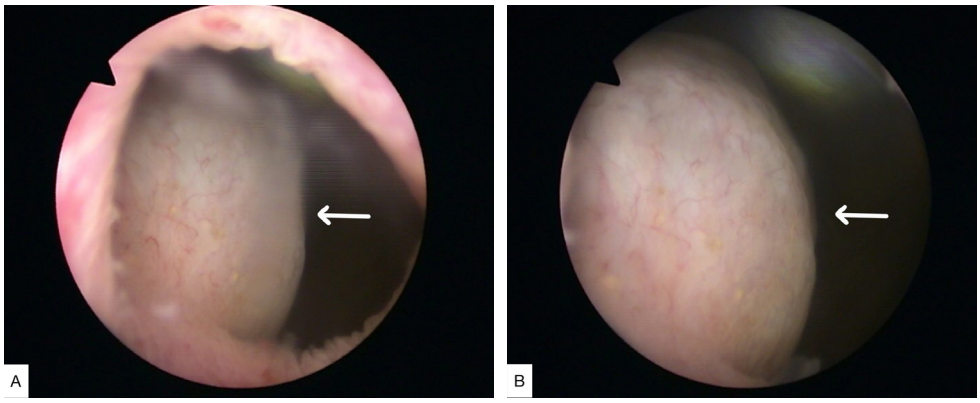

Figure 2. 2A and B. Cystoscopic view of bladder neck cystic mass (arrows indicating mass).

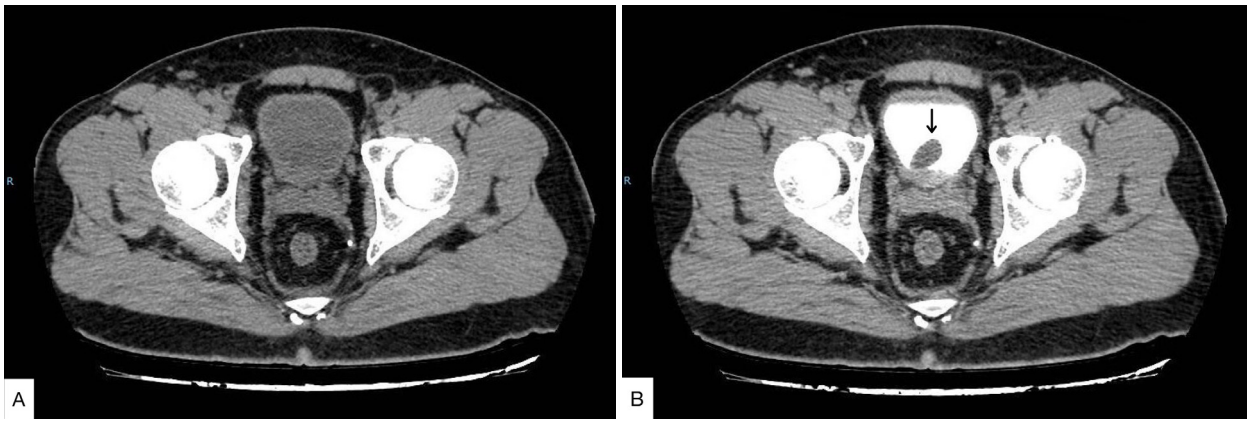

Figure 3. CT scans post contrast (A) and delayed phase (B) show Brunn's cyst (arrow).

on delayed phase (Figure 3). The prostate gland and seminal vesicles were normal. A provisional diagnosis of Brunn's cyst was based on the ultrasonography, CT scan and cystoscopic examination.

