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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 Second issue of Insight Urology (ISU) has been published on time, despite the COVID-19 pandemic. It contains 13 papers including 11 original articles, 1 review article, and 1 case report, covering many topics in urology. Interestingly, most of them are about endourology, oncology, and general urology. All of the papers are well-written and have been critically reviewed by our team. The Editorial Committee would like to thank all the authors for their great support and you, the reader, for your continued interest. Thanks to our authors and readers we have this important official journal of the Thai Urological Association under the Royal Patronage (TUA).

While working towards becoming an international journal, we have gained an energetic new managing editor and have welcomed some more members to our editorial committee, editorial board, and advisory board. We have also broadened our editorial team to include some more international editors in the fields of endourology and kidney transplantation. Additionally, several of the papers contained in this issue of ISU have, for the first time in its history, been reviewed by international urologists. We are a member of Crossref, a Digital Objective Identifier (DOI) Registration Agency (RA). This is the first issue in which every paper has its own individual DOI. I, as the Editor in Chief of Insight Urology, really appreciate all the work that has been done by my productive team, especially my international colleagues.

The COVID-19 pandemic situation is still of cause for concern worldwide, every country is facing the challenges presented by it, with many new cases every day. The world's governments have created many protocols to keep all of us safe, healthy, and prosperous. Physical distancing and wearing masks are the main practices advised by the World Health Organization (WHO). The Editorial Committee would like to offer respect and peace to every sufferer and casualty of COVID-19. Our true feelings are represented by the black cover of this issue. We really hope that everybody will overcome this difficult situation safely after vaccination.

No reserve, No retreat, No regret.

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

Contents

Original Article

Contents

Original Article

Predicting factors for improvement of serum creatinine after percutaneous nephrostomy in adults with bilateral hydronephrosis associated with malignancy

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Keywords:
Bilateral hydronephrosis, percutaneous nephrostomy, serum creatinine, renal function

Abstract

Objective: Improvement of renal function in obstructive uropathy is a main goal of urinary diversion. In cases of failed internal diversion, percutaneous nephrostomy (PCN) is used to divert urine from the obstructed kidney. PCN also affect on quality of life, particularly having both sides. The objective of this study was to identify a predicting factor associated with improvement of renal function after bilateral PCNs and to avoid performing bilateral PCNs.

Materials and Methods: Data of all patients with bilateral hydronephrosis associated with malignancy who were performed bilateral PCNs in Siriraj Hospital between December 2011 and December 2016 were reviewed and collected. Success with PCN was defined as a serum creatinine less than 2 mg/dl or decreased more than 95% of initial serum creatinine.

Results: A total of 240 patients met the criteria. Mean age was 64.6 ± 14.9 years old. Most common organ of malignancy was cervix. Mean initial serum creatinine (iCr) and nadir serum creatinine (nCr) were 7.7 and 1.9 mg/dl, respectively. On multivariate analysis, no significant predicting factors were demonstrated but only iCr tended to have a statistically significant ($p = 0.058$). From receiver operating characteristics analysis, at cut-off value of iCr 5 mg/dl could demonstrate significant difference between success and failure ($p = 0.027$). Sensitivity and specificity were 72.4% and 44.0%, respectively.

Conclusion: Only the iCr was more likely to be a predicting factor. At cut-off value of iCr 5 mg/dl, if a patient presented with iCr more than 5 mg/dl and unilateral PCN at dominant side did not improve serum creatinine, performing contralateral PCN might not help.

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Introduction

Approximately 10% of renal failure is caused by urinary tract obstruction and is known as obstructive uropathy[1]. A common cause of upper urinary tract obstruction is malignancy, particularly pelvic organ malignancy[2,3] or as a result of treatments, for example pelvic radiation. After a patient has developed a bilateral upper urinary tract obstruction, they may initially be asymptomatic but clinical presentations depend on etiology, location, degree and timing of the obstruction. Consequently, once overall renal function had declined, symptoms would manifest including uremia, oliguria, anuria, and volume overload[4]. Almost all cases require urinary diversion which reroute or bypass the urine. This procedure is a key step to improving renal function and stabilizing a patient. The rationale behind urinary diversion is to relieve symptoms and alleviate complications from renal insufficiency as well as facilitate systemic therapy[4,5].

Percutaneous nephrostomy (PCN) is an external urinary diversion, used to decompress and divert urine directly from the obstructed kidney[6]. Complications of PCN include bleeding, infection, and catheter related problems[7]. All PCN consequences have impact on quality of life because the patient is unable to adequately perform normal daily activity as a result of a catheter at the flank or back. In addition, the catheter needs changing regularly which is in itself restrictive. In order to avoid all associated issues of PCN, internal urinary diversion such as ureteric stent is always considered as a first step. When it fails, external urinary diversion such as PCN will be considered. The aim of this study was to identify a predicting factor that resulted in an improvement in serum creatinine after PCN in adults with bilateral hydronephrosis associated with malignancy.

Materials and Methods

All patients with bilateral hydronephrosis associated with malignancy who were performed bilateral PCNs between December 2011 and December 2016 at our hospital were retrospectively reviewed. The study was approved by Ethical committee of Siriraj Hospital. All data including

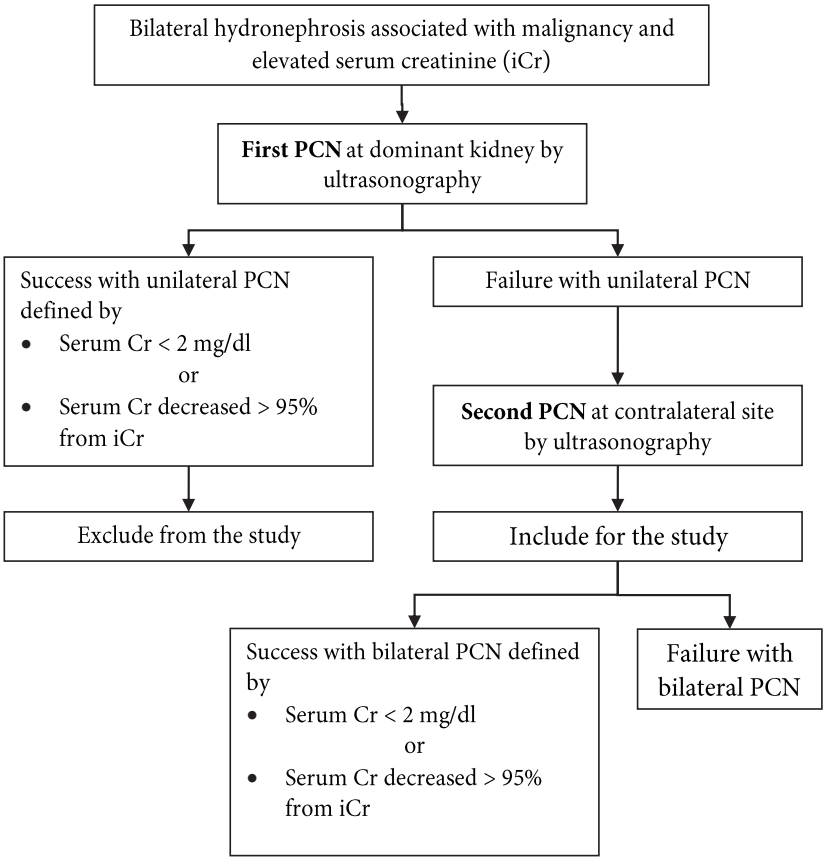

Figure 1. Flow chart demonstrated patient selection in this study .

age, gender, degree of hydronephrosis using The Society of Fetal Urology (SFU) grading system[8], organ of malignancy, initial serum creatinine (iCr), and nadir serum creatinine (nCr) were collected. iCr was defined as the last serum creatinine before PCN was performed as well as nCr was defined as the lowest serum creatinine after PCN was successfully performed. Most cases did not have baseline serum creatinine before occurring of bilateral hydronephrosis and timing from baseline to iCr was not completely recorded so that we had to define success PCN as serum creatinine was less than 2 mg/dl or decreased more than 95% of iCr after performing PCN to demonstrate a predicting factor which associated with improvement of serum creatinine and referred to renal function. A dominant kidney was defined by a greater cortical thickness or less degree of hydronephrosis on ultrasonography.

A patient who had history of previous renal and/or ureteral surgery, previous ureteric stent, diagnosed chronic kidney disease or single functional kidney or congenital anomalies in urinary tract before PCN and incomplete information was excluded from the study. PCN was performed by using ultrasound guidance. All patients with bilateral hydronephrosis were initially performed unilateral PCN on the dominant kidney. Serum creatinine was checked before first PCN and followed until stable at least 2 days. If it was still more than 2 mg/dl, contralateral PCN would be performed. After successfully performed bilateral PCNs, serum creatinine was followed until it was reached the lowest level, called nadir serum creatinine (nCr) (Figure 1).

Statistical analysis

Statistical Package for Social Sciences (SPSS) version 17.0 was used to calculate and analyze the data set. In order to determine predicting factors, the Student T-test and ANOVA were used for normal distribution data as well as the Mann-Whitney U test was used for abnormal distribution data. The Chi-square test or Fisher Exact test was used for qualitative comparison. P-value less than 0.05 was indicated a statistical significance.

Table 1. Demographic data of 240 patients.

Demographic data	Results
Gender, n (%)	
Male	85 (35.4)
Female	155 (64.6)
Mean age ± SD (range) (years)	64.6 ± 14.9 (21-95)
Mean iCr ± SD (mg/dl)	7.7 ± 5.2
Mean nCr ± SD (mg/dl)	1.9 ± 2.1
Organ of malignancy – n (%)	
Urologic malignancy	88 (36.7)
• Bladder	66 (27.5)
• Prostate	22 (9.1)
Gynecologic malignancy	119 (49.6)
• Cervix	98 (40.8)
• Endometrium	14 (5.8)
• Ovary	7 (2.9)
Miscellaneous	33 (13.8)
• Colon	11 (4.5)
• Rectum	10 (4.1)
• Unknown	5 (2.0)
• Pancreas	4 (1.6)
• Lymphoma	2 (0.8)
• Breast	1 (0.4)
Degree of hydronephrosis by SFU grading system – n (%)	
• Grade 1	7 (2.9)
• Grade 2	90 (37.5)
• Grade 3	127 (52.9)
• Grade 4	16 (6.7)
Dominant kidney – n (%)	
• Right	105 (43.7)
• Left	135 (56.3)
Success with bilateral PCNs – n (%)*	182 (75.8)

*Success with bilateral PCNs defined by serum Cr < 2 mg/dl or serum Cr decreased > 95% from iCr

Results

A total of 251 patients with bilateral hydronephrosis associated with malignancy were performed bilateral PCNs and 11 patients were excluded from the study. All data of 240 patients who met the criteria were analyzed. Demographic data were demonstrated on Table 1. Mean age was 64.6 years and majority of cases was female (64.6%). Most common malignancy was cervical cancer (40.8%). Most common degree of

Table 2. Determining of predicting factors for improvement of serum creatinine.

Predicting factors	Success with bilateral PCNs	Failure with bilateral PCNs	P-value
Mean age ± SD	61.7 ± 14.1	62.3 ± 12.4	0.798
Mean iCr ± SD	7.4 ± 5.0	8.8 ± 5.6	0.058
Organ of malignancy – n (%)			0.680
• Urological malignancy	62 (34.0)	21 (36.2)	
• Gynecologic malignancy	88 (48.4)	29 (50.0)	
• Miscellaneous	32 (17.5)	8 (13.7)	
Degree of hydronephrosis – n (%)			0.388
• Grade 1	4 (2.1)	2 (3.4)	
• Grade 2	53 (29.1)	15 (25.8)	
• Grade 3	104 (57.1)	31 (53.4)	
• Grade 4	21 (11.5)	10 (17.2)	
Dominant kidney – n (%)			0.884
• Right	93 (50.5)	29 (50.0)	
• Left	89 (48.9)	29 (50.0)	

Table 3. Success and failure with bilateral PCNs at cut-off iCr 5 mg/dl .

Initial creatinine (mg/dl)	Equal or less than 5 mg/dl n (%)	Greater than 5 mg/dl n (%)	P-value
Success	80 (83.3)	102 (70.8)	0.027
Failure	16 (16.7)	42 (29.2)	

hydronephrosis was SFU grade 3 (52.9%) and most common of dominant kidney was left side (56.3%). Mean iCr was 7.7 mg/dl as well as mean nCr was 1.9 mg/dl. Comparing between iCr and nCr, there was statistically significant improvement ($p < 0.05$).

On multivariate analysis, there was no statistically significant correlation among mean age, organ of malignancy groups, dominant kidney and success with bilateral PCNs. Only mean iCr was more likely to reach statistically significance. There was also no statistically significant correlation between degree of hydronephrosis and success with bilateral PCNs (Table 2).

Receiver operating characteristics (ROC) curve analysis was used to identify the cut-off value of iCr which was able to predict improvement of serum creatinine. If cut-off value of iCr was 5 mg/dl, it would demonstrate statistically significant difference between success and failure with bilateral PCNs ($p = 0.027$). If iCr was equal or less than 5 mg/dl, failure with bilateral PCNs was 16.7%. On the other hand, if iCr was greater than 5 mg/dl, failure with bilateral PCNs was 29.2% (Table 3). Sensitivity and specificity were 72.4% and 44.0%, respectively.

Discussion

PCN was usually a treatment of bilateral ureteral obstruction associated with malignancy. This procedure can improve renal function and alleviate the symptoms of uremia. PCN did not impact on quality of life in advanced stage malignancy with short survival[6] and suitable for palliative setting. Major concern of PCN was quality of life in long-term use particularly bilateral PCNs. Another study indicated that bilateral PCNs allowed significant improvement of renal function and was superior to unilateral PCN[9]. From our study, bilateral PCNs could significantly improve renal function ($p < 0.05$) but we did recommend to initially perform unilateral PCN at dominant side and waited for improvement of renal function for few days. If renal function was achieved, contralateral PCN would be avoided.

The study which compared renal function improvement between unilateral and bilateral PCNs in bilateral ureteral obstruction demonstrated that unilateral PCN at the greater cortical thickness may appropriate for improving renal function[6]. In our study excluded a patient who was success with unilateral PCN so that the degree of hydronephrosis classified by SFU grading system was not a significant predicting factor (p = 0.388). In fact, degree of hydronephrosis depends on degree (complete or partial) and duration of obstruction. Longer period of complete ureteral obstruction was associated with diminished return of glomerular filtration rate[10, 11]. Moreover, there are many other factors that influence returning of renal function after relief of obstruction including compliance of the collecting system and presence of pyelolymphatic backflow[12]. However, the degree of hydronephrosis on ultrasonography may not strongly correlate with renal function as DMSA renal scintigraphy[13], it was used to initially and practically evaluate the dominant site and reasonably consider urinary diversion. This study may help urologists to make a better decision for performing bilateral PCN in daily basis.

In this study, only one factor that might correlate the improvement of renal function from bilateral PCNs was iCr but it did not reach statistically significance (p = 0.058). Therefore, ROC curve was used to identify a cut-off value of iCr that might guide need of bilateral PCNs. At iCr 5 mg/dl, the failure rate was significant difference (p = 0.027) as well as sensitivity and specificity were 72.4% and 44.0%, respectively. For clinical application, if a patient presented with iCr more than 5 mg/dl and first unilateral PCN did not achieve the improvement of serum creatinine, contralateral PCN should be avoided.

Because of retrospective design, some expectedly significant factors such as timing from baseline to iCr and iCr to nCr were not recorded as well as some important information would be missed. Therefore, robust conclusion could not be drawn. Further prospective study would thoroughly answer this question.

Conclusion

Bilateral PCNs were an effective treatment for improving renal function in bilateral hydronephrosis associated with malignancy. Only an initial serum creatinine (iCr) was more likely to be a predicting factor. At cut-off value of iCr 5 mg/dl, if a patient presented with iCr more than 5 mg/dl and unilateral PCN at dominant side did not improve serum creatinine, performing contralateral PCN might not help.

Conflict of Interest

The authors declare no conflict of interest.

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Original Article

Long term outcomes between adjuvant radiotherapy and combined radiotherapy with hormonal treatment after radical prostatectomy in high risk prostate cancer

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Keywords:
Prostate cancer, locally advanced, high risk, adjuvant radiotherapy, combined treatment, hormonal treatment

Abstract

Objective: To determine the oncological outcome of adjuvant treatment between radiotherapy (RT) alone and combined radiotherapy with androgen deprivation therapy (ADT) in high risk prostate cancer patients after radical prostatectomy (RP).

Materials and Methods: All medical records of high risk-prostate cancer patients (including PSA > 20 ng/ml, pT3-pT4 or Gleason score 8-10) who underwent RP in Siriraj Hospital between 2000 and 2016 were retrospectively reviewed. Demographic data, pathological staging, types of adjuvant treatment, time to follow up and time to biochemical recurrence (BCR) were analyzed.

Results: Undetectable PSA after RP was achieved in 1009 out of 1221 high risk prostate cancer patients who had been followed up at least 6 months after surgery. Pathological staging pT2, pT3, pT4 and N1 was 23.8%, 73%, 0.8% and 4.7%, respectively. Forty one percent received adjuvant treatment (41 adjuvant RT alone, 74 combined adjuvant RT and ADT, 303 ADT alone). Median follow up time in the adjuvant RT group and combined treatment group was 63.8 months (8.9 - 210.7). BCR rates were 22% (9 of 41) for adjuvant RT and 12.2% (9 of 74) for adjuvant combined treatment. 10-year BCR-free survival in the two groups was 70.2% and 83.8%, respectively. There was no statistical difference between adjuvant RT and adjuvant combined treatment in terms of survival benefit (Hazard Ratio 0.40; p = 0.057).

Conclusion: Adjuvant radiotherapy after radical prostatectomy increases long term survival outcomes for high risk prostate cancer patients. This study shows that combined adjuvant RT and ADT may improve BCR-free survival.

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Introduction

Radical prostatectomy (RP) is one of the standard treatments in localized high-risk prostate cancer patients. Between 25 and 40 percent of patients who undergo RP have biochemical recurrence or disease progression, especially patients with adverse pathological features which include extracapsular extension, a positive surgical margin and seminal vesicle involvement[1,2]. Several trials have shown that adjuvant radiation therapy (ART) after RP conferred benefits with regard to long-term biochemical progression-free survival (PFS) and metastasis-free survival (MFS)[2-5]. On the contrary the data from two large randomized trials (RTOG 96-01 and GETUG-AFU 16) indicated that salvage radiation therapy (SRT) combined with short or long term of androgen deprivation therapy (ADT) was advantageous and improved PFS and MFS in patients with disease recurrence. However, at the start of this investigation there was no consensus regarding the role and duration of ADT in combination with ART or SRT in post RP patients[6-8]. Therefore, this study was conducted to determine the oncological outcome of adjuvant treatment between ART alone and combined radiotherapy with androgen deprivation therapy (ART plus ADT) in high risk prostate cancer patients after RP.

Materials and Methods

All charts of patients who were diagnosed with high risk prostate cancer and underwent radical prostatectomy with pelvic lymphadenectomy at Siriraj Hospital between 2000 and 2016 were retrospectively reviewed. All patients had pathological confirmation of adenocarcinoma with a Gleason score of 8-10, pathological staging T3-T4 or preoperative PSA > 20 ng/ml with adverse pathological features (positive surgical margin, bladder neck involvement or seminal vesicle invasion). Patients who had postoperative detectable PSA (PSA > 0.2 ng/ml) or a follow up time of less than 6 months were excluded. Eligible patients were categorized into two groups: the adjuvant radiation therapy group including patients who received postoperative radiotherapy alone without any ADT and patients who received combined radiation therapy with ADT (Figure 1).

Both groups underwent external beam radiation therapy (EBRT) at the Radiation Oncology Division, Department of Radiology, Faculty of Medicine Siriraj Hospital. Most of these were given three-dimensional conformal radiotherapy (3D-CRT) or intensity modulated radiotherapy (IMRT) within the 12 months after surgery. The radiation doses ranged from 66 to 72 Gray (Gy) given in 33 to 36 daily fractions at the surgical bed. ADT was given including a GnRH agonist,

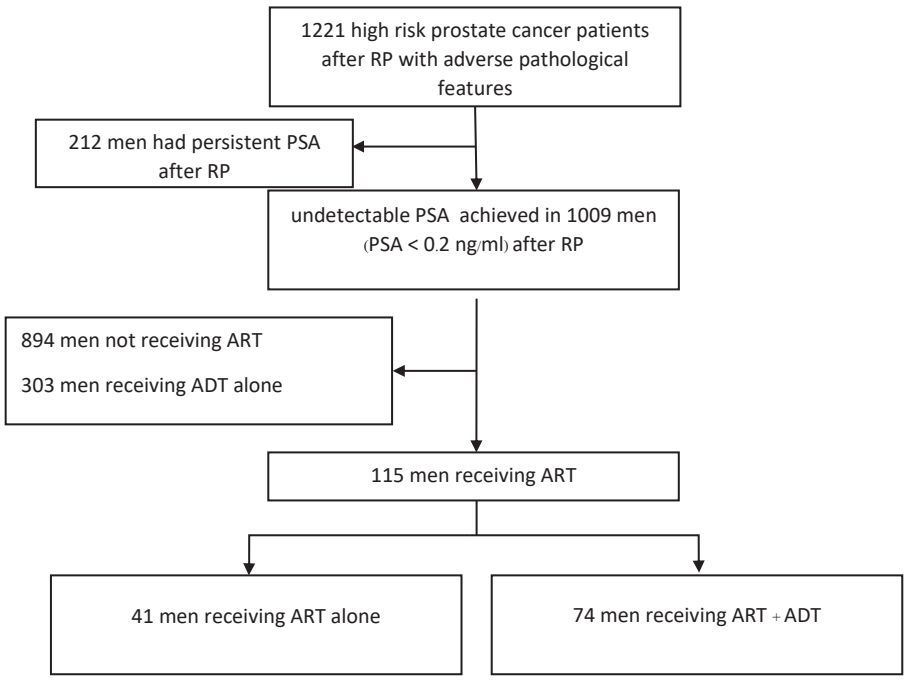

Figure 1. Study design

an antiandrogen and a bilateral orchiectomy. The period of ADT in patients who underwent a bilateral orchiectomy was recorded to the last follow up time or biochemical recurrence occurred. Demographic data, tumor characteristics and types of adjuvant treatment were reviewed. Time to events were calculated starting from date of operation to the documented time of recurrence or metastasis. Biochemical recurrence was defined by two consecutive PSA values of increases of more than 0.2 ng/ml[9]. Distant metastasis was evaluated using CT and bone scans. The primary outcome was biochemical recurrence-free (BCR) survival between the two groups of adjuvant treatment after RP. The secondary outcome was metastasis-free survival.

Statistical analysis was carried out using SPSS version 21.0. Demographic data are showed as mean and median. The Kaplan-Meier method was used to analyze survival time. A log-rank test was used to compare the two groups. Quantitative data was analyzed using a Mann Whitney U test and independent t-tests, and a Chi-square test was used for categorical data.

Results

Undetectable PSA after RP was achieved in 1009 out of 1221 high risk prostate cancer patients who had been followed up at least 6 months after surgery. One hundred and fifteen men received ART regardless of adjuvant ADT, 41 patients (35.7%) underwent ART alone, 74 patients (64.3%) received a combination of ART plus ADT.

Demographic data and tumor characteristics in both groups are shown in Table 1. A comparison between the ART alone group and the combined treatment group showed there was no statistical difference in age, preoperative PSA level or pathological staging. Mean age in both groups was 65 years. Median preoperative PSA levels were 19 ng/ml in both groups. Median follow up time was 56.7 months (Range 9.5 to 154.9) and 73.7 months (Range 8.9 to 210.7) in the ART alone group and combined group respectively. Positive surgical margin rates were 70.7% vs 81.1%, BCR rates were 22% vs 12.2%, distant metastasis rates were 2.4% vs 2.7%, between ART alone group and combined group respectively. Four patients in the adjuvant combined treatment group had regional lymph node metastasis (pN1).

Survival analysis is shown in Figure 2. Ten year BCR-free survival of adjuvant RT alone and the combined treatment group was 70.2% and 83.8% respectively (Hazard ratio 0.40; 95% confidence interval 0.16 to 1.03, p = 0.057). Ten

Table 1. Demographic data and tumor characteristics

Characteristics	Adjuvant RT alone (n = 41)	Adjuvant RT + ADT (n = 74)	P-value
Age (years)	65.3 ± 6.6	65.4 ± 8.7	0.923
PSA (ng/ml)	19.15 (5 to 60)	19.0 (2 to108)	0.28
Follow up time (months)	56.7 (9.5 to 154.9)	73.7 (8.9 to 210.7)	0.01
Gleason grade group (N = 109) n (%)	n = 38	n = 71	0.089
1	1 (2.6)	1 (1.4)	
2	11 (28.9)	12 (16.9)	
3	11 (28.9)	11 (15.5)	
4	8 (21.1)	18 (25.4)	
5	7 (18.4	29 (40.8)	
Surgical margin status			0.204
Positive n (%)	29 (70.7)	60 (81.1)	
Pathological staging n (%)			0.696
pT2	3 (7.3)	7 (9.5)	
pT3	38 (92.7)	67 (90.5)	
Node n (%)			0.111
pN1	0 (0)	4 (6)	
Biochemical recurrence n (%)	9 (22)	9 (12.2)	0.166
Metastasis n (%)	1 (2.4)	2 (2.7)	0.932

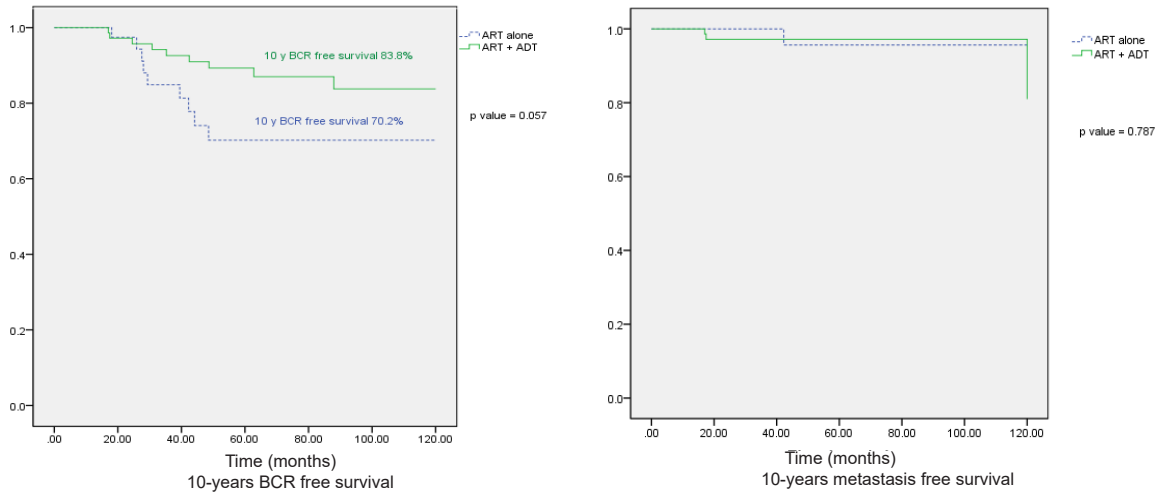

Figure 2. Kaplan-Meier curves of biochemical recurrence free survival and metastasis free survival

Table 2. Details of comparative analysis

Study	Siriraj study	GETUG-AFU-16	RTOG 9601
Years (no. of patients)	2000-2016 (115)	2006-2010 (743)	1998-2003 (760)
Inclusion criteria	pT2-T4 preop PSA > 20 ng/ml Gleason grade group 4-5 Adverse pathologic features	PT2-T4a Pre SRT PSA 0.2-2.0 ng/ml Undetectable PSA postop	pT3N0 or T2 with positive margin Pre SRT PSA 0.2-4.0 ng/ml
Treatment arms	ART vs ART + ADT	SRT vs SRT + ADT	SRT vs SRT + ADT
RT dose (Gy)	66-72	66	64.8
Hormone therapy type	GnRH agonist; Antiandrogen Bilateral orchiectomy	GnRH agonist (goserelin)	Antiandrogen (bicalutamide)
ADT duration (mo)	28	6	24
Median follow-up (yr)	5.3	9.3	13
High-risk features (%)	T3 : 91.3 SM+ : 77.4 Persistent PSA : 0	T3 : 46 SM+ : 51 Persistent PSA : 0	T3 : 67 SM+ : 75 Persistent PSA : >12
Biochemical control (%)	9.8 improvement (10 yr)	17 absolute improvement (9.3 yr)	24 absolute improvement (12 yr)
Distant metastasis (%)	No significant improvement	7 absolute improvement (9.3 yr)	9 absolute; improvement (12 yr)

years metastasis-free survival was 95.7% and 81% respectively (p = 0.787).

