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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 fourth issue of Insight Urology (ISU) has now been published online in full. It is comprised of 10 original articles, three review articles, one case report, and one surgical technique, and covers several fields of urology, namely oncologic urology, pediatric urology, endourology, female urology, andrology, and kidney transplantation. Two articles were submitted by the international authors: "Kidney health for all: bridging the gap in kidney health education and literacy" and "Rotational labial and inferior pudendal artery based inner thigh flaps for vaginal defects after reconstructive surgery". All 15 articles are of superb quality. We are certain that you will enjoy reading and applying the articles' content to your present urological treatment.

What is an invited review article? It is an article in which we invite various authors to make a review. The topics that are renowned and popular will be selected, and the experts in that field will be invited by the Editor in Chief of ISU. Then the submitted manuscripts will be reviewed by peer reviewers. We aim to publish two invited review articles per issue so there will be 4 invited review articles per year. We acknowledge the help of the Thai Urological Association under the Royal Patronage (TUA) for its strong support of all the expenses involved in this important process. We hope that this new section will benefit our readers and assist the ISU to achieve the international standard of Scopus in the future.

The COVID-19 pandemic is declining both in terms of its virulence and cases worldwide after vaccinations and our adaptation to the disease. However, there are new challenges such as wars, monkey pox, and economic disruptions in many countries. These poor situations cause difficulties in living, medical care, and education. But do not forget that every new risk comes with new opportunities. Mindfulness, concentration, and deep looking is good practice for learning to cope with these hard tasks. The Editorial Board of ISU hopes that the silver cover of this issue with the light at the end of the tunnel will represent our hope for peace for everyone in the world.

No reserve. No retreat. No regret.

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

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Original Article

Prediction of a novel prostate-specific antigen density cutoff value and use of transrectal ultrasound-guided prostate biopsy for diagnosis of prostate cancer in Thailand

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Keywords:
PSAD, prostate-specific antigen density, prostate cancer detection

Abstract

Objective: The measurement of prostate-specific antigen density (PSAD) is a noninvasive and inexpensive practice, which may improve the accurate diagnosis of prostate cancer. The incidence of prostate cancer in Thailand is relatively low compared with that in Western countries. Therefore, a blanket adoption of the Western cutoff value (PSAD 0.15 ng/ml/cm^3) is inapplicable and can lead to unnecessary biopsies. The aim of this study was to determine an optimal PSAD cutoff value for effective diagnosis in Thai men.

Materials and Methods: We retrospectively studied transrectal ultrasound-guided prostate biopsies from 542 men with intermediate PSA concentrations ranging from 4 to 10 ng/ml, carried out from January 2011 to January 2017. The area under the receiver operating characteristic curve (AuROC) was used to evaluate the efficacy of PSAD for the diagnosis of prostate cancer.

Results: In Thai men who had intermediate PSA concentrations, the AuROC was higher for PSAD in comparison to that of PSA (0.692 vs 0.544). The AuROC using the PSAD cutoff value = 0.20 ng/ml/cm^3 was higher than that using the PSAD cutoff value = 0.15 ng/ml/cm^3 (0.652 vs 0.626). The sensitivity, specificity, positive predictive value, and negative predictive values were 67.33%, 62.13%, 29.95%, and 89.15%, respectively.

Conclusion: PSAD improved the diagnosis of prostate cancer in Thai men with intermediate PSA concentrations. The optimal cutoff value was 0.20 ng/ml/cm^3.

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Introduction

The level of prostate-specific antigen (PSA) is used extensively for the detection of prostate cancer.[1] However, the diagnostic power of the PSA test shows an insufficient sensitivity or specificity, particularly at intermediate concentrations (4–10 ng/ml).[2] More recently, prostate-specific antigen density (PSAD) has served as a useful tool for the diagnosis of prostate cancer[3] in patients with a normal digital rectal exam (DRE) and gray-zone (intermediate) PSA concentrations.[4] The PSAD value is easily calculated (PSA concentration divided by the volume of the prostate gland).[4] The most recent clinical practice guidelines support the use of PSAD in combination with other new biomarkers when deciding to avoid a prostate biopsy.[5] The advantages of using PSAD over other tests are its lower cost and simplicity, which enable its use in low-income countries or provincial hospitals.

The prevalence of prostate cancer, which varies worldwide, is relatively low in Asian countries compared with that in Western countries. For example, the incidence of prostate cancer is 2.87 per 100,000 persons in Thailand[6] compared with 109.2 per 100,000 persons in the United States.[7] Furthermore, the PSA cutoff value should be higher for Thai patients compared with that for patients residing in Western countries.[8]

The present study therefore aimed to determine an optimal cutoff value of PSAD for Thai patients with intermediate PSA concentrations and a normal DRE. From the data collected we propose a higher cutoff value than that used in Western countries (0.15 ng/ml/cm^3).[9-11]

Materials and Methods

We collected data from January 2011 to January 2017 retrospectively from Ramathibodi Hospital, Thailand. The inclusion criterion was a prostate biopsy. Exclusion criteria were data from patients with an abnormal DRE with a PSA < 4 ng/ml and >10 ng/ml. Serum PSA concentrations were measured using an automated electrochemiluminescence immunoassay method (Cobase 601, Roche) immediately before biopsy. Prostate volume was measured using transrectal ultrasound (TRUS) (BK Medical Flex Focus 400). PSAD = PSA/prostate volume (ng/ml/cm^3). Prostate tissue biopsies were carried out using a Pro-Mag 18-gauge biopsy needle and a BK Medical Type 8812 equipped with an end-firing TRUS probe and samples were sent for review by pathologists who specialize in urology.

A receiver operating characteristic (ROC) curve was generated to evaluate the performance characteristic of PSAD according to the areas under the ROC curve (AuROC) as a primary outcome. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were evaluated as secondary outcomes.

We analyzed data using a t test median regression and Pearson's chi-square test to evaluate the significance of differences in mean and median values. The research protocol was approved by the Ethical Committee of the Faculty of Medicine Ramathibodi Hospital, Mahidol University (Protocol Number: 06-61-66).

Results

Out of the 1,577 patients who underwent a prostate biopsy at Ramathibodi Hospital from 2011 until 2017, 542 with a normal DRE met the inclusion criteria with PSA concentrations within the gray (intermediate) zone. These patients included 441 without detectable prostate cancer and 101 with histopathologically confirmed prostate cancer (mean ages 66.6 years and 67.4 years, respectively). The mean PSA concentration of those with prostate cancer was 6.91 ng/ml vs 6.68 ng/ml in those without. However, the volume of the prostate glands of patients with prostate cancer, measured by ultrasound during performance of the transrectal prostate biopsy, were significantly smaller in comparison to those of patients without (33.38 ml vs 45.56 ml) (Table 1).

The cutoff value of PSAD with the highest AuROC (0.652) was 0.20 ng/ml/cm^3. The AuROC was 0.626 when we used the cutoff value of PSAD = 0.15 ng/ml/cm^3. When we used the cutoff value of PSAD = 0.20 ng/ml/cm^3, the sensitivity, specificity, positive predictive value, and negative predictive values were 67.33%, 62.13%, 29.95%, and 89.15%, respectively (Table 2). The AuROC of PSAD was higher compared with that of PSA (0.69 and 0.54, respectively) (Figure 1).

Discussion

Benson et al.[3] first reported the advantages of PSAD in differentiating prostate cancer from other benign prostate diseases in patients with a normal DRE patient with serum PSA concentra-

Table 1. Clinical characteristics of DRE-negative patients with intermediate serum PSA concentrations

Data	Total (n = 542)	Non-cancer (n = 441)	Cancer (n = 101)	P-value
Patients (PSA 4–10 ng/ml/cm^3)				
Age (years)				
Mean ± SD	66.72 ± 7.72	66.56 ± 7.88	67.40 ± 6.98	0.344
Median ± (IQR)	67 (62, 72)	67 (62, 72)	67 (62, 71)	
PSA ng/ml				
Mean ± SD	67.2 ± 1.64	6.68 ± 1.64	6.91 ± 1.61	0.202
Median ± (IQR)	6.52 (5.36, 8.12)	6.43 (5.34, 8.00)	6.97 (5.60, 8.12)	
Prostate volume ml				
Mean ± SD	43.29 ± 26.25	45.56 ± 27.46	33.38 ± 16.99	0.001
Median ± (IQR)	39.1 (28.4, 52.0)	41.0 (31.8, 54.0)	28.8 (23.0, 39.1)	

PSA = prostate-specific antigen, SD = standard deviation, IQR = interquartile range

Table 2. Cutoff values and diagnostic variables associated with PSAD

PSAD (ng/ml/cm^3)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AuROC
0.10	94.06	13.15	19.84	90.64	0.5361
0.15	85.15	40.14	24.53	92.20	0.6264
0.20	67.33	62.13	29.95	89.15	0.6521

PSAD = prostate-specific antigen density, PPV = positive predictive value, NPV = negative predictive value

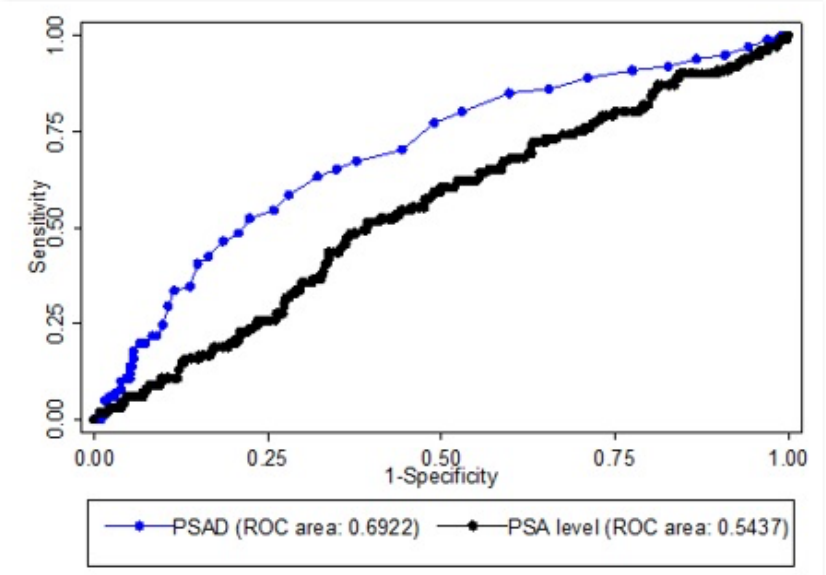

Figure 1. The areas under the receiver operating characteristic curve for prostate-specific antigen (PSA) and PSA density as continuous variables used to predict prostate cancer

tions ranging from 4.0 ng/ml to 10 ng/ml.[3] This concept is supported by the findings of numerous subsequent studies. As in other low-income countries, standard practice in Thailand is to employ a PSAD cutoff value = 0.15 ng/ml/cm^3, which was adopted from the experience of Western countries because of insufficient data available for Thai patients.[12] In this study we determined a new cutoff value for the PSAD of DRE-negative Thai men with intermediate concentrations of serum PSA. This cutoff value = 0.2 ng/ml/cm^3, which is higher in comparison to the Western cutoff value, and is consistent with reports for men from other Asian countries.[13-15] For example, Lin et al.[16] reported PSAD cutoffs as high as 0.35 ng/ml/cm^3 for men of Chinese ethnicity.

A disadvantage of using PSAD is that the procedures of measuring prostate volume and

performing a DRE need to be carried out by skilled technicians or clinicians,[17,18] and these specialists must have sufficient experience in the identification of an abnormal prostate.[19] Other diagnostic methods are available including multiparametric magnetic-resonance imaging for the measurement of prostate volume and a range of practices to facilitate the measurement of biomarkers including the %free PSA,[20] the Prostate Health Index,[21] PCA3,[22] and the 4K score.[23] However the benefits of these practices in routine clinical use in low-income countries have not been realized because of limited availability and high cost. Another Thai study reported using extended 14-core schematic diagram mapping prostate biopsy which also increased the detection rate of prostate cancer and increased the accuracy of the Gleason score from biopsy.[24]

Conclusion

Determining the PSAD in individuals is inexpensive and noninvasive, making it a feasible and efficacious option for use by provincial hospitals. The new cutoff value reported here (0.20 ng/ml/cm^3) may contribute to improving the management of Thai patients with intermediate serum PSA concentrations and a normal DRE.

Conflicts of Interest

The authors declare no conflicts of interest.