The patient was taken to the operation room for a transurethral resection of the bladder neck cyst (Figure 4). At a follow-up appointment 3 weeks after surgery, his obstructive voiding symptoms were completely resolved. The pathology report showed a large submucosal cyst lined by a mixture of urothelial and columnar cells. The adjacent area displayed invagination of a sub-

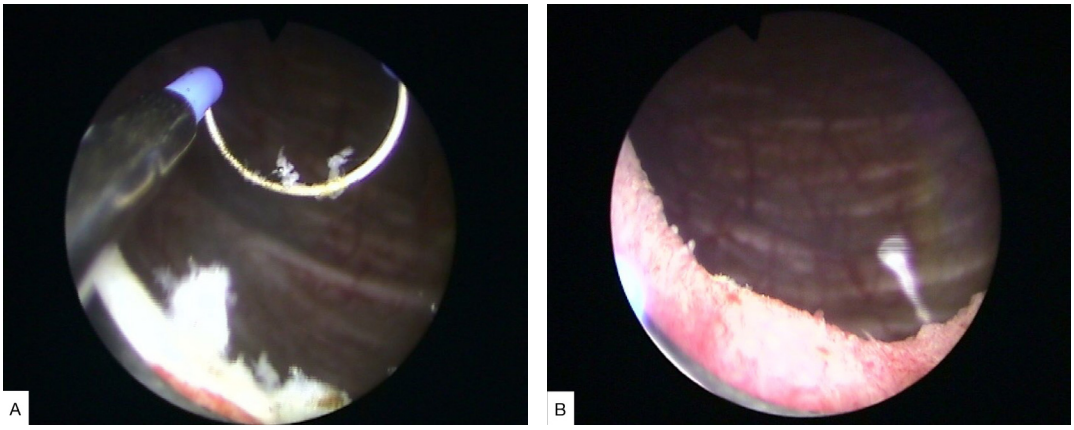

Figure 4. Transurethral resection of the bladder neck cyst. (A) Resecting and (B) Resected.

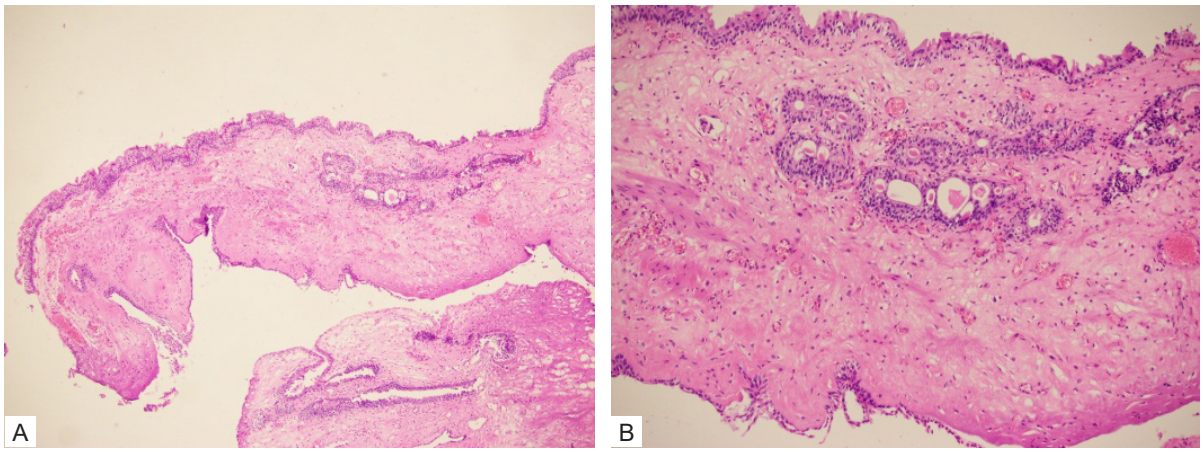

Figure 5. A and B. Final pathology findings consistent with Brunn's cyst.

mucosal Brunn's nest. The finding was consistent with Brunn's cyst (Figure 5). The final diagnosis of this case was a Brunn's cyst.

Discussion

Bladder outlet obstruction in the elderly is usually caused by enlargement of the prostate gland, but in younger men is caused by urethral stricture. Our patient had a rare cause of bladder outlet obstruction secondary to a Brunn's cyst at the bladder neck.[1-6]

The differential diagnosis of a cystic lesion near the bladder neck is presence of an intraurethral prostatic cyst[7] or ureterocele[8], which can cause irritative or obstructive voiding symptoms. Transurethral resection of the cyst only at the base of the cyst is the primary mode of treatment in a young patient.[7]

The main diagnosis of Brunn's cyst is by ultrasonography and cystoscopic examination. Transurethral resection of the cystic lesion is the first line of treatment. This operation has resulted in a resolution of the symptoms.[1-6] Due to the benign nature of the pathology in this case, routine surveillance in the absence of the symptoms would appear to be unnecessary[5].