Discussion

Locally advanced prostate cancer with high risk features is a complex condition which needs a multidisciplinary approach to increase a positive outcome. Long term ADT plays a major role in combination with radiotherapy as an effective primary treatment which improves survival in high risk prostate cancer patients with intact prostate[10-12]. By contrast, surgical treatment alone may be insufficient in long life expectancy patients. Previous randomized studies demonstrated the benefits of adjuvant radiotherapy alone after RP in high risk pathological cases. Unfortunately, there is no strong evidence to support the benefits of additional ADT in patients who underwent radical prostatectomy.

Bolla et al. and Wiegel et al. reported biochemical recurrence rates of about 40% in cases where ART alone was given after a 10-year follow up[2-4]. RTOG 9601 and GETUG-AFU 16 reported that a combination of SRT with ADT increased PFS and MFS in patients with BCR after RP[7,8]. The duration of ADT in these trials was 24 months of bicalutamide and 6 months of goserelin respectively. A comparative analysis is shown in table 2. This study shows a 9.8% improvement in biochemical control after 10 years of follow up whereas 24% and 17% absolute improvement were discovered in RTOG 9601 and GETUG-AFU 16 respectively. The 10-year PFS in GETUG-AFU 16 was 64% for patients in the radiotherapy plus goserelin group. Our results emphasize that a combination of ART plus ADT improved BCR-free survival in high risk patients with adverse pathological features after RP (70.2% vs 83.8% in ART alone vs ART plus ADT). Some recent data showed an overall survival improvement after a combination of ART plus ADT vs observation or ADT alone in high risk and node-positive patients after RP (HR 0.77, 95% CI 0.64-0.94; p = 0.008)[13]. This may guide us how to improve survival rates in the context of adjuvant combination therapy after RP in men with adverse pathological features.

Major limitations of this study include its retrospective nature which can lead to a selection bias and lack of matched controls causing a level of variation in types and duration of ADT in the combination treatment cohort. Phase III AFU-GETUG-20 (NCT01442246) and ERADICATE trials (NCT04484818) will help us to understand the benefits and the optimum duration of hormonal treatment in adjuvant therapies.

Conclusion

Multimodality treatment increases long term survival rates for high risk prostate cancer patients. A combination of radiotherapy and hormonal treatment after radical prostatectomy appears to improve biochemical recurrence-free survival in patients with adverse features when compared with adjuvant radiation therapy alone.

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Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Cost-effective analysis and budget comparison of laparoscopic radical prostatectomy and robotic-assisted radical prostatectomy for prostate cancer treatment in a health insurance system in Thailand

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Keywords:
Prostate cancer, cost-effectiveness, laparoscopic radical prostatectomy, robot-assisted laparoscopic radical prostatectomy

Abstract

Objectives: To compare the total medical cost and post-operative quality of life between laparoscopic radical prostatectomy (LRP) and robotic-assisted laparoscopic radical prostatectomy (RALP) and to discuss the cost differences of each approach.

Materials and Methods: Data were retrospectively reviewed from patients diagnosed with prostate cancer and who underwent LRP (n=68) or RALP (n=104) during a 36-month period. The prostate cancers of all patients were classified as low, intermediate, or high risk. Patient variables, inpatient hospital charges, outpatient total medical costs within 24 months and post-operative quality of life were compared.

Results: The baseline patient characteristics were similar between each group. Rates of positive margins and the need for further cancer treatment were correlated with the burden of disease (highest in the high risk group). The RALP inpatient hospital charges were higher in all risk groups. However, the mean total outpatient hospital charges were comparable. The RALP group demonstrated a trend towards better sexual-related quality of life in all risk groups. However, urinary incontinence, urinary-related, bowel-related, vitality-related quality of life were not significantly different between LRP and RALP.

Conclusion: From the payer's perspective, RALP costs are higher than LRP costs. The clinical and quality of life benefits associated with RALP may not convert into a net savings of total medical costs within 24 months after surgery.

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Introduction

Prostate cancer is one of the emerging healthcare burdens in Thailand[1] and is the fourth most common cancer in males. However, the trend toward early stage presentation due to public awareness and PSA screening now means that early stage prostate cancer can be cured by radical prostatectomy. In the last decade, laparoscopic radical prostatectomy (LRP) and robotic-assisted laparoscopic radical prostatectomy (RALP) have become the dominant surgical approaches due to the benefits of minimally invasive surgery.

LRP has been performed in many large university or tertiary hospitals; however, this procedure has a steep learning curve for surgeons and several technological limitations, including the use of two-dimensional imaging, restrictive movement of the surgical instrument, and a long operative time[2]. The first generation of the "Da Vinci System" was a robotic surgical device designed by Intuitive Surgical Inc. (Sunnyvale, CA, USA) in 1995. The machine consisted of robotic arms that could move freely. The surgeon remained seated at a console unit and had a 3D high-definition view of the surgical field[3].

In Thailand, RALP was introduced in 2007. Since then, it has gradually become a more favored surgical approach both for surgeons and patients. This may be the result of aggressive marketing by the surgical robot manufacturer and the hospital[4], and the eagerness of patients for new technology that claimed superior results. However, robotic systems come with a hefty price, and their high cost has led authorities into a reimbursement program and insurance companies to question their clinical value.

There is a large volume of evidence to indicate that the most consistent perioperative clinical benefits of RALP over LRP are lower blood loss, fewer transfusions, and a shorter length of stay[5,6]. However, the available data are insufficient to draw conclusions regarding the effect of cancer-related outcomes, complications, and quality of life[7]. Therefore, whether the benefits of RALP can outweigh its higher costs remain unclear.

Previous studies in this area usually compare the costs of LRP and RALP using theoretical economic modeling or they address only the costs of the procedure but exclude most of the costs associated with surgical complications, side effects, and cancer-related outcomes[4,7-9]. The aim of the present study was to determine whether the extra cost of RALP can decrease the total expenditure of medical care and result in a better post-operative quality of life in real-world practice. We sub-classified our patients into prostate cancer risk groups and compared the results between each surgical approach in terms of clinical outcomes, total medical costs, and post-operative quality of life.

Materials and Methods

The study was conducted in a single institute, Ramathibodi Hospital, which is a tertiary referral center for prostate cancer in Thailand. LRP was performed in all cases by the intraperitoneal approach with various laparoscopic instruments from different manufacturers. RALP was all performed by intraperitoneal approach with the three-arm da Vinci Si HD surgical system model SS3000 (Intuitive Surgical, Inc., Sunnyvale, CA, USA). In our study, no patient underwent Retzius-sparing prostatectomy. All three surgeons (Sangkum P, Kongchareonsombat W, and Kijvikai K) performed both operations and were specialized in the field of prostate cancer treatment, with experience beyond the initial learning curve. All surgeons have successfully performed a nerve-sparing dissection, which is usually done as an interfascial dissection. The decision whether to perform LRP or RALP, the nerve sparing dissection and pelvic lymphadenectomy depended on the surgeon who operated on each case. The decision of any given post-operative treatment (e.g. radiation therapy, chemotherapy, androgen deprivation therapy (ADT) or other medicine were dependent on the decision of the individual surgeon.

Data were retrospectively reviewed from 238 patients who were diagnosed with prostate cancer and underwent radical prostatectomy between January 2013 and December 2015. Initially, 14 patients were excluded because they had undergone open radical prostatectomy. In addition, 9 patients in the LRP group and 15 patients in the RALP group were lost to follow up during the 24 month follow-up period and were excluded from the study. Another 28 patients in the RALP group were excluded because of the use of discounted promotion instruments from the robotic manufacturer. These exclusions resulted in a total of 68 patients remaining in the LRP group

and 104 patients in the RALP group (Figure 1). All patients were then sub-classified in terms of their prostate cancer risk as low risk (including the NCCN very low and low risk), intermediate risk, and high risk (including the NCCN high and very high risk) groups based on preoperative PSA level and Gleason score from preoperative biopsy results[10].

Baseline patient characteristics and post-operative variables, such as preoperative PSA, total hospital stay, positive margin rate, and biochemical recurrence within 24 months, were collected separately for each risk group from the information system of the hospital.

Direct costs were used in this study to estimate the cost effectiveness because they are associated with hospitalization and subsequent treatments which represent major expenditures. We used hospital charges to represent the direct medical costs. Hospital charges gave the advantage of accuracy and objective values, but they may have incorporated direct costs and profit margins[4]. Indirect costs were highly varied due to many factors and we were unable to determine objective values; therefore, we omitted the effects of indirect costs under the assumption that no significant differences existed in terms of the opportunity costs of work loss or reduced productivity. The cost components associated with hospital care were more feasibly represented by the costs from a payer's perspective.

We examined the total medical costs by using all hospital charges from the surgical admission period to the end of the 24-month period following the prostate cancer surgery. Notably, the costs of adjuvant or salvage radiation therapy, chemotherapy, androgen deprivation therapy (ADT), and surgical consequential treatment (e.g. re-operation due to complications, cystoscopy, and urethral dilatation) were included. No patient in our study underwent any male sling procedure after prostatectomy. We did not include the cost of preoperative hormonal treatment in the analysis. The cost was discounted at an annual rate of 3.5%.

Following radical prostatectomy, the patients either entered surveillance or received adjuvant treatment. Adjuvant treatment (RT or ADT) were usually given to men at high risk of cancer recurrence[10]. Both RT and ADT can cause significant side effects which affect urinary, sexual, bowel, or hormonal quality of life. Recovery from prostatectomy could be complicated by bladder neck contracture, urinary incontinence, and sexual dysfunction[10]. We compared the quality of life between each approach using the expanded prostate cancer index composite for clinical practice (EPIC-CP), which specifically measures 5 prostate cancer-related quality of life items. This questionnaire enabled real-time and point-of-care scoring[11]. Cross-sectional data were collected at a time beyond the 24 month period after prostate surgery. A higher score indicated greater impairment of quality of life. Scores out of 12 in each domain and total scores out of 60 were used to compare each surgical approach.

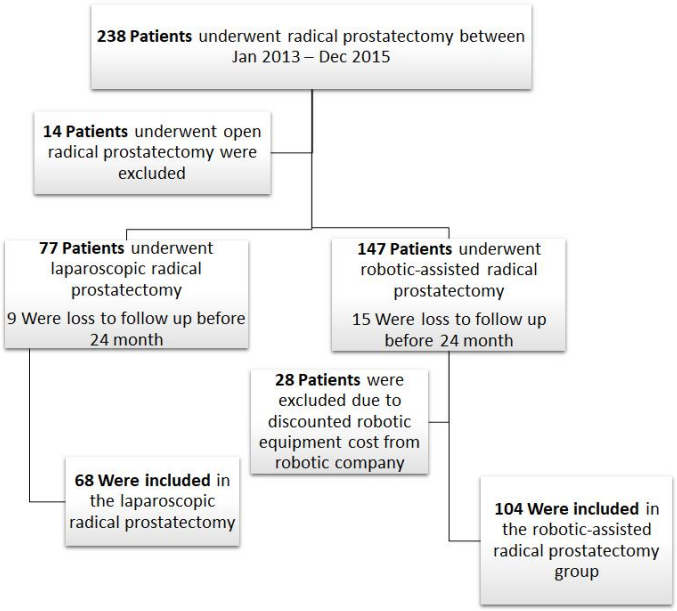

Figure 1. Patient classification.

Statistical analysis was performed using the Stata program version 14.1 (StataCorp, Texas). Quantitative variables were presented as mean ± standard deviation and data were compared between groups with the Independent t-test. Categorical variables were presented as numbers (percentage, %) and data were compared between groups with the Fisher's exact test. A p-value < 0.05 was considered statistically significant.

Results

In all risk groups, each surgical approach had similar pre-operative baseline characteristics. The mean age of patients in all risk groups ranged from 65 to 69 years. The mean PSA level was lowest in the low risk group (7.00 ± 1.97 ng/ml) and highest (36.00 ± 23.40 ng/ml) in the high risk group.

Between LRP and RALP, the comparisons of post-operative variables for all three risk groups showed no statistically significant differences in terms of total hospital stay, rate of neurovascular preservation, rate of positive margins, and the need for further cancer treatment (RT or ADT) (Table 1). After the follow-up period of up to 24 months from the prostate cancer surgery, the rate of biochemical recurrence was also similar between the LRP and RALP groups. (Biochemical recurrence was defined as undetectable PSA after radical prostatectomy with subsequent detectable PSA that increased in 2 or more determinations[10].)

A majority of patients were enrolled in the civil servant medical benefit scheme (CSMBS) (56.72% in the LRP group and 56.31% in the RALP group). The fewest patients in this study were

Table 1. Baseline patient characteristics and post-operative variables. (Classified based on prostate cancer risk-groups)*

Patient risk group/ patient characteristic	Low risk group			Intermediate risk group			High risk group		
	LRP	RALP	P-value**	LRP	RALP	P-value**	LRP	RALP	P-value**
Number of patients: n (%)	10 (40.0)	15 (60.0)	-	32 (41.0)	46 (59.0)	-	25 (37.3)	42 (62.7)	-
Age (years): mean ± SD ∂	68.7±6.3	67.0±4.7	0.501	67.2±7.3	66.8±6.6	0.806	67.2±5.1	65.9±6.9	0.413
Preoperative PSA level (ng/ml): mean ± SD Δ	7.0±2.6	7.0±1.4	0.995	10.3±3.6	10.1±3.8	0.796	33.7±27.5	37.4±20.5	0.571
Total hospital stay (days): mean ± SD ∏	7.2±1.5	7.9±3.3	0.558	6.7±2.9	7.0±2.4	0.525	7.0±2.6	7.9±2.6	0.155
Neurovascular Preservation: n (%) ∑	4 (40.0)	8 (53.3)	0.688	10 (31.3)	21 (45.7)	0.244	3 (12.0)	1 (2.4)	0.143
Positive Margin of prostate specimen: n (%) ∞	2 (20.0)	1 (6.7)	0.543	10 (31.3)	21 (45.7)	0.244	14 (56.0)	18 (42.9)	0.324
Need for further cancer treatment: n (%) ∫	3 (30.0)	4 (26.7)	1.000	9 (28.1)	11 (23.9)	0.793	15 (60.0)	25 (59.5)	1.000
Radiation therapy: n (%) **	2 (20.0)	1 (6.7)	0.543	5 (15.6)	3 (6.5)	0.262	9 (36.0)	13 (31.0)	0.789
ADT: n (%) =	3 (30.0)	3 (20.0)	0.653	9 (28.1)	11 (23.9)	0.793	15 (60.0)	23 (54.8)	0.800
Biochemical recurrence within 24 months: n (%)‡	3 (30.0)	1 (6.7)	0.267	5 (15.6)	13 (28.3)	0.276	9 (36.0)	15 (35.7)	1.000

*Patients were classified based on NCCN guidelines risk-group (Version 2.2016),
NCCN criteria from very low and low risk were combined and labelled as "low risk group",
NCCN criteria from intermediate risk was labelled as "intermediate risk group"
NCCN criteria from high and very high risk were labelled as "high risk group".
**Boldfaced p-value denote statistical significance (p-value < 0.05)
∂ Age at the time of surgery
Δ Preoperative PSA level within 3 months
∏ count from the day of admission until the day of hospital discharge within operation visit
∑ the decision whether to perform neurovascular preservation was based on the surgeon
∞ positive margin from the final pathologic specimen
∫ the rate of patient need to receive radiation therapy and androgen deprivation therapy within 24 months post-operative period
++ including both adjuvant and salvage RT
= Androgen Deprivation Therapy (ADT) included any forms of medical or surgical therapy that aim to block the effects of androgens
‡ Biochemical recurrence defined as undetectable PSA after radical prostatectomy with subsequent detectable PSA that increase on 2 or more determinations

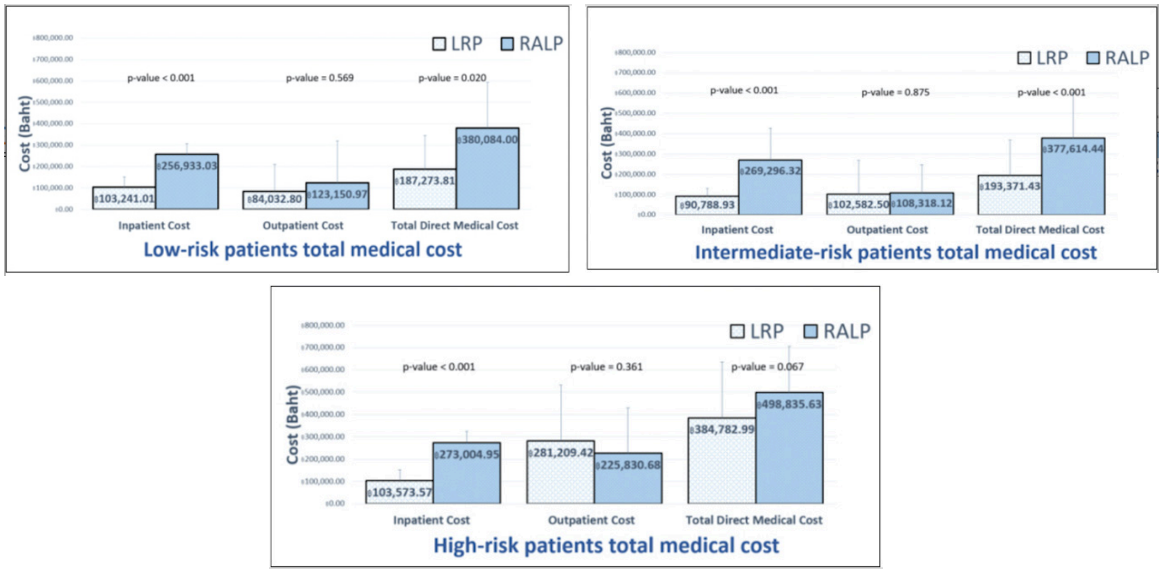

Figure 2. Total medical cost comparison between LRP and RALP

enrolled in the social security scheme (SSS) (5.97% in the LRP group and 0.97% in the RALP group).

The da Vinci Si HD surgical system model SS3000 was purchased in 2013 at a cost of approximately 52.5 million baht (1.75 million US dollars, in 2013). However, in our cost analysis, we used the section of "medical equipment and medical procedures cost" in the hospital bills to represent the divided cost of purchasing both laparoscopic and robotic systems. These costs were consistent for each surgical approach (22,500฿ in LRP and 105,000฿ in RALP). Calculating the true costs of system purchasing and maintenance was troublesome and potentially inaccurate when included in the analysis.

We observed that the risk group had no impact on the inpatient hospital charges. In the LRP cohort, the mean inpatient hospital charges were 103,241.01฿, 90,788.93฿, and 103,573.57฿ for the low, intermediate, and high risk groups, respectively. In the RALP cohort, the inpatient hospital charges were 256,933.03฿, 269,296.32฿, and 273,004.95฿ for the low, intermediate, and high risk groups, respectively (Figure 2). The RALP inpatient hospital charges were significantly higher for all risk groups (with $p < 0.001$). The higher costs of RALP could be explained by the "prosthesis devices cost," which represents the apportioned cost of disposable instruments per case. In the LRP cohort, the mean expenditure in this section was 32,052.75฿, compared to 146,467.65฿ in the RALP cohort.

The mean total outpatient hospital charges between each surgical approach showed no statistically significant difference. Nonetheless, we observed that, in the high risk group, the mean outpatient cost was lower in the RALP than in the LRP cohort, although the difference was not statistically significant (281,209.42฿ in LRP vs. 225,830.68฿ in RALP; $p = 0.361$).

The quality of life assessment, determined by the EPIC-CP scores, demonstrated comparable quality of life domains within the risk groups. Urinary irritation, urinary incontinence, bowel symptoms, and hormonal symptoms domains did not differ between the LRP and RALP cohorts (Figure 3).

In the sexual symptoms domain, RALP showed a consistent trend towards a better post-operative quality of life assessment. Nonetheless, combining all the quality of life domains did not reveal a statistically significant difference. We presumed that the incremental cost-effectiveness ratio cannot further contribute to the quality of life analysis in this scenario.

Discussion

Our study did not observe any clinically significant benefits of RALP. Previous studies on this topic have demonstrated inconsistent results. For example, a review by Caceres et al. suggested that RALP may be associated with a reduced incidence of sexual dysfunction (22–85%, median 61%) when compared with LRP, when the rates of positive surgical margins are similar[11]. Similarly, the meta-analysis by Ficarra et al. of 37 comparative studies between open retropubic

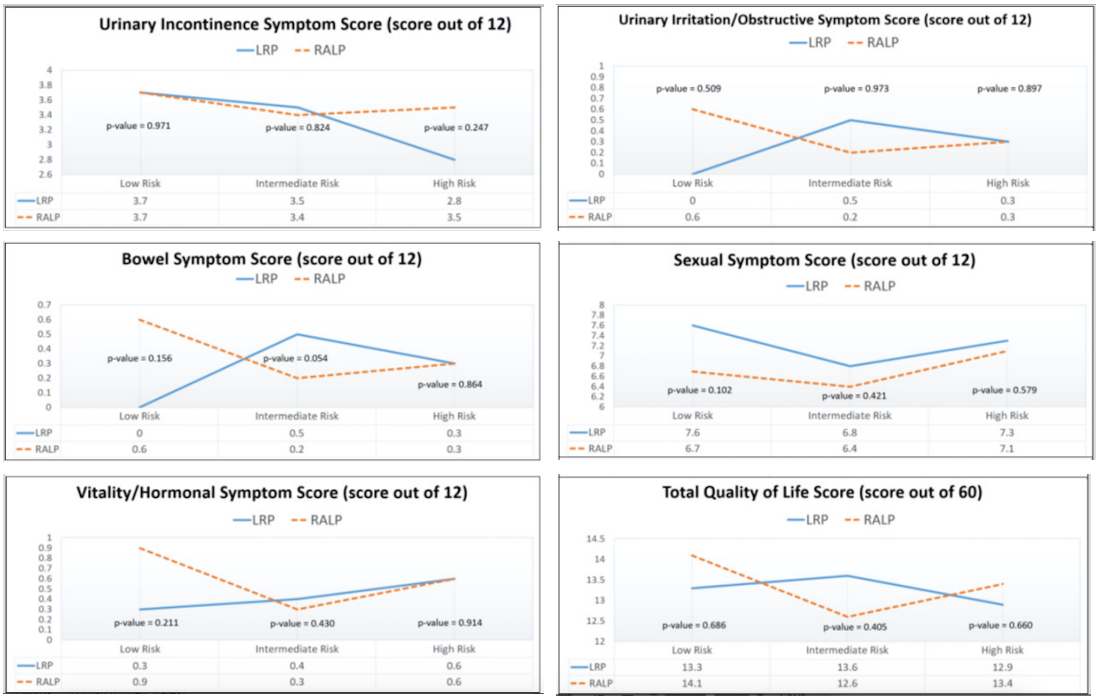

Figure 3. Prostate cancer related quality of life comparison between LRP and RALP.

radical prostatectomy (RRP), LRP, and RALP compared functional and oncologic outcomes, surgical complications, time to continence, potency rate, quality of life and cancer recurrence. Their analysis showed no differences in functional outcomes or in oncologic outcomes[5].

Our data must be viewed with some caution because we focused solely on the outcomes of the post-operative period and did not include the perioperative period outcomes. We cannot draw a conclusion that RALP had no clinical benefits in any manner. Some previous studies reported that the rate of perioperative morbidity was lower for RALP than for LRP. For example, the systematic review conducted by Ramsay et al. demonstrated that RALP had a lower rate of major adverse events, such as blood transfusion and organ injury. These researchers also predicted a probability of a positive margin of 17.6% following RALP, compared with 23.6% following LRP[7].

Some advantages of robotic surgery may not be measurable based on their clinical endpoints. For example, it is claimed that robotic surgery improves visualization, facilitates dissection and suturing, reduces the technical complexity, and shortens the learning curve when compared with traditional LRP. However, there is only limited evidence to confirmed these benefits or the impact of robotic surgery on clinical and economic outcomes. For this reason, our cost-effectiveness analysis had to be based principally on costs.

The high cost of RALP has been recognized since its introduction, and previous studies have explored the cost differences between LRP and RALP. For example, Bolenz et al. compared 643 consecutive radical prostatectomy operations (262 RALP, 220 LRP, and 161 RRP) and found a significantly higher median direct cost for RALP than for either LRP or RRP. The higher cost was predominantly due to the increased costs of surgical supplies and operation rooms.

In our study, we observed that the risk grouping did not have any impact on the inpatient hospital charges. In both the LRP and RALP cohorts, the low risk groups had similar mean inpatient costs to those observed for the high risk groups. This finding could reflect the fact that a majority of the expenditure was the fixed costs of each procedure and that the additional surgical or medical expenditures did not differ significantly among the risk groups. The fixed cost was largely due to the cost of purchasing the system and the cost of disposable surgical instruments, in agreement with previous studies[4,9,13,14]. The costs of drugs, blood transfusions, laboratory tests, doctors' fees, and anesthesia had a negligible impact on the total inpatient cost. We concluded that any benefits from RALP cannot be converted into net savings in terms of inpatient costs.

By contrast, the outpatient costs, which were highest in the high risk group, directly varied according to risk groups. This finding could be explained by the add-on costs of adjuvant treatments, as well as the higher rate of biochemical recurrence. The outpatient costs did not show statistically significant differences between the LRP and RALP cohorts. In the high risk group, the mean outpatient cost was slightly lower for RALP than for LRP. Future studies could explore this point by performing a prospective study or by increasing the number of patients in the high risk group. We did not take into account the indirect costs because the mean age of the patients in our study was the mid to late sixties. We assumed that the majority of these patients were retired from work. Therefore, we focused solely on the total direct medical costs.