References

1. Catalona WJ, Smith DS, Ratliff TL, Dodds KM, Coplen DE, Yuan JJ, et al. Measurement of prostate-specific antigen in serum as a screening test for prostate cancer. N Engl J Med 1991;324:1156-61.
2. Lavallée LT, Binette A, Witiuk K, Cnossen S, Mallick R, Fergusson DA, et al. Reducing the Harm of Prostate Cancer Screening: Repeated Prostate-Specific Antigen Testing. Mayo Clinic Proc 2016;91:17-22.
3. Benson MC, Whang IS, Olsson CA, McMahon DJ, Cooner WH. The use of prostate specific antigen density to enhance the predictive value of intermediate levels of serum prostate specific antigen. J Urol 1992;147:817-21.
4. Aus G, Bergdahl S, Lodding P, Lilja H, Hugosson J. Prostate cancer screening decreases the absolute risk of being diagnosed with advanced prostate cancer--results from a prospective, population-based randomized controlled trial. Eur Urol 2007;51:659-64.
5. National Comprehensice Cancer Network [Internet]. Prostate Cancer Early Detection (Version 2.2019) [cited 2021 Jan 1]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/prostate_detection.pdf.
6. Hospital-based cancer registry 2017. In: Services DoM, editor. Bangkok: Institute NC; 2017.
7. Andrew J, Stephenson EAK. Epidemiology, Etiology, and Prevention of Prostate Cancer. In: Wein AJ, Kavoussi LR, Partin AW, Peters CA, editors. Campbell-Walsh Urology. 11th ed. Philadelphia: Elsevier; 2020. p. 3458-77.
8. Sirisopana K, Sirisreetreerux P, Viseshsindh W, Kijvikai K, Kongcharoensombat W, Pacharatakul S, et al. Optimal prostate-specific antigen (PSA) cut-off value and transrectal ultrasound guided prostate biopsy in the diagnosis of prostate cancer in Ramathibodi Hospital: first study in South East Asia. J Med Assoc Thai 2019;102:52-5.
9. Akdas A, Tarcan T, Türkeri L, Cevik I, Biren T, Ilker Y. The impact of prostate-specific antigen density in predicting prostate cancer when serum prostate-specific antigen levels are less than 10 ng/ml. Eur Urol 1996;29:189-92.
10. Rico L, Contreras P, Vitagliano G, Rios Pita H, Ameri C, Blas L. Value of prostate-specific antigen density in negative or equivocal lesions on multiparametric magnetic resonance imaging. Turk J Urol 2020;46:367-72.
11. Faisal FA, Sundi D, Pierorazio PM, Ball MW, Humphreys EB, Han M, et al. Outcomes of men with an elevated prostate-specific antigen (PSA) level as their sole preoperative intermediate- or high-risk feature. BJU Int 2014;114:e120-9.
12. Saema A, Kochakarn W, Lertsithichai P. PSA density and prostate cancer detection. J Med Assoc Thai 2012;95:661-6.
13. Gohji K, Nomi M, Egawa S, Morisue K, Takenaka A, Okamoto M, et al. Detection of prostate carcinoma using prostate specific antigen, its density, and the density of the transition zone in Japanese men with intermediate serum prostate specific antigen concentrations. Cancer 1997;79:1969-76.
14. Muangman V. Vasectomy: clinical aspects and reversibility. J Thai Assoc Volunt Steriliz 1979:79-83.
15. Rahardjo D, Kamil ST, Pakasi LS. Rationale for using serum prostate-specific antigen (PSA) level and PSA density (PSAD) to detect prostatic malignancy in a country with low prostate cancer incidence. Gan To Kagaku Ryoho 2000;27:563-70.
16. Lin YR, Wei XH, Uhlman M, Lin XT, Wu SF, Diao PF, et al. PSA density improves the rate of prostate cancer detection in Chinese men with a PSA between 2.5-10.0 ng ml (-1) and 10.1-20.0 ng ml (-1): a multicenter study. Asian J Androl 2015;17:503-7.

17. Matthews GJ, Motta J, Fracehia JA. The accuracy of transrectal ultrasound prostate volume estimation: clinical correlations. J Clin Ultrasound 1996;24:501-5.
18. Sajadi KP, Terris MK, Hamilton RJ, Cullen J, Amling CL, Kane CJ, et al. Body mass index, prostate weight and transrectal ultrasound prostate volume accuracy. J Urol 2007;178:990-5.
19. Pinsky PF, Kramer BS, Crawford ED, Grubb RL, Urban DA, Andriole GL, et al. Prostate volume and prostate-specific antigen levels in men enrolled in a large screening trial. Urology 2006;68:352-6.
20. Catalona WJ, Partin AW, Slawin KM, Brawer MK, Flanigan RC, Patel A, et al. Use of the percentage of free prostate-specific antigen to enhance differentiation of prostate cancer from benign prostatic disease: a prospective multicenter clinical trial. JAMA 1998;279:1542-7.
21. Filella X, Giménez N. Evaluation of [-2] proPSA and Prostate Health Index (phi) for the detection of prostate cancer: a systematic review and meta-analysis. Clin Chem Lab Med 2013;51:729-39.
22. Gittelman MC, Hertzman B, Bailen J, Williams T, Koziol I, Henderson RJ, et al. PCA3 molecular urine test as a predictor of repeat prostate biopsy outcome in men with previous negative biopsies: a prospective multicenter clinical study. J Urol 2013;190:64-9.
23. Vedder MM, de Bekker-Grob EW, Lilja HG, Vickers AJ, van Leenders GJ, Steyerberg EW, et al. The added value of percentage of free to total prostate-specific antigen, PCA3, and a kallikrein panel to the ERSPC risk calculator for prostate cancer in prescreened men. Eur Urol 2014;66:1109-15.
24. Nravejsakul K, Na song-kha B, Raksakul W, Wongumpornwat T, Nuanthaisong U. Extended 14-core schematic diagram mapping prostate biopsy increases both the cancer detection rate and the accuracy of Gleason Score. Insight Urol 2020;41:75-80.

Original Article

Prostate-specific antigen age-specific reference ranges and the effect of metabolic syndrome factors in a Thai population

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Keywords:
PSA, age specific PSA, prostate cancer, metabolic syndrome

Abstract

Objectives: An appropriate prostate specific antigen (PSA) cut-off value in Thailand has not been investigated, nor has an age-specific PSA reference range. This study aims to evaluate the correlation between metabolic syndrome, metabolic factors, and age specific PSA level.

Materials and Methods: A cross-sectional study in men who underwent medical checkups from September 2019 to December 2019. The 95th percentile PSA value was applied to the normal age-specific reference range. Correlations between PSA levels and a variety of factors were determined using linear regression.

Results: A total of 507 men met the criteria to be included in the analysis. Age-specific PSA reference ranges for men aged 40-49, 50-59, and 60-70 years were 0-2.3, 0-3.4, and 0-4.2 ng/ml, respectively. The multivariate adjusted geometric mean PSA model indicated that the factors related to PSA were age, higher body mass index (BMI) and serum fasting blood sugar (FBS) ≥ 100 mg/dl. The age group 50-59 and 60-70 have a 43% and 99% increase in mean PSA compared to the age group 40-49, respectively ($p < 0.001$). A higher BMI was associated with lower PSA ($p < 0.001$). And the serum FBS ≥ 100 mg/dl showed a 15% reduction in mean PSA compared to FBS < 100 mg/dl ($p = 0.018$).

Conclusion: The age-specific PSA reference in Thai men was lower than reported in a previous study. Use of the lower PSA cut-off may increase the sensitivity of prostate cancer screening. This study demonstrates that age, BMI, and FBS may all influence the clinical interpretation of serum PSA levels. Screening for prostate cancer using PSA should be carried out with caution in those who have those risk factors.

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Introduction

Prostate cancer is one of the most frequently diagnosed cancers in males globally. In Thailand, prostate cancer is the fourth most common cancer in men, with nearly 6,500 new cases in 2018 and nearly 3,000 deaths in 2018.[1]

Prostate cancer is usually asymptomatic at diagnosis. Early detection of disease whilst still organ-confined would dramatically improve patient outcomes. Prostate cancer screening is carried out via the use of serum prostate specific antigen (PSA) in conjunction with digital rectal examination, followed by biopsy of the prostate when levels of PSA are over 4 ng/ml.[2] However, the PSA level presents several limitations due to the lack of a universal threshold level.[3] In addition, prostate biopsy for cancer diagnosis is an invasive technique with numerous consequences such as bleeding and infection.[4] Two recent studies have shown multiple factors such as age, prostatitis, ejaculation, certain lifestyles, and comorbidities influence PSA level.[5,6]

The age-specific PSA reference ranges were first given by Oesterling et al in 1993.[2] Several studies of age-specific PSA reference ranges have been carried out in populations of different races and have found that racial differences affect the PSA levels.[7,8] Currently, no studies have been conducted on age-specific PSA reference ranges in healthy Thai men.

The metabolic syndrome is a condition consisting of a group of disorders that occur concurrently and significantly increase risk of heart disease, stroke, and type 2 diabetes. These problems include hypertension, diabetes, abdominal obesity, and elevated cholesterol or triglyceride levels. Worldwide, metabolic syndrome and prostate cancer are extremely widespread disorders.[9] Several studies have reported a relationship between metabolic syndrome and prostate cancer.[10-12] A meta-analysis of the effects of metabolic syndrome on the incidence of prostate cancer showed that metabolic syndrome is just a weak and non-significant risk factor for prostate cancer. However, certain components, such as hypertension and greater waist circumference, are related to an increased risk of prostate cancer.[13]

Numerous studies have been undertaken to evaluate the relationship between metabolic syndrome and PSA levels. One study found that PSA level decreased in a group of individuals with metabolic syndrome. The study reported that the metabolic syndrome patients would be less likely to have significantly higher PSA results than the non-metabolic syndrome patients. This meant that they would be less likely to have a prostate biopsy facilitating an early diagnosis for prostate cancer.[14] However, few studies have been conducted to determine the relationship between the metabolic components and PSA levels. Therefore, this study aims to investigate and evaluate the correlation between metabolic syndrome, metabolic components, and age specific PSA level in Thailand.

Materials and Methods

The study population consisted of men who underwent medical check-ups at the Institute of Pathology Phramongkutklao Medical Center from September 2019 to December 2019. The research protocol was approved by the Ethical Committee of the Faculty of Medicine, Phramongkutklao Medical Center (Protocol Number: R057q/62_Exp).

The inclusion criterion was all men aged 40 to 70 years old. The participants who had a history of prostate cancer, prostate surgery, recent sexual intercourse, or ejaculation (7 days), hematuria and pyuria in urinalysis were excluded.

Anthropometric measurements (height, weight, and waist circumference), a blood test (complete blood cell count, basic chemistry), fasting blood sugar, triglyceride and HDL levels, stool/urine analysis, and details of a full clinical assessment were gathered from participants. In addition, all patients were asked to complete a questionnaire regarding sociodemographic characteristics, comorbidities, the last time they engaged in sexual activity, current or previous medication, and a history of prostate surgery.

Out of the 595 men recruited, 12 men who had engaged in sexual activity in the previous seven-day period were excluded from the study. Fifty-seven with a history of medication for benign prostatic hyperplasia were also excluded, as were 8 with a history of prostate surgery and 3 with known cases of prostate cancer. Data from eight individuals were removed from the study due to the discovery of microscopic pyuria on urinalysis. Consequently, the final population numbered 507.

To diagnose metabolic syndrome, we followed the recommendations by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III).[15] The NCEP ATP III criteria were defined as a person having three or more of the following features:

1. waist circumference in male ≥ 102 cm (≥ 40 inches) or female ≥ 88 cm (≥ 35 inches)
2. triglyceride level ≥ 150 mg/dl
3. HDL cholesterol, male < 40 mg/dl, female < 50 mg/dl
4. Blood pressure (systolic ≥ 130 mmHg or diastolic ≥ 85 mmHg) or persons taking antihypertensive medicine.
5. Fasting blood sugar (FBS) (≥ 100 mg/dl) or previously diagnosed with type 2 diabetes.

The Statistical Package for the Social Sciences (SPSS), Version 20 was used to conduct the statistical analysis (IBM Corp. Chicago, Illinois, USA). For categorical variables, the findings are presented as frequency and percentage, whilst continuous variables are expressed as mean and standard deviation. Correlation between PSA levels and a variety of factors were determined using linear regression, with a significance level of $p < 0.05$ regarded as statistically significant.