Conclusion

The presence of a Brunn's cyst is rare but should be kept in mind as a potential differential diagnosis in a patient with bladder outlet obstruction and a cystic lesion at the bladder neck. In this case transurethral resection of the cyst resulted in resolution of the obstructive voiding symptoms.

Conflict of Interest

The authors declare no conflict of interest.

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Case Report

Penile prosthesis in an organ transplanted diabetic: a challenging case

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Keywords:
Penile prosthesis, organ transplantation, diabetic, recipient

Abstract

Most patients with erectile dysfunction have various comorbidities. These may lead to an increase in postoperative complications after penile prosthesis implantation especially with regard to prosthesis infection. This case study reports on the outcome of a penile prosthesis implantation in an immunocompromised patient with underlying comorbidities of diabetes and post kidney transplantation. A literature review regarding surgical site infection after this procedure reinforce the finding that the incidence of infection need be no greater than a non-immunocompromised patient.

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Introduction

Erectile dysfunction (ED) is defined as the inability to attain or maintain penile erection sufficient for satisfactory sexual performance. The prevalence of ED is estimated to be around 10% to 20% worldwide,[1,2] the prevalence increasing in patients with comorbidities including type 2 diabetes mellitus, obesity, cardiovascular disease, hypertension, dyslipidemia, and depression.[3,4] Although there are various non-surgical treatments for ED, many patients are still not satisfied with the treatment response and seek other options. A penile prosthesis (PP) remains the standard surgical treatment for ED patients who have no response to the other treatments. PP aims for the creation of penile rigidity that differs from a physiologic or pharmacologically induced erection. Malleable (semirigid) and inflatable (hydraulic) devices are both currently available for this purpose.

Infection following implant of a penile prosthesis remains a rare but devastating complication of urologic prosthetic surgery that results in loss of sexual function, increased healthcare costs, and physical and emotional morbidity for patients. The majority of ED patients have several comorbidities related to the etiologies of ED common ones being diabetes, neurological disorders, and pelvic organ surgery. These conditions may increase the risk of infection. However, there are currently no guidelines to assist surgeons in identifying the patients at high risk of infection and giving clear recommendations for the treatment. This article presents a case study of a complex patient undergoing PP implantation with a focus on infection risk.

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Case Report

A 41-year-old man had experienced ED for many years and had no effective response from any phosphodiesterase type 5 (PDE5) inhibitors and was seeking alternative treatment. He had a history of type I diabetes mellitus for 25 years and end stage renal disease for 5 years before he underwent living-donor kidney transplantation 4 years ago. His diabetes was not well-controlled. He had suffered from chronic diabetic foot ulcers for 2 years and had had a right below knee amputation 2 years ago. The current medication taken for diabetic control were insulin lispro (Humalog®) 20-20-20 units and insulin glargine (Lantus®) 25 units before bed. His HbA1c was 8.9% and fasting blood sugar was 150-160 mg/dl. Immunosuppressive drugs taken were mycophenolate mofetil (Cellcept®) 500 mg twice daily, tacrolimus (Prograf®)1mg twice daily and prednisolone 5 mg once daily. His tacrolimus level was 9.50 ng/ml.

After careful evaluation and counselling, PP implantation was recommended to the patient. We elected to use a malleable implant to reduce risk of infection, malfunction and avoid reservoir placement. His diabetes was carefully controlled before the operation. On the morning of the operation, the patient was advised to take a shower with chlorhexidine. Parenteral antibiotics vancomycin 1 gm and amikacin 500 mg were administered half an hour before the incision was made. Hair was clipped in the operating room. The operative site was scrubbed with povidone iodine scrub for 15 minutes. A Foley catheter was inserted. A three-centimeter skin incision was made at the penoscrotal junction and the dartos tissue was opened. Corpora tissue and urethra were identified and dissected. Buck's fascia was incised and released, giving direct access down to the urethra and corpus spongiosum until the corpus cavernosum was clearly bilaterally exposed. An avascular plane was created leading to the inferior pubic rami. A corporotomy was performed. Corpora tissue was dilated and measured. Careful dilation was taken to ensure no crural crossover. A coloplast Genesis 11-mm in diameter and 16-cm in length device was inserted into the corpora tissue after irrigation with antibiotics. The corpora was closed with absorbable sutures. The dartos and skin were subsequently closed with absorbable sutures.