We observed no significant benefit of RALP in terms of prostate cancer-related quality of life. This result was similar to that of the previous study by Hohwu et al., which included readmissions and adjuvant treatments within the first post-prostatectomy year. They retrospectively matched 77 consecutive RALPs with 154 RRPs based on the D'Amico risk, and they concluded that RALP was more effective with regard to cancer removal, continence, and erectile function. However, the health economic evaluation did not show any quality of life (QALY) gain 1 year after RALP[15]. A study by Close et al. found a small margin of QALY benefit over 10 years, with a mean (95% CI) of 0.08 (0.01–0.15). They concluded that RALP costs may be offset by modest health gains that result from a lower risk of early harm and positive margins, if RALP is performed on >150 cases each year[8].

In Thailand, the three major medical insurance schemes are: (1) the social security scheme (SSS) for private sector employees (16% of the total population), (2) the civil servant medical benefit scheme (CSMBS) for government employees as well as their families (8% of the total population), and (3) the universal health-care coverage scheme (UCS) (75% of the population). These facts complicated the cost-effective analysis from the Thailand health-care perspective when compared to developed countries, where most of the population is covered by compulsory health insurance and everyone has the right to the same benefits package and usually has equal access to prostate cancer treatment[16,17].

We acknowledge that cost of the procedures varies not only among institutions but also between centers and health care systems[14]. We conducted our study in a large teaching-university hospital (>1,000 beds). The findings in our study that a majority of patients had the CSMBS (56.72% in LRP group and 56.31% in RALP group) may reflect their privilege of having a free choice of public hospitals and reimbursement of almost all medical expenditures. By contrast, the patients with SSS had the least access to LRP and RALP (5.97% in LRP group and only 0.97% in RALP group) because they were limited by the contracted network and could only be reimbursed when they received their treatment within the network area. Although the data were not well collected, most of the patients in the SSS and the UCS received primary ADT (usually done by surgical castration) for the treatment of localized prostate cancer in provincial hospitals[1]. There is clearly a lot of room for improvement.

Will RALP ever be cost effective? An increase in case volumes or even extension of the criteria for surgery may lead to lower charges, and this has been proposed as a way to increase cost effectiveness of RALP[7,8]. The high cost of the robotic system may also change in the near future. Before 2012, the Intuitive surgical system held a market monopoly on robotic systems, so negotiating discounts or lowering the purchasing price was difficult[18]. The increasing competition among medical companies may lower the price. For example, the Revo-i robot by Meere Company (South Korea) had already been used for the Retzius-sparing RALP and data on 17 patients has been published; surgery cost cuts of 42 percent are expected[19,20]. The new Versius robotic system, designed and built by CMR surgical (Cambridge, UK), is expected to be used on patients for the first time in 2019. We encourage surgeons to keep abreast of robotic technology, because the price may be affordable for mid-sized or provincial hospitals in the upcoming years.

Our study was limited by the retrospective data collection, which possibly imposed a recall bias in the quality of life assessment. The lack of patient randomization or propensity score matching of the patients is an area of improvement to consider in future studies.

Conclusion

From the payer's perspective, RALP costs, which are attributable to the robotic equipment and supplies, are higher when compared to LRP costs. The clinical and quality of life benefits associated with RALP may not convert into a net savings in terms of total medical costs within 24 months after surgery.

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Conflict of Interest

The authors declare no conflict of interest.

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Original Article

Predictive factors of stone-free status in renal stone treatment with flexible ureterorenoscopy

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Keywords:
Flexible ureterorenoscopy, stone-free status, renal stone

Abstract

Objective: Flexible ureterorenoscopy (fURS) is one of the standard treatments for renal calculi up to 20 mm. This study aims to identify factors associated with stone-free status.

Materials and Methods: We included patients undergoing fURS for treatment of small to medium-size renal stone (no single stone larger than 20 mm) from April 2017 to September 2019 at King Chulalongkorn Memorial Hospital. All patients had a preoperative CT scan and postoperative imaging for comparison. We collected patient characteristics (sex, age, previous ipsilateral urinary tract surgery, preoperative ureteral stent placement), stone factors (total stone burden, stone number, stone density) and renal factors (anatomical abnormalities, stone location in a lower pole, number of caliceal involvement) and correlated the data against postoperative stone-free status (defined as residual fragment ≤ 2 mm).

Results: The overall stone-free rate was 53.3%. From the univariate analysis, previous surgery, total stone burden, stone number, stone location in the lower pole, and the number of caliceal involvement were associated with stone-free status. However, only the total stone burden remained statistically significant in the multivariate analysis (p-value < 0.05). The stone-free rates were 75.9%, 57.1%, and 11.1% in the total stone burden ≤ 10 mm, 11-20 mm, > 20 mm, respectively.

Conclusion: Following treatment of renal stones ≤ 20 mm with fURS, the stone-free rate was 53.3% and was significantly associated with the preoperative total stone burden.

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Introduction

Flexible fiber-optic ureterorenoscopy was first introduced in the 1960s for diagnostic purposes but the technique was unable to apply any therapeutic procedure due to a lack of a deflecting system and working channel[1-3]. Later, the development of the deflecting system, working channel, and holmium: YAG laser made it possible to treat renal stones[1,2,4]. However, poor durability of the fiber optics was a major limitation from a wide adoption of this procedure. Subsequent development of flexible digital ureterorenoscopy in the 2010s had a significant impact on renal stone treatment. The digital system improved the stone visualization, scope durability and offered improved ergonomics[1,2].

According to the European Association of Urology (EAU) guidelines on urolithiasis, flexible ureterorenoscopy (fURS) is one of the standard treatments for renal stone up to 20 mm. Depending on stone size and location, fURS is suitable for a non-lower pole < 20 mm, lower pole stone < 10 mm, and lower pole stone 10-20 mm, which is unfavorable for SWL[5]. However, the treatment selection is more complicated in real-life practice. Many patients, especially in Thailand, have a complex stone burden beyond the guideline algorithm. In addition, fURS is invasive and potentially leads to perioperative complications such as urinary tract infection, ureteral injury and ureteral stricture[5,6].

This study primarily aims to identify predictive factors associated with stone-free status for treatment of renal stone up to 20 mm. The secondary purpose is to determine the correlation between the stone-free rate and the predictive factors.

Materials and Methods

Patients

This study was a retrospective cross-sectional study of adult patients undergoing fURS for stone treatment at King Chulalongkorn Memorial Hospital from April 2017 to September 2019. All patients had small to medium-size kidney stones with no single stone larger than 20 mm based on a preoperative CT scan. Exclusion criteria were patients at the extremity of age (< 18 or > 80 years old), presence of any single stone larger than 20 mm, failure to approach into the renal pelvis, and incomplete perioperative imaging. We collected patient characteristics (sex, age, previous ipsilateral urinary tract surgery, preoperative ureteral stent placement), stone factors (total stone burden, stone number, stone density), renal factors (anatomical abnormalities, number of caliceal involvement) and lower pole factors (infundibulum width, infundibulum length, infundibulopelvic angle) if stone was presenting in the lower pole. Stone size was defined as the longest axis of each stone (millimeters), stone density was defined as a mean of three times the measurement of stone density (Hounsfield Unit). For patients with multiple stones, the total stone burden was a sum of all stone sizes, and stone density was a mean density of all stones.

Operation techniques

All procedures were performed under general anesthesia in a lithotomy position by a single surgeon. Fluoroscopic guidance was utilized for instrumental navigation, and a 12/14 French ureteral access sheath (Bi-Flex EVO, Rocamed, Monaco) was applied in all cases. We only used flexible digital ureterorenoscope (URF-V, Olympus Medical System, Tokyo, Japan). Lithotripsy was performed with a 30-watt holmium: YAG laser machine (Sphinx Holmium Laser, LISA Laser Products GmbH, Katlenburg-Lindau, Germany), either with a fragmenting or dusting technique. Active stone retrieval was done with a 1.3 French tip-less nitinol basket (Optiflex, Boston Scientific Marlborough, MA, USA). At the end of the procedure, the ureteral access sheath was removed under vision, and a double-J stent was placed based on surgeon decision.

Follow up

All patients did not receive any medical chemolysis and underwent postoperative imaging (plain KUB, renal ultrasonography, or non-contrast CT scan) two months after the procedures. Stone-free status was defined as no fragment left or residual stone fragment ≤ 2 mm.

Data analysis

Patients were classified into two groups; the stone-free group and the non-stone-free group. Patient characteristics were compared between the two groups. Qualitative data are presented as number (%). Quantitative data are shown as mean (standard deviation) or median (interquartile

range). Statistical significance between the two groups was determined. Categorical variables were analyzed using a chi-square test, and continuous variables were analyzed with a two-sample independent t-test and Wilcoxon rank-sum test. Statistical significance was considered at p-value < 0.05. Binary logistic regression was applied for univariate analysis. Factors with a p-value < 0.1 from the univariate analysis were subsequently included in the multivariate analysis. Binomial distribution was applied to calculate the stone-free rate and 95% confidence interval from significant factors. Statistical analysis was carried out using STATA version 15.1 (StataCorp, College Station, TX, United States).

Table 1. Patient's characteristics.

Characteristic	Total (N=75)	Stone free (N=40)	Non-stone free (N=35)	P-value
Patient's baseline				
Sex ----- no. (%)				0.23
Male	31 (41.3)	14 (35)	17 (48.6)	
Female	44 (58.7)	26 (65)	18 (51.4)	
Age ----- mean years (SD)	52.8 (13.5)	51.4 (13.7)	54.5 (13.4)	0.31
Previous urinary tract surgery ----- no. (%)				0.006
Yes	28 (37.3)	9 (22.5)	19 (54.3)	
Endoscopic ureteric procedure	19 (25.3)	9 (22.5)	10 (28.6)	
PCNL	4 (5.3)	0 (0)	4 (11.4)	
Open renal procedure	3 (4)	0 (0)	3 (8.6)	
Endoscopic ureteric procedure and PCNL	1 (1.3)	0 (0)	1 (2.9)	
Open ureteric procedure and PCNL	1 (1.3)	0 (0)	1 (2.9)	
No	47 (62.7)	31 (77.5)	16 (45.7)	
Preoperative ureteral stent placement				0.1
Yes	23 (30.7)	9 (22.5)	14 (40)	
No	52 (69.3)	31 (77.5)	21 (60)	
Stone factor				
Total stone size ----- median mm. (IQR)	12 (8-20)	10 (6-14.5)	19 (12-28)	< 0.001
Stone number ----- median no. (IQR)	2 (1-3)	1 (1-2)	2 (2-3)	< 0.001
Stone density ----- median HU (IQR)	705 (482-954)	668 (447-996)	820 (584-949)	0.28
Anatomical factor				
Anatomical abnormality ----- no. (%)				0.01
Yes	6 (68)	0 (0)	6 (17.1)	
UPJO	1 (1.3)	0 (0)	1 (2.9)	
Bifid renal pelvis	3 (4)	0 (0)	3 (8.6)	
Kidney malrotation	2 (2.7)	0 (0)	2 (5.7)	
No	69 (92)	40 (100)	29 (82.9)	
Stone location in lower pole ----- no. (%)				0.005
Yes	50 (66.7)	21 (52.5)	29 (82.9)	
Lower pole and non-lower pole	23 (30.7)	7 (17.5)	16 (45.7)	
Only lower pole*	27 (36)	14 (35)	13 (37.1)	
No	25 (33.3)	19 (47.5)	6 (17.1)	
Number of caliceal involvement ----- median no. (IQR)	1 (1-2)	1 (1-2)	2 (1-3)	0.001
***Only lower pole stone**	**Total (N = 27)**	**Stone free (N = 14)**	**Non-stone free (N=13)**	**P-value**
Infundibulum width ----- mean mm. (SD)	5.2 (2.7)	5 (2.8)	5.5 (2.6)	0.66
Infundibulum length ----- mean mm. (SD)	25.7 (4.3)	25.4 (3.7)	26.1 (5)	0.7
Infundibulopelvic angle ----- median degrees (IQR)	33 (21.2-55.1)	33.7 (21.3-55.1)	32.9 (16.7-51.2)	0.72

Results

A total of 133 flexible ureterorenoscopy procedures was reviewed during the study period. Nineteen procedures were excluded due to them being in the non-target population. Thirty-nine procedures were excluded due to incomplete clinical or imaging data. Finally, a total of 75 procedures were analyzed and classified into a stone-free group (n = 40, 53.3%) and a non-stone-free group (n = 35, 46.7%) (Figure 1). Females (n = 44) slightly predominated males (n = 31), and the mean age at operation was 52.8 years. The majority of clinical characteristics of both groups were similar, exceptions being previous ipsilateral urinary tract surgery, total stone burden, stone number, anatomical abnormality, presence of stone in the lower pole, and a number of caliceal involvement (Table 1).

Univariate analysis revealed five clinical factors were significantly associated with stone-free status including the absence of previous ipsilateral urinary tract surgery (OR = 4.09, p-value = 0.006), a total stone burden less than 20 mm (OR = 25.14, p-value < 0.001 for stone burden ≤ 10 mm and OR = 10.67, p-value = 0.005 for stone burden 11-20 mm), the presence of a single stone (OR = 6, p-value = 0.001), the absence of stone in the lower pole (OR = 4.37, p-value = 0.007), and the presence of stone in a single calyx (OR = 3.98, p-value < 0.001) (Table 2).

Subsequently, these five factors were included in the multivariate analysis. The only factor sig-

Table 2. Odds ratio of factors in the univariate and multivariate analysis.

Parameter	Total (N=75)	Stone free (N=40)	Non-stone free (N=35)	Univariate analysis			Multivariate analysis		
				Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value
Previous urinary tract surgery									
No	47	31	16	4.09	1.51-11.08	0.006	correlate with stone number		
Yes	28	9	19		reference				
Preoperative ureteral stent placement									
Yes	23	9	14	0.44	0.16-1.18	0.11	-		
No	52	31	21		reference				
Total stone size									
≤ 10 mm	29	22	7	25.14	4.60-137.4	< 0.001	11.14	1.67-74.1	0.01
11-20 mm	28	16	12	10.67	2.05-55.52	0.005	6.72	1.20-37.76	0.03
> 20 mm	18	2	16		reference			reference	
Stone number									
1	31	24	7	6.00	2.11-17.01	0.001	2.25	0.66-7.60	0.19
≥ 2	44	16	28		reference			reference	
Stone density									
< 500 HU	19	12	7	0.69	0.15-3.04	0.62	-		
500-999 HU	42	18	24	0.30	0.08-1.11	0.07			
≥ 1000 HU	14	10	4		reference				
Anatomical abnormality									
No	69	40	29		n/a				
Yes	6	0	6		reference				
Stone location in lower pole									
No	25	19	6	4.37	1.49-12.82	0.007	2.04	0.61-6.86	0.25
Yes	50	21	29		reference			reference	
Number of caliceal involvement									
1	39	27	12	3.98	1.52-10.41	0.005	correlate with stone number		
≥ 2	36	13	23		reference				

Table 3. Significant factors related to stone-free percentage rates.

Parameter	n/N	Stone free rate (%)	95% CI	P-value
Total stone size				< 0.001
≤ 10 mm	22/29	75.9	56.5-89.7	
11-20 mm	16/28	57.1	37.2-75.5	
> 20 mm	2/18	11.1	1.4-34.7	

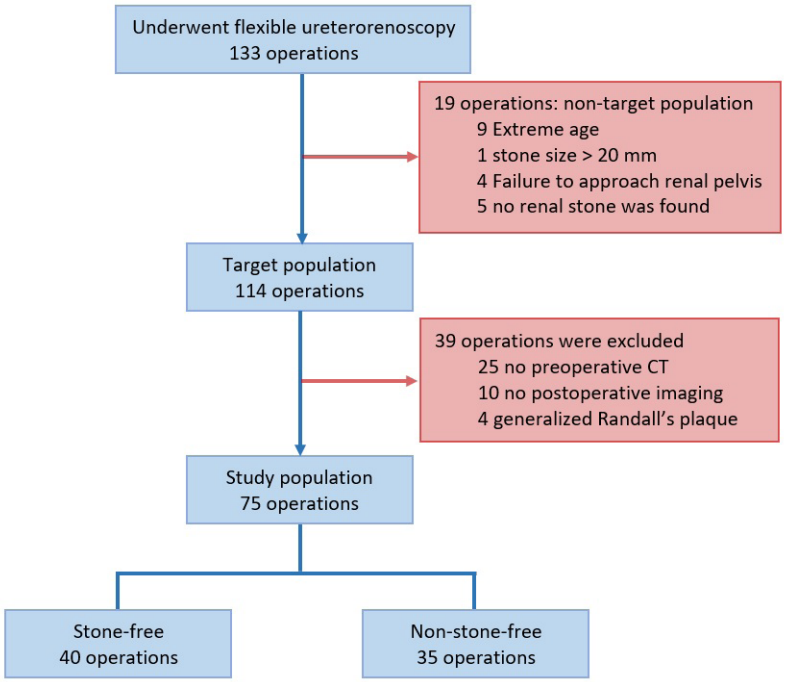

Figure 1. Flow chart

nificantly correlated to stone-free status was the total stone burden less than 20 mm (OR = 11.14, p-value = 0.01 for stone burden ≤ 10 mm and OR = 6.72, p-value 0.03 for stone burden 11-20 mm) (Table 2). The stone-free rates were 75.9%, 57.1%, and 11.1% for the total stone burden ≤ 10 mm, 11-20 mm, and > 20 mm, respectively (Table 3).

Stone-free status was not affected by the learning curve of the physicians. We divided 75 procedures into three groups chronologically: the first case to the twenty-fifth case, the twenty-sixth case to the fiftieth case, and the fifty-first case to the seventy-fifth case. The stone-free rates were 60%, 60% and 40%, respectively.

Discussion

Previous studies have determined several factors to be associated with stone-free status. Some studies have proposed a scoring system predictive for stone-free status. The Resorlu-Unsal Stone Score (RUSS) includes four clinical conditions (stone size > 20 mm, lower pole stone location with infundibulopelvic angle < 45°, stone involvement in more than one calyx, and abnormal renal anatomy)[7]. The modified S-ReSC score included the number of caliceal involvement from 9 sites[8]. The R.I.R.S scoring system consisted of stone density, stone in the lower pole with infundibulopelvic angle < 30°, infundibulum length, and stone burden[9]. One study by Tonyali et al. proposed that the lower pole stone location and the use of a ureteral access sheath were significant factors[10].

We included almost all of these potential factors in our analysis, which finally revealed that the total stone burden of less than 20 mm was the only factor significantly correlated to stone-free status. This finding is consistent with others and is stated in the current guidelines issued by the EAU and AUA/Endourological Society. These guidelines mention that the stone-free rate of fURS declines with increased stone burden, and a staged procedure might be required in cases of stone burden more than 20 mm[5,11].

The main limitation to our study was the relatively small number of included patients. One-third of total patients undergoing fURS during the study period were excluded due to incomplete data. Further limitations were that the study results were derived from a single institution, which makes generalization of the findings difficult and also a variety of imaging modalities was used to assess stone-free status, and an interpretation bias may be unavoidable.

Conclusion

Stone-free rate of fURS for treatment of renal stone < 20 mm was 53.3%. The only predictive factor for stone-free status was the total stone burden, which revealed a stone-free rate of 75.9%, 57.1%, and 11.1% for the total stone burden ≤ 10 mm, 11-20 mm, and > 20 mm, respectively.

Conflict of Interest

The authors declare no conflict of interest.

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Original Article

The association between relative leukocyte telomere length of prostate cancer patients at diagnosis with cancer prognostic parameters

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Keywords:
Leukocyte telomere length, prostate cancer, castration resistance, metastasis, survival

Abstract

Objectives: In this study, relative leukocyte telomere length (LTL) was investigated as a prognostic marker to evaluate association of LTL at the time of diagnosis and prostate cancer-specific survival, metastasis-free survival, overall survival, with castrate-resistant prostate cancer (CRPC).

Materials and Methods: In this retrospective cohort study, pertinent data from 81 patients were collected. Patients underwent prostate cancer (PCa) treatment procedures determined by staging and current recommendation. Blood samples from suspected PCa patients were obtained before the initiation of diagnosis and treatment. LTL was determined by the quantitative polymerase chain reaction method. Relative LTL was compared to the main clinical outcome measures. Prostate cancer-specific survival, metastasis-free survival, overall survival and CRPC were calculated retrospectively, for a mean follow-up period of 30 months.

Results: This analysis showed relative LTL was not associated with tumor stage, Gleason score, grade group, metabolic disease, or smoking. However, older age was significantly associated with short LTL ($p < 0.001$). All main outcomes were not associated with LTL. In contrast, a subgroup analysis of patients who underwent primary androgen deprivation therapy (ADT) showed a CRPC association with relatively long LTL ($p = 0.039$). To our knowledge, these results are novel and give further strength to our hypothesis that relative LTL might be used as a prognostic marker in PCa especially in patients who will receive primary ADT.

Conclusion: Aging was significantly associated with relatively short LTL. There was no significant association between LTL in PCa patients at diagnosis and cancer-specific survival, metastasis-free survival, or overall survival. However, patients who underwent ADT treatment alone showed CRPC associated with relatively long LTL.

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Introduction

At present, aging is an important risk factor in relation to disease development. Malignancy, degenerative diseases, metabolic syndrome and cardiovascular disease are associated with advanced age. The length of telomere is a known marker of biological aging[1]. Metabolic diseases, cardiovascular diseases, and heavy smoking are also associated with shortened telomere length[2-5].

Current research has produced varying results regarding relative leukocyte telomere length (LTL). One study showed that telomere length of prostatic cancer cells was shorter than in normal prostatic cells[6]. Nevertheless, other studies reported that LTL between prostate cancer (PCa) patients and non-PCa patients, benign prostatic hypertrophy and prostatitis, were not significantly different[7,19]. A meta-analysis demonstrated that shortened LTL is associated with the risk of cancer[8]. Some studies showed an association between shorter LTL and worse cancer outcomes[9-11], but several prospective studies showed an association between long LTL and the increasing risk of certain cancers[12-15]. Some studies demonstrated a null association between cancer risk and LTL[16,17]. The most probable explanation of differences between the results included genetics, epigenetics, immune components, hormones and stress[18]. Moreover, differences in study design (retrospective vs prospective), type of cancer, and technical variability of LTL measurement by real time polymerase chain reaction could have impact on the results and create variation.

Currently, the prevalence of PCa is increasing and is one of the most common male cancer mortalities, therefore, diagnostic and prognostic factors for PCa are very important in enabling early diagnosis and informing choice of treatment dependent on risk classification. Unfortunately, to date, past and ongoing studies have not furnished significant data on the potential association of relative LTL with prognostic markers of PCa. In one prospective cohort study, longer LTL at baseline was a significant PCa risk factor[15]. Another study found that patients with long LTL (median) had a significantly worse prostate cancer–specific and metastasis-free survival rate compared to patients with short LTL[19]. However, another recent study found shorter LTL was associated with a significantly increased risk of biochemical recurrence in localized PCa patients receiving radical prostatectomy and radiotherapy[20]. This study aimed to elucidate the association of relative LTL as a prognostic marker of various aspects of prostate cancer including cancer-specific survival, overall survival, metastasis-free survival and relation of CRPC.

Materials and Methods

This study was conducted in the Division of Urology, Department of Surgery, Maharaj Nakorn Chiang Mai Hospital, Chiang Mai, Thailand. The study protocol was approved by the Research Ethics Committee, Faculty of Medicine, Chiang Mai University. This was a retrospective study including data from 87 patients diagnosed with PCa between March 2017 and December 2018 in Maharaj Nakorn Chiang Mai Hospital. Data from six cases was excluded due to missing key parameters including TNM stage, Gleason score, PSA at diagnosis, PSA nadir level, month of death, or month of CRPC. The LTL from genomic DNA (20 ng/mL) was evaluated at baseline before initiation of any treatment by the monochromic multiplex-quantitative real-time polymerase chain reaction method (MMQPCR), as previously described in Cawthon RM. and Shen M. et al[21,22].

Briefly, the T/S value was calculated as the ratio of telomere repeat copies (T) to single-copy-gene number and albumin gene (S) to represent the average length of telomere. In each sample, the quantity of telomere repeats, and single-copy-gene copies were determined and compared to the reference samples. All samples were assayed in triplicate to minimize the sample-to-sample variation. Once the PCR was completed, the Applied Biosystems QuantStudio™ 6 Flex Real-Time PCR analysis software was used to determine the T and S values for each experimental sample based on the standard curve method (Applied Biosystems, Foster City, CA, USA). The results were expressed in terms of T/S ratio or LTL.

Clinical data including age, weight, height, waist circumference, underlying diseases and current medication were collected. The laboratory data including serum PSA, fasting blood glucose, LDL, HDL, triglycerides, Gleason score and grade group reported were recorded.

Data from PCa patients included choice of treatment (radical prostatectomy, external beam radiation therapy, androgen deprivation therapy), stage after follow-up, time to metastasis,

time to death, time to castration resistance and cause of death. Details of pathologic stage and pathologic grade group were collected if the patient underwent radical prostatectomy. Decline in velocity, time to PSA nadir and PSA nadir were collected if the patient underwent primary ADT.

Fisher's exact test was used to compare LTL to clinical parameters including age, smoking, metabolic syndrome, Gleason score, T stage, stage of cancer, metastatic cancer and CRPC. All parameters were observed retrospectively, for a mean follow-up period of 30 months. Survival analysis was performed using Kaplan–Meier survival curves with the log-rank test; univariate comparison was investigated to determine if they carry any prognostic information. The patients were subdivided into two groups, with the median LTL (value 5.3) as the cut-off and with PC-specific death, overall death, time to metastasis, and time to castration resistance as the event. Statistical significance was determined as p-value < 0.05.

Results

Complete data from 81 patients were collected. Baseline characteristics of patients are reported in Table 1. The mean age of prostate cancer patients was 69.35 years old. 43.2% were aged over 70 years of age. Only 27.5% patients had smoked more than 15-pack-years. About 39% were diagnosed with metabolic syndrome. Notably, many cases in this study were locally advanced (45.7%) and metastasis had occurred (34.6%).

Median LTL was 5.3 which became a cut-off point to dichotomize the data. As expected, patients over 70 years old were significantly associated with short LTL ($p < 0.001$). In contrast, other factors including smoking, metabolic syndrome, Gleason score, T stage, stage of cancer, metastatic cancer and castrate resistant cancer were not associated with LTL with p values of 0.45,1.0, 0.51, 0.59, 0.41, 0.24 and 0.57 respectively (Table 2). In line with current studies, factors including T stage, stage, Gleason score, CRPC and metastasis were factors which significantly impact overall survival with p-values < 0.001, 0.009, 0.018, 0.008 and < 0.001 respectively. The main outcome of this study was that prostate cancer-specific survival and overall survival were not associated with relative LTL with p values of 0.769 and 0.206 respectively (Figure 1 and 2). Four patients developed metastasis in the median follow-up time, so metastasis-free survival could not be analyzed or interpreted.