Results

Baseline characteristic of the population are shown in Table 1. The mean age and standard deviation (SD) of the population was 53.93±6.9 years old. Overweight status taken from BMI (> 25.0) were 30% and for metabolic syndrome was 15%. Serum PSA more than 4 ng/ml was found in 13 men (3%). As in the study by Oesterling, the 95th percentile PSA value is applied to the normal reference range for the age group.[2] Thus, the PSA levels for men aged 40-49, 50-59, and 60-70 years were 0-2.31, 0-3.44, and 0-4.25 ng/ml, respectively (Table 2).

Demographic and metabolic characteristic data were analyzed to investigate any potential correlation with PSA by linear regression (Table 3). Following analysis, it was determined that increasing age was associated with an increase in the geometric mean PSA. Presence of metabolic syndrome and higher BMI were associated with lower geometric mean PSA levels. The components of metabolic syndrome that correlated with lower geometric mean PSA levels were waist circumference ≥ 90 cm, serum triglyceride concentration ≥ 150 mg/dl, high blood pressure (systolic ≥ 130 mmHg or diastolic ≥ 85 mmHg), and serum FBS ≥ 100 mg/dl.

In building the multivariate adjusted geometric mean PSA model, the factors that were found to be related to PSA were age, higher BMI and serum fasting blood sugar ≥ 100 mg/dl. The age group 50-59 and 60-70 had a 43% and 99% increase in mean PSA compared to the 40-49 age group, respectively ($p < 0.001$). The higher BMI was associated with lower PSA ($p < 0.001$). The serum FBS ≥ 100 mg/dl had a 15% reduction in mean PSA in comparison to FBS < 100 mg/dl ($p = 0.018$).

Discussion

There is a growing awareness regarding prostate cancer screening around the world, including in Thailand. PSA levels have been shown to vary by ethnicity, Asian men having lower levels, whereas European men and African Americans have higher values. In Thailand, prostate cancer screening is based on the American or European guidelines, but the PSA cut-off values of these guidelines may be inappropriate for the Thai population. To date an appropriate PSA cut-off value specific to Thai males has not been investigated,

Table 1. Baseline characteristics of the population (total population = 507)

Characteristic	Number (%) N = 507
Age (years)	53.93±6.9 (mean±SD)
40-49	162 (32)
50-59	216 (43)
60-70	129 (25)
BMI	24.50±2.9 (mean±SD)
Less than 23	226 (45)
23-24.9	125 (25)
25-29.9	117 (23)
30 or greater	39 (7)
PSA (ng/ml)	1.25±1.1 (mean±SD)
Less than 1	269 (53)
1-1.99	156 (30)
2-2.99	44 (9)
3-3.99	25 (5)
4 or greater	13 (3)
Metabolic syndrome	
Yes	78 (15)
No	429 (85)

SD = standard deviation, BMI = body mass index, PSA = prostate specific antigen

Table 2. Mean, median, and 95th percentile PSA among the population

PSA	Age group (years)			
	40-49	50-59	60-70	All
Mean PSA (ng/ml)	0.642	1.285	1.973	1.255
Median PSA (ng/ml)	0.425	0.9770	1.600	0.941
95th percentile PSA (ng/ml)	2.311	3.443	4.250	3.240

PSA = prostate specific antigen

Table 3. Association of PSA with demographic and metabolic characteristics (Linear regression)

Characteristic		Geometric mean				Adjusted geometric mean		
	No (%)	PSA	95%CI	RGM	P-value	95% CI	RGM	P-value
Age (years)								
40-49	162 (32)	0.643		1			1	
50-59	216 (43)	1.286	0.952-1.121	1.033	0.433	1.321-1.565	1.438	< 0.001
60-70	129 (25)	1.974	1.521-1.848	1.676	< 0.001	1.823-2.185	1.996	< 0.001
BMI (kg/m^2)								
< 23	226 (45)	1.758		1			1	
23.0-24.9	125 (25)	0.921	0.667-0.831	0.745	< 0.001	0.51-0.644	0.573	< 0.001
25.0-29.9	117 (23)	0.902	0.58-0.757	0.662	< 0.001	0.482-0.631	0.551	< 0.001
≥ 30.0	39 (7)	0.476	0.35-0.483	0.411	< 0.001	0.32-0.436	0.374	< 0.001
Metabolic syndrome								
Absence	429 (85)	1.337		1			1	
Presence	78 (15)	0.806	0.506-0.703	0.597	< 0.001	0.758-1.036	0.886	0.128
WC								
< 90 cm	408 (80)	1.341		1			1	
≥ 90 cm	99 (20)	0.904	0.535-0.733	0.626	< 0.001	0.938-1.391	1.142	0.185
Triglycerides								
< 150 mg/dl	350 (69)	1.352		1			1	
≥ 150 mg/dl	157 (31)	1.039	0.652-0.834	0.737	< 0.001	0.821-1.048	0.927	0.227
HDL-C								
≥ 40 mg/dl	417 (82)	1.269		1			1	
< 40 mg/dl	90 (18)	1.195	0.743-1.024	0.872	0.094	0.809-1.018	0.907	0.097
Blood pressure								
< 130/85 mmHg	354 (70)	1.292		1			1	
≥ 130/85 mmHg	153 (30)	1.171	0.74-0.95	0.838	0.006	0.856-1.072	0.958	0.452
Fasting blood sugar								
< 100 mg/dl	388 (77)	1.38		1			1	0.018
≥ 100 mg/dl	119 (23)	0.848	0.533-0.703	0.612	< 0.001	0.748-0.973	0.854	

PSA = prostate specific antigen, RGM = relative geometric mean, BMI = body mass index, WC = waist circumference

nor has an age-specific PSA reference range for the Thai population.

Age-specific PSA reference ranges were first given by Osterling et al.[2] The possible benefits of applying age-adjusted PSA criteria include boosting the sensitivity of the test in younger men, facilitating early detection of curable, organ-confined cancers, and decreasing the proportion of negative biopsies in older men.

Table 4. Comparison of age-specific prostate-specific antigen (PSA) reference ranges (95% confidence interval [CI]) with China, Korea, Japan and Singapore.

Age (years)	95th percentile PSA values (ng/ml)					
	Study group	Oesterling[2] (US)	China[15]	Korea[16]	Japan[17]	Singapore[18]
40-49	2.3	2.5	2.15	2.0	2.0	2.3
50-59	3.4	3.5	3.20	2.4	3.0	4.0
60-70	4.2	4.5	4.10	3.9	4.0	6.3

The age-specific PSA reference range uses a 95th percentile PSA value for each profile. The standard values from the reference study for men aged 40-49, 50-59, 60-69, and 70-79 years, respectively, are 0-2.5 ng/ml, 0-3.5 ng/ml, 0-4.5 ng/ml, and 0-6.5 ng/ml.[2] According to this study, the age-specific PSA reference ranges for Thai men aged 40-49, 50-59, and 60-70 years were 0-2.3, 0-3.4, and 0-4.2 ng/ml, respectively. It was found that the age-specific PSA reference range obtained in this study was lower than the reference study.

Comparing age-specific serum PSA values in Asian populations from other studies suggests that men of Asian ethnicity have lower total PSA and age-specific PSA values than those of American men and demonstrates that race, nationality, and environment may have an influence on PSA values.[16-19] As a result, incorporating age-specific PSA results for each ethnicity would increase the sensitivity and specificity of PSA testing in the screening of men over the age of 40 for prostate cancer.

The results of this study showed a correlation of the reduction in PSA with higher BMI, and FBS ≥ 100 mg/dl after adjusting for confounding factors such as age and BMI. In addition, higher BMI levels were associated with significantly lower PSA levels. With regard to the metabolic components, there was a clear correlation between FBS ≥ 100 mg/dl with decreased serum PSA.

A previous study was carried out in obese men and PSA, dihydrotestosterone (DHT), and testosterone levels and found that obese males had lower PSA, DHT, and testosterone levels.[20] It was hypothesized that the lower PSA levels were the result of reduced circulating DHT and testosterone. Additionally, the dilution of serum as a result of increased plasma volume in obese men could be another cause of lower PSA levels. This study result agrees with the study by Werny DM et al, which concludes that PSA levels are lower in obese men than in men with weight within normal limits, which could be due to obesity-related hemodilution or a decrease in circulating androgens in obese men.[21] In the obese men, the PSA density cut-off for prostate biopsy was lower than in males with a normal BMI.[22]

To explain the causes of PSA reduction in the high FBS group, studies have shown that there are several potential causes. The diabetic patients have low testosterone levels, which can lead to a lower PSA than that in the non-diabetic group.[23,24] Another study found that in men with diabetes with poor glycemic control, based on their HbA1C levels, there was a correlation between higher HbA1C levels and lower PSA levels.[25] This association was found to be independent of age, BMI, androgen levels, medication use, and severity of diabetes, implying that parameters associated with glycemia may have a direct effect on PSA levels. Another study concluded that lower PSA levels in diabetics appear to be related to factors such as duration of diabetes, disease severity, or use of either oral diabetes medication or insulin rather than an actual diagnosis of diabetes.[26]

There are several limitations to our study. For example, this study excluded prostate volume and digital rectal examination as potential predictors of PSA levels. Secondly, the study did not assess testosterone levels, which would have been beneficial in determining the relationship between various factors and PSA levels. Finally, the study demonstrates a correlation between risk variables and PSA levels but does not demonstrate a difference in the likelihood of high-grade prostate cancer across groups due to a lack of follow-up PSA and prostate biopsy for cancer diagnosis.

Conclusions

This study adds weight to the findings of prior studies that serum PSA levels vary in accordance with age, race, and ethnic origin. The age-specific PSA reference ranges reported in this study may be more appropriate for Thai men than the ones

currently used based on men, for example, of American ethnicity. The identification of a specific reference range could increase the sensitivity of prostate cancer screening and decrease the need for prostate biopsy in Thailand.

This study demonstrates that age, BMI, and FBS may all influence the clinical interpretation of serum PSA levels. Screening for prostate cancer should be interpreted with caution in those who have the risk factors identified in this study. The PSA threshold levels may need to be re-evaluated for men of Thai ethnicity, however additional research is essential to identify the extent of the effect of these factors on the prognosis of prostate cancer.

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Conflict of Interest

The authors declare no conflict of interest.

References

1. National Cancer Institute Department of Medical Services Ministry of Public Health Thailand. Hospital-Based Cancer Registry 2019. Bangkok: New Thammada Press (Thailand); 2020.
2. Oesterling JE, Jacobsen SJ, Chute CG, Guess HA, Girman CJ, Panser LA, et al. Serum prostate-specific antigen in a community-based population of healthy men. Establishment of age-specific reference ranges. JAMA 1993;270:860-4.
3. Shakir NA, George AK, Siddiqui MM, Rothwax JT, Rais-Bahrami S, Stamatakis L, et al. Identification of threshold prostate specific antigen levels to optimize the detection of clinically significant prostate cancer by magnetic resonance imaging/ultrasound fusion guided biopsy. J Urol 2014;192:1642-8.
4. Jiraanankul V ,Choeypan N, Thunyaharn S, Lerdpraiwan W. Prevalence of fluoroquinolone-resistant Enterobacteriaceae in the normal rectal flora of patients undergoing transrectal prostate biopsy in Phramongkutklao Hospital, Thailand . J Southeast Asian Med Res 2018:1:1-6.
5. Hatakeyama S, Yoneyama T, Tobisawa Y, Ohyama C. Recent progress and perspectives on prostate cancer biomarkers. Int J Clin Oncol 2017;22:214-21.
6. Hsing AW, Devesa SS. Trends and patterns of prostate cancer: what do they suggest? Epidemiol Rev 2001;23:3-13.
7. Lin KJ, Pang ST, Chang YH, Wu CT, Chuang KL, Chuang HC, et al. Age-related reference levels of serum prostate-specific antigen among Taiwanese men without clinical evidence of prostate cancer. Chang Gung Med J 2010;33:182-7.
8. Shah S, Jha B, Khanal MP. Effects of aging and ethnicity on serum free prostate specific antigen. Asian Pacific J Cancer Prev 2011;12:2509-12.
9. Alberti KGMM, Eckel RH, Grundy SM, Grundy SM, Zimmet PZ, Cleeman JI, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009;120:1640-5.
10. Tande AJ, Platz EA, Folsom AR. The metabolic syndrome is associated with reduced risk of prostate cancer. Am J Epidemiol 2006;164:1094-102.
11. Xiang YZ, Xiong H, Cui ZL, Jiang SB, Xia QH, Zhao Y, Li GB, Jin XB. The association between metabolic syndrome and the risk of prostate cancer, high-grade prostate cancer, advanced prostate cancer, prostate cancer-specific mortality and biochemical recurrence. J Exp Clin Cancer Res 2013;32:9.
12. Gacci M, Russo GI, De Nunzio C, Sebastianelli A, Salvi M, Vignozzi L, Tubaro A, Morgia G, Serni S. Meta-analysis of metabolic syndrome and prostate cancer. Prostate Cancer Prostatic Dis 2017;20:146-55.
13. Esposito K, Chiodini P, Capuano A, Bellastella G, Maiorino MI, Parretta E, et al. Effect of metabolic syndrome and its components on prostate cancer risk: meta-analysis. J Endocrinol Invest 2013;36:132-9.
14. Pierce BL. Why are diabetics at reduced risk for prostate cancer? A review of the epidemiologic evidence. Urol Oncol Semin Orig Invest 2012;30:735-43.
15. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005;112: 2735-52.
16. Liu ZY, Sun YH, Xu CL, Gao X, Zhang LM, Ren SC. Age-specific PSA reference ranges in Chinese men without prostate cancer. Asian J Androl 2009;11: 100-3.
17. Lee SE, Kwak C, Park MS, Lee CH, Kang W, Oh SJ. Ethnic differences in the age-related distribution of serum prostate-specific antigen values: a study in a healthy Korean male population. Urology 2000;56: 1007-10.
18. Oesterling JE, Kumamoto Y, Tsukamoto T, Girman