On post-operative day 1, the patient had minor surgical wound pain, the Foley catheter was removed and he could spontaneously pass the urine. Serum glucose was well-controlled with insulin. An oral antibiotic, amoxicillin/clavulanic acid (Amoxiklav®) 1 gm twice daily, was continued for 1 month. At the 1-month follow-up, the patient was doing well with no sign of surgical site infection. He was satisfied with the girth and length of the penis.

Discussion

Although ED is not a severe life-threatening condition, this spectrum of disease has a high impact on the quality of life in men. PP implantation is now a popular procedure for ED treatment worldwide, however, surgical site infection along with prosthesis infection are common complications following this procedure. According to a previous report focusing on immunocompromised patients, studies on infection rates among medically immunosuppressed patients are currently limited.[1]

The overall complication rate was found to be significantly higher in transplant patients (22%) than in non-transplant patients (7.9%) receiving prostheses ($p < 0.01$). The difference in the rate of malfunction was statistically significant ($p < 0.001$) when comparing the three-piece prosthesis in the transplant and non-transplant patients ($p < 0.001$).

Cuellar et al followed 46 organ transplanted patients for 2 years after PP implantation. In this series, the incidence of infection was no different to patients without organ transplant. Also, in 2018, Sun et al found no significant increase in infection rate after a 30 month follow up of transplant recipients.[5] Based on these limited data, it is reasonable to consider transplant recipients on immunosuppression therapy as potentially good candidates for penile prostheses.

Regarding the patients with diabetes, implanters have long considered diabetic patients as high risk for prosthesis infection. In 1998, Wilson et al conducted a 2 year prospective study of 389 patients, including 114 diabetics, who underwent 3-piece penile prosthesis implantation[6]. There was no statistically significant increased infection risk with increased levels of glycosylated hemoglobin A1C among all patients or among only the diabetics. The same result was concluded

by Montague et al.[7] In contrast, Habous et al reported that an HbA1c threshold level of 8.5% predicted infection with a sensitivity of 80% and a specificity of 65%.[8]

Perioperative serum glucose has also been found to play an important role. Balen et al[6] retrospectively collected data from diabetic patients for 12 years and found that glucose levels higher than 200 mg/dl at the time of the procedure showed a positive correlation with postoperative infection.[9] Ussapol et al reported on a case of penile prosthesis implantation in a patient with poorly controlled diabetes mellitus necessitating post paraffinoma excision. This case showed a good result without wound infection.[10]

In summary, we can report a good result of PP implantation in an immunocompromised patient without any infectious complications. However, we recommend some strategies to prevent this sequela as follows: firstly, appropriate systemic prophylactic antibiotic usage is mandatory, secondly, copious irrigation with antibiotic-containing solution is recommended throughout the surgery and finally a 'no touch technique' or minimal touching of the skin in the operative field is advised. In a case of the development of infection early recognition and treatment are the mainstays of a successful outcome and minimize the burden of the complication.

Conclusion

The infection of a surgical site after PP implantation can be devastating for both the patients and implanters. However, this operation can be performed safely in an immunocompromised patient at a high risk of infection. Careful patient selection, appropriate counselling and thorough surgical care during the operation are the mainstays of success in this area.

Conflict of Interest

The author declares no conflict of interest.

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3. Case report

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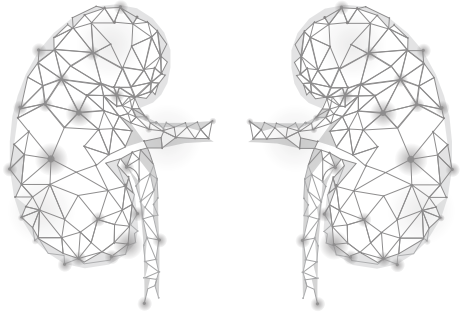

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