Table 1. Demographic data

Parameters	N=81
Age (years)	
Mean (SD)	69.35 (8.09)
Median	68
Age group (years) n (%)	
≤ 70	46 (5679)
> 70	35 (43.21)
Label smoker n (%)	
Yes	22 (27.50)
No	58 (72.50)
Metabolic syndrome n (%)	
Yes	30 (38.96)
No	47 (61.04)
Telomere length mean (SD) median	5.43 (0.72), 5.3
Telomere length	
≤ 5.3	44 (54.32)
> 5.3	37 (45.68)
Stage n (%)	
IIa, IIb and IIc	16 (19.75)
IIIa, IIIb, IIIc, IVa and IVb	65 (80.25)
Gleason score n (%)	
< 7	14 (17.28)
≥ 7	67 (82.72)
Metastasis n (%)	
Yes	28 (34.57)
No	53 (65.43)
Treatment n (%)	
ADT	37 (45.68)
RP	33 (40.74)
EBRT+ADT	7 (8.64)
WW	2 (2.47)
AS	2 (2.47)
CRPC n (%)	
Yes	15 (18.52)
No	66 (81.48)
Survival n (%)	
Survived	67 (82.72)
Death	14 (17.28)

There were 37 patients (45.7%) who underwent primary androgen deprivation therapy (ADT). In the subgroup analysis of this group, CRPC was significantly ($p = 0.039$) associated with long LTL. However, decline velocity (≤ 9 month) and time to PSA nadir (≤ 11ng/mL/month) showed no correlation with LTL (Table 3). However, CRPC was associated with decline velocity (≤ 9 month), time to PSA nadir (≤ 11ng/

Table 2. Association of relative LTL and other parameters.

Parameters	Telomere length		P-value
	≤ 5.3 (n=44)	> 5.3 (n=37)	
Age (years) n (%)			< 0.001
≤ 70	17 (38.64)	29 (78.38)	
> 70	27 (61.36)	8 (21.62)	
Smoker			0.452
Yes (%)	14 (31.82)	8 (22.22)	
No (%)	30 (68.18)	28 (77.78)	
Metabolic syndrome n (%)			1.000
Yes	16 (39.02)	14 (38.89)	
No	25 (60.98)	22 (61.11)	
T stage n (%)			0.586
T1c, T2a, T2b and T2c	17 (38.64)	18 (48.65)	
T3a, T3b	12 (27.27)	10 (27.03)	
T4	15 (34.09)	9 (24.32)	
Stage n (%)			0.407
IIa, IIb and IIc	7 (15.91)	9 (24.32)	
IIIa, IIIb, IIIc, IVa and IVb	37 (84.09)	28 (75.68)	
Gleason score			0.407
≤ 7	18 (40.91)	18 (48.65)	
> 7	26 (59.09)	19 (51.35)	
Metastasis			0.243
Yes	18 (40.91)	10 (27.03)	
No	26 (59.09)	27 (72.97)	
CRPC			0.574
Yes	7 (15.91)	8 (21.62)	
No	37 (84.09)	29 (78.38)	
Survival			0.126
Survived	30 (68.18)	31 (83.78)	
Dead	14 (31.82)	6 (16.22)	

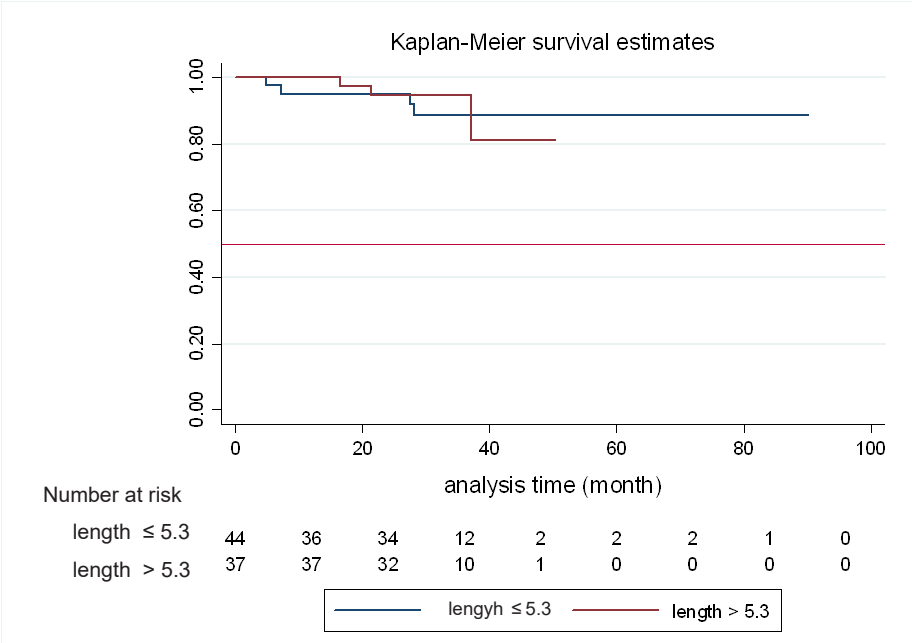

Figure 1. Cancer specific free survival estimates by relative leukocyte telomere length.

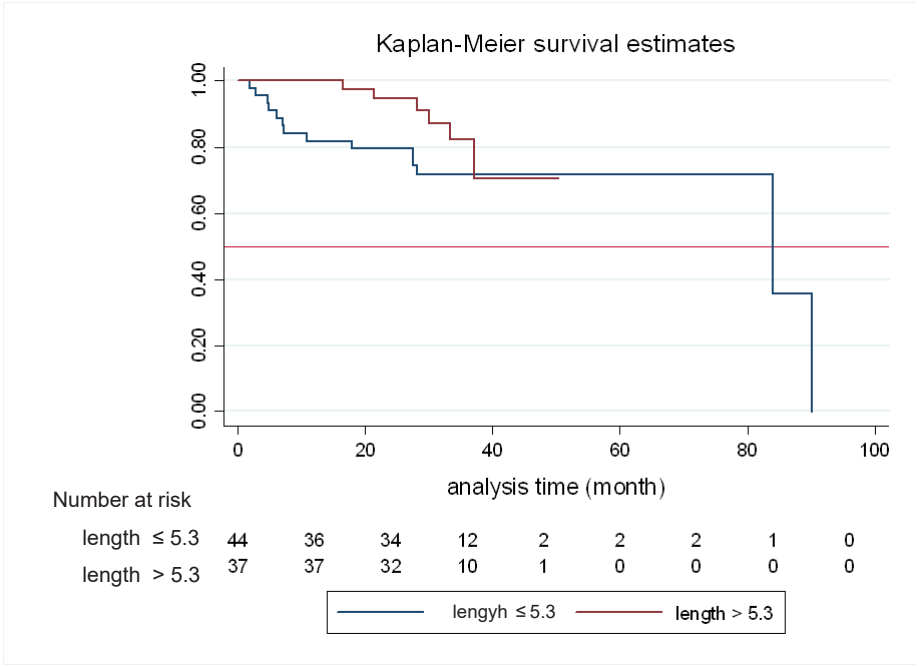

Figure 2. Overall survival estimates by relative leukocyte telomere length.

Table 3. Subgroup analysis of patients who underwent primary ADT compared with relative LTL and other parameters.

Parameters	Telomere length		P-value
	≤ 5.3 (n=24)	> 5.3 (n=13)	
CRPC n (%)			0.039
Yes	6 (25.00)	8 (61.54)	
No	18 (75.00)	5 (38.46)	
Time to PSA nadir n (%)			0.091
≤ 9 months	11 (45.83)	10 (76.92)	
> 9 months	13 (54.17)	3 (23.08)	
Decline velocity n (%)			0.300
≤ 11 ng/ml/month	13 (54.17)	4 (30.77)	
> 11 ng/ml/month	11 (45.83)	9 (69.23)	
PSA nadir			0.512
Mean (SD)	26.82 (72.84)	51.15 (151.00)	
Median	1.05	4.50	

mL/month) and PSA nadir ≥ 0.2 ng/mL with P-values of 0.007, 0.040 and 0.007 respectively (Table 4).

Discussion

In this study, we investigated the association between relative LTL and prognostic markers of various aspects of prostate cancer including cancer-specific survival, overall survival, metastasis-free survival, and castrate-resistant prostate cancer. We found that the only factor which affects the LTL was old age (more than 70 years old).

Patients who undergo ADT inevitably show progression to CRPC[23]. We are reporting a novel finding, specifically that a relatively long LTL measurement in newly diagnosed patients with primary ADT may be correlated with an increased risk of progression to CRPC. In this group, patients with long LTL had significantly more CRPC in 30 months of follow-up. CRPC was correlated with decreased PCa-specific survival, metastasis-free survival, and overall survival. This finding was in line with data from Svenson et al.[19] and Renner et al.[24]

Svenson et al.[19] measured LTL in 272 PCa patients (162 controls and 110 newly diagnosed PCa). This study excluded high-grade prostatic intraepithelial neoplasia (PIN) and other cancers.

Table 4. Subgroup analysis of patients who underwent primary ADT compared with CRPC and other parameters.

Parameters	CRPC		P-value
	Yes (n=14)	No (n=23)	
Telomere length n (%)			0.039
≤ 5.3	6 (42.86)	18 (78.26)	
> 5.3	8 (57.14)	5 (21.74)	
Time to PSA nadir n (%)			0.007
≤ 9 months	12 (85.71)	9 (39.13)	
> 9 months	2 (14.29)	14 (60.87)	
Decline velocity n (%)			0.040
≤ 11 ng/ml/month	3 (21.43)	14 (60.87)	
> 11 ng/ml/month	11 (78.57)	9 (39.13)	
PSA nadir			0.007
< 0.2 ng/ml	0 (0.00)	9 (39.13)	
≥ 0.2 ng/ml	14 (100.00)	14 (60.87)	

LTL was evaluated in relation to PCa diagnosis, risk classification and level of serum PSA. This study is reporting that PCa patients with long LTL(≥ median) had a significantly worse PCa-specific and metastasis-free survival compared to those with short LTL and confirmed the use of LTL as a prognostic marker for PCa. Another study by Renner et al.[24] reported that longer LTL predicts higher overall mortality in patients with PCa on EBRT +/- ADT.

Ji G. et al.[25] studied 185 patients with PCa who had received ADT as the primary therapy. That study reported the presence of distant metastasis before ADT, higher PSA nadir, and a velocity of PSA decline > 11ng/mL per month. They further determined that a time to PSA nadir ≤ 9 months was significantly associated with an increased risk of progression to CRPC. In line with our findings from the subgroup analysis of patients who underwent primary ADT, a higher PSA nadir of more than 0.2 ng/mL, a velocity of PSA decline > 11ng/mL per month, and a time to PSA nadir ≤ 9 months were significantly associated with an increased risk of progression to CRPC (Table 4). However, we were unable to demonstrate a significant correlation of these parameters with LTL but not CRPC which may be associated with long LTL.

Due to a limitation of the study, we could not show a significant main outcome related to PC-specific death, overall death, or time to metastasis. We had a small number of patients compared with prior studies. In addition, the short follow-up (median time only 30 months) may have affected our outcomes, especially the time to metastasis and time to death. Furthermore, only baseline blood samples were taken; thus, no analyses of LTL such as telomere shortening dynamics were available during follow-up. In future studies these limitations would need to be addressed to add weight to the findings.

Conclusion

In this study, aging was significantly associated with relatively short LTL. We found no significant association between telomere length of prostate cancer patients at diagnosis, cancer specific survival, metastasis-free survival, or overall survival. However, the subgroup analysis of patients who underwent ADT treatment alone showed castrate-resistant prostate cancer may associated with relatively long LTL. Future large, prospective-longitudinal studies are needed to confirm these initial findings.

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Conflict of Interest

The authors declared no conflict of interest.

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Original Article

Renal function of bladder cancer patients after urinary diversion by ileal conduit in Rajavithi Hospital

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Keywords:
Renal function, bladder cancer, urinary diversion, ileal conduit

Abstract

Objectives: Our objectives were to evaluate the long-term renal function after radical cystectomy (RC) and ileal conduit diversion (ICD) and to analyze year-by-year the estimated glomerular filtration rate (eGFR) and morphologic upper urinary tract changes.

Materials and Methods: We retrospectively identified 214 patients who had undergone RC and ICD from 2012 to 2018, with regular postoperative follow-up visits. The eGFR was calculated using the Modification of Diet in Renal Disease equation at baseline and during follow-up. A renal function decrease was defined as a greater than 10 mL/min/1.73 m^2 reduction in the estimated glomerular filtration rate.

Results: The median follow-up period after RC was 24 months (range, 6-60 months). The median eGFR decreased from 64 mL/min/1.73 m^2 (range, 9-125 mL/min/1.73 m^2) to 61.5 mL/min/1.73 m2 (range, 8-125 mL/min/1.73 m^2). A decline in renal function occurred during the first postoperative years (2.74 mL/min/1.73 m^2 and 3.95 mL/min/1.73 m^2 in the first and second year, respectively), with a slight decrease in the subsequent years. The strongest predictor of an eGFR decline was CKD stage 1 or 2 (> 60 mL/min/1.73 m^2). Urinary obstruction was diagnosed in 6 patients (2.8%). Among the patients who underwent prompt interventional treatment, we did not find any association with the eGFR decline.

Conclusion: Patients with urinary ICD have a lifelong risk of chronic kidney disease. Regular monitoring of renal function and the morphologic upper urinary tract will permit early diagnosis and treatment of modifiable factors, avoiding irreversible kidney damage.

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Introduction

Chronic kidney disease (CKD) has been identified as an independent risk factor of death, cardiovascular events, and use of specialized healthcare. It is probable that commonly used drugs and surgical intervention can adversely affect several aspects of kidney function.

Although it remains the reference standard treatment of muscle invasive and high-risk urothelial bladder carcinoma, radical cystectomy (RC) is associated with significant risks of perioperative and long-term morbidity and mortality, notably due to renal function impairment. Despite the variety of diversion techniques used, either continent or incontinent, patients undergoing RC have a life-long risk of CKD[1]. Several factors have been identified to explain the renal function decrease, including nonmodifiable parameters such as age, the nephrotoxicity of chemotherapy or medical treatment, chronic hypertension, and diabetes mellitus, and potentially modifiable factors, including mechanical obstruction and urinary tract infection[2].

However, the natural history and long-term follow-up data of renal function decline in patients treated by RC for urothelial bladder cancer have been poorly reported[3,4]. Furthermore, most of the studies have evaluated variation in renal function using serum creatinine as a surrogate value for the estimated glomerular filtration rate (eGFR). Although the reference standard for renal function evaluation is the measured GFR, equations estimating the GFR have been considered to be the better measure of overall kidney function in routine clinical practice. In this study, we analyzed the year-by-year eGFR variations and morphologic upper urinary tract changes in patients who had undergone RC and urinary ICD for urothelial bladder cancer

Materials and Methods

This research was an observational study approved by Rajavithi Hospital Ethics Committee. Data was collected from the medical records of bladder cancer patients which had undergone Radical Cystectomy for localized muscle-invasive bladder cancer in Rajavithi Hospital, from 1 Jan 2012 - 31 December 2018.

Exclusion criteria

- End stage kidney disease which required renal replacement therapy
- Preoperative eGFR < 15 mL/min/1.73 m^2
- Cutaneous ureterostomy
- Ureterosigmoidostomy

The clinical variables evaluated included age, gender, diabetes mellitus, preoperative chronic hypertension, preoperative hydronephrosis, baseline and follow-up eGFR, and receipt of perioperative systemic chemotherapy.

Surgical technique

All patients underwent pelvic lymphadenectomy before RC was performed. An ileal segment 15 to 20 cm long was isolated approximately 15 cm proximal to the ileocecal valve. The ureters were split and anastomosed separately in the ileal segment. Ureteroileal anastomoses were performed using either the direct implantation Bricker (23%) or the Wallace technique (77%). The ureteral catheter was brought directly through the ileal segment and secured to the abdominal skin. The ileal segment was oriented in the isoperistaltic direction and anastomosed to the abdominal wall in a nipple-tostoma fashion. The ureteral catheters were removed on the 13^{th} or 14^{th} day postoperative.

Patient follow-up data and data collection

The patients were followed up regularly at our department or their local hospital at 1, 3, and 6 months, and annually thereafter. At each visit, the patients' blood pressure, complete blood count, and serum creatinine, were determined and urine culture was completed. Renal ultrasonography or abdominopelvic computed tomography were performed alternatively every 6 months for 2 years and annually thereafter. The radiologists diagnosed hydronephrosis by measuring the anteroposterior diameter of the renal pelvis. The images of the upper urinary tract were compared with previous images to determine the presence of any radiologic changes. We focused our evaluation on postoperative complications, including mechanical urinary obstruction, urinary tract infection, and urolithiasis. Urinary tract obstruction was documented in patients with hydronephrosis secondary to ureteroileal stricture and/or stomal obstruction. In these instances patients underwent repeat surgery, and the obstruction resolved. The designation of recurrent urinary tract infection was determined by bacteriuria of % 10^5 colony-forming units lasting ≥ 3 months per year, whether or not symptomatic.

Pyelonephritis was defined as a febrile episode with a positive urine culture after excluding any other cause for the fever.

Renal function evaluation

The GFR was the primary outcome measured. It was calculated using the Modification of Diet in Renal Disease (MDRD) equation[5].

GFR (mL/min/1.73 m^2) = 175 × (serum creatinine) - 1.154 × (age) - 0.203 × (0.742, if female)

To be consistent with previous studies, decreased renal function was defined as a reduction in the GFR > 10 mL/min/1.73 m^2 after surgery[3]. To evaluate the factors associated with an eGFR decrease, we compared the preoperative values with those obtained at the subsequent postoperative visits. The CKD stage was also used to classify renal function. Similar to the method in a recent analysis we compared the preoperative eGFR with the values obtained at the subsequent postoperative visits. At the 1-year postoperative point, we evaluated serum creatinine, measured 9 to 18 months postoperatively. In addition, we accounted for all subsequent values obtained within each subsequent year.

Statistical analysis

Continuous, normally distributed and non-normal distributed variables are reported as the median and range. Univariate statistical analyses were performed with a Student's t test for quantitative variables and Fisher's exact test for qualitative variables. Linear regression analysis was used to test the liaison between the quantitative variables. For all statistical analyses, a 2-sided p-value < 0.05 was considered statistically significant. All data were analyzed using the Statistical Package for Social Sciences, version 25.0 (SPSS, Chicago, IL).

Results

Patient characteristics

The clinicopathologic features of the patients at surgery are reported in Table 1. All 214 patients with serum creatinine measurements available at baseline and regular follow-up visits after surgery, were evaluated. The median follow-up period after RC for patients alive at the last visit was 24 months (range, 6-60 months). The overall survival rate was 80% at 5 years. Median patient age was 63 years (range, 27-87 years), and the gender ratio was 3 : 1. Of the 214 patients, 70 (31%) received platinum-based chemotherapy. Postoperative complications included ureteroenteric stricture (n = 1), recurrent urinary tract infection (n = 2), and urolithiasis (n = 3)

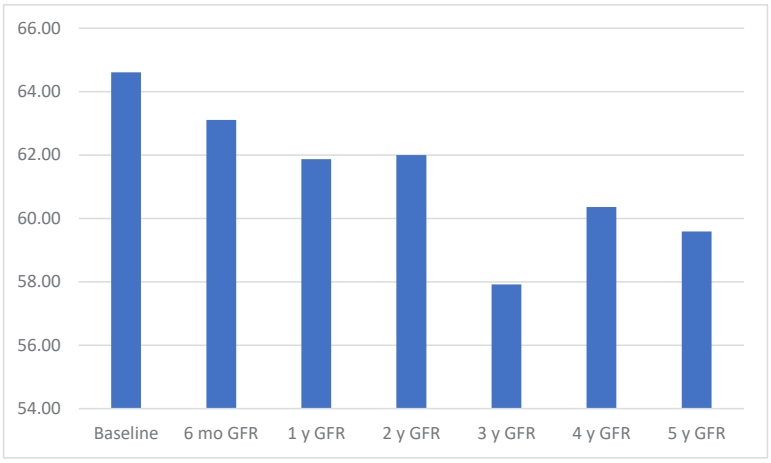
Changes in eGFR

The median estimated glomerular filtration rate (eGFR) significantly decreased from 64 mL/min/1.73 m^2 to 61.5 mL/min/1.73 m^2 (p = 0.008) between preoperative and final F/U.

Figure 1 shows the median eGFR evolution from baseline to event analysis. At 5 years postoperative, median GFR deceased 2.74 mL/min/1.73 m^2 in the first year before decreasing slowly in the subsequent years.

Table 1. Demographic data.

Patient characteristics (N = 214)	n (%)
Patients	214 (100)
Age (years)	
- Median	63
- Range	27-87
Gender	
- Male	161 (75)
- Female	53 (25)
Comorbidity	
- Chronic hypertension	89 (42)
- Diabetes mellitus	36 (17)
Preoperative hydronephrosis	93 (44)
Adjuvant chemotherapy	53 (25)
Neoadjuvant chemotherapy	14 (7)
Years followed up (mean±sd)	2.04 (1.36)
Type of anastomosis	
- Wallace	164 (76.6)
- Bricker	50 (23.4)
Preoperative eGFR (mL/min/1.73 m^2)	
- Median	64
- Range	8-125
Patients with eGFR > 90 mL/min/1.73 m^2	37 (17)
Patients with eGFR 60-90 mL/min/1.73 m^2	89 (42)
Patients with eGFR 30-59 mL/min/1.73 m^2	68 (32)
Patients with eGFR < 30 mL/min/1.73 m^2	20 (9)
Pathologic stage	
pT1	58 (27)
pT2	60 (28)
pT3	58 (27)
pT4	37 (17)
pN+	57 (26)



N=214		Baseline	6 mo GFR	1 y GFR	2 y GFR	3 y GFR	4 y GFR	5 y GFR
n	Valid	214	213	196	112	60	33	22
	Missing	0	1	18	102	154	181	192
Mean GFR (mL/min/1.75 m^2)		64.61	63.10	61.87	62.00	57.92	60.36	59.59

Figure 1. Change in median estimated glomerular filtration rate (eGFR) after radical cystectomy across the postoperative period.

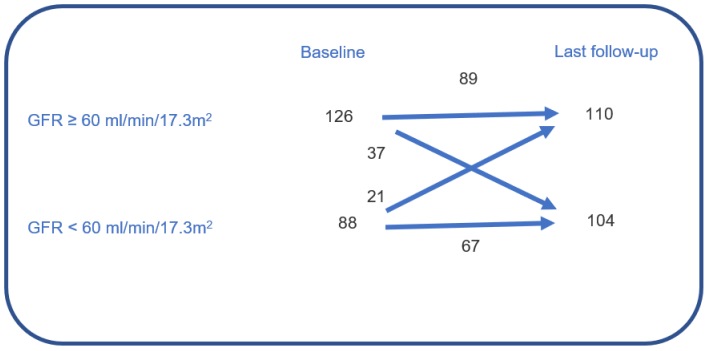


Figure 2. Chronic kidney disease (CKD) stage in patients with ileal conduit diversion before surgery and at last follow-up visit.

Figure 2 shows the evolution of CKD stage from baseline to the last follow-up visit. At baseline, 126 out of 214 patients (58%) had normal renal function (eGFR > 60 mL/min/1.75 m^2) and 88 (42%) had CKD stage 3, defined as an eGFR of < 60 mL/min/1.73 m^2. Of the 126 patients with a normal preoperative eGFR, new-onset stage 3 CKD was detected postoperatively in 37 (17%). In contrast, in 21 of 88 patients (26%) with a preoperative eGFR of > 15 but < 60 mL/min/1.73 m^2 the functional capacity of their kidneys improved.

Factors influencing renal function

The variables associated with renal function deterioration are reported in Table 2 and Table 3. A normal preoperative eGFR at baseline (> 60 mL/min/1.73 m^2) was independently associated with worse renal outcome in both univariate and multivariate analysis ($p < 0.001$). However, preoperative hydronephrosis was associated with worse renal outcome only in the univariate analysis.

Diabetes (n = 22), chronic hypertension (n = 57), gender, age, pathological stage, type of anastomosis and adjuvant chemotherapy were not associated with a poor renal function outcome ($p > 0.05$).

Discussion

The standard treatment of muscle invasive bladder cancer is radical surgery with urinary diversion and chemotherapy[8]. Ileal conduit is the type of urinary diversion that is most frequently used in Rajavithi Hospital. Decreased renal function has been noted in most patients during long-term follow-up after urinary diversion. However, long-term data evaluating the risk factors associated with worsening renal function

Table 2. Univariate analysis of clinicopathologic variables and complications associated with renal function deterioration.

	Decrease in renal function	No decrease in renal function	Odds ratio	P-value
Gender n (%)			0.66	0.235
Male	101 (72.7)	60 (80.0)		
Female	38 (27.3)	15 (20.0)		
Age (years) Mean±SD	62.2(10.95)	64.3 (10.19)		0.24
Preoperative GFR n (%)			3.96	< 0.001
> 60 mL/min/1.73 m^2	59 (78.7)	67 (48.2)		
< 60 mL/min/1.73 m^2	16 (21.3%)	72 (51.8)		
Diabetes mellitus n (%)	22 (15.8)	14 (18.7)	0.82	0.596
Hypertension n (%)	57 (41.00)	32 (42.70)	0.93	0.814
Preoperative hydronephrosis n (%)	22 29.3	72 51.8	0.37	0.002
pT stage (≥ pT2 vs pT1 stage) n (%)			0.52	0.034
pT1	27 (36.0)	31 (22.5)		
≥ pT2	48 (64.0)	107 (77.5)		
Type of anastomosis n (%)			0.52	0.034
Wallace	59 (78.7)	105 (75.5)		
Bricker	16 (21.3)	34 (24.5)		
Adjuvant chemotherapy n (%)	37 (26.60)	16 (21.30)	1.34	0.393

Table 3. Multivariate analysis of clinicopathologic variables and complications associated with deterioration in renal function.

	HR	Lower	Upper	P-value
Gender	1.039	1.005	1.074	0.025
Age	0.616	0.292	1.298	0.203
Preoperative eGFR > 60 mL/min/1.73 m^2	5.871	2.614	13.188	< 0.001
DM	1.588	0.653	3.864	0.308
HT	1.098	0.541	2.229	0.796
Preoperative hydronephrosis	0.930	0.449	1.927	0.846
pT stage (> pT2 vs pT1 stage)	0.682	0.332	1.401	0.298
Type of anastomosis	0.961	0.455	2.027	0.916
Adjuvant chemotherapy	0.982	0.460	2.100	0.963

in patients with urinary diversion are lacking.

Eisenberg et al reported the first study evaluating renal function decrease-free survival with long-term follow up in a large cohort of patients treated by RC and urinary diversion. They reported that the renal function decline approached 49% and 72% at 5 and 10 years after urinary diversion, respectively. They found a statistically significant association between older age, higher preoperative eGFR, chronic hypertension, postoperative hydronephrosis, ureteroenteric anastomotic stricture, and pyelonephritis and an increased risk of subsequent decreased renal function[3].

Jin et al found renal function decrease in 25% of patients after RC at a minimum of a 10-year follow-up period. The incidence of urinary tract obstruction was significant and that diabetes and hypertension were contributing factors associated with renal function deterioration in patients with incontinent diversion[4].

Osawa et al, reported that 34.2% of their patients had reduced renal function after the mid-term follow-up period after RC[6].

Mathieu Rouanne et al, found the overall rate of renal function had decreased by 51% at 5 years after urinary diversion by ileal conduit. They considered a significant annual decline in GFR of > 1 mL/min/1.73 m^2. They found that a normal preoperative eGFR > 60 mL/min/1.73 m^2 was associated with decreased renal function postoperatively. However, neither chronic hypertension nor diabetes mellitus was associated with the eGFR decline[7].