CJ, Guess HA, Masumori N, et al. Serum prostate-specific antigen in a community-based population of healthy Japanese men: lower values than for similarly aged white men. Br J Urol 1995;75:347-53.
19. Saw S, Aw TC. Age-related reference intervals for free and total prostate-specific antigen in a Singaporean population. Pathology 2000;32:245-9.
20. Tande AJ, Platz EA, Folsom AR. The metabolic syndrome is associated with reduced risk of prostate cancer. Am J Epidemiol 2006;164:1094-102.
21. Werny DM, Thompson T, Saraiya M, Freedman D, Kottiri BJ, German RR, et al. Obesity is negatively associated with prostate-specific antigen in U.S. men, 2001-2004. Cancer Epidemiol Biomarkers Prev 2007;16:70-6.
22. Tritipwanit S, Chotikawanich E, Nualyong C, Leewansangtong S, Taweemonkongsap T, Phinthusophon K. Diagnostic Accuracy of BMI and PSA Density in Screening Prostate Cancer Patients in the PSA Diagnostic Gray Zone (4-10 ng/ml). Thai J Urol 2015;36:1-10.
23. Andersson B, Mårin P, Lissner L, Vermeulen A, Björntorp P. Testosterone concentrations in women and men with NIDDM. Diabetes Care 1994;17:405-11.
24. Waters KM, Henderson BE, Stram DO, Wan P, Kolonel LN, Haiman CA. Association of diabetes with prostate cancer risk in the multiethnic cohort. Am J Epidemiol 2009;169:937-4.
25. Sarma AV, Hotaling J, Dunn RL, Cleary PA, Braffett BH, Kim C, et al. Poor glycemic control is associated with reduced prostate specific antigen concentrations in men with type 1 diabetes. J Urol 2015;193:786-93.
26. Bernal-Soriano M, Lumbreras B, Hernández-Aguado I, Pastor-Valero M, López-Garrigos M Parker L. Untangling the association between prostate-specific antigen and diabetes: a systematic review and meta-analysis. Clin Chem Lab Med 2020;59:11-26.

Original Article

Development and validation of a score for the screening of Loei urolithiasis patients

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Keywords:
Water spinach, Bamboo shoot, Laab/Koi, score, screening urolithiasis

Abstract

Objective: To evaluate risk factors associated with stone formation and development and validation of a score for screening Loei urolithiasis patients.

Materials and Methods: This cross-sectional study included 1008 individuals, 466 of which were urolithiasis patients and 542 non-urolithiasis, with no history of stone and no evidence of stone from investigations at Loei Hospital between July 2014 and January 2019. This group was used effectively as a control group. Questionnaires were used to collect information regarding demographic parameters, food and water intake and frequency. The information was used to identify any associations with stone formation using logistic regression analysis. Univariable and multivariable analysis were carried out in order to build a predictive model for the likelihood of stone formation. The strength of the classifier from the predictive model was evaluated using the area under the receiver operating characteristics (ROC) curve.

Results: Multivariable analysis showed increasing BMI (adjusted odds ratio (aOR) =1.06; 95% CI: 1.01-1.1, p = 0.01); male gender (aOR = 2.09; 95%CI: 1.46-2.98, p < 0.001); family history of urolithiasis (a OR = 2.81; 95% CI: 1.78-4.42, p < 0.001); farmer (aOR = 3.59; 95% CI: 2.44-5.29, p < 0.001); working time > 8 hours/day (aOR = 2.19; 95%CI: 1.47-3.27, p < 0.001); drinking more than 2 liters per day of water (aOR = 1.58; 95%CI: 1.13-2.22, p = 0.01); always eat water spinach (aOR = 3.37; 95% CI: 1.47-7.74, p = 0.01); always eat bamboo shoots (aOR = 9.53; 95% CI: 4.54-19.99, p < 0.001); eat Laab/Koi (a local Thai spicy salad made of raw meat and fish) more than or equal to 3 times per week (aOR = 1.75; 95% CI: 1.05-2.9, p = 0.03) and drink bottled water (aOR = 0.17.; 95% CI: 0.12-0.24, p < 0.001) were statistically significant for stone formation. The predictive model for the likelihood of stone formation has a cut-off value greater than or equal to 0.46 for a sensitivity of 72.41%, a specificity of 79.52%, and area under the ROC curve of 0.83.

Conclusions: Increasing BMI, being of male gender, a family history of urolithiasis,

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farmers, working time > 8 hours/day, regular consumption of water spinach, regular consumption of bamboo shoots, eat Laab/Koi more than or equal to 3 times per week were associated significantly with stone formation. We developed and validated a predictive model to indicate the likelihood of stone formation, which can be utilized for the screening of Loei urolithiasis patients facilitating early detection and early treatment.

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Introduction

Urolithiasis is a longstanding health problem and is of major concern in Thailand, especially in the northeast part with a prevalence of 16.9%.[1] Loei is a province in the northeast that has many urolithiasis patients. Urinary tract calculi causing pain, infection, renal failure, and death have increased annually. There has been a concordant increase in government healthcare expenditure. The major problems of urolithiasis are seen in patients with complications as a result of urolithiasis, many having large stones that are difficult to treat in comparison to small stones, and also a high recurrence of stone formation.

To date the etiology of stone formation is still not clear. Stone formation occurs as a result of multifactorial factors, urolithiasis patients in different places having differences in stone analysis.[2,3] Analysis of the risk factors for stone formation which could be used as a guide for the prevention of urolithiasis and the development of a score for screening for Loei urolithiasis patients could reduce the number of patients with complications regarding urolithiasis. The guide could also reduce the costs of treatment of stones, for example if the screening tool could be used to identify small size stones before they increased in size stone the costs would be much reduced. Therefore this research was conducted in order to develop a screening test.

Materials and Methods

Ethics statement

The study was approved by the Ethical Committee for Research in Human Subjects of Loei Hospital (Study Number: EC 009/2559).

Study design and patient selection

This research was a cross-sectional study conducted in Loei Hospital between July 2014 and January 2019. 1,008 patients were divided into 2 groups. Group 1 included urolithiasis patients, defined as having a stone in any urinary tract from radiographic or urologic investigation and group 2 included patients who were not urolithiasis. The patients in Group 2 had no history of either urolithiasis radiologic investigation, for example, ultrasound whole abdomen, and CT whole abdomen or urologic investigations such as cystoscopy, and ureterorenoscopy which had not found a stone in the urinary tract.

Data collection

Data collected included: [1] baseline characteristics and demographic data: sex, age, body mass index, comorbidities, history of family urolithiasis, previous stone treatment, occupation, education, income per month, working time and place; [2] Consumption of types of food and water related to urolithiasis

Evaluation variables

The questionnaire was used for data collection by direct interview. The workplace was divided into either an outdoor occupation (getting sunlight exposure), or an indoor occupation (e.g. office, hospital). The amount of drinking water was estimated using the question: How many glasses of water do you drink per day (1 glass of water equals 250 ml). Questions regarding frequency of consumption of specific foods were used to assess dietary risk factors for urolithiasis. Frequency of consumption was divided into 4 categories: [1] Never defined as never to eat; [2] Seldom defined as eat monthly; [3] Sometimes defined as eat weekly; [4] Always defined as eat daily. Patients were asked to recall all their consumption of the specific foods within 1 year.

Statistical analysis

Continuous variables are reported as mean and standard deviation if there is a normal distribution. Other variables are reported as median and interquartile ranges. The normality of distribution was tested using the Shapiro-Wilk test. Categorical variables are reported by frequency and percentage. Comparison of characteristics between urolithiasis and non-urolithiasis patients for the categorical variables were analyzed using Fisher's exact test and the continuous variables using the student T-test. All analyses used a $p < 0.05$ as a measure of statistical significance and the analysis was carried out using IBM SPSS Statistics for Windows version 23.0 (IBM Corp, 2015).

Model development

Variables that could potentially be statistically and clinically significant were identified from the review literature for inclusion in the analysis by univariable logistic regression. Then the variables with a $p < 0.15$ were selected to determine the potential factors affecting urolithiasis in the multivariable analysis. Complete-case analysis and backward elimination were used in this analysis. The variable with the largest p-value was deselected in each iteration until only variables with $p < 0.05$ remained in the multivariable model. The final multivariable model then included only factors that affect urolithiasis. The likelihood model was set up in exponential function (Probability = $1/e^{-y}$, when y = the multivariable model with coefficients) for predicting the likelihood of urolithiasis formation. The area under the receiver operating characteristic (AUROC) was performed by all cutoff points. We evaluated the suitable probability cutoff from the intersecting line between sensitivity and specificity versus probability cutoff. The selected cutoff point indicates the optimal maximum sensitivity and specificity.

Model validation

Datasets from other sources represented values into the multivariable model which developed from the model development stage using the training dataset. Each dataset was used to generate sensitivity, specificity, and AUROC from the model. The multiple AUROC was tested for equality using an algorithm by DeLong and Clarke-Pearson (1988). When compared models differ statistically significantly, the highest AUROC was considered the best model for predicting the likelihood of the formation of urolithiasis.

Results

Data from 1,008 individuals was divided into 466 urolithiasis patients and 542 classed as non-urolithiasis, with no history of stone and no evidence of stone from investigation. The male to female ratio in urolithiasis patients was 3.1:1, and in the non-urolithiasis group was only 1.1:1. 23.6% of urolithiasis patients had a family history of stones while only 10.5% of non-urolithiasis patients had a family history. 52.1% had a history of previous treatment for stones. Most urolithiasis patients were farmers (Table 1).

Rain water was the most frequent source of water consumed by urolithiasis patients (71.7%) while most non-urolithiasis patients drank bottled water (68.6%). Both groups favored papaya salad with pickled fish (Table 2).

Types of high oxalate vegetables[4] eaten by Loei patients are shown in table 3.

Logistic regression analysis found increasing BMI, male gender, family history of urolithiasis, farmers, working time > 8 hours/day, drinking water more than 2 liters/day, outdoor work, eating peanuts, amaranth, pea eggplant, eggplant, betel, small eggplant, Cha-om, water spinach, paprika, neem, bamboo shoots, dill and Laab/Koi, papaya salad with pickled fish, spicy shredded bamboo-shoot 3 times/week or more, and drinking rain water was significant for stone formation. Underlying disease, an income of more than 30,000 baht per month, eating fish, drinking bottled and filter water were statistically significantly associated with the prevention of stone formation as shown in table 4. These factors were selected as variables for multivariable logistic regression.

The multivariable model showed BMI, male gender, family history of urolithiasis, farmer, working time > 8 hours/day, drinking more than 2 liters of water /day, always eating water spinach, and bamboo shoots, and eating Laab/Koi 3 or more times/week were significant risk factors for stone formation. But drinking bottled water is a preventative factor for stone formation as shown in table 4.

Table 1. Demographic data of urolithiasis and non-urolithiasis (control) patients (N = 1,008)

Characteristics	Urolithiasis patients (n = 466)	Non-urolithiasis patients (n = 542)
Sex		
Male	353 (75.8)	292 (53.9)
Female	113 (24.2)	250 (46.1)
Age, median (IQR)	55 (47-63)	57 (44-69)
BMI, median (IQR)	23 (20.6-25.4)	22.1 (19.6-25.1)
Underlying diseases	174 (37.3)	285 (52.6)
Diabetes mellitus[1]	55 (11.8)	98 (18.1)
Hypertension[1]	98 (21)	151 (27.9)
Dyslipidemia[1]	19 (4.1)	53 (9.8)
Gout[1]	34 (7.3)	14 (2.6)
Chronic kidney disease[1]	9 (1.9)	28 (5.2)
History of family urolithiasis	110 (23.6)	57 (10.5)
Previous stone treatment	179 (38.4)	0 (0)
Occupations		
Farmer	376 (80.7)	230 (42.4)
Self-employed/labor	29 (6.2)	67 (12.3)
Others	61 (13.1)	245 (45.2)
Education		
Equal to or lower than Bachelor's degree	463 (99.4)	540 (99.6)
Higher than Bachelor's degree	3 (0.6)	2 (0.4)
Income per month		
≤ 10,000 Baht	358 (76.8)	429 (79.2)
10,001-20,000 Baht	79 (17.0)	64 (11.8)
20,001-30,000 Baht	20 (4.3)	24 (4.4)
> 30,000 Baht	9 (1.9)	25 (4.6)
Working times (missing 1 case-0.1%)		
≤ 8 hours/day	306 (65.8)	449 (82.8)
> 8 hours/day	159 (34.2)	93 (17.2)
Workplace		
Outdoors	406 (87.1)	292 (53.9)
Indoors	29 (6.2)	249 (45.9)
Other	31 (6.7)	1 (0.2)
Amount of water intake (missing 1 case-0.1%)		
≤ 1 liter/day	33 (7.1)	61 (11.3)
1-2 liters/day	179 (38.5)	285 (52.6)
> 2 liters/day	253 (54.4)	196 (36.2)

Data expressed as n (%) unless otherwise stated
IQR = interquartile range, BMI = body mass index
1% calculated from 466 from urolithiasis patients and 542 non-urolithiasis patients

Model development and validation

Excluded from the predictive model for stone formation is a water intake of more than 2 liters/day and drinking bottled water, which were not of clinical significance. We constructed a model to predict the probability of stone formation (Table 5) which can be seen at https://3557-171-102-53-178.ngrok.io/stone/ or scan (Figure 1A) The cut-off of probability for stone formation is 0.46 with a sensitivity of 72.41%, a specificity of 79.52%, and an area under the ROC curve of 0.83 (Figure 2). For example, a 65-year-old male, weight 65 kg, height 1.66 m (BMI = 23.59), with no family history of urolithiasis, a farmer, working time > 8 hours/day, never eats water spinach, sometimes consumes bamboo shoots, and eats Laab/Koi less than 3 times/week had a probability of stone formation

Table 2. Type of food and water-related to urolithiasis in the patient group and control group.

Characteristics	Urolithiasis patients (n = 466) n (%)	Non-urolithiasis patients (n = 542) n (%)
Type of water		
Tap water[1]	40 (8.6)	30 (5.5)
Ground water[1]	19 (4.1)	27 (5.0)
Boiled water[1]	15 (3.2)	29 (5.4)
Rain water[1]	334 (71.7)	209 (38.6)
Bottled water[1]	104 (22.3)	372 (68.6)
Filtered water[1]	11 (3.4)	42 (7.7)
Other[1]	4 (0.9)	2 (0.4)
Food that is eaten 3 or more times/week		
Noodles[1]	68 (14.6)	97 (17.9)
*Laab/Koi[1]	87 (18.7)	41 (7.6)
Papaya salad with pickled fish[1]	252 (54.1)	219 (40.4)
Chilli fried rice with holy basil (missing 1 case-0.1%)[1]	73 (15.7)	83 (15.3)
Spicy shredded bamboo-shoots[1]	201 (43.1)	110 (20.3)
Rice noodles in fish curry sauce with vegetables[1]	38 (8.2)	64 (11.8)
Chilli paste[1]	11 (2.4)	5 (0.9)
Fish[1]	36 (7.7)	64 (11.8)
Other[1]	8 (1.7)	9 (1.7)

1% calculated from 466 from urolithiasis patients and 542 non-urolithiasis patients
*Laab/Koi is a local Thai spicy salad made of raw meat and fish

Table 3. Type of high oxalate vegetable[4] and frequency to eat.

Characteristics	Urolithiasis patients (n = 466) n (%)	Non-urolithiasis patients (n = 542) n (%)
Peanut (missing 1 case-0.1%)		
Never	307 (56.6)	226 (48.6)
Seldom	188 (34.7)	150 (32.3)
Sometimes	42 (7.7)	80 (17.2)
Always	5 (0.9)	9 (1.9)
Amaranth (missing 1 case-0.1%)		
Never	362 (66.8)	265 (57)
Seldom	121 (22.3)	107 (23)
Sometimes	50 (9.2)	73 (15.7)
Always	9 (1.7)	20 (4.3)
Water fern (missing 1 case-0.1%)		
Never	480 (88.6)	373 (80.2)
Seldom	47 (8.7)	71 (15.3)
Sometimes	12 (2.2)	18 (3.9)
Always	3 (0.6)	3 (0.6)
Vietnamese coriander (missing 1 case-0.1%)		
Never	402 (74.2)	317 (68.2)
Seldom	101 (18.6)	104 (22.4)
Sometimes	37 (6.8)	36 (7.7)
Always	2 (0.4)	8 (1.7)

Table 3. Type of high oxalate vegetable and frequency to eat (continue).

Characteristics	Urolithiasis patients (n = 466) n (%)	Non-urolithiasis patients (n = 542) n (%)
Pea eggplant (missing 2 cases-0.2%)		
Never	199 (36.7)	115 (24.8)
Seldom	217 (40)	145 (31.3)
Sometimes	111 (20.5)	157 (33.8)
Always	15 (2.8)	47 (10.1)
Eggplant (missing 1 case-0.1%)		
Never	270 (49.8)	186 (40)
Seldom	194 (35.8)	168 (36.1)
Sometimes	73 (13.5)	98 (21.1)
Always	5 (0.9)	13 (2.8)
Betel (missing 2 cases-0.2%)		
Never	305 (56.3)	250 (53.9)
Seldom	173 (31.9)	130 (28)
Sometimes	58 (10.7)	75 (16.2)
Always	6 (1.1)	9 (1.9)
Small eggplant (missing 2 cases-0.2%)		
Never	246 (45.5)	165 (35.5)
Seldom	171 (31.6)	152 (32.7)
Sometimes	107 (19.8)	114 (24.5)
Always	17 (3.1)	34 (7.3)
Cha-om (missing 1 case-0.1%)		
Never	205 (37.8)	142 (30.5)
Seldom	193 (35.6)	138 (29.7)
Sometimes	130 (24)	149 (32)
Always	14 (2.6)	36 (7.7)
Water spinach (missing 1 case-0.1%)		
Never	191 (35.2)	138 (29.7)
Seldom	184 (33.9)	132 (28.4)
Sometimes	149 (27.5)	156 (33.5)
Always	18 (3.3)	39 (8.4)
Paprika (missing 1 case-0.1%)		
Never	222 (41)	132 (28.4)
Seldom	62 (11.4)	70 (15.1)
Sometimes	68 (12.5)	49 (10.5)
Always	190 (35.1)	214 (46)
Tomato (missing 3 cases-0.3%)		
Never	224 (41.4)	198 (42.7)
Seldom	173 (32)	136 (29.3)
Sometimes	115 (21.3)	93 (20)
Always	29 (5.4)	37 (8)

Table 3. Type of high oxalate vegetable and frequency to eat (continue).

Characteristics	Urolithiasis patients (n = 466) n (%)	Non-urolithiasis patients (n = 542) n (%)
Neem (missing 2 cases-0.2%)		
Never	346 (63.8)	254 (54.7)
Seldom	140 (25.8)	136 (29.3)
Sometimes	50 (9.2)	62 (13.4)
Always	6 (1.1)	12 (2.6)
Bamboo shoots (missing 1 case-0.1%)		
Never	214 (39.5)	84 (18.1)
Seldom	186 (34.3)	97 (20.9)
Sometimes	131 (24.2)	198 (42.6)
Always	11 (2)	86 (18.5)
Green pepper (missing 1 case-0.1%)		
Never	282 (52)	231 (49.7)
Seldom	175 (32.3)	138 (29.7)
Sometimes	74 (13.7)	77 (16.6)
Always	11 (2)	19 (4.1)
Basil (missing 1 case-0.1%)		
Never	199 (36.7)	170 (36.6)
Seldom	195 (36)	144 (31)
Sometimes	131 (24.2)	129 (27.7)
Always	17 (3.1)	22 (4.7)
Bean sprouts (missing 1 case-0.1%)		
Never	266 (49.1)	237 (51)
Seldom	167 (30.8)	136 (29.2)
Sometimes	100 (18.5)	84 (18.1)
Always	9 (1.7)	8 (1.7)
Dill (missing 2 cases-0.2%)		
Never	138 (25.5)	121 (26)
Seldom	193 (35.7)	115 (24.7)
Sometimes	164 (30.3)	160 (34.4)
Always	46 (8.5)	69 (14.8)

Table 4. Factors associated with stone formation using a univariable and multivariable logistic model

Variables	Univariable analysis		Multivariable analysis	
	OR (95% CI)	P-value	adjusted OR (95% CI)	P-value
Characteristics				
Age (years)	1.00 (0.99-1.01)	0.88		
BMI (kg/m^2)	1.05 (1.02-1.08)	< 0.001	1.06 (1.01-1.10)	0.01
Sex: male vs. female	2.67 (2.04-3.51)	< 0.001	2.09 (1.46-2.98)	< 0.001
Underlying disease: Yes vs. No	0.54 (0.42-0.69)	< 0.001		
Family history of urolithiasis: Yes vs. No	2.63 (1.86-3.72)	< 0.001	2.81 (1.78-4.42)	< 0.001
Education		0.54		
Equal to or below Bachelor's degree	Ref			
Higher than Bachelor's degree	1.75 (0.29-10.51)			

Table 4. Factors associated with stone formation using a univariable and multivariable logistic model (continue)

Variables	Univariable analysis		Multivariable analysis	
	OR (95% CI)	P-value	adjusted OR (95% CI)	P-value
Occupation		< 0.001		< 0.001
Other	Ref		Ref	
Farmer	6.57 (4.74-9.09)		3.59 (2.44-5.29)	
Self-employed/laborer	1.74 (1.04-2.92)		1.01 (0.55-1.90)	
Income per month Baht)		0.02		
> 30,000	Ref			
20,001-30,000	2.31 (0.88-6.08)			
10,001-20,000	3.43 (1.49-7.86)			
≤ 10,000	2.32 (1.07-5.03)			
Working time: > 8 vs. < 8 hours/day	2.51 (1.87-3.37)	< 0.001	2.19 (1.47-3.27)	< 0.001
Workplace: outdoors vs. indoors	5.79 (4.21-7.97)	< 0.001		
Amount of water intake: > 2 vs. < 2 liters/day	2.11 (1.64-2.71)	< 0.001	1.58 (1.13-2.22)	0.01
High oxalate vegetables and frequency eaten				
Peanuts		< 0.001		
Never or seldom	Ref			
Sometimes	2.51 (1.69-3.73)			
Always	2.37 (0.79-7.13)			
Amaranth		< 0.001		
Never or seldom	Ref			
Sometimes	1.9 (1.29-2.78)			
Always	2.89 (1.3-6.41)			
Pea eggplant		< 0.001		
Never or seldom	Ref			
Sometimes	2.26 (1.7-3.02)			
Always	5.01 (2.75-9.15)			
Eggplant		< 0.001		
Never or seldom	Ref			
Sometimes	1.76 (1.26-2.46)			
Always	3.41 (1.2-9.65)			
Betel		0.02		
Never or seldom	Ref			
Sometimes	1.63 (1.13-2.35)			
Always	1.89 (0.67-5.35)			
Small eggplant		< 0.001		
Never or seldom	Ref			
Sometimes	1.4 (1.04-1.89)			
Always	2.63 (1.44-4.79)			
Cha-om		< 0.001		
Never or seldom	Ref			
Sometimes	1.63 (1.23-2.16)			
Always	3.66 (1.94-6.9)			