In our study, we noted that the overall rate of renal function had decreased after surgery. We considered as significant a decline in GFR of > 10 mL/min/1.73 m^2 because we could not monitor the year-by-year eGFR. We found normal preoperative eGFR > 60 mL/min/1.73 m^2 and no preoperative hydronephrosis were associated with decreased renal function postoperatively. This situation can be explained as relative improvement due to the regression of preoperative hydronephrosis in patients with preoperative eGFR < 60 mL/min/1.73 m^2. Diabetes, chronic hypertension, gender, age, pathological stage, type of anastomosis and adjuvant chemotherapy were not associated with a poor renal function outcome.

Our study is limited by its retrospective, nonrandomized design. We further acknowledge the potential for underestimating renal related postoperative complications, given the tertiary referral nature of our center, since patients frequently undergo follow up locally. Additionally, excluding patients from analysis when they did not have long term RF data available may have introduced selection bias. Those on whom RF data were and were not recorded in our registry may have had clinically relevant clinicopathological differences that would have impacted an RF decrease and we could not examine the effects of medical or surgical intervention for renal related complications.

eGFR is not the gold standard measures of inulin clearance or creatinine clearance under diuretic conditions. It has limited accuracy in measuring serum creatinine in patients after UD due to creatinine reabsorption.

Conclusion

Most patients experienced a decrease in RF during long-term follow up after RC. The long-term renal function in patients with an ileal conduit urinary tract can be adversely affected by both diversion and non- diversion-related factors. These data emphasize the importance of continuing to monitor eGFR after RC and identifying and treating renal related complications early to limit renal function deterioration to prevent irreversible kidney damage.

Conflict of Interest

The authors declare no conflict of interest.

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Original Article

Safety of a first-day catheter removal after transurethral resection of the prostate (TURP): a propensity score-matched historical control study

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Keywords:
TURP, early postoperative catheter removal, community-based hospital

Abstract

Objective: Transurethral resection of the prostate (TURP) is the standard surgical management for patients with benign prostatic hyperplasia (BPH). Postoperative maintenance of bladder catheterization is a routine procedure. However, the timing of catheter removal varies. Our objective is to evaluate the safety of early catheter removal (less than 24 hours) whilst maintaining efficacy, especially in an overcrowded community-based hospital, which has a high rate of preoperative catheterization (47.7%).

Materials and Methods: This was a prospective and retrospective observational cohort study of 399 TURP indicated patients from February 2014 to September 2019. Since October 2017, the urological unit protocol has changed the process of removal of the catheter to less than 24 hours after monitoring for safety. Data from 95 patients after October 2017 was prospectively collected as the less than 24 hours group. The information from 2014 to October 2017 was collected and used as the control group. Data was then studied retrospectively for three years. The primary outcome, morbidity, and postoperative stay were compared with a 1:1 nearest neighbor propensity score-matched analysis.

Results: After the score was matched and balanced, there was no difference as regards complications between the two groups (Odd ratio (OR): 1, (95% Confidence interval (95% CI): 0.14-7.10, p-value: 1.00). Acute urinary retention and postoperative bleeding were also comparable (OR: 0.5, 95% CI: (0.05-5.51), p-value: 0.57, and p-value: 0.99). The postoperative hospital stay was significantly less in the < 24 hours group (38.1 less hours, 95% CI: (41.82- 34.31), p-value: < 0.01).

Conclusion: After TURP early catheter removal was safe even in the hospital with a high preoperative catheterization rate. Experienced surgeons, well-educated and compliant patients without contraindications (neurogenic bladder, urethral stricture, stroke, and some intraoperative complications: urinary bladder perforation, urinary tract infection, prostatic capsule perforation, or intraoperative bleeding) are our recommendation for adopting this protocol.

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Introduction

Benign prostatic hyperplasia (BPH) is a common condition of the elderly male. The incidence can be as high as 70 to 80 % in males older than 70 years old[1,2]. Symptomatic BPH in Thailand could be around 41.3 % in men aged more than 60[3]. The disease can cause a decrease in the quality of life of the affected individual[4,5].

In less symptomatic cases of the disease, pharmacologic treatment (alpha-blocker or 5-alpha reductase inhibitor) is the first-line treatment[6,7]. In more severe cases, Transurethral resection of the prostate (TURP) is a gold standard surgical management[8]. The indications are: resistance to drug therapy, recurrent urinary retention, complications from obstruction (such as vesicle stone, renal failure, urinary tract infection), or recurrent prostatic bleeding.

After surgery, bladder catheterization is routinely performed, the catheter being retained for around 1 to 5 days[9-12]. The tamponade effect, reduction of incidence of blood clotting, and urine drainage are positive attributes of its usefulness. Although many studies have supported early removal as a policy[13,14], an extensive review could not reach a definitive conclusion and endorse the practice of rapid removal[15]. In our hospital, maintaining catheterization for at least 3 to 5 days has been the rigorous approach. This approach caused crowding in the inpatient ward and caused extended discomfort to patients. There is one more feature of our hospital. As a tertiary government hospital, the extent of the case burden is a problem. Timely surgery cannot always be achieved, a factor reflected by the high rate of preoperative catheterization (47.7%). For the reasons mentioned above, we attempted to answer the question that in an overcrowded hospital, the approach of early catheter removal can be effective, ethical and still be safe.

Materials and Methods

This study was approved by the Sawanpracharak Hospital ethics committee. This was a prospective and retrospective observational cohort study of TURP indicated patients in Sawanpracharak hospital, Nakhon Sawan, Thailand, from February 2014 to September 2019. From October 2017 to September 2019, the urological unit protocol has changed to that of removal of a urinary bladder catheter after TURP to less than 24 hours. In the early period of changing to the protocol, the introduction of the rapid catheter removal practice was closely monitored until it was shown to be safe for patients, and the whole urology team felt confident with the approach. The data of this group (< 24 hours group) of 95 patients were prospectively collected. The information of the control group (304 patients) was then retrospectively reviewed for three years (the rigorous 3 to 5 days catheter retention group) (historical control) from the medical records. Neurogenic bladder, urethral stricture, and stroke patients, which were preoperative contraindications for early catheter removal, were excluded from both groups. There are also indications for prolonged maintenance of the catheter postoperatively from some intraoperative complications, which are urinary bladder perforation, urinary tract infection, prostatic capsule perforation, or intraoperative bleeding. These particular intra-operative complications, however, were not excluded as we decided to analyze them as the intention-to-treat basis.

All TURPs were performed with monopolar energy with sterile water irrigation by three certified urologists. A 24 Fr sized with 30-milliliter inflated balloon catheter was postoperatively inserted, tractioned, and attached to a thigh from 2 to 6 hours. Normal saline irrigation was then performed until drainage fluid was cleared. Catheter removal time was in accordance with the group. Although some instruments have changed during the five years, there was, nevertheless, no difference in equipment technology between the two groups.

Baseline data collection was age, comorbidity, indications for TURP, type of anesthesia, operative time, resected prostate weight, intraoperative complications, and postoperative traction time. Outcomes were complications (acute urinary retention, postoperative bleeding, and septicemia) and length of hospital stay. Data distribution analysis was carried out using Fisher's exact test for categorical data and a t-test or Mann-Whitney U test for continuous data.

Propensity score matching was utilized to compare the main results. Table 2 represents the chosen confounders to calculate the scores using logistic regression. With abundant control numbers (around three times), 1:1 nearest neighbor matching was used[16]. The balance of confounder distribution was checked with a propensity score

distribution mirrored histogram and standardized mean differences (SMD) which are presented in Figure 1 and also in Table 2. Estimation of treatment effect was analyzed using conditional logistic regression for the categorical outcome and paired t-test for the continuous results. Statistical analysis was performed using statistical software. < 0.05 of p-value was considered to be statistically significant.

Results

Table 1 represents the baseline data distribution between the two groups with its uni-variable analysis results. With raw unmatched data, the operative time was faster in the < 24 hours group (p-value < 0.01).

Table 2 presents the outcomes. It also shows a list of confounders used to calculate the scores. The balance of the covariates can be checked by comparing before and after the procedure matching the propensity score mirrored histogram (Figure 1) and SMD (Table 2). After matching, the graph showed fairly balanced scores, and mean differences of all factors were around and less than 10 % (0.010). Interpretation of these analyses, after matching, indicates that our data scores and covariate distribution were comparable[16,17]. According to the results, there was no difference as regards complications between the two groups (Odds ratio (OR): 1, (95% Confidence interval (95% CI): 0.14-7.10, p-value: 1.00). Acute urinary retention and postoperative bleeding, which are the main theoretical benefits of maintaining a catheter, were also the same (OR: 0.5, 95% CI: (0.05-5.51), p-value: 0.57, and p-value: 0.99). The OR for postoperative bleeding couldn't be calculated due to there being zero incidence in the control group. The < 24 hours group had a significantly shorter length of postoperative hospital stay (38.1 less hours, 95% CI: (41.82-34.31), p-value: < 0.01).

Discussion

TURP by monopolar energy is a gold standard for BPH indicated patients because it is effective and safe[8]. Catheterization time after the operation varies in accordance with experience and surgeon opinion. Around three days of balloon tamponade were traditionally recommended. Maintenance time, however, can range from less than 48 hours to up to four to five days[18-20].

Bladder catheterization and continued irrigation, although theoretically sound, reduces patient mobility which has associated problems and causes discomfort. Prolonged retention of the catheter can also cause urethral stricture, catheter-associated urinary tract infection (CAUTI)[21], increase the length of hospital stay, and increase

Table 1. Baseline data distribution (N=399)

	Control group (n = 304)	< 24 hours group (n = 95)	P-value
Age (years) mean (±SD)	72.0 (8.1)	72.5 (8.5)	0.61
Comorbidity n (%)	144 (47.4)	55 (57.9)	0.08
Preoperative catheterization n (%)	145 (47.7)	44 (46.3)	0.91
Operative time (minutes) median (range)	40 (10 -120)	35 (15-110)	< 0.01
General anaethesia n (%)	21 (6.9)	11 (11.6)	0.19
Resected Wt (grams) median (range)	15 (2-60)	12 (3-84)	0.39
Intraoperative complications n (%)	24 (7.9)	2 (2.1)	0.05
Bleeding	10 (3.3)	1 (1.1)	
Capsule perforate	7(2.3)	1(1.1)	
Bladder perforate	7(2.3)	0 (0)	
TURP syndrome	2 (0.7)	0 (0)	
Cardiovascular	0 (0)	0 (0)	
Septicemia	3 (1.0)	0 (0)	
PRC transfusion (n (%))	7 (2.3)	1 (1.1)	0.70
Traction time (hours), Median (range)	4 (0-19)	4 (2-6)	0.81

Mean (±SD) = mean ± standard deviation, Resected Wt = intraoperative resected prostate weight, PRC transfusion = Packed red cell transfusion

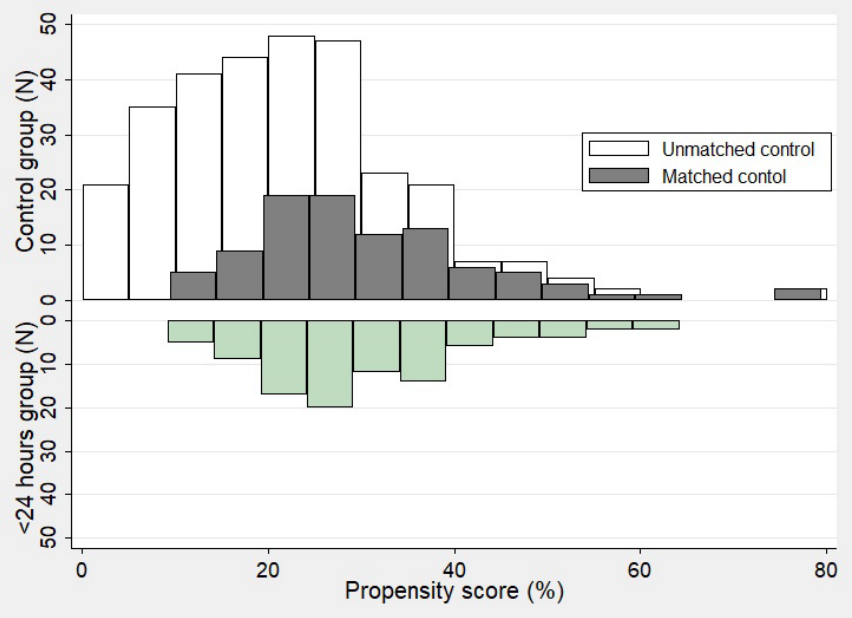

Figure 1. Mirrored histogram of the propensity score distribution.

Table 2. Main results of the study.

	Control group (N = 304)	< 24 hours group (N = 95)	SMD before matching	Control group (N = 95)	< 24 hours group (N = 95)	SMD after matching
Age (years) mean (±SD)	72 (8.1)	72.5 (8.5)	0.059	72.5 (8.2)	72.5 (8.5)	0.001
Comorbidity n (%)	144 (47.4)	55 (57.9)	0.211	50 (52.6)	55 (57.9)	0.106
Preop cath n (%)	145 (47.7)	44 (46.3)	0.028	39 (41.1)	44 (46.3)	0.105
Intra-op complication n(%)	24 (7.9)	2 (2.1)	0.268	1 (1.1)	2 (2.1)	0.049
OR time (minutes), median (range)	40 (10-120)	35 (15-110)	0.399	30 (10-90)	35 (15-110)	0.102
GA N (%)	21 (6.9)	11 (11.6)	0.161	10 (10.5)	11 (11.6)	0.036
Resected Wt (gm), median (range)	15 (2-60)	12 (3-84)	0.009	13 (2-60)	12 (3-84)	0.077
Traction time (hours), median (range)	4 (0-19)	4 (2-6)	0.141	4 (0-12)	4 (2-6)	0.084
Estimation of treatment effect			**P-value**		**P-value**	
PO complication n (%)	10 (3.3)	2 (2.11)	0.74	2 (2.11)	2 (2.11)	1.00
			Odds ratio (95% CI)		1 (0.14-7.10)	
AUR n (%)	6 (2.0)	1 (1.1)	1.00	2 (2.11)	1 (1.1)	0.57
			Odds ratio (95% CI)		0.5 (0.05-5.51)	
PO bleeding n (%)	2 (0.7)	1 (1.1)	0.56	0 (0.0)	1 (1.1)	0.99
			Odds ratio (95% CI)		NA	
PO stay (hours), median (range)	68 (18-216)	22 (20-72)	< 0.01	68 (20-142)	22 (20-72)	< 0.01
			Less hours (95% CI)		38.1 (41.82- 34.31)	

SMD = standardized mean differences; preop cath = preoperative catheterization; intra-op complication = intraoperative complication; OR time = operative time; GA = general anaethesia; Resected Wt = intraoperative resected prostate weight; AUR = acute urinary retention; PO = postoperative

treatment cost[22,23].

With advancements in surgical technique, anesthesia, and perioperative care, the long catheterization time may not necessary[24]. Catheterization time has gradually decreased. Until recently, a retaining hour with hospitalization less than 24 hours can be achieved[13,14], mainly applied as ambulatory care[25].

After close monitoring of the safety aspects, the early catheter removal protocol has been used in our urological unit. Our results could add weight to the confirmation that the practice was safe, even in an overcrowded community-based hospital. Benefits from the protocol were less discomfort to patients, early mobilization and a decrease in length of hospital stay. CAUTI incidence, however, was not collected in our data.

There were, nevertheless, limitations to our study. Firstly, operative time was significantly lower in the < 24 hours group. Although all surgeons have already progressed through the traditionally accepted learning curve five years ago (all have practiced for more than three years with high volume) the level of skill can still probably improve further. The high skill level could be reflected by the shorter operative time in the later years. Better results in the treatment group can be expected even if all factors are balanced. Secondly, the rate of re-admission was not included in our study. The data concerning readmission could be more reassuring as regards safety if it were available. Thirdly, the level of patient education and compliance level were not collected, a practice which in future studies needs to be included and requires effective interaction with and cooperation from patients.

Conclusion

The practice of catheter removal less than 24 hours after TURP was safe and feasible, even in an overcrowded hospital with high levels of preoperative catheterization. To adopt the protocol, we recommend surgeons need a high level of experience and patients should be well-educated and compliant. Our contraindications were patients with neurogenic bladder, urethral stricture, stroke, and some intraoperative complications, which are urinary bladder perforation, urinary tract infection, prostatic capsule perforation, or intraoperative bleeding.

Conflict of Interest

The authors declare no conflict of interest.

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Original Article

Feasibility study of relative renal function assessment by contrast-enhanced abdominal CT in comparison to 99mTc-MAG3 renal scintigraphy

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Keywords:
Relative renal function, computed tomography, renal scintigraphy, 99mTc-MAG3

Abstract

Objective: To determine the feasibility of using contrast-enhanced abdominal CT to assess relative renal function.

Materials and Methods: This retrospective study reviewed data from 32 patients who had had investigations by contrast-enhanced abdominal CT and 99mTc-MAG3 renal scintigraphy, within a period of not more than 30 days. Post-processing CT images of kidneys were by manual segmentation and calculated to interpret the relative renal function.

Results: There was strong correlation between CT derived relative renal function and 99mTc-MAG3 renal scintigraphy ($r = 0.971$, $p < 0.001$) and no statistically significant difference in renal function between the two techniques ($p = 0.572$).

Conclusion: Contrast-enhanced abdominal CT can determine relative renal function as accurately as renal scintigraphy. It is an appropriate alternative method, especially in hospitals where renal scintigraphy is not available.

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Introduction

Relative renal function is the most important preoperative parameter to inform the decision making process and give guidance to enable optimal management of patients with kidney pathologies, such as atrophic kidney, ureteropelvic junction obstruction and renal malignancy. It is also vital in the assessment of potential kidney donors[1,2].

The gold standard to determine relative renal function (RRF) is Renal scintigraphy[3]. At present, Technetium-99m-mercaptoacetyltriglycine is the most frequently used isotopes due to its higher extraction fraction and it results in a high quality of gamma camera image[4]. However, renal scintigraphy is less available, time-consuming, relatively expensive, and has additional costs therefore it is less practical for use in all except tertiary hospitals.

In practice, contrast-enhanced abdominal computed tomography (CE-CT) is commonly used for preoperative assessment of the anatomy of the kidney. Computed tomography is now available in most hospitals and the physiologic properties of the Iodinated contrast agent have many benefits, specifically nearly complete glomerular excretion, less tubular excretion, and less extrarenal excretion, which make it suitable for assessing renal function during renal scintigraphy[5].

The aim of this study is to determine the feasibility of efficacy of using CE-CT to assess RRF in comparison to ^{99m}Tc-MAG3 renal scintigraphy (MAG3).

Materials and Methods

Patients

Data was collected for this retrospective study between January 2012 and December 2019 in Rajavithi Hospital. One hundred thirty-four patients who had had both MAG3 and CE-CT at least both plain phase and arterial phase performed were enrolled onto this study. The exclusion criteria were a longer than 30 day period between CE-CT and MAG, single kidney and surgical intervention between CE-CT and MAG3. Ninety-eight patients were excluded due to the longer than 30 day gap. One patient was excluded due to having a single kidney. Three patients did not meet the exclusion criteria but were excluded due to incomplete imaging data records in the database. Therefore 32 patients met the inclusion criteria and their data was included in the analysis.

Theory of equations

In the pharmacokinetic model, contrast enhancement is directly related to iodine concentration in tissue. Attenuation value of contrast enhancement (CE_{att}) can be calculated by subtracting total attenuation value of region of interest in the plain phase (PP_{att}) from total attenuation value of region of interest in the arterial phase (AP_{att}) which will represent iodine concentration. The proportion of CE_{att} of the right kidney ($^{RK}CE_{att}$) to both kidneys can be used to represent relative renal function of the right kidney (RRF_{RK}) as in Eq. 2. And relative renal function of the left kidney (RRF_{LK}) can be calculated in the same way as shown in Eq. 3.

$$CE_{att} = AP_{att} - PP_{att} \quad \text{(Eq. 1)}$$

$$RRF_{RK} = [{}^{RK}CE_{att} / ({}^{RK}CE_{att} + {}^{LK}CE_{att})] \quad \text{(Eq. 2)}$$

$$RRF_{LK} = [{}^{LK}CE^{att} / ({}^{RK}CE_{att} + {}^{LK}CE_{att})] \quad \text{(Eq. 3)}$$

All Digital Imaging and Communications in Medicine (DICOM) Files were analyzed using Slicer 4.10.2, an open source software. A region of interest (ROI) was drawn around the kidney cortex, which was performed in the arterial phase, in all slices as shown in figure 1. Mean attenuation of the arterial phase of each kidney in Hounsfield units (HU) and kidney cortex volume were registered. The ROI previous created was used to analyze Plain CT to calculate mean attenuation. In some cases where there was motion of the artifact, image transformation function in software was used to correct images to near equivalence in the arterial phase. Total attenuation was calculated by multiplying the mean attenuation and kidney cortex volume. All measurements were carried out by a resident of urology and were reviewed by a radiologist.

Statistical analysis was performed using the IBM SPSS version 20.0.0. Pearson's correlation coefficient was used to establish the correlation of RRF results from CE-CT and MAG3. A two-sided paired t-test was used to establish statistical equivalence.

Results

Of the 32 patients, 10 patients (31.25%) were male and twenty-two patients (68.75%) were female. The age ranged from 15 to 90 years

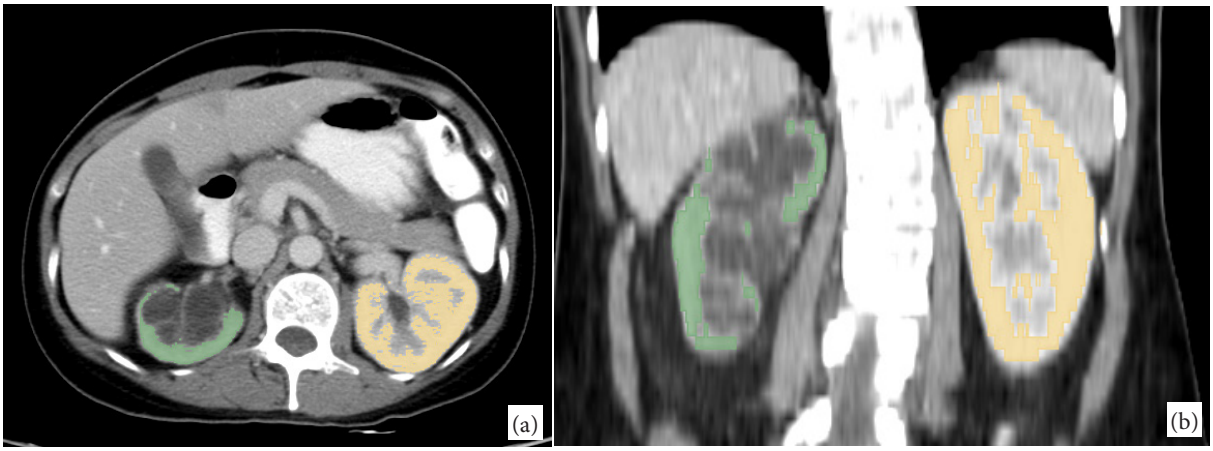

Figure 1. CT image in arterial phase. (a) A region of interest (ROI) was drawn around kidney cortex in every slice of axial image. (b) Coronal view of CT image reconstructed from axial image after ROI was drawn

Table 1. Demographic data.

Demographic data	
Sex, n (%)	
Male	10 (31.25)
Female	22 (68.75)
Mean Age (years) mean (±SD)	46.69±18.97
Mean eGFR (mg/dL) mean (±SD)	88.094±23.32
Diagnosis, n (%)	
Ureteropelvic junction obstruction	10 (31.25)
Renal stone	8 (25.00)
Non-obstructive hydronephrosis	5 (15.63)
Stricture ureter	3 (9.38)
Donor kidney	2 (6.25)
Retrocaval ureter	2 (6.25)
Abdominal aortic aneurysm	1 (3.12)
Renal infarction	1 (3.12)

(mean, 46.69 ± 18.97 years). The average eGFR was 88.094 ± 23.32 mg/dL.

Diagnoses of all patients were as follows: 10 patients ureteropelvic junction obstruction (31.25%), 8 patients renal stones (25%), 5 patients non-obstructive hydronephrosis (15.63%), 3 patients stricture of the ureter (9.38%), 2 patients donor kidneys (6.25%), 2 patients retrocaval ureter (6.25%), 1 patient abdominal aortic aneurysm (3.12%), and 1 patient renal infarction (3.12%).

The relative renal function of right kidney from MAG3 and CE-CT were 48.06 ± 26.67% and 48.70 ± 26.07%, respectively. From left kidneys were 51.95 ± 26.67% and 51.92 ± 26.07%. RRF between two studies showed a strong correlation ($r = 0.971$, $p < 0.001$) and there was no significant different in the paired t-test ($p = 0.572$). Mean different between two studies was 0.65%.

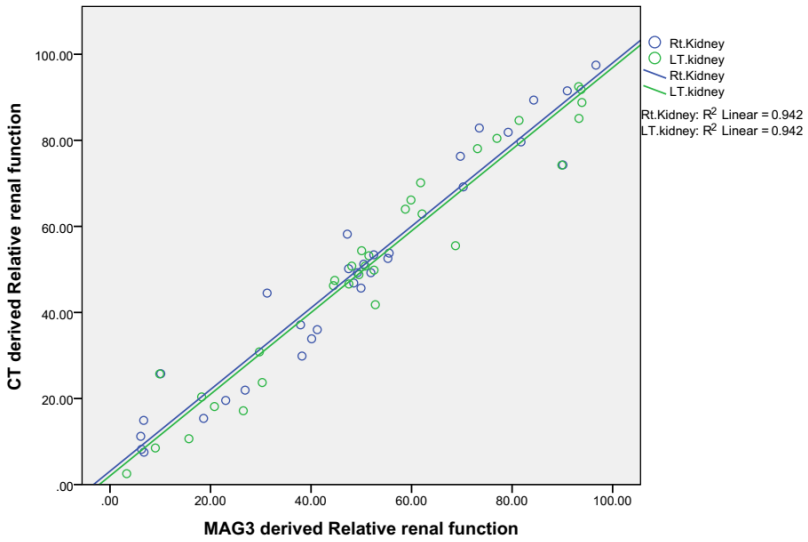

Figure 2. Correlation between RRF derive from CE-CT and MAG3.

Discussion

Although renal scintigraphy is the standard investigation to evaluate RRF it is less available, time consuming, and adds additional costs. In addition, there are several confounding factors when it comes to interpretation of the RRF for example depth of skin, poor renal function, and operator dependence on drawn ROI of kidney with a possible poor demarcation, especially in cases where there is low glomerular filtration rate.

In general, most patients would have a CE-CT performed, usually a triple phase CT, to access the anatomy of the kidney and pathology before surgery. In theory, CE-CT could be used to interpret the RRF as efficiently as renal scintigraphy due to pharmacodynamic of the iodinated contrast material which has a nearly 100% excretion rate by glomerular filtration[4].

There are a few studies which have investigated the feasibility of using a CT scan to interpret RRF. Most studies show that the excretory phase of the CE-CT has a high correlation with renal scintigraphy derived RRF[6-9]. Nilsson H, et al[7] compared the excretory phase and arterial phase to investigate RRF. The results show that the excretory phase was more accurate than the arterial phase in investigation of RRF. The author explain that the conventional CT scan takes time to complete a scan of both kidneys.

This time lag could cause overestimation of the efficacy of the right kidney because it usually appears inferior to the left kidney which has more time to accumulate the contrast during the complete CT scan. In modern time the majority of CT scanners are multidetector. This effect will be considerably less important in the calculation of RRF.