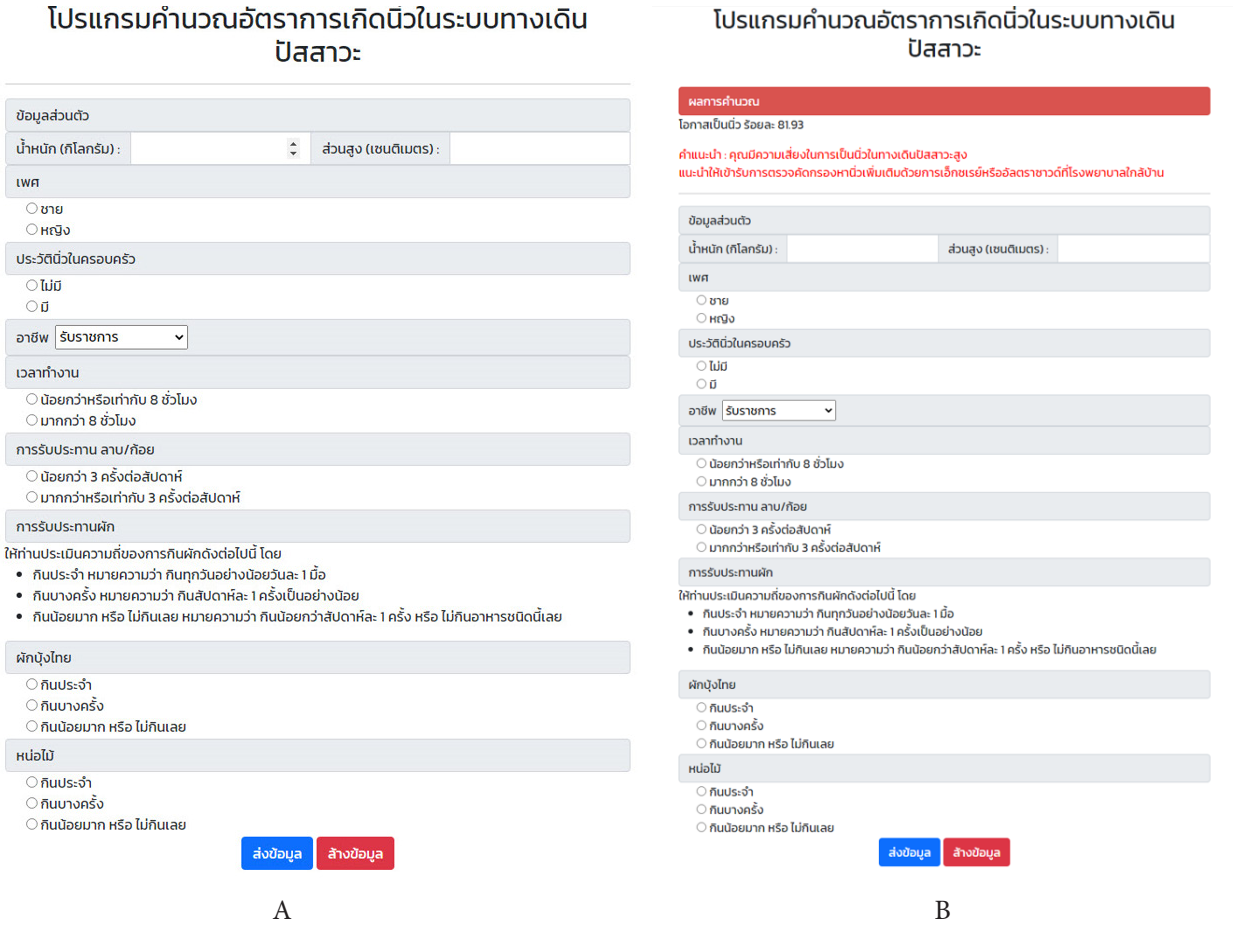
Table 4. Factors associated with stone formation using a univariable and multivariable logistic model (continue)

Variables	Univariable analysis		Multivariable analysis	
	OR (95% CI)	P-value	adjusted OR (95% CI)	P-value
Water spinach		< 0.001		0.01
Never or seldom	Ref		Ref	
Sometimes	1.45 (1.11-1.91)		1.32 (0.92-1.89)	
Always	3.01 (1.68-5.37)		3.37 (1.47-7.74)	
Paprika		< 0.001		
Never or seldom	Ref			
Sometimes	1.01 (0.67-1.53)			
Always	1.58 (1.21-2.07)			
Neem		0.02		
Never or seldom	Ref			
Sometimes	1.55 (1.04-2.3)			
Always	2.49 (0.93-6.7)			
Bamboo shoot		< 0.001		< 0.001
Never or seldom	Ref		Ref	
Sometimes	3.34 (2.52-4.43)		2.56 (1.81-3.62)	
Always	17.28 (9-33.15)		9.53 (4.54-19.99)	
Dill		< 0.001		
Never or seldom	Ref			
Sometimes	1.37 (1.04-1.80)			
Always	2.10 (1.40-3.17)			
Type of food eaten 3 or more times/week				
Laab/Koi: Yes vs. No	2.81 (1.89-4.16)	< 0.001	1.75 (1.05-2.90)	0.03
Papaya salad with pickled fish: Yes vs. No	1.74 (1.35-2.23)	< 0.001		
Spicy shredded bamboo-shoot: Yes vs. No	2.98 (2.26-3.93)	< 0.001		
Fish: Yes vs. No	0.63 (0.41-0.96)	0.03		
Type of drinking water				
Rain water: Yes vs. No	4.03 (3.09-5.26)	< 0.001		
Bottled water: Yes vs. No	0.13 (0.10-0.17)	< 0.001	0.17 (0.12-0.24)	< 0.001
Filtered water: Yes vs. No	0.42 (0.21-0.84)	0.01		

OR = odds ratio, BMI = body mass index

Table 5. Probability of stone formation.

Probability stone formation = $1 / (1+e^{-\{-3.800+[0.842*Male]+[0.042*BMI]+[0.962*Family\ history\ of\ urolithiasis]+[1.597*Farmer]+[0.108*(Self\text{-}employed/Laborer)]+[0.826*(Working\ time > 8\ hours/day)]+[0.214*sometimes\ eats\ water\ spinach]+[1.032*\ always\ eats\ water\ spinach]+[1.056*\ sometimes\ eats\ bamboo\ shoots]+[2.581*\ always\ eats\ bamboo\ shoots]+[0.693*eats\ Laab/Koi\ 3\ or\ more\ times/week]\}}$



A B

Figure 1 A. A web-based application for the calculation of the probability stone formation was posted at https://3557-171-102-53-178.ngrok.io/stone/. B. For example: a 65-year-old male, weight 65 kg, height 1.66 m (BMI = 23.59), no family history of urolithiasis, farmer, working time > 8 hours/day, never eats water spinach, sometimes consumes bamboo shoots, and eats Laab/Koi less than 3 times/week. There was a probability of stone formation of 0.8193 (81.93%) that more than 0.46 (46%) advised further investigation for urolithiasis

of 0.8193(81.93%) (Figure 1B) that more than 0.46 (46%) advised further investigation for urolithiasis

Discussion

Urolithiasis is major health problem at Loei Hospital which has recorded an average of 3,083 urolithiasis patients per year.[5]

Urolithiasis has a range of risk factors, including intrinsic factors (age, gender, ethnicity, family history of stone) and extrinsic factors (climate, lifestyle, dietary habits, occupation, and education).[6] We conducted this research at Loei Hospital in order to discover the risk factors for stone formation with the aim of decreasing the incidence and severity of urolithiasis in Loei province.

Aegukkatajit found the most frequent age range of urolithiasis patients in the North east of Thailand was between 41-50 years old[7] which differed from the range of 51-60 found in this study. This is probably due to Loei urolithiasis patients first presenting with symptoms at 42-43 years of age but only beginning to seek treatment 3-4years after that resulting in Loei patients being older than average.[5]

The male to female ratio of Loei urolithiasis patients was 3.1 : 1 which is similar to the male to female ratio of 2.3-4 : 1 found in a study in the Ubonratchathani province.[8] This higher frequency of urolithiasis in males can be explained by the effect of testosterone which increases the synthesis of oxalate in the liver. The inhibitory effect by estrogen on urinary citrate in females also results in lower oxalate levels than in males.[9]

In this study we found that increasing BMI can increase the incidence of stone formation. A study by Taylor, Semin, and Kim[10-12] offers evidence to show that obesity can produce hyperinsulinemia which results in a significant increase

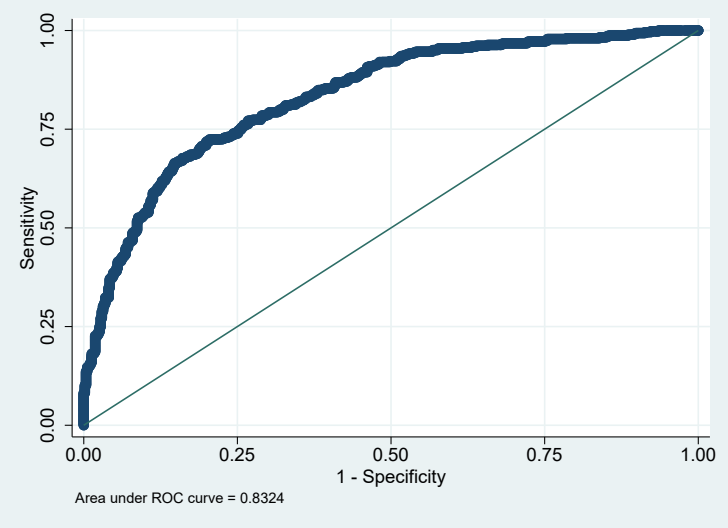


Figure 2. The ROC curve for the predictive model

in urinary calcium excretion.[13] A family history of urinary tract calculi has been shown in several studies to increase the risk of stone formation by 16-37%.[14,15] In this study in Loei urolithiasis patients a family history was also found to be a statistically significant risk for stone formation.

Having an outside occupation, farming in this study, was a significant risk factor for stone formation. This can be explained by working at the high temperatures typical of the Loei climate and also having a working time of more than 8 hours per day. These factors cause sweating and hence increasing the concentration of oxalate in the urine, increasing the risk of stone formation.

Dietary factors are important factors in stone formation.[16] Drinking more than 2 liters of water per day can prevent stone formation[17] but interestingly our study found that most urolithiasis patients drank more than 2 liters of water per day. This may be due to changes in the behavior of patients after a diagnosis of urolithiasis. Drinking bottled water was a statistically significant factor for stone prevention but drinking bottled water was just a favor in Loei within 5 years that Bottled water was may not real factor for stone prevention.

Stone analysis in Loei shows that oxalate is the most common component.[5] Therefore we explored the rate of consumption of high oxalate vegetables which were favored by the Loei population and found water spinach and bamboo shoots were statistically significant for stone formation and it was found that an increase in frequency intake resulted in an increased risk of urolithiasis. Laab/Koi eaten 3 or more times per week was statistically significant for stone formation. Laab/Koi is made from several vegetables high in oxalate such as paprika, betel, Vietnamese coriander, basil, small eggplant, and Neem[4] which can increase the risk of stone formation. Also the daily lifestyle of the Loei population frequently includes a high carbohydrate, low fat, low citric acid diet resulting in hypocitrauria[18,19] and these dietary factors may increase the incidence of urolithiasis in the Loei population.

In this study, we conducted logistic regression model in order to predict the chance of stone formation in Loei enabling screening for urolithiasis to facilitate early detection and early treatment. Our model has several strengths. First, the predictive model is easy to use, not only for urologists, but also for nurses and even the general population. Secondly, the predictive scoring system can be applied from the patient's history rather than by investigations such as scans, facilitating its use in less well-equipped facilities.

However, some limitations need to be addressed. First, in the case of the non- urolithiasis patients the ultrasound scans may have missed tiny stones meaning these patients should have been in the other group. Secondly, a food frequency questionnaire was used for data collection which could potentially result in recall bias.

Conclusion

Increasing BMI, male gender, family history of urolithiasis, farmer, working time > 8 hours/day, eating water spinach and bamboo shoots, and eating Laab/Koi 3 or more times per week were found to be significant factors for stone forma-

tion. This study is the first to publish a method of calculating a score which can be used to screen urolithiasis patients in Thailand facilitating early detection and early treatment of urolithiasis.

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Conflict of Interest

The authors declare no conflict of interest.