Although the excretory phase reflects the level of iodine contrast passing through the glomeruli it is more user dependent on the drawn ROI because the iodine contrast will present as being present in the renal collection system (renal calyx, renal pelvis, and ureter) which are less demarcated than the drawn ROI. In addition, when the contrast has been excreted to the renal collecting system, it will obscure the renal stone which usually reduces the overestimation of RRF. Since the timing of the excretory phase varies, ranging from 90 to 180 second after IV contrast injection, confirmed in previous studies[6-9], it is usually not included in the standard protocol of CE-CT. It needs to be performed additionally to the standard protocol of CE-CT which increases cost and causes additional radiation exposure in the patient while the arterial phase is usually performed using the standard protocol of CE-CT.

The advantage of arterial phase is well demarcating of kidney cortex cause less user dependence and can easily to refrain pathology in renal correcting system. This phase has primary reflect to renal blood flow. As result of El-Diasty TA, et al[10] study, renal perfusion parameter will be accurate if ROI should draw only kidney cortex.

Renal scintigraphy in the arterial phase doesn't represent the true GFR because the contrast medium has not yet passed through glomeruli. However, the renal physiology between renal perfusion and GFR have a linear relationship[11] which means that the proportion of renal perfusion will be equal to the proportion of renal GFR in both kidneys.

In this study, the results showed a very strong correlation between the RRF derived from the arterial phase of the CE-CT and that derived from the MAG3 ($r = 0.971$, $p < 0.001$). These findings were similar to those found in a previous study by Nilsson H, et al which investigated the excretory phase of the CE-CT, which was even better than the RRF derived from the arterial phase CE-CT[7]. There was no significant difference in the RRF derived from the CE-CT when compared to the MAG3 ($p = 0.572$).

This study is retrospective in design and hence one of the limitations is the lack of control of the time factor in the investigations. If there is a longer time between studies the results of the RRF may be affected if the pathology causes an ongoing decrease in kidney function. Further studies need to be prospective in nature and ensure that both the CECT and MAG3 are performed within a short period of time.

The performance of segmentation of both kidneys in post-process imaging of CE-CT is time consuming which makes it hard to apply in clinical practice. In the Artificial Intelligence era, the timing of this process will become increasingly reduced and maybe it can be used more easily in clinical practice in the future.

Conclusion

Contrast-enhanced abdominal CT can determine relative renal function as accurately as

renal scintigraphy. It is an appropriate alternative method, especially in hospitals where renal scintigraphy is not available. However, it cannot entirely replace renal scintigraphy because of the consequences of the higher radiation dose and its limited use in cases where there is a low glomerular filtration rate

Conflict of Interest

The authors declare no conflict of interest.

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Original Article

Comparison between circumferential local anesthesia and dorsal penile nerve block in circumcision procedure

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Keywords: Circumferential, local anesthesia, dorsal penile nerve block, circumcision

Abstract

Objectives: To compare circumferential local anesthesia and dorsal penile nerve block with regard to pain control during adult circumcision.

Materials and Methods: A randomized, controlled clinical trial was conducted and 30 men were randomly assigned into one of the following groups: circumferential local anesthesia (LA) and dorsal penile nerve block (DNB). Patients in both groups were injected with 0.2 ml/kg of 2% lidocaine without epinephrine before circumcision using the different techniques. During the operation, pain score was evaluated in accordance with the Numerical Rating Scale (NRS) and the data were compared using the Mann-Whitney test.

Results: The patients in the LA group felt more pain than those in the DNB group during anesthetic injection (4.73 vs 3.7, $p<0.05$) but the pain scores were lower than in the DNB group during the outer prepuce incision (0.47 vs 3.93, $p<0.05$), inner prepuce incision (0.33 vs 1.47, $p<0.05$) and incision near/at Frenulum (0.33 vs 4.47, $p<0.05$). Overall pain score was higher in the dorsal penile nerve block group (1.53 vs 2.6, $p<0.05$). The circumferential local anesthesia is equally effective through all stages of the circumcision whereas the dorsal penile nerve block was not effective at the ventral surface of penis.

Conclusion: For pain control in circumcision, circumferential local anesthesia is more effective than dorsal penile nerve block.

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Introduction

Male circumcision (MC) is the surgical removal of skin covering the tip of penis. This operation can improve penile hygiene, reduce incidence of penile cancer and has the potential to decrease the risk of sexual transmitted diseases such as human papilloma virus and human immune deficiency virus[1-3]. It is considered a treatment option for recurrent urinary tract infection, phimosis, paraphimosis and recurrent balanitis or for social, cultural, personal or religious purposes[4,5].

Although considerable controversy exists regarding the medical value of circumcision, the evidence is overwhelming that it is acknowledged to be a painful procedure. The dorsal penile block (DPNB) is an effective technique for regional anesthesia of the penis[6,7]. It is done by injecting anesthetic solution deep into Buck's fascia where the nerves emerge from under the pubic bone. Two injection sites are identified over the inferior edge of the pubic bone at approximately 10 o'clock and 2 o' clock relative to the base of the penis. The needle is inserted and directed ventrally until contact is made with the pubic bone. It is then withdrawn slightly and redirected to pass below the pubic symphysis, slightly laterally and approximately 3 to 5 mm deeper to enter the appropriate space.

Several studies have documented the effectiveness of dorsal penile nerve block but as circumcision only involves the skin that covers the glans penis it is not necessary to control pain in the entire penis with dorsal penile nerve block and there is the possibility that circumferential local anesthesia would be equally if not more appropriate. This study was undertaken to compare the efficacy of circumferential LA with DNB.

Materials and Methods

Patient selection

This clinical trial was approved by the Ministry of Public Health and the patients provided written informed consent before undergoing the procedures. All enrolled patients were adult men of 18 to 70 years of age who came for circumcision due to phimosis or for religious reasons.

The exclusion criteria included patients who might have sensory deficit such as peripheral neuropathy or paralysis, patients who were allergic to lidocaine, and patients who preferred general anesthesia. Other exclusion criteria were acute infection of the genitalia (acute posthitis or balanitis), a thickened prepuce secondary to chronic inflammation, severe foreskin adhesion, or other contraindications to MC such as anomalies of the penis (e.g. chordee, or curvature of the penis), hypospadias, epispadias, concealed or buried penis, micropenis, webbed penis, and ambiguous genitalia.

In total, 30 patients were prospectively enrolled onto the study and randomized by drawing lots. The anesthetic techniques were written on 30 pieces of paper, LA group (n = 15) and DNB group (n = 15). The papers were put in a box and patients selected one blindly before the operation. All anesthesia and circumcision procedures were performed by the same surgeon.

Surgical technique

The patient was placed in the supine position. After preparation of the skin the anesthetic injection was given.

For the regional anesthesia, the dorsal penile nerve block was administered as described by Kirya and Werthmann[6]. Using a 24-gauge syringe, 0.2 ml/kg of 2% lidocaine without epinephrine[8,9] was divided into 2 and injected into both sides at the 10- and 2-o'clock positions at the base of the

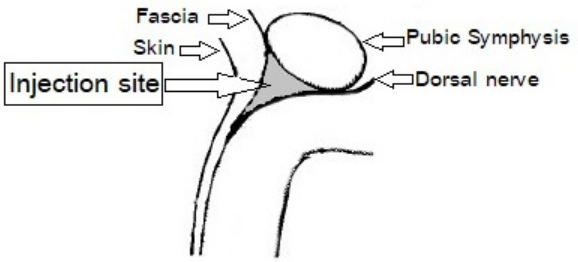

Figure 1. Lateral view of dorsal penile nerve block.

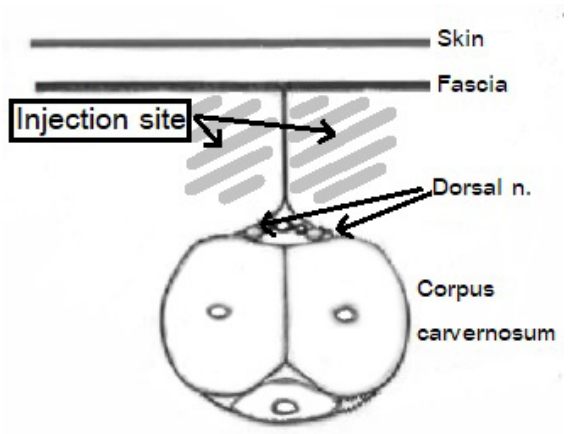

Figure 2. Transverse section of dorsal penile nerve block.

penis inferior to pubic symphysis (Figure 1 and 2).

In the LA group, circumferential local anesthesia was performed by injecting 0.2 ml/kg of 2% lidocaine without epinephrine[8,9] subcutaneously in the outer and inner surface at the level of the corona (Figure 3).

The sleeve technique circumcision was done with the following steps: circumferential outer foreskin incision, circumferential inner foreskin incision, frenulum incision, dorsal slit, foreskin excision and wound suture[10]. If the patients could not tolerate the level of pain, additional anesthetic solution would be injected directly at that area. Patient pain scores were evaluated again immediately and 5 minutes after the operation.

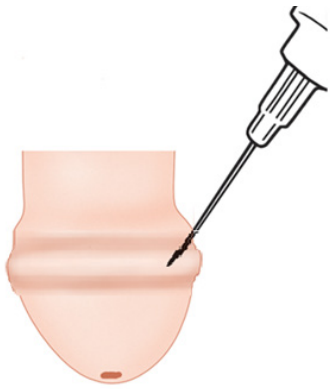

Figure 3. Circumferential local anesthesia (both outer and inner surface of prepuce).

Data collection

After anesthesia, patient sensation would be tested with forceps before starting the operation. Pain score was evaluated before, at each step and after the operation.

We used the internationally accepted Numerical Rating Scale (NRS) to evaluate pain[11]. To record the NRS, patients were asked to circle the number between 0 and 10 that best described their pain intensity. Zero usually represents "no pain at all" whereas the upper limit represents "the worst pain ever possible".

Statistical analysis

A T-test was used to compare age and BMI between two groups. We used the nonparametric Mann-Whitney test to compare pain scores[12]. Statistical significance was defined as a p-value of < 0.05.

Results

Patient characteristics were well balanced between the two groups. There were no statistically significant differences in age ($p = 0.9161$) and BMI ($p = 0.926$). Table 1 lists the characteristics of all patients in this study.

During anesthesia injection, LA was more painful than DNB (4.73 vs 3.7, $p < 0.05$). For each step of circumcision, in comparison with the dorsal penile nerve block group, the pain score was less in the LA group during the three procedural intervals: outer incision (0.47 vs 3.93, $p < 0.05$), inner incision (0.33 vs 1.47, $p < 0.05$) and incision near/at frenulum (0.33 vs 4.47,

Table 1. Comparison between local anesthesia (LA) group and dorsal penile nerve block (DNB) group.

	LA	DNB	P-value
Age (years)	43.53 +/- 20.97	42.73 +/- 20.23	0.9161
Body mass index (BMI) (kg/m^2)	22.59 +-/ 2.46	21.75 +/- 2.6	0.926
Circumcision steps	Pain score		
• Injection	4.73 +/- 1.22	3.7 +/- 0.96	0.04
• Outer incision	0.47 +/- 0.52	3.93 +/- 1.22	< .00001
• Inner incision	0.33 +/- 0.48	1.47 +/- 1.06	< .00001
• Frenulum incision	0.33 +/- 0.49	4.47 +/- 1.19	< .00001
• Dorsal slit	0.27 +/- 0.46	0.27 +/- 0.46	0.98
• Foreskin excision	0.27 +/- 0.46	1.33 +/- 0.35	0.59
• Suturing	0.73 +/- 0.70	1.00 +/- 0.76	0.37
• Post-op	0.267 +/- 0.46	0.2 +/- 0.41	0.77
• Post-op 5 minutes	0.13 +/- 0.35	0.13 +/- 0.35	0.98
• Overall pain score	1.53 +/- 0.64	2.6 +/- 1.24	.01278

Age and BMI are reported as mean ± SD. There were no significant differences between groups. The Numerical Rating Scale was used to evaluate pain. The Mann-Whitney test was used for statistical analyses.

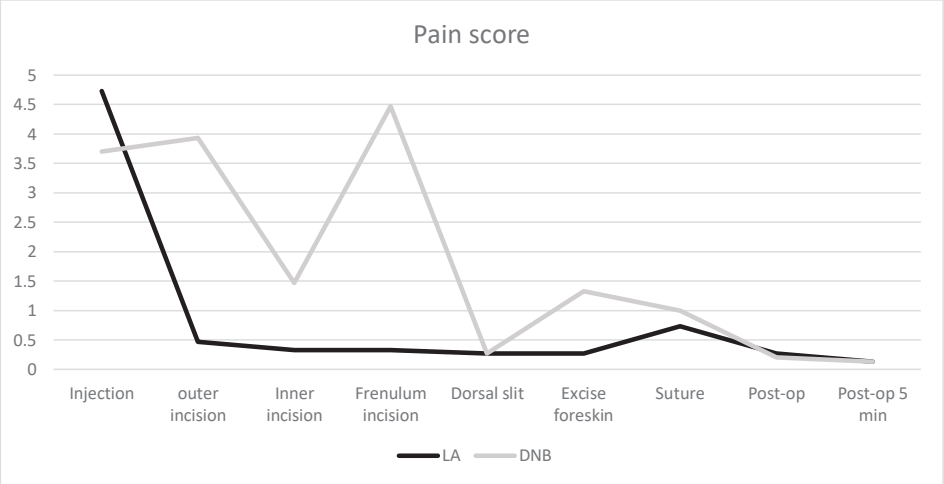

Figure 4. Pain score at each step of circumcision between the two groups.

$p < 0.05$). But there was no significant difference during dorsal slit, foreskin excision, suture, and post-operative pain. Overall pain score was higher in the dorsal penile nerve block group (1.53 vs 2.6, $p < 0.05$). Figure 4 shows the pain score at each step of circumcision between the groups.

Throughout the circumcision, the patients in the LA group had the highest pain score during anesthetic injection but showed little change in pain score compared with the DNB group during every step of circumcision and immediately afterwards. The DNB group had the highest pain score during frenulum incision, injection and outer foreskin incision.

Discussion

Our study has shown that circumferential LA is associated with higher pain score than DNB during anesthetic injection but lower scores during the operation. In the circumferential LA group there was a requirement of more injection sites than in the dorsal penile nerve block group to cover both outer and inner foreskin. This might be the cause of the pain score being higher in the circumferential LA during injection.

In the DNB group it appears that the dorsal penile nerve block was less effective at the three steps: outer incision, inner incision and incision near/at frenulum. However, during these steps, most of the patients did not feel pain at the dorsal side but began to feel pain and required additional anesthesia when the operation shifted to the ventral side especially near/at the frenulum. This might be the cause of the overall pain score being higher in the dorsal penile nerve block group.

Sensory innervation of the penis is through the dorsal nerve. The nerves richly supply the glans. The dorsal nerves travel alongside the dorsal arteries. In addition to receiving supply from the dorsal penile nerves the penis also receives innervation from small branches of the perineal nerve at the ventral side[13]. If DNB is used more anesthetic is needed in this area. The dorsal penile nerve block is technically more difficult than the local anesthesia as the depth and location of the dorsal nerve has to be estimated. The local anesthesia involves an injection of lidocaine directly at the surgical site so it can be performed more easily and accurately. In addition, in this study, we found that the duration for the anesthetics to take effect was shorter in the LA group. This might be due to the difference in technical difficulty as mentioned before.

There are a few limitations to our study, firstly there was no pain score threshold for additional anesthesia. We injected additional anesthesia only when the patients could not tolerate pain. Some patients requested additional anesthesia when NRS was 3 while others did not request it at the same pain score, so the real pain score might be higher. The variation in human tolerance of pain is difficult to control. The other principal weakness is that, statistically NRS does not have ratio qualities. Numerically equal intervals on the scale (e.g., the difference between 1 and 3 and the difference between 7 and 9) may not represent equivalent intervals in terms of scaling the intensity of pain.

In this study no complications were found in either group. But by reviewing the literature on dorsal penile nerve block, there are potentially two minor complications: bleeding and hematoma, both due to penetration of the superficial penile vein. Sara and Lowry have reported two cases of gangrene of the glans following circumcision using dorsal penile nerve block in a 13-month-old and a 3-year-old[14]. The authors postulated that trauma to the dorsal vessels caused bleeding into the restricted space between the Buck fascia and the corpora cavernosa, resulting in tamponade of the dorsal arteries and subsequent ischemia. Using the local anesthesia technique, the anesthetic is injected away from any major vessels and consequently would be less likely to result in bleeding or intravascular injection.

Conclusion

Circumferential local anesthesia is more effective in controlling pain during circumcision. Local anesthesia is also a simple technique and is theoretically less likely to result in serious complications. In the case of dorsal penile nerve block, it should be combined with ventral infiltration of local anesthesia at the site of incision.

Conflict of Interest

The author declares no conflict of interest.

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Original Article

Factors associated with urosepsis following percutaneous nephrolithotomy

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Keywords:
Factor, PCNL, urosepsis, staghorn stone, pelvic urine culture

Abstract

Objective: To evaluate factors associated with urosepsis after percutaneous nephrolithotomy (PCNL).

Materials and Methods: Seventy-six upper tract urinary calculi patients underwent PCNL at Loei Hospital between July 2014 to January 2019, all were enrolled onto the study. The following data were collected: demographics, type and size of stone, intraoperative data, pelvic urine culture and urosepsis complications after the procedure. Association of factors with urosepsis after PNCL were identified using a binary logistic regression model with a bootstrap estimation.

Results: Urosepsis complications occurred in 7 patients (9.2%). Mean (SD) of age was 54.4 (10.3) years. Of all patients, 2% with staghorn stone and 22% positive urine culture. Multivariable analysis indicated that staghorn stone (a OR =6.75; 95%CI: 1.59-28.63, p=0.01) and positive pelvic urine culture (a OR =7.51; 95%CI: 1.35-41.77, p=0.02) were associated with urosepsis after PCNL.

Conclusion: There was no mortality after PCNL in this study. Staghorn stone and positive pelvic urine culture may be associated with an increased risk of urosepsis complication.

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Introduction

Urolithiasis is one of the most problematic health issues worldwide. Loei Hospital encounters many patients with urolithiasis. There are multiple modalities to treat stones, one of which is percutaneous nephrolithotomy (PCNL). PCNL is the treatment of choice for large upper urinary tract stones.

PCNL is a safe, minimally invasive procedure, in comparison to open surgery; however, some patients may develop complications including fever, hemorrhage, urosepsis or death after PCNL. Urosepsis occurred in only 1% of cases but mortality in these cases was high at 66-80%[1]. Rashid concluded that risk factors for sepsis after PCNL were number of stones, operative time, intraoperative bleeding and presence of residual stones[2]; these findings differed from those reported by Basal et al who found that stone size more than 2.5 cm and intraoperative hemorrhage requiring transfusion were the risk factors[3].

No conclusions about risk factors for sepsis after PCNL have been drawn to date. This study was conducted with the aim of identifying risk of post-PCNL sepsis in Loei Hospital.

Materials and Methods

This was a retrospective study of medical records of 76 urolithiasis patients who underwent PCNL in Loei hospital between July 2013 and January 2019. Exclusion criteria were patients with incomplete medical records and patients with conversion from PCNL to open surgery.

The operations were performed by one urologist. A single dose of prophylactic antibiotic was given 30 minutes to 1 hour prior to surgery. After intubation and induction of anesthesia, the patient would be turned into the lithotomy position and a ureteric catheter was inserted at the site where stones were present. In the prone position, renal access was achieved under fluoroscopic guidance. After successful access pelvic urine was aspirated and collected for bacterial culture, A guide wire was inserted into the collecting system, followed by tract dilatation with metal dilatation up to 30 Fr. An Amplatz sheath was used in all cases. A nephroscope was introduced and stones were disintegrated by pneumatic lithotripsy. After the procedure a JJ stent was inserted via the nephroscope and a decision was made whether to insert the nephrostomy tube again.

Urosepsis complication was defined by SIRS criteria plus evidence of urologic sources. SIRS criteria in this study were defined by two or more of the following: 1. Body temperature > 38 °C or < 38 °C; 2. heart rate > 90 bmp; 3. respiratory rate > 20 breaths/min; 4. white blood cell count > 12,000 cells/ml or < 4,000 cells/ml[4].

Data collected and recorded included demographic data (including sex, age, body mass index (BMI), underlying disease, history of urinary tract infection), stone data, intraoperative data and complication data. Categorical data are reported as number and percentage. Continuous data are reported as mean and standard deviation, normality distribution being ascertained by the Shaphiro-Wilk test. For inter-group comparison of Urosepsis a t-test was used for continuous data and Fisher's exact test for categorical variables. Factors affecting urosepsis were assessed using a binary logistic regression model. From the univariable analysis, variables which had a $p < 0.15$ were entered in the multivariable analysis by forward selection. The multivariable model only included significant factors with the forward selection method. Coefficients were estimated using the bootstrap method to improve the precision of estimation in a small sample size. A $p < 0.05$ was considered statistically significant. All analyses were performed using IBM SPSS Statistics for Windows version 23.0 (IBM Corp, 2015).

Table 1. Clinical characteristics of study population.

Parameters	Number (%) (N=76)
Sex	
Male	54 (71.1)
Female	22 (28.9)
Age (year), mean ±SD	54.43 ± 10.27
BMI (kg/m^2), mean ± SD	22.89 ± 3.46
Underlying diseases	44 (57.9)
Diabetes mellitus	13 (17.1)
Hypertension	24 (31.6)
Dyslipidemia	6 (7.9)
Gout	3 (3.9)
Chronic kidney disease*	21 (27.6)
Past history UTI	21 (27.6)

*Chronic kidney disease is defined by a glomerular filtration rate less than 60 ml/min/1.73 m^2 for at least 3 months[5]

Results

Twenty-one patients (27.6%) had a history of urinary tract infection. Demographic data is shown in Table 1 and stone data is presented in Table 2. Staghorn stone was found to be the most common type of stone operated on by PCNL in this study and the median size of stone was 4.05 cm (IQR: 3.20-6.00). The univariate analysis found that the type of stone was a pre-operative risk factor for urosepsis, as shown in Table 3 and a positive renal pelvic culture was an intra-operative risk factor for urosepsis (Table 4). Multivariate analysis showed staghorn stone and renal pelvic culture positive were associated with urosepsis as shown in Table 5.

Table 2. Stone data.

Parameters	Number (%) (N=76)
RC	75 (98.7)
Renal pelvis stone	4 (5.3)
Multiple caliceal stone	2 (2.6)
Pelvic caliceal stone	14 (18.42)
Partial staghorn stone*	23 (30.3)
Staghorn stone**	32 (42.1)
Diverticulum stone	1 (1.3)
UC	3 (3.95)
Stone burden***, Median (IQR) (n=72)	4.05 (3.20-6.00)
Hydronephrosis	
Present	71(94.67)
Absent	4 (5.33)
Degree of hydronephrosis	
No hydronephrosis	4 (5.33)
Mild	9 (12.00)
Moderate	22 (29.33)
Severe	41 (54.67)

*Partial staghorn stone defined as a renal pelvic stone extending to only one calyx[6]

**Staghorn stone defined as a renal pelvic stone extending to at least two calices[6]

***Stone burden defined as the sum of the longest axial diameter of all stones[7]

Discussion

PCNL has become one of the preferred treatment options for upper urinary tract stones and PCNL is recommended as the first line treatment of larger stones > 2 cm. PCNL is a minimally invasive and safe procedure; however, it can be complicated by urosepsis which although is found infrequently it can prove lethal after PCNL. Several studies showed post-PCNL sepsis occurred in 0.3%-9.3% of cases[8,9]. In this study we found 9.2% of patients studied developed post-PCNL sepsis with no mortality.

Urosepsis after PCNL can be caused by bacterial growth in the renal pelvic urine or infected calculi. A biofilm can form which protects the bacteria from the antibiotic hence some bacteria remain active[10] during the manipulative actions and endotoxins will be released from stones[11]. The use of pressure irrigation during the process can result in bacteria and endotoxins from stones entering the bloodstream during stone manipulation through pyelovenous, pyelolymphatic and pyelotubular back flow and forniceal rupture[12].

Several studies have reported risk factors for post-PCNL sepsis including female gender, age, diabetes mellitus, history of UTI, white blood cells in the urine preoperatively, stone size, staghorn stone, degree of hydronephrosis, number of stones, amount of blood loss, operative time, and number of residual stones[2,13-15]. In this study, only pre-operative positive pelvic culture and staghorn morphology were found to be associated with urosepsis complications.

Many reports found that renal pelvis culture positive was a risk factor for fever, systemic inflammatory response syndrome (SIRS) and sepsis[13,16,17]. In this study we found that *E. Coli* (43.8%) was the most common organism in a positive renal pelvis culture. This was in line with previous reports[16-18] half of the organisms in urosepsis patients with a positive renal pelvis culture being *E. Coli*. In this study, patients with urosepsis were investigated by hemoculture. The findings were that out of the urosepsis patients one patient had an inconsistency in the organisms between the hemoculture and pelvic urine culture and 4 patients had negative hemocultures (Table 6).

Staghorn stone was associated with urinary tract infection with urease producing bacteria[19]. Several reports have reported the outcome of stone culture from staghorn stones and urease producing organisms were found in 44%-75.9% of cases[17,18,20]. It is difficult to conclude whether the UTI was caused by urea splitting bacteria as no examination of the culture stone was performed to confirm that urea splitting bacteria cause UTI in staghorn stone cases.

Selection of the antibiotic in post-PCNL urosepsis is important. This study found isolated

Table 3. Pre-operative factors related to urosepsis (N=76).

Characteristics	No (n=69)	Yes (n=7)	Total	P-value
Sex n (%)				0.40[b]
Male	50 (73)	4 (57)	54 (71)	
Female	19 (24)	3 (43)	22 (29)	
Age (years) mean ± SD	54.2 ± 10.6	57 ± 6.9	54.4 ± 10.3	0.49[a]
BMI (n=66)	2.2 ± 0.7	2.1 ± 0.7	2.2 ± 0.7	0.46[a]
Underlying disease n (%)				0.23[b]
No	31 (45)	1 (14)	32 (42)	
Yes	38 (55)	6 (86)	44 (58)	
Diabetes mellitus n (%)				1.0[b]
No	57 (83)	6 (68)	63 (83)	
Yes	12 (17)	1 (14)	13 (17)	
CKD n (%)				0.09[b]
No	52 (75)	3 (43)	55 (72)	
Yes	17 (25)	4 (57)	21 (28)	
Previous UTI n (%)				0.39[b]
No	51 (74)	4 (57)	55 (72)	
Yes	18 (26)	3 (43)	21 (28)	
Size of stone ≥ 4.2 cm n (%)				0.24[b]
No	39 (57)	2 (29)	41 (54)	
Yes	30 (44)	5 (71)	35 (46)	
Type of stone n (%)				0.04[b]
Non-staghorn stone	21 (30)	0 (0)	21 (28)	
Partial staghorn stone	22 (32)	1 (14)	23 (30)	
Staghorn stone	26 (38)	6 (86)	32 (42)	
Hydronephrosis (n=75) n (%)				1.0[b]
No	4 (6)	0 (0)	51 (68)	
Yes	64 (94)	7 (100)	71 (95)	

P-values were calculated from a Student t-test[a] and Fisher's exact test[b]. Data are expressed as mean (± SD) and number (%) depending on type of variable.

Table 4. Intra-operative factors related to urosepsis (N=76).

Characteristics	No (n=69) n (%)	Yes (n=7) n (%)	Total	P-value
Renal pelvic culture (n=72)				0.02[b]
Negative	54 (82)	2 (33)	56 (78)	
Positive	12 (18)	4 (67)	16 (22)	
Operative time (minutes)				1.0[b]
< 120	12 (17)	1 (14)	32 (17)	
≥ 120	57 (87)	6 (86)	63 (83)	
Number of access tracts				1.0[b]
1 tract	63 (91)	7 (100)	70 (92)	
> 1 tract	6 (8.7)	0 (0)	6 (8)	
Blood transfusion				0.06[b]
No	54 (78)	3 (43)	57 (75)	
Yes	15 (22)	4 (57)	19 (25)	
Residual stones (n=74)				0.58[b]
No	11 (16)	0 (0)	11 (15)	
Yes	56 (84)	7 (100)	63 (85)	

P-values were calculated from a Student t-test[a] and Fisher's exact test[b]. Data are expressed as mean ± SD and number (%) according to the types of variable.

Table 5. Univariable and multivariable analysis of post-PCNL urosepsis.

Variables	Univariable analysis		Multivariable analysis	
	OR (95%CI)	P-value	aOR (95%CI)	P-value
Underlying disease		0.02		
No	Ref			
Yes	4.89 (1.28 - 18.65)			
Blood transfusion		0.07		
No	Ref			
Yes	4.80 (0.89 - 25.76)			
Staghorn stone		<0.001		0.01
No	Ref		Ref	
Yes	9.92 (2.68 - 36.74)		6.75 (1.59 - 28.63)	
Hydronephrosis		0.12		
< Severe	Ref			
> Severe	0.33 (0.08 - 1.32)			
Size of stone (cm)		0.12		
< 4.2	Ref			
≥ 4.2	3.25 (0.73 - 14.54)			
Previous UTI		0.37		
No	Ref			
Yes	2.13 (0.41 - 11.06)			
Renal pelvic culture		0.01		0.02
Negative	Ref		Ref	
Positive	9.00 (1.63 - 49.77)		7.51 (1.35 - 41.77)	
CKD		0.10		
No	Ref			
Yes	4.08 (0.77 - 21.69)			
Diabetes mellitus	Ref	0.75		
No	0.79 (0.19 - 3.26)			
Yes				
Sex		0.42		
Male	Ref			
Female	1.97 (0.37 - 10.46)			
Operative time (minutes)		0.75		
< 120	Ref			
≥ 120	1.26 (0.30 - 5.40)			

aOR, adjusted odds ratio; The variables in univariable analysis were included by forward selection ($p < 0.15$). These consisted of underlying disease, blood transfusion, staghorn stone, hydronephrosis, size of stone, renal pelvic culture, and CKD. Those variables were excluded from the multivariable model due to their non-significance ($p > 0.05$) leaving only two variables which were significant ($p < 0.05$): staghorn stone and renal pelvic culture. The multivariable model was adjusted for staghorn stone and renal pelvic culture.

bacteria from urosepsis patients were more resistant to ampicillin, ceftriaxone, and ciprofloxacin while being relatively more sensitive to amoxycillin/clavulanate, ceftazidime, amikacin, gentamicin, and meropenam (Table 7). The drug of choice following PCNL needs to be from the following list amoxycillin/clavulanate, ceftazidime, amikacin, gentamicin, and meropenem.

This study does have some limitations, specifically that due to the retrospective nature of the study there were some incomplete data and also that the population studied was relatively small.

Table 6. Bacterial species detected in the cultures.

Variables	Urine culture non urosepsis n (%)	Urine culture urosepsis n (%)	Hemoculture non urosepsis n (%)	Hemoculture urosepsis n (%)
Not sent	5 (6.8%)	1 (1.3%)	69 (90.8%)	0 (0%)
Negative culture	52 (68.4%)	2 (2.6%)	7 (9.2%)	4 (57.1%)
Positive culture	12 (15.8%)	4 (5.3%)	0 (0%)	3 (42.9%)
Isolated organism				
Escherichia Coli	5 (31.3%)	2 (12.5%)	-	1 (33.3%)
Acinetobacter spp.	1 (6.3%)	1 (6.3%)	-	1 (33.3%)
Staphylococcus spp.	2 (12.5%)	-	-	-
Streptococcus spp.	2 (12.5%)	-	-	1 (33.3%)
Pseudomonas spp.	1 (6.3%)	-	-	-
Klebsiella spp.	-	1 (6.3%)	-	-
Mixed (Proteus+*E. coli*)	1 (6.3%)	-	-	-

Table 7. Intraoperative antibiogram-resistogram patterns of bacteria detected in the cultures.

Bacteria	Ampicilin	Amoxycillin/ clavulanate	Ceftriaxone	Ceftazidime	Meropenam	Ciprofloxacin	Amikacin	Gentamicin
E. coli								
1	R	I	R	R	S	R	S	S
2	R	S	R	R	S	R	S	S
*3	R	S	R	S	S	R	S	S
4	R	S	S	S	S	S	S	S
5	R	S	R	S	S	R	S	R
*6	R	S	R	S	S	R	S	S
7	ND	ND	ND	ND	ND	ND	ND	ND
Acinetobacter								
*1	ND	ND	R	R	R	R	S	S
2	ND	ND	R	R	S	R	I	S
Staphylococcus								
1	ND	ND	ND	ND	ND	S	ND	S
2	S	ND	ND	ND	ND	I	ND	S
Streptococcus								
1	ND	ND	R	ND	ND	ND	ND	ND
2	ND	ND	S	ND	ND	ND	ND	ND
Pseudomonas	ND	S	R	R	S	R	I	R
Klebsiella	ND	I	S	S	S	S	S	S
Mixed								
E. coli	R	I	S	S	S	R	S	S
Proteus	S	R	S	S	S	S	S	S

S = sensitivity, R = resistance, I=intermediate, ND = not done
*Urosepsis patients

Conclusion

PCNL is a safe operation for treatment of large upper urinary tract calculi; however, it can be complicated by urosepsis. This study found staghorn stone and a positive intraoperative pelvic culture to be risk factors for urosepsis complications. An intraoperative pelvic culture is important in caring patients with urosepsis particularly in UTI's which do not respond to previous antibiotics.

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Conflict of Interest

The author declares no conflict of interest.

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Original Article

Urine neutrophil gelatinase-associated lipocalin (NGAL) measurement is not predictive for ureteral patency in pediatric patients following pyeloplasty: a pilot study

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Keywords:
Biomarker, neutrophil gelatinase associated lipocalin, pyeloplasty, ureteropelvic junction obstruction

Abstract

Objective: To evaluate the benefit of urine neutrophil gelatinase-associated lipocalin (NGAL) measurement to predict the ureteral patency in pediatric patients undergoing pyeloplasty.

Materials and Methods: Ureteropelvic junction obstruction patients who underwent unilateral dismembered pyeloplasty had urine NGAL measurements taken intraoperatively during pyeloplasty and postoperatively at six months following surgery. All patients were evaluated preoperatively and postoperatively with renal scans. Pairwise comparisons and correlation analyses were performed to determine the dynamics and benefits of urine NGAL measurement.

Results: Thirteen patients were included in this pilot study with a mean age of 3.2 years at surgery. Mean intraoperative bladder urine level was 4.43 ng/mL, and median intraoperative renal pelvic urine NGAL level was 3.70 ng/mL. There was no significant difference between these two levels (p-value = 0.76). Six months after pyeloplasty, 9/13 patients demonstrated significant reduction in the bladder urine NGAL level (at least 50% reduction), and 5/13 patients showed ureteral patency based on postoperative renal scan (more than 5% improvement in differential renal function or the conversion of diuretic half time. However, the finding of significant reduction of urine NGAL level did not correlate with ureteral patency (r = -0.50, p-value = 0.08).

Conclusion: Although bladder urine NGAL level reduces in most pediatric patients following pyeloplasty, this decline is not reflective of the finding of ureteral patency from renal scanning. The benefits of urine NGAL measurement in this context remain unclear and require further large-scale investigation.

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Introduction

Prenatal hydronephrosis is one of the most common abnormalities found using ultrasound[1]. Although spontaneous resolution occurs in most cases, in some instances various degrees of permanent kidney injury can occur and it may lead to renal deterioration if left untreated[2]. Out of the different etiologies of prenatal hydronephrosis, ureteropelvic junction obstruction (UPJO) accounts for 19-25% and is usually identified in clinical practice[3]. Currently, two management pathways for UPJO are generally advocated: watchful waiting and surgical correction known as pyeloplasty[4]. In most situations, the latter is usually selected for patients who demonstrate one or more of the indications for surgery which include: the presence of symptoms associated with obstruction, impairment of overall function, progressive impairment of ipsilateral function, development of stones or infection and rarely, casual hypertension[5]. Of the various surgical techniques used in UPJO correction, dismembered pyeloplasty has been most frequently adopted by urologists and pediatric surgeons because of its simplicity and adaptability to almost all scenarios[6,7].

Although most patients are symptom-free following pyeloplasty, one question is paramount – how to determine whether the obstruction is corrected and the urine drainage from renal pelvis to ureter is no longer restricted. In general, these outcomes are evaluated using a combination of renal ultrasonography and renal scan[8]. Nevertheless, these imaging techniques are far from perfect. Resolution of hydronephrosis visualized from renal ultrasound is not always predictive of successful pyeloplasty, since most patients will demonstrate residual hydronephrosis. Renal scan images may be more reflective of an improvement in differential renal function (DRF), but it inevitably exposes pediatric patients to a significant amount of ionizing radiation, requires intravenous contrast injection, and sometimes necessitates sedation during the imaging procedure[9].

Recently, researchers have found several plasma and urine biomarkers potentially associated with obstructive uropathy, which are potentially useful in the evaluation of patients with urinary tract obstruction[10]. Neutrophil gelatinase-associated lipocalin (NGAL) is a promising one that has been widely investigated. Earlier studies have reported that urine NGAL levels were significantly higher in children with UPJO than in control groups[11,12]. This increase was also followed by a decrease to the same levels as the controls after surgical correction of UPJO[12]. However, whether this pattern of urine NGAL reduction reflects an actual "ureteral patency" remains unknown, and this was the exploratory aim of this study.

Materials and Methods

This prospective pilot study was carried out at King Chulalongkorn Memorial Hospital, Bangkok, Thailand. After approval was obtained from the institutional review board (IRB# 310/57), guardians of all consecutive eligible UPJO patients were informed about this study. If there was agreement to participate, written consent was acquired. Inclusion criteria were patients below 18 years of age who were diagnosed with unilateral UPJO requiring treatment with dismembered pyeloplasty. Exclusion criteria were bilateral UPJO patients, those diagnosed with posterior urethral valve (PUV), single functioning kidney patients, or those who had prior surgery on the ipsilateral kidney. We also excluded patients who had had a prior urinary diversion either with ureteral stent or percutaneous nephrostomy tube and those with complications caused by urinary tract infection within the last three months. Based on a previous finding that bladder urine NGAL level decreased by approximately 50% following UPJO correction, a sample size of 13 patients was required for this study[12].

Patient demographic parameters were prospectively collected including patient age at surgery, gender, associated urinary tract anomalies, and history of renal surgery. Within the month prior to surgery, an MAG-3 renal scan was performed to determine the differential renal function (DRF) and diuretic half-time. At the time of surgery, two urologists (C.B. and M.U.) conducted the open dismembered pyeloplasty surgical technique proposed by Anderson-Hynes[13]. Initially, a urethral catheter was inserted, and a 10 mL bladder urine specimen (BU1) was collected for research purposes. Then, the patient was turned into the lateral decubitus position, and a small flank incision was made to enter the retroperitoneal space. Once the renal pelvis and proximal ureter were dissected free from the surrounding tissue, another 10 ml of renal pelvic urine (PU)

was aspirated from the affected kidney via an 18-gauge needle. Resection of the stenotic part was carried out, and pyeloureterostomy anastomosis was performed over an indwelling 4.6 Fr ureteral stent which was subsequently removed after 6 weeks.

At six months, a voided midstream urine specimen (BU2) was collected at the clinic, and MAG-3 renal scan was performed to measure the postoperative DRF and the diuretic half-time clearance. In this study, ureteral patency was defined by the improvement of more than 5% of DRF[14] or the conversion of diuretic half time to less than 20 minutes.

All three urine specimens (BU1, PU, and BU2) were delivered to the laboratory facility within one hour of collection. They were centrifuged at 3000 cycles per minute at room temperature. Subsequently, the supernatant parts were drawn, divided into three tubes, and stored at -80°C. At the time of analysis, these specimens were defrosted, and NGAL level was measured using the NGAL Test™ Reagent Kit which uses enzyme-linked immunosorbent assay (BioPorto Diagnostics A/S, Hellerup, Denmark). The different assays were strictly quality controlled by the manufacturer with an inter-assay variation of well below 5%. All urine NGAL levels were expressed as an absolute value.

Comparison of NGAL levels was made using a paired t-test and a Mann-Whitney test. Significant NGAL reduction was noted if the NGAL level decreased by at least 50% following pyeloplasty. This outcome was further correlated against postoperative ureteral patency using Spearman's correlation. Statistical analyses were performed using Stata/SE version 14.1 (StataCorp, College Station, TX, USA). Data are expressed as mean± tandard deviation or percentage with statistical significance being assumed at $p < 0.05$.

Results

Sixteen pediatric patients were newly diagnosed with UPJO at our institution during the study period. However, three were excluded due to bilateral obstruction, single functioning kidney, and persistent urinary tract infection requiring preoperative ureteral stent placement. The remaining 13 patients were included in the analysis. The mean age at surgery was 3.2 ± 3.4 years (range 0.6-10.4 years), males predominated (n=8), females (n=5), and the majority of obstructions were on the left side (69.2%). Preoperative renal scans revealed a mean DRF of 43.1 ± 9.5% in the affected kidney, and the diuretic half-time was prolonged (> 20 minutes) in all patients (Table 1).

The mean intraoperative bladder urine (BU1) NGAL level was 4.43 ± 3.93 ng/mL, and the median intraoperative renal pelvic urine (PU) NGAL level was 3.70 ng/mL (Table 1). There was no statistically significant difference between bladder urine and renal pelvic urine NGAL levels (p-value = 0.76). All patients underwent dismembered pyeloplasty without any major perioperative complication and recovered uneventfully.

At six months after surgery, the mean postoperative bladder urine (BU2) NGAL level was 1.00±0.90 ng/mL, which was significantly lower than the intraoperative BU1 NGAL level (p-value = 0.01). Overall, 11/13 patients demonstrated some degree of NGAL reduction, and 9/13 patients demonstrated significant reduction (at least a 50% decrease from baseline level). Five out of 13 patients showed ureteral patency from the renal scan profiles specifically: 1) at least 5% elevation in DRF (3 patients), or 2) conversion of half-time to less than 20 minutes (3 patients) (Table 2).

Despite no clinical deterioration being found after surgery, the dynamics of urine NGAL did not show a significant correlation with postoperative radiologic outcome assessment. Following pyeloplasty, the demonstration of significant NGAL reduction (n = 9) was not significantly correlated

Table 1. Demographics and perioperative biochemical and radiological parameters.

Parameters	Value
Age at surgery, mean±SD (years)	3.2 ± 3.4
Gender, n (%)	
- Male	8 (61.5)
- Female	5 (38.5)
Laterality, n (%)	
- Left	9 (69.2)
- Right	4 (30.8)
Preoperative DRF, mean±SD (%)	43.1 ± 9.5
Preoperative half time, n (%)	
- > 20 minutes	13 (100)
Intraoperative bladder urine NGAL level, mean±SD (ng/mL)	4.43 ± 3.93
Intraoperative renal pelvic urine NGAL level, median (ng/mL)	3.70

Table 2. Postoperative biochemical and radiological parameters.

Parameters	Value
Postoperative DRF, mean±SD (%)	43.3 ± 11.7
At least 5% elevation in postoperative DRF, n (%)	
- Presence	3 (23.1)
- Absence	10 (76.9)
Postoperative half time, n (%)	
- 10-20 minutes	3 (23.1)
- < 10 minutes	0
- > 20 minutes	10 (76.9)
Postoperative bladder urine NGAL level, mean±SD (ng/mL)	1.00 ± 0.90
Reduction in postoperative bladder urine NGAL level, n (%)	
- Presence	11 (84.6)
- Absence	2 (15.4)
Significant reduction (at least 50%) in postoperative bladder urine NGAL level, n (%)	
- Presence	9 (69.2)
- Absence	4 (30.8)

to the finding of ureteral patency based on postoperative renal scan (r = -0.50, p-value = 0.08). Even looking at any degree of NGAL reduction (n = 11), this factor did not correlate well with postoperative ureteral patency (r = -0.37, p-value = 0.22).

Discussion

The goal of follow-up in UPJO patients after pyeloplasty is to identify those who are in danger of losing renal function from recurrent or unresolved obstruction[15]. To date, there has been no consensus regarding an appropriate surveillance strategy in this group of patients[16]. The majority of urologists commonly utilize a combination of clinical well-being, renal ultrasonography, and renal scan. Nevertheless, these tools are yet to be perfected and have certain drawbacks. Recurrent symptoms after surgery are usually detectable at a late phase of renal deterioration, and persistent symptoms such as pain may not correlate to anatomical obstruction[17]. In the case of ultrasonography, long-term evolution of residual hydronephrosis is relatively common[16]. A significant number of patients demonstrate stable hydronephrosis on ultrasound, while renal scanning shows an improved DRF[15]. In general, the renal scan is accepted as a gold standard for evaluating improvement in renal function after pyeloplasty, with a change of 5% considered as significant[14]. However, this imaging modality requires a significant exposure of ionizing radiation to the patients[18] which may negatively affect organ maturation in the long-term. Thus, when selecting a surveillance imaging modality following pyeloplasty, the radiation risks versus the diagnostic benefits should be weighed properly.

To overcome the complexity of imaging procedures and the associated radiation issue, several urine biomarkers have been investigated in the setting of obstructive uropathy[19]. They include Epidermal Growth Factor (EGF), Normal T- cell Expressed and Secreted (RANTES), Osteopontin (OPN), Neutrophil Gelatinase-Associated Lipocalin (NGAL), Cystatin C (CyC), β2-Microglobulin (β2-M), Kidney Injury Molecule-1 (KIM-1), and Carbohydrate Antigen 19-9 (CA-19-9), with various sensitivity, specificity and receiver operating characteristic (ROC) curves being reported in determining their clinical diagnostic and prognostic values[19]. Among these biomarkers, urine NGAL has demonstrated a promising diagnostic profile in numerous studies[11,12,20]. It is a 25-kDa protein secreted into urine via the thick ascending limb and collecting duct[21]. An increase in urine NGAL level is a well-established biomarker of kidney injury[22,23], and its role has also been examined in various kidney diseases such as diabetic nephropathy and nephritic syndrome[22,24].

Cost et al. have demonstrated that median bladder urine NGAL level was significantly higher in children with UPJO compared to controls (18.6 versus 8.3 ng/mg, p-value = 0.004). Within the subset of UPJO patients, renal pelvic urine NGAL was significantly higher than bladder urine NGAL, a finding that differed to ours. That study group also found that NGAL levels correlated well with their corresponding DRF (r = -0.359, p-value = 0.004). However, there was no published data regarding surgical outcomes or comparison to postoperative urine NGAL level[20]. Wasilewska et al., on the other hand, investigated the effect of pyeloplasty on urine NGAL levels of 20 children with unilateral UPJO. Similar to our findings, they found no difference between bladder urine and renal pelvic urine NGAL levels. A statistically significant correlation between preoperative urine NGAL level and differential renal function was also found when evaluating by MAG-3 renal

scan (r = -0.422, p-value <0.05). Three months after surgery, the bladder urine NGAL level had significantly decreased; however, there was no data published with regards to postoperative DRF, clinical outcomes, or other radiologic parameters of obstructive uropathy[11].

The major strength of our study is the comparison of NGAL dynamics to postoperative radiologic outcome assessment. Despite the low rates of significant improvement in DRF and half-time conversion, our surgical outcomes were comparable to others[14,25]. This may correspond to the fact that, although widely utilized, follow-up with a renal scan is still controversial, and its clinical benefits are considerably uncertain. Similarly to findings in previous studies, we found that bladder urine NGAL level reduced in most patients following pyeloplasty[11,12]. Nevertheless, this change was not associated to any of the ureteral patency parameters including improved DRF and diuretic half-time conversion.

Several limitations of this study should be addressed in future research. First, although prospectively conducted, the subject number was relatively small, and all findings need to be interpreted carefully. Second, we did not assign a group of matched controls to enable comparison of urine NGAL level. Third, one study has shown a daily biological variation of 27% for urine NGAL level in healthy young subjects[26] and we measured urine NGAL only once for every specimen. The intermediate variation levels would not be accounted for if there were changes. Finally, we did not standardize urine NGAL with urine creatinine level (urine NGAL/Creatinine ratio) a useful parameter previously described in other published literature[11,20]. However, this practice is still controversial. For example, one study indicated that urine NGAL/Creatinine ratio had a higher daily variation compared to absolute NGAL level[26]. This should be minimized in our study as we compared NGAL level from various specimens in a pairwise fashion, therefore interpersonal variability should be limited.

Conclusion

Bladder urine NGAL levels reduced in the majority of pediatric UPJO patients after pyeloplasty. However, our study did not demonstrate that the NGAL decline showed a significant correlation to the finding of ureteral patency obtained from renal scan. Whether urine NGAL measurement has a clinical benefit in the evaluation of post-operative ureteral patency remains unclear and requires further large-scale investigation.

Conflict of Interest

The authors declare no conflict of interest.

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Review Article

Living well with kidney disease by patient and care-partner empowerment: kidney health for everyone everywhere

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Abstract

Living with chronic kidney disease (CKD) is associated with hardships for patients and their care-partners. Empowering patients and their care-partners, including family members or friends involved in their care, may help minimize the burden and consequences of CKD-related symptoms to enable life participation. There is a need to broaden the focus on living well with kidney disease and re-engagement in life, including an emphasis on patients being in control. Every second Thursday in March, World Kidney Day (WKD) is celebrated. This year, it is on 11th March 2021. The WKD Joint Steering Committee has declared 2021 the year of "Living Well with Kidney Disease" in an effort to increase education and awareness on the important goal of patient empowerment and life participation. This calls for the development and implementation of validated patient-reported outcome measures to assess and address areas of life participation in routine care. It could be supported by regulatory agencies as a metric for quality care or to support labelling claims for medicines and devices. Funding agencies could establish targeted calls for research that address the priorities of patients. Patients with kidney disease and their care-partners should feel supported to live well through concerted efforts by kidney care communities including during COVID-19 pandemics. In the overall wellness program for kidney disease patients, the need for prevention should be reiterated. Early detection with a prolonged course of wellness despite kidney

disease, after effective secondary and tertiary prevention programs, should be promoted. WKD 2021 continues to call for increased awareness of the importance of preventive measures throughout populations, professionals, and policy makers, applicable to both developed and developing countries.

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Patient priorities for living Well: a focus on life participation

CKD, its associated symptoms, and its treatment, including medications, dietary and fluid restrictions, and kidney replacement therapy can disrupt and constrain daily living, and impair the overall quality of life of patients and their family members. Consequently, this can also impact treatment satisfaction and clinical outcomes[1]. Despite this, the past several decades have seen limited improvement in the quality of life of people with CKD[1]. To advance research, practice, and policy, there is increasing recognition of the need to identify and address patient priorities, values, and goals[1].

Several regional and global kidney health projects have addressed these important questions including the Standardised Outcomes in Nephrology (SONG) with more than 9,000 patients, family members, and health professionals from over 70 countries[2,3]. Across all treatment stages, including CKD, dialysis, and transplantation, SONG participating children and adults with CKD consistently gave higher priority to symptoms and life impacts than health professionals[2,3]. In comparison, health professionals gave higher priority to mortality and hospitalization than patients and family members. The patient-prioritized outcomes are shown in Figure 1. Irrespective of the type of kidney disease or treatment stage, patients wanted to be able to live well, maintain their role and social functioning, protect some semblance of normality, and have a sense of control over their health and wellbeing.

Life participation, defined as the ability to do meaningful activities of life including, but not limited to, work, study, family responsibilities, travel, sport, social, and recreational activities, was established a critically important outcome across all treatment stages of CKD[1,2]. The quotations from patients with kidney disease provided in Box 1. demonstrates how life participation reflects the ability to live well with CKD[4]. According to the World Health Organization (WHO), participation refers to "involvement in a life situation."[5] This concept is more specific than the broader construct of quality of life. Life participation places the life priorities and values of those affected by CKD and their family at the center of decision-making. The World Kidney Day Steering Committee calls for the inclusion of life participation, a key focus in the care of patients with CKD, to achieve the ultimate goal of living well with kidney disease. This calls for the development and implementation of validated patient-reported outcome measures, that could be used to assess and address areas of life participation in routine care. Monitoring of life participation could be supported by regulatory agencies as a metric for quality care or to support labelling claims for medicines and devices. Funding agencies could establish targeted calls

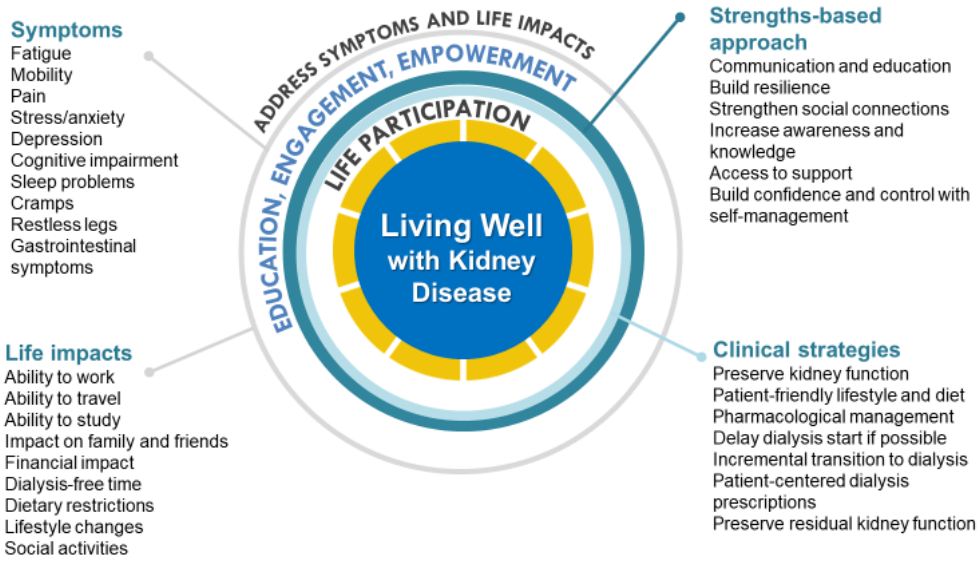

Figure 1. Conceptual framework of "Living Well with Kidney Disease" based on patient centeredness and empowering patient with focus on effective symptom management and life participation

Box 1. Quotations from patients with CKD related to priorities for living well

"I don't want to think about dying from my disease. I want to be able to live well with my disease." – Patient with CKD
"Life participation is most important because without it, you can't do anything." – Child with CKD
"Maybe it's as simple as asking patients whether, how well they are able to participate in the life that they want to lead because it's going to be different for different people" – Kidney transplant recipient
"Everyone has to face death, what I would like to have is a good quality of life rather than to face death." – Kidney transplant recipient
"So, it doesn't actually really matter what the numbers say, and some of my numbers should have suggested that I should be feeling a lot worse than what I actually was, it's about how much I feel I can do and participate in my life and feel normal." – Patient with CKD
"I'm still living. I get out of bed, and I'm still living and still breathing. As long as I can do that, I'm going to carry on and be positive because life is short." Patient with CKD
"I put life participation because I know that looking from the outside, I know [his kidney disease] stops [him] from thinking bigger. . .Although that's really big, there's this life that has to happen at the same time." – Family member
"Amazed at comments from professional(sic) about travel, free time, etc they seem to think the mechanics of dialysis far more important. Dialysis is a treatment which keeps us alive to live a life, not just to wait for death. – Patient receiving dialysis
"I prefer to be above ground, then below ground. So why not enjoy life whilst being above ground." Adam Martin
"Over the years, I have learned to worry less, control my emotions, and not fear death. I keep my mind active. I follow the advice of the philosopher-emperor Marcus Aurelius to 'love the hand that fate (has dealt me) and play it as (my) own'. Living well with CKD means to live the best life I can in the time I have available….Living well with CKD is the same as living well." – Tess Harris
"While CKD brings me some limitations, I can maximize the possibility to live well. I kept working when I was doing hemodialysis. After transplant, I could live: study, work, travel, marry, have children, and service the community." – Maggie Ng

for research that address the priorities of patients, including life participation.