References

1. Yanagawa M, Kawamura J, Onishi T, Soga N, Kameda K, Sriboonlue P, et al. Incidence of urolithiasis in northeast Thailand. Int J Urol 1997;4:537-40.
2. Tosukhowong P, Boonla C, Ratchanon S, Tanthanuch M, Poonpirome K, Supataravanich P, et al. Crystalline composition and etiologic factors of kidney stone in Thailand: update 2007. Asian Biomedicine 2007;1:87-95.
3. Laohapan A, Nuwatkrisin K, Ratchanon S, Usawachintachit M. Study of urinary stone composition in a university-based hospital. Insight Urol 2020;41:48-56.
4. Tosukhowong P, Phansin P, Shotiksatit J, Selahapan N, Tungsahya K, et al. Study of organic acid and mineral contents in fruits and vegetables in northeastern of Thailand and impact on nephrolithiasis. Research report quality of life improvement project. Chula Med J 1991;35:32-43.
5. Santanapipatkul K, Jantakun W, Tanthanuch M. Urinary tract stone analysis in Loei province. Thai J Urol 2019;40:9-18.
6. Liu Y, Chen Y, Liao B, Luo D, Wang K, Li H, et al. Epidemiology of urolithiasis in Asia. Asian J Urol 2018;5:205-14.
7. Aegukkatajit S. Epidemiology of stone diseases in north-eastern Thailand. In: Urolithiasis: current status. Proceeding of the 17th Academic Meeting of the Royal College of Surgeons of Thailand; 2003; Pattaya: Bangkok; 2003. p. 1-17.
8. Lamphetthapong C, ChuaSathuchon C, Pongparit N, Sanguanwongwan W, Jenwittaya T, Chaowaratet S, et al. The urinary tract stone disease in Ubonratchathani province. Med J Ubon Hosp 1993;14:17-8.
9. Fan J, Chandhoke PS, Grampsas SA. Role of sex hormones in experimental calcium oxalate nephrolithiasis. J Am Soc Nephrol 1999;10:S376-80.
10. Taylor EN, Stampfer MJ, Curhan GC. Obesity, weight gain, and the risk of kidney stones. JAMA 2005;293:455-62.
11. Semins MJ, Shore AD, Makary MA, Magnuson T, Johns R, Matlaga BR. The association of increasing body mass index and kidney stone disease. J Urol 2010;183:571-5.
12. Kim MS, Moon Y. The relationship between obesity and the risk factors of urolithiasis. Korean J Urol 2007;48:505-11.
13. Kerstetter J CB, O'Brien K, Wurtman R, Allen L. Mineral homeostasis in obesity: effects of euglycemic hyperinsulinemia. Metabolism 1991;40:707-13.
14. Curhan GC, Willett WC, Rimm EB, Stampfer MJ. Family history and risk of kidney stones. J Am Soc Nephrol 1997;8:1568-73.
15. Edvardsson VO, Ingvarsdottir SE, Palsson R, Indridason OS. Incidence of kidney stone disease in Icelandic children and adolescents from 1985 to 2013: results of a nationwide study. Pediatr Nephrol 2018;33:1375-84.
16. Taylor EN, Curhan GC. Diet and fluid prescription in stone disease. Kidney Int 2006;70:835-9.
17. Agarwal MM, Singh SK, Mavuduru R, Mandal AK. Preventive fluid and dietary therapy for urolithiasis: An appraisal of strength, controversies, and lacunae of current literature. Indian J Urol 2011;27:310-9.
18. Tosukhowong P, Borvonpadungkitti S, Prasongwatana V, Tungsanga K, Jutuporn S, Dissayabutr T, et al. Urinary citrate excretion in patients with renal stone: roles of leucocyte ATP citrate lyase activity and potassium salts therapy. Clin Chim Acta 2002; 325:71-8.
19. Tungsanga K, Sriboonlue P, Borwornpadungkitti S, Tosukhowong P, Sitprija V. Urinary acidification in renal stone patients from northeastern Thailand. J Urol 1992;147:325-8.

Original Article

Long-term survival of upper tract urothelial carcinoma patients in a tertiary care hospital

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Keywords:
Survival analysis, transitional cell carcinoma, upper tract urothelial carcinoma

Abstract

Objective: Upper urinary tract urothelial carcinoma (UTUC) is an uncommon but rapidly progressive disease associated with a high mortality rate. Despite the advancement in surgical and medical treatment during the last decade, long-term clinical data pertinent to UTUC are still limited in Thailand. The objectives of this study were to identify the long-term survival rate and factors affecting the survival of UTUC patients.

Materials and Methods: We reviewed medical records of UTUC patients treated at King Chulalongkorn Memorial Hospital from 2004 to 2019. We calculated 5-year survival rate using the Kaplan-Meier method and investigated its correlation with various clinicopathological factors through the Cox hazard regression model.

Results: One hundred and twenty-seven UTUC patients were included in this study. There was a slight predominance of females (55.1%), and the mean age at diagnosis was 68.2 years. The majority of patients were TNM stage I (43.3%) followed by stage III (26.9%). The 5-year overall and cancer-specific survival rates were 62.2% and 75.6%, respectively. Based on univariable analysis, TNM stage, pathological T stage, pathological N stage, and lymph node dissection status were associated with the overall survival and cancer-specific survival. However, none of these factors remained statistically significant in the multivariate analysis.

Conclusion: The 5-year overall survival rate of UTUC patients was 62.2%. TNM stage, pathological T stage, pathological N stage, and lymph node dissection status were associated with the overall survival. A further study with a higher population number is warranted to add weight to these findings and investigate their potential clinical use further.

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Introduction

Upper tract urothelial carcinoma (UTUC) or transitional cell carcinoma is cancer of the urothelial lining of the upper urinary tract which is taken to consist of the renal calyces, renal pelvis, and ureter. Although only found in 5-7% of all renal cancer patients,[1] UTUC is associated with a poor prognosis due to a rapid progression, delayed diagnosis, and treatment complexity. Risk factors for UTUC include smoking and contact with aromatic amines.[2] Studies have shown that 60% of UTUC patients were diagnosed with invasive or high-grade tumors compared to 15-25% of those with urinary bladder cancer.[3,4]

The fundamental basis of UTUC treatment is radical nephroureterectomy with bladder cuff excision and lymph node dissection. The traditional open surgical technique has been increasingly replaced by minimally invasive techniques such as laparoscopic or robotic-assisted approaches, which offer rapid recovery with lower levels of morbidity. Among patients presenting with locally advanced or metastatic disease, adjuvant treatment with radiation, systemic chemotherapy, or even immunotherapy is usually offered.

Since the incidence of UTUC is low, and patients received treatment in different centers, there is a lack of long-term clinical data in Thailand. Hence, the authors conducted this study to identify the survival rate of UTUC patients and explore clinicopathologic factors associated with long-term survival in a single center.

Materials and Methods

This is a retrospective analysis of UTUC patients older than 18 years old who were treated at King Chulalongkorn Memorial Hospital, Bangkok, Thailand, from January 2004 to November 2019. Approval from the institutional review board with a waiver of informed consent was obtained prior to the study (IRB No. 493/62). The authors searched for eligible patients from the electronic medical records by using the 10th International Classification of Diseases (ICD-10) codes of "C64 (malignant neoplasm of kidney, except renal pelvis)", "C65 (malignant neoplasm of renal pelvis)", and "C66 (malignant neoplasm of ureter)". Patients with confirmed diagnoses of UTUC from histopathology or cytopathology were included in the study. The authors excluded patients with a history of bladder cancer, patients with concurrent bladder cancer or other malignancies at the time of UTUC diagnosis, and patients with inadequate medical records.

Demographic data were collected including age at diagnosis, sex, body mass index, and comorbidities. The date of diagnosis was defined as the date of pathological or cytological confirmation of UTUC. The clinical presentation was defined as symptomatic or asymptomatic, and computed tomography or magnetic resonance imaging were utilized for the clinical diagnosis. Data regarding the surgical procedure, surgical approach, and lymph node dissection were collected.

Tumor characteristics, including size and location, were primarily classified based on histopathological findings. Tumor size was measured at the maximal dimension and tumors were divided into < 2 cm and ≥ 2 cm. Tumor location was categorized as renal calyx, renal pelvis, proximal ureter, middle ureter, and distal ureter. Multifocal tumor was recorded if the tumor was present in at least two locations. Histopathological data including tumor grade, T-stage, N-stage, and TNM stage grouping were reported in accordance with the 8th edition of the American Joint Committee on Cancer TNM staging for renal pelvis and ureter. In cases where histopathological data was unavailable, tumor characteristics and clinical staging were estimated based on findings from computed tomography or magnetic resonance imaging.

Living status, the date of death, and cause of death were obtained from the hospital medical records. If the data was unavailable, the authors interviewed the patient's family by telephone or obtained the data from the Bureau of Registration Administration. Overall and cancer specific survivals (reported in months) were calculated from the date of diagnosis to the date of death by all-causes, and cancer-specific death, respectively.

Continuous variables were reported as mean ± standard deviation, and categorical variables were presented as frequency and percentage. Overall and cancer-specific survival rates were estimated using the Kaplan-Meier method. Each clinicopathological factor was correlated to overall and cancer-specific survival by univariate and multivariate analysis using the Cox regression. Statistical analysis was performed with IBM SPSS Statistics version 22.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was considered at $p < 0.05$.

Results

Medical records of 207 UTUC patients were reviewed. Fifty-eight patients were excluded due to a previous or concurrent diagnosis of bladder cancer. Six patients were diagnosed with other concurrent malignancies and were also excluded. Sixteen patients were excluded due to incomplete data collection. The remaining total of 127 patients was analyzed in this study.

Out of all patients, there was a slight predominance of females (55.1%) over males (44.9%). The mean age at UTUC diagnosis was 68.2±11.9 years, and the mean body mass index was 23.1±4.4 kg/m^2. The most common comorbidities were hypertension (64.6%), diabetes mellitus (28.3%), and dyslipidemia (25.2%). Almost all patients (89.8%) were symptomatic at the initial presentation, with gross hematuria (86.0%) as the most common presenting symptom, following by flank pain or abdominal pain (14.9%) (Table 1).

Three patients did not undergo surgical treatment due to an advanced stage of disease.

Table 1. Demographics and perioperative data of UTUC patients

Parameters (n = 127)		Value
Preoperative data (n = 127)	Age at diagnosis, mean±SD (years)	68.2±11.9
	Sex, n (%)	
	- Male	57 (44.9)
	- Female	70 (55.1)
	Body mass index, mean±SD	23.1±4.4
	Comorbidity, n (%)	
	- Diabetes mellitus	36 (28.3)
	- Hypertension	82 (64.6)
	- Dyslipidemia	32 (25.2)
	- Ischemic heart disease	9 (7.1)
	- Stroke/CVA	9 (7.1)
	- COPD	2 (1.6)
	Clinical presentation, n (%)	
	- Asymptomatic	13 (10.2)
	- Gross hematuria	98 (86.0)
	- Microscopic hematuria	2 (1.8)
	- Flank pain/abdominal pain	17 (14.9)
	- Palpable abdominal mass	3 (2.6)
	Laterality, n (%)	
	- Right	64 (50.4)
	- Left	57 (44.9)
	- Bilateral	6 (4.7)
Intraoperative data (n = 124)	Aim of surgery, n (%)	
	- Curative aim	117 (94.4)
	- Palliative aim	7 (5.6)
	Surgical procedure, n (%)	
	- Radical nephroureterectomy with bladder cuff excision	121 (97.6)
	- Radical nephrectomy	1 (0.8)
	- Distal ureterectomy	2 (1.6)
	Surgical approach, n (%)	
	- Open approach	70 (56.5)
	- L aparoscopic approach	54 (43.5)
	Lymph node dissection, n (%)	
	- Performed	25 (20.2)
	- Not performed	99 (79.8)

UTUC = upper tract urothelial carcinoma, SD = standard deviation, CVD = cerebrovascular accident, COPD = chronic obstructive pulmonary disease

Table 2. Pathological data of UTUC patients

Parameters (n = 127)	Value
Tumor size (cm), mean±SD	4.3±2.9
Tumor size, n (%)	
- < 2 cm	20 (15.7)
- ≥ 2 cm	107 (84.3)
Tumor location, n (%)	
- Renal calyx	50 (40.3)
- Renal pelvis	60 (48.4)
- Proximal ureter	33 (26.6)
- Middle ureter	15 (12.1)
- Distal ureter	38 (30.6)
Multifocal tumor, n (%)	
- Absence	78 (61.4)
- Presence	49 (38.6)
Tumor grade, n (%)	
- Low grade	22 (17.3)
- High grade	105 (82.7)
Concurrent upper tract CIS, n (%) (n = 124)	
- Absence	114 (91.9)
- Presence	10 (8.1)
T-stage, n (%)	
- Ta	24 (18.9)
- Tis	1 (0.8)
- T1	31 (24.4)
- T2	20 (15.7)
- T3	42 (33.1)
- T4	9 (7.1)
N-stage, n (%)	
- N0	112 (88.2)
- N1	4 (3.1)
- N2	10 (7.9)
- N3	1 (0.8)
M-stage, n (%)	
- M0	123 (96.9)
- M1	4 (3.1)
Distant metastasis, n (%)	
- Liver	3 (75)
- Lung	1 (25)
TNM stage grouping, n (%)	
- Stage 0is	1 (0.8)
- Stage I	55 (43.3)
- Stage II	19 (15.0)
- Stage III	33 (25.9)
- Stage IV	19 (15.0)

UTUC = upper tract urothelial carcinoma,
SD = standard deviation, CIS = carcinoma in situ

Table 3. Survival data of UTUC patients

Parameters (n = 127)	Value
Living status, n (%)	
- Alive	62 (48.8)
- Dead	65 (51.2)
Cause of death, n (%) (n = 65)	
- UTUC-related causes	38 (58.5)
- Other causes	27 (41.5)
Overall survival rate %	48.8
- 1-year overall survival rate	81.9
- 5-year overall survival rate	62.2
Cancer-specific survival rate %	70.1
- 1-year cancer-specific survival rate	88.2
- 5-year cancer-specific survival rate	75.6
Overall time to death (months), mean (95% confi-dence interval)	93.8 (78.5 to 109.0)
Cancer-specific time to death (months), mean (95% confidence interval)	129.3 (113.0 to 145.7)
Follow-up duration (months), mean (95% confi-dence interval)	49.7 (0.3-187.4)

UTUC = upper tract urothelial carcinoma

Out of 124 patients who underwent surgical treatment, curative surgery was the aim in 117 patients (94.4%). Radical nephroureterectomy with bladder cuff excision was performed in the majority of cases (97.6%). An open surgical approach (56.5%) was used more commonly than laparoscopy (43.5%). Lymph node dissection was performed in 25 patients (20.2%) One patient received neoadjuvant chemotherapy, 17 patients received adjuvant chemotherapy, and 16 patients underwent adjuvant postoperative radiation (Table 1).