Patient empowerment, partnership and a paradigm shift towards a strengths-based approach to care

Patients with CKD and their family members including care-partners should be empowered to achieve the health outcomes and life goals that are meaningful and important to them. The WHO defines patient empowerment as "a process through which people gain greater control over decisions or actions affecting their health,"[6] which requires patients to understand their role, to have the knowledge to be able to engage with clinicians in shared decision-making, skills, and support for self-management. For patients receiving dialysis, understanding the rationale for a lifestyle change, having access to practical assistance and family support promoted patient empowerment, while feeling limited in life participation undermined their sense of empowerment[7].

The World Kidney Day Steering Committee advocates for strengthened partnership with patients in the development, implementation, and evaluation of interventions for practice and policy settings, that enable patients to live well with kidney diseases. This needs to be supported by consistent, accessible, and meaningful communication. Meaningful involvement of patients and family members across the entire research process, from priority setting and planning the study through to dissemination and implementation, is now widely advocated[8]. There have also been efforts, such as the Kidney Health Initiative, to involve patients in the development of drugs and devices to foster innovation[9].

We urge for greater emphasis on a strengths-based approach as outlined in Table 1, which encompasses strategies to support patient resilience, harness social connections, build patient awareness and knowledge, facilitate access to support, and establish confidence and control in self-management. The strengths-based approach is in contrast to the medical model where chronic disease is traditionally focussed on pathology, problems, and failures[10]. Instead, the strengths-based approach acknowledges that each individual has strengths and abilities to overcome the problems and challenges faced,

Table 1. Suggested strategies for "living well with CKD" using a strengths-based approach.

Strengths-based approach	Suggested strategies
Build resilience	• Identify or provide strategies and resources to manage stress and functioning when encountering challenges, adversity and trauma (e.g. commencement of dialysis)
Harness social connections	• Facilitate connections with other patients to learn coping strategies and for support • Support family members/caregivers
Build awareness and knowledge	• Provide education (including practical advice) on diet and lifestyle modifications • Understand, identify, and address the potential impacts of CKD (e.g. cognitive function). • Encourage patients to ask questions. • Encourage the use of knowledge to empower and prepare for the future.
Facilitate access to support	• Refer to allied health care professionals (e.g. dietitian, social worker, mental health professionals, occupation therapists) • Provide support that enables the patient to participate in important life activities e.g. work.
Establish confidence and control in self-management	• Support informed and shared decision-making (including dialysis, kidney transplantation, conservative or non-dialytic care) • Encourage patients to learn to "get in tune" with what works well for them and to voice any concerns, and work together to develop better management strategies to enable patients to feel better. • Provide strategies to prevent or manage complications (e.g. infection) • Support open communication regarding goals, concerns, and priorities

Abbreviations: CKD: chronic kidney disease (not receiving kidney replacement therapy)

and requires collaboration and cultivation of the patient's hopes, aspirations, interests, and values. Efforts are needed to ensure that structural biases, discrimination, and disparities in the health care system also need to be identified, so all patients are given the opportunity to have a voice.

The role of care-partner

A care-partner is often an informal caregiver who is also a family member of the patient with CKD[11]. They may take on a wide range of responsibilities including coordinating care (including transportation to appointments), administration of treatment including medications, home dialysis assistance, and supporting dietary management. Caregivers of patients with CKD have reported depression, fatigue, isolation, and also burnout. The role of the care-partner has increasingly become more important in CKD care given the heightened complexity in communicative and therapeutic options including the expansion of telemedicine under the COVID-19 pandemic and given the goal to achieve higher life expectancy with CKD[12]. The experience of caring for a partially incapacitated family member with progressive CKD can represent a substantial burden on the care-partner and may impact family dynamics. Not infrequently, the career goals and other occupational and leisure aspects of the life of the care-partner are affected because of CKD care partnership, leading to care-partner overload and burnout. Hence, the above-mentioned principles of life participation need to equally apply to care-partners as well as all family members and friends involved in CKD care.

To provide assistance or improve the quality of life of these caregivers, some aspects should be considered including medical, psychological, and socio-economic aspects. Since kidney patients may need assistance physically from their caregivers, maintain and support the health and well-being of the caregivers are important. Healthcare providers may take the opportunity when educate the kidney patients to offer some advice that may be helpful for caregivers. Sometimes, anxiety for the caregivers to patients can persistently affect caregivers' psychological burden. This may result from a lack of knowledge about the patients' disease or on the other hand misunderstand about the patients' diseases. Providing

the caregivers education, establishing trust, and improving access to a healthcare provider may relieve the anxiety and help the caregivers to plan their life and time for caring for themselves and their patients. Lastly, financial problems from an inability to fully work of the caregivers need to be considered. Dialysis and transplant social workers should provide advice and resource to help the caregivers be able to financially support themselves. Hopefully, these supports for the caregivers can mitigate their burden and lead the caregivers to provide better care partnerships with the patients and healthcare providers.

Living with kidney disease in low-income regions

In low and lower-middle-income countries (LICs and LMICs) including in sub-Saharan Africa, South East Asia, and Latin America, patient's ability to self-manage or cope with the chronic disease vary but may often be influenced by internal factors including spirituality, belief system, and religiosity, and external factors including appropriate knowledge of the disease, poverty, family support system, and one's grit and social relations network. The support system comprising healthcare providers and caregivers plays a crucial role as most patients rely on them in making decisions, and for the necessary adjustments in their health behavior[13]. Specifically, among the majority of LIC, there are remaining unequal opportunities to access care for kidney health especially in rural areas. Patients and their caregivers may not be well-educated about kidney diseases and tend to trust and follow their doctors' decisions. However, in LIC regions, where there are often a relatively low number of physicians and an even lower number of kidney care providers per population especially in rural areas. On the other hand, patients in urban areas are generally well-educated and likely participate in making treatment decisions with trained nephrologists condensed practicing in the big city. This geographic injustice leads to the lack of education and access to kidney care in rural areas may contribute to late or inadequate therapeutic implementation to slow CKD progression and complications including CKD-related symptoms.

A suggested stepwise approach can involve local and national stakeholders including both non-governmental organizations and government agencies to mitigate the injustice in a sustainable fashion by 1) extending patient education in the rural areas with the assistance from local community leaders to periodically arrange educational campaigns by local health care providers, 2) adapting telehealth technologies if feasible with implementing info-communications technology to educate patients and train local community healthcare providers to be capable of providing kidney care,[14] 3) implementing effective retention strategies[15] for rural kidney health providers by changing educational structures and adapting career plans and competitive incentives for the new generation of physicians to return or remain in their local communities after their completion of specialist training to meet with the expectation of local community stakeholders,[16] and 4) promoting prevention of CKD progression by an emphasis on patient and family education and distributing medical and financial resources to healthcare facilities in the rural areas to improve care accessibility.

In addition to empowerment for kidney patients and family, both government and private stakeholders can contribute to improving not only the patient quality of life but also patient survival by promoting kidney transplantation. For example, the number of kidney transplantation in Thailand was significantly increased in 2003 and 2007 when there were two royal charity programs for free kidney transplantation initiated by the Kidney Foundation of Thailand[17].

Many patients in low resource settings present in very late stage needing to commence emergency dialysis[18]. The very few fortunate ones to receive kidney transplantation may acquire an indescribable chance to normal life again, notwithstanding the high costs of immunosuppressive medications in some countries. For some patients and care-partners in low-income regions, spirituality and religiosity may engender hope, when ill they are energized by the anticipation of restored health and spiritual wellbeing. For many patients, informing them of a diagnosis of kidney disease is a harrowing experience both for the patient (and caregivers) and the healthcare professional. Most patients present to kidney physicians (usually known as "renal physicians" in many of these countries) with trepidations and apprehension. It is rewarding therefore to see the patient's anxiety dissipate after reassuring him or

her of a diagnosis of simple kidney cysts, urinary tract infection, simple kidney stones, solitary kidneys, etc., that would not require extreme measures like kidney replacement therapy. Patients diagnosed with glomerulonephritis who have an appropriate characterization of their disease from kidney biopsies and histology; who receive appropriate therapies and achieve remission are relieved and are very grateful. Patients are glad to discontinue dialysis following resolution of AKI or acute on CKD.

Many CKD patients who have residual kidney function appreciate being maintained in a relatively healthy state with conservative measures, without dialysis. They experience renewed energy when their anemia is promptly corrected using erythropoiesis-stimulating agents. They are happy when their peripheral oedema resolves with treatment. For those on maintenance hemodialysis who had woeful stories from emergency femoral cannulations, they appreciate the construction of good temporary or permanent vascular accesses. Many patients in low resource settings present in very late stage needing to commence emergency dialysis. Patients remain grateful for waking from a uremic coma or recovering from recurrent seizures when they commence dialysis.

World Kidney Day 2021 Advocacy

World Kidney Day 2021 theme on 'Living Well with Kidney Disease' is deliberately chosen to have the goals to redirect more focus on plans and actions towards achieving patient-centred wellness. "Kidney Health for Everyone, Everywhere" with emphasis on patient-centred wellness should be a policy imperative that can be successfully achieved if policy makers, nephrologists, health care professionals, patients, and care partners place this within the context of comprehensive care. The requirement of patient engagement is needed. World Health Organization (WHO) in 2016 put out an important document on patient empowerment (WHO 2016): 'Patient engagement is increasingly recognized as an integral part of health care and a critical component of safe people-centred services. Engaged patients are better able to make informed decisions about their care options. In addition, resources may be better used if they are aligned with patients' priorities and this is critical for the sustainability of health systems worldwide. Patient engagement may also promote mutual accountability and understanding between patients and health care providers. Selecting kidney replacement therapy modalities is a common situation that sometimes is limited by healthcare resources resulting in an inability to provide therapy as per the patients' preference such as "Peritoneal dialysis First" in Thailand. However, planning and educating the patients and caregivers in advance should provide them guidance to be able to adequately make a reasonable and appropriate decision for each individual when those opportunities and resources exist. Informed patients are more likely to feel confident to report both positive and negative experiences and have increased concordance with mutually agreed care management plans. This not only improves health outcomes but also advances learning and improvement while reducing adverse events.' In the ISN Community Film Event at World Congress of Nephrology (WCN) 20 (ISN Community Film Event 2020), it is good to see a quote in the film from patients: "Tell me. I will forget; Show me. I will remember; Involve me. I will understand." ISN Global Kidney Policy Forum 2019 included a patient speaker Nicki Scholes-Robertson from New Zealand: 'Culturally appropriate and sensitive patient information and care are being undertaken in New Zealand to fight inequities in kidney health, especially in Maori and other disadvantaged communities.'

World Kidney Day 2021 would like to promote to the policy makers on increasing focus and resources on both drug and non-drug programmes in improving patient wellness. Examples include funding for erythropoiesis-stimulating agents and anti-pruritic agents for managing anemia and itchiness respectively, just name but a few[19,20]. Home dialysis therapies have been consistently found to improve patient autonomy and flexibility, quality of life in a cost-effective manner, enhancing life participation. Promoting home dialysis therapies should tie in with appropriate 'assisted dialysis' programs to reduce patient and care partner fatigue and burnout. Also, examples like self-management programmes, cognitive behavioural therapy, and group therapies for managing depression, anxiety, and insomnia should be promoted before resorting to medications[21]. The principle of equity recognizes that different people with different levels of disadvantage require different approaches and

resources to achieve equitable health outcomes. The kidney community should push for adapted care guidelines for vulnerable and disadvantaged populations. The involvement of primary care and general physicians especially in LICs and LMICs would be useful in improving the affordability and access to services through the public sector in helping the symptom management of CKD patients and improve their wellness. In the overall wellness program for kidney disease patients, the need for prevention should be reiterated. Early detection with a prolonged course of wellness despite kidney disease, after an effective secondary prevention program, should be promoted[22]. Prevention of CKD progression can be attempted by lifestyle and diet modifications such as a plant-dominant low protein diet and by means of effective pharmacotherapy including administration of sodium-glucose transport protein 2 (SGLT2) inhibitors[23]. WKD 2021 continues to call for increased awareness of the importance of preventive measures throughout populations, professionals, and policy makers, applicable to both developed and developing countries[22].

Successful of WKD campaign will not be possible unless there is a strong private-public partnership to continuously support the campaign around the world for example dialysis program as a part of the National Health policy providing free dialysis service to patients especially under representative or poor people, private pharmaceutical companies specializing in research, development, and commercialization of kidney-related products involving patient symptoms relieve by adhering to U.S. Food and Drug Administration regulations, and charity and non-profit organizations initiating activities that promote patient support and empowerment by launching fundraising to directly support kidney patients or kidney-related organizations, educational and research grants. Moreover, to extending the world of the 2021 WKD, partnership with scientific journals in different target audiences around the world has been helping to announce and spread the word of WKD annually. Lastly, national kidney foundations and organizations from different countries around the world may take the opportunity during the WKD campaign to meet and share their experiences for caring kidney patients as well as extend their partnership to LIC to support the care system in the aspects that may be limited in those countries such as home hemodialysis, kidney transplantation as well as to promote education that will benefit to patients and family and empower them to participate in their care.

Conclusions

Effective strategies to empower patients and their care-partners strive to pursue the overarching goal of minimizing the burden of CKD related symptoms in order to enhance patient satisfaction, health-related quality of life, and life participation. To celebrate the WKD every second Thursday in March, and this year's WKD is on 11th March 2021, World Kidney Day 2021 theme on 'Living Well with Kidney Disease" is deliberately chosen to have the goals to redirect more focus on plans and actions towards achieving patient-centered wellness. Notwithstanding the COVID-19 pandemic that had overshadowed many activities in 2020 and beyond, the World Kidney Day Steering Committee has declared 2021 the year of "Living well with Kidney Disease" in an effort to increase education and awareness on the important goal of effective symptom management and patient empowerment. Whereas the World Kidney Day continues to emphasize the importance of effective measures to prevent kidney disease and its progression,[22] patients with preexisting kidney disease and their care-partners should feel supported to live well through concerted efforts by kidney care communities and other stakeholders throughout the world even during a world-shattering pandemic as COVID-19 that may drain many resources[24]. Living well with kidney disease is an uncompromisable goal of all kidney foundations, patient groups, and professional societies alike, to which the International Society of Nephrology and the International Federation of Kidney Foundation World Kidney Alliance are committed at all times.

Conflict of Interest

K.K.-Z. reports honoraria from Abbott, Abbvie, ACI Clinical, Akebia, Alexion, Amgen, Ardelyx, Astra-Zeneca, Aveo, BBraun, Cara Therapeutics, Chugai, Cytokinetics, Daiichi, DaVita, Fresenius, Genentech, Haymarket Media, Hospira, Kabi, Keryx, Kissei, Novartis, Pfizer, Regulus, Relypsa, Resverlogix, Dr Schaer, Sandoz, Sanofi, Shire, Vifor, UpToDate, and ZS-Pharma.

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This article is being published in Kidney International and reprinted concurrently in several journals. The articles cover identical concepts and wording, but vary in minor stylistic and spelling changes, detail, and length of manuscript in keeping with each journal's style. Any of these versions may be used in citing this article. Note that all authors contributed equally to the conception, preparation, and editing of the manuscript.

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Case Report

Burkholderia pseudomallei infection in the genitourinary tract: a case report

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Keywords:
Melioidosis, genitourinary tract infection, renal abscesses, healthy, Thailand

Abstract

Melioidosis, caused by the gram-negative bacillus *Burkholderia pseudomallei*, is an infectious disease which is endemic in areas like Southeast Asia and Northern Australia. Urogenital involvement is less common in Thailand. This is a case study of a 60-year-old Thai male who had no underlying diseases and developed a renal abscess from melioidosis. He presented with a high grade fever for about 2 weeks. Physical examination disclosed costovertebral angle tenderness but otherwise was unremarkable. Laboratory and imaging investigations revealed leukocytosis in the complete blood count. White blood cells and red blood cells were detected in urinalysis. There was no growth in either the hemoculture or urine culture but melioidosis antibody level was positive (1:5, 120). Computerized tomography of the whole abdomen showed multiple areas of hypodensity lesions at mid and lower pole extended to the right perirenal space indicating likely renal abscesses. The final diagnosis was melioidosis with renal abscesses.

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Introduction

Melioidosis is an infectious disease, caused by the gram-negative bacillus *Burkholderia pseudomallei*. This disease is usually endemic in specific areas including Southeast Asia and Northern Australia[1]. However, there are increasing numbers of reported cases from many countries. Risk factors for this disease are diabetes mellitus, thalassemia, chronic renal disease, chronic lung disease and excessive alcohol use[2] and involve many organ systems including the respiratory tract, skin and soft tissue, intraabdominal organs, and the skeletal system. The genitourinary tract could be affected but there have been few reported cases worldwide.

Case Report

A 60-year-old healthy Thai male, a farmer from a Northeastern part of Thailand, presented with high grade fever and dysuria for 2 weeks. He also had right flank pain and nausea for 3 days. He denied any underlying diseases. His personal history included social alcohol drinking. The history of steroid use was negative. At Buriram hospital, he was febrile (38.9 °C) and exhibited tachycardia with a pulse rate of 120 beats per minute. His blood pressure was 127/90 mmHg. He had right costovertebral angle tenderness. His urine output was 2,400 ml/day, the remainder of the physical examination was unremarkable.

Due to the clinical findings, it was suspected that he had a urinary tract infection. His complete blood count showed anemia (hemoglobin 9.3 g/dl) and neutrophil leukocytosis (white blood cell 23,400/ul, neutrophils 95%). Fasting blood sugar was normal (97 mg%). Urinalysis showed many red and white blood cells in the urine. Both hemoculture and urine culture were negative. Due to the history of the subacute fever, melioidosis antibody levels were investigated and were found to be positive for a titer of 1:5, 120.

A computerized tomography (CT) scan of the whole abdomen was used to find the affected organs. The scan detected multiple areas of hypodensity lesions, involving the fat strand of the right kidney, perinephric collection (mid and lower pole of right kidney) and extending to the right perirenal space. These findings indicated potential right renal abscesses, there was no evidence of renal stones (Figure 1). From the clinical findings and laboratory investigations, the patient was diagnosed with melioidosis with renal abscesses and received high dose intravenous 2 gm meropenem every 8 hours for 21 days, continuing with oral trimethoprim/sulfamethoxazole (80/400 mg) 3 tabs per oral every 12 hours for 3 months in the eradication phase.

Discussion

Renal abscess is the one of the resulting complications from urinary tract infection[3]. The organisms commonly causing the infection are aerobic bacteria such as *Escherichia coli*, *Klebsiella* spp., *Proteus* spp., and also gram-positive bacte-

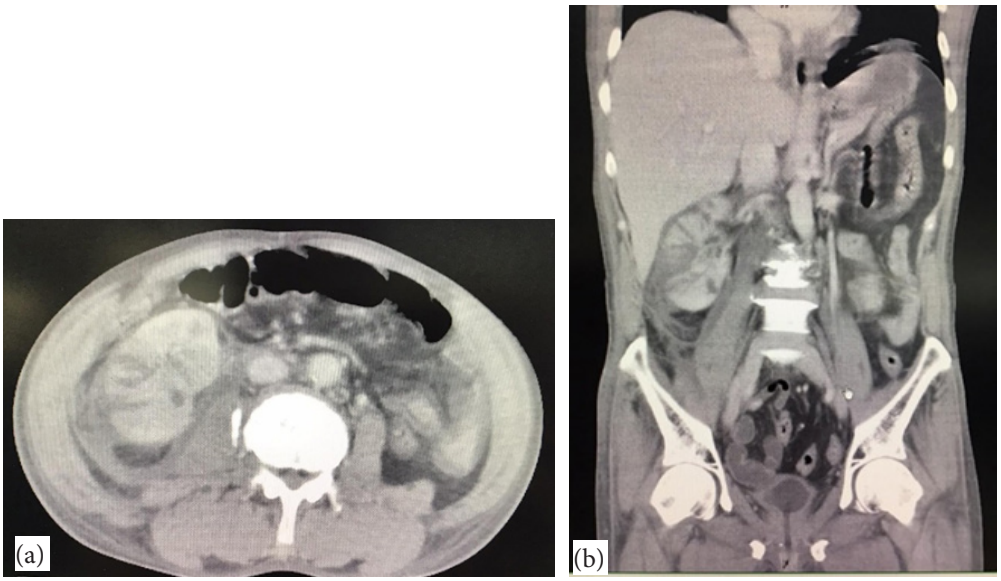

Figure 1. The coronal view (a) and sagittal view (b) of computerized tomography of the whole abdomen detected multiple areas of hypodense lesions involving the fat strand of the right kidney, perinephric collection (mid and lower pole), extending to the right perirenal space. Right renal abscesses were suspected.

ria such as *Enterococcus spp*. and *Staphylococcus aureus*. It is a difficult-to-treat condition and serious complications may develop including septic shock. The treatment is dependent on abscess size. Antibiotic administration, depending on the type of organism, is indicated in small abscesses of a diameter less than 3 cm. Drainage (percutaneous or surgical) is recommended in the case of large abscesses (diameter more than 5 cm). Both approaches can be applied in medium-sized abscesses (3-5 cm)[4].

Melioidosis may infect the genitourinary tract mostly involving the prostate and kidney. Renal abscess from melioidosis is a rare condition. Predisposing factors in adults are diabetes mellitus and urinary tract abnormalities (mainly lithiasis and ureteral obstruction). Currently few cases have been reported cases[5]. The isolation and identification of cultures from the infected site remains the gold standard for diagnosis. However, melioidosis titers which have a sensitivity of 73% and specificity of 64% with a cut-off point = 1:160 could be used as alternative investigations for diagnosis[6]. Treatment of melioidosis consists of 2 phases; an intensive phase and eradication phase.

To the best of our knowledge, this is the first Thai case of renal abscess from melioidosis in a patient who was healthy. Although, hemoculture and urine culture which are the gold standard for diagnosis were negative, melioidosis was still a possibility due to his risk factors, which included living in an endemic area and exposure to soil. The outcome of the melioidosis antibody titers revealed a high positive titer (1:5,120) added weight to the diagnosis. The CT scan, the tool for diagnosis and assessment of the severity of the complications, detected findings compatible with renal abscesses[7]. The abscesses were not collected in this case due to their small size. Thus, melioidosis was diagnosed in this patient. The patient received meropenem for the intensive phase of treatment for 21 days and then oral trimethoprim/sulfamethoxazole (80/400 mg) 3 tabs per oral every 12 hours for 3 months in the eradication phase.

In summary, the genitourinary tract may be affected in cases of melioidosis. A high level of clinical suspicion of clinicians from the personal history, risk factors and physical examination is mandatory. Early diagnosis could reduce the complications and mortality. Despite the negative cultures for melioidosis, the other laboratory investigations should be further studied such as melioidosis antibody titers. A CT scan may also help diagnosis and can be used to assess the severity of this disease.

Conflict of Interest

The authors declare no conflict of interest.

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The Insight Urology (ISU) is the official journal of Thai Urological Association under the Royal Patronage (TUA). The Editorial Board welcomes all scientific manuscripts from physicians and various specialties which are of interest and of benefit to the urological society. The submitted manuscripts must not be in the process of submission or have been previously published in any other journal.

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1. Original article

Requirements:

1.1 Abstract
- Objective (s)
- Materials and Methods
- Results
- Conclusion (s)

1.2 Full text
- Introduction
- Objective (s)
- Materials and Methods
- Results
- Discussion
- Conclusion (s)
- Acknowledgement (optional)
- Conflict of Interest
- References

1.3 Table (s) and legend (s)

1.4 Figure (s) and legend (s)

2. Review article

Requirements:

2.1 Interesting and pertinent

2.2 Include standard of treatment

3. Case report

Requirements:

3.1 Interesting

3.2 Not previously published

3.3 Indicates the important case aspects

4. Letter to the editor

Requirements:

4.1 Questions, discussions, and opinions to published articles

4.2 Creative and beneficial to all readers

4.3 Negative opinions must include reference (s) for the opposing opinion

5. Surgical technique

Requirements:

5.1 Reports of surgical technique

5.2 The technique provides beneficial to readers

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The Insight Urology will be maintained according to the international standards set by the International Committee of Medical Journal Editors for the conduct, reporting, editing and publication of scholarly work in medical journals.

1. Manuscripts should be typed on paper size A4 (212 X 297 mm) using Times New Roman 12 font. All borders should be at least 25 mm. Page numbers should be in the top right corner. The first page must be the title page, followed by abstract, text, tables, and figures.
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The authors must use Vancouver style and use Arabic numbers as seen in the manuscript. The number of references should be put in braces/parentheses. The short name of the journal must follow Index Medicus format.

Examples for references

1. English article: List all authors' names if less than seven. If seven or more authors, list only the first six names and follow by et. al.

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If the authors are committees, groups, or institutes:

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Table

1. Each table should be placed on a separate page. One page for one table.
2. All tables should have the table number with table description on the top of the table.
3. Additional explanations should put *, ¥, etc., in the table and then give more detail on the bottom of the table.
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Figure

1. Hand-drawn figures must be drawn with thick, black lines.
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Abbreviation and measurement

1. Use standard abbreviations. Should not use abbreviation in the Title or Abstract. All abbreviations must be first typed in entirety with the abbreviation in parentheses/braces before continued use in abbreviated form.
2. Use metric units for length, height, weight, and volume (meter, kilogram, and litter), with only 2-decimal accuracy.
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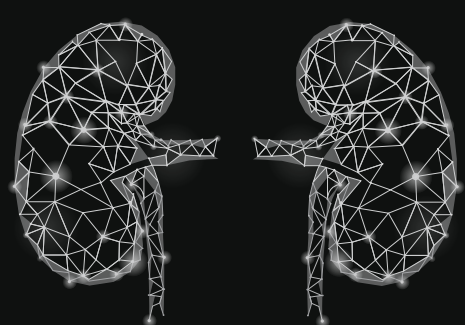

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