The mean tumor size was 4.3±2.9 cm, with 84.3% of the tumors being larger than 2 cm. In the majority of cases the tumor was located in the renal pelvis (48.4%), followed by the renal calyx (40.3%) and the distal ureter (30.6%). Multifocal tumors were found in 38.6% of the patients. High grade tumors were found in 82.7%, and concurrent upper tract CIS were found in 8.1%. The most common T-stage was T3 (33.1%), followed by T1 (24.4%), and Ta (18.9%). Lymph node status was negative for most patients (88.2%); however; this data was only available in one-fifth of the patients. The proportion of TNM stage grouping was 0.8%, 43.3%, 15.0%, 25.9%, and 15.0% for stage 0is, I, II, III, and IV, respectively (Table 2).

At the end of the study, 62 patients were alive, and 65 patients were dead (38 had died from UTUC-related causes, and 27 from other causes). The median follow-up duration was 49.7 months. The mean overall survival was 93.8 months, and the mean cancer-specific survival

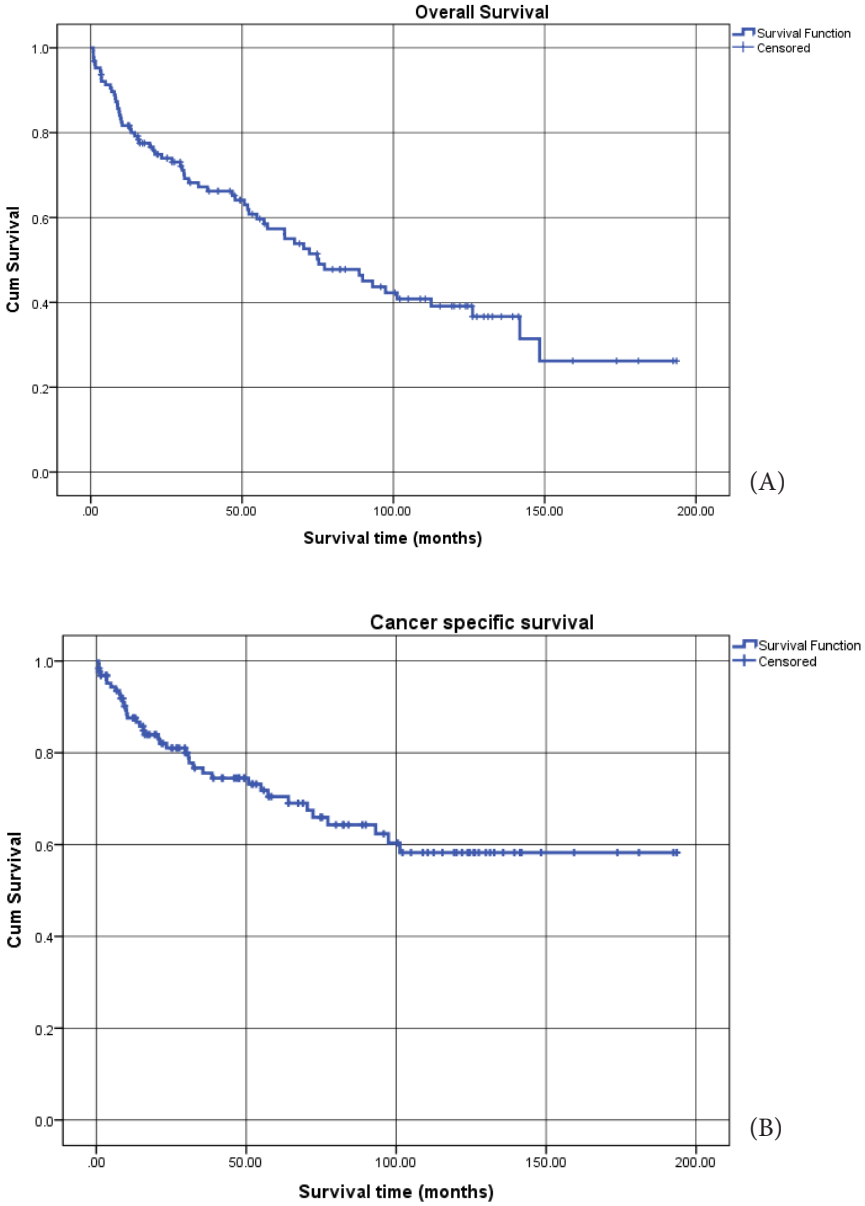

Figure 1. Kaplan-Meier plot of overall survival (A) and cancer-specific survival (B)

was 129.3 months (Table 3). The Kaplan-Meier plot showed an overall survival rate of 48.8% and a cancer-specific survival rate of 70.1%. The 5-year overall and cancer-specific survival rates were 62.2% and 75.6%, respectively (Figure 1).

Univariate analysis using Cox regression was performed to ascertain any correlation between each clinicopathological factor and the overall and cancer-specific survivals. Overall survival showed a significant correlation with lymph node dissection status ($p = 0.037$), T-stage ($p = 0.034$), N-stage ($p = 0.000$), and TNM stage grouping ($p = 0.034$). Cancer-specific survival showed a significant correlation with lymph node dissection status ($p = 0.010$), tumor grade ($p = 0.016$), T-stage ($p = 0.001$), N-stage ($p = 0.000$), and TNM stage grouping ($p = 0.001$) (Table 4). Subsequently, a prediction model with multivariate analysis was performed involving significant clinicopathological factors identified from the univariate analysis. However, none of these factors remained statistically significant when adjusted with the multivariable analysis (Table 5).

Discussion

UTUC is an uncommon disease with limited long-term data on survival. It accounts for 5-10% of all urothelial cancers with an estimated annual incidence of 1-2 cases per 100,000 in the United States.[1] The recorded incidence has been

Table 4. Univariate analysis of overall and cancer-specific survivals

Parameters	Overall survival, p-value	Cancer-specific survival, p-value
Sex (male versus female)	0.125	0.181
Surgical approach (open versus lapa-roscopic approach)	0.133	0.141
Lymph node dissection (performed versus not performed)	0.037*	0.010*
Tumor size (< 2 cm versus ≥ 2 cm)	0.212	0.090
Tumor location (renal calyx/renal pelvis versus proximal/middle/ distal ureter)	0.428	0.713
Multifocal tumor (absence versus presence)	0.255	0.589
Tumor grade (low grade versus high grade)	0.344	0.016*
Concurrent upper tract CIS (absence versus presence)	0.965	0.435
T-stage (Ta/Tis/T1 versus T2-T4)	0.034*	0.001*
N-stage (N0 versus N1-N3)	0.000*	0.000*
TNM stage grouping (stage 0is/stage I versus stage II-IV)	0.034*	0.001*

*, statistically significant, CIS = carcinoma in situ

Table 5. Multivariate analysis of overall and cancer-specific survivals

Parameters	Overall survival, P-value (hazard ratio)	Cancer-specific survival, P-value (hazard ratio)
Tumor grade (low grade versus high grade)	N/A	0.132
T-stage (Ta/Tis/T1 versus T2-T4)	0.769	0.732
N-stage (N0 versus N1-N3)	0.268	0.819
Lymph node dissection (performed versus not performed)	0.752	0.937

increasing during the last few decades mainly due to improvements in imaging, diagnostic endoscopy, and cytopathology. Epidemiological data in Thailand about this condition is markedly limited mainly due to rarity of the disease and inadequacy of the national tumor registry. In addition, UTUC is sometimes under-reported or miss-interpreted due to the difficulty in diagnosis.

The data for this study were retrospectively collected over 16 years and have shown some interesting epidemiological findings. We found the ratio between male and female patients to be similar (44.9% versus 55.1%). In contrast, other studies from Western countries have shown the majority of patients, ranging from 64 to 68.4%, to be male.[5-7] One study from Thailand found 61.5% out of 65 UTUC patients undergoing radical nephroureterectomy to be male.[8] Another study from central China found 53.7% out of 439 UTUC patients to be male.[9] Hypothetically, there could be a genetic gender predilection among different ethnicities, with a slightly lower male predominance in Asia. Another possible explanation may be the exclusion criteria used in our study. We excluded all patients with a concurrent or subsequent diagnosis of bladder cancer. These were predominantly male. In our study, the most common tumor location was the renal pelvis, following by the renal calyx. Multifocal tumors were found in 38.6% of patients, this incidence being higher than in a previous study by Favaretto et al., which showed an incidence of 25%.[10]

Based on the observations from 127 UTUC patients from 2007 to 2019, we calculated a 5-year cancer-specific survival of 75.6%. This survival rate is comparable to findings from other previous studies. Wheat et al. retrospectively reviewed 1,387 UTUC patients undergoing radical nephroureterectomy from 13 institutions between 1987 and 2007. They found a cancer-specific survival of 85% at 1 year, 75% at 3 years and 70% at 7 years.[6] Munoz and Ellison identified 9,072 UTUC

patients in a Surveillance, Epidemiology and End Results (SEER) program from 1973 to 1996. They demonstrated a 5-year cancer-specific survival of 75%.[11] Interestingly, although the surgical techniques and adjuvant treatment modalities have been improved during the last two decades, the cancer-specific survival is still unchanged. Whether this finding results from more aggressive tumor behavior or not is still under debate.

Several prognostic factors for cancer-specific survival have been identified from the univariate analysis. They included the lymph node dissection status, tumor grade, T-stage, N- stage, and TNM stage grouping. However, T-stage and TNM stage grouping were significantly correlated and together could be a covariate. Thus, we decided not to include TNM stage grouping in the further analysis. The subsequent multivariate analysis revealed no statistically significant factors. However, contrary to our findings, a large retrospective cohort study of 13,800 UTUC cases from the SEER database reported multiple factors significantly associated with poorer overall survival using multivariate analysis. These factors included increasing patient age, male gender, black non-Hispanic race, bilateral UTUC, and regional or distant disease.[7] Another study by Wheat et al. found that concomitant CIS was predictive of cancer specific mortality in 1,387 patients with organ confined UTUC.[6] However, in their study, 26.7% of patients had concomitant CIS, compared to only 8.1% in our study. In addition, Wheat et al. also included patients with a previous history of bladder cancer in their analysis, which may have a different natural history.

We found that different surgical approaches, specifically open or laparoscopic technique, did not affect long-term survival of the patients. This finding is consistent with the study by Taweemonkongsap et al., which reported similar 2-year cancer-specific survivals of 92.5% and 86.3% after open and laparoscopic techniques, respectively.[12]

Some limitations were encountered in this study. The retrospective nature of the design inevitably leads to incomplete data collection and selection bias. Owing to the rarity of the disease, the sample size is relatively limited, which may negatively affect the statistical power of the data. Moreover, the decision as to whether to perform lymph node dissection (LND) was in accordance with the discretion of each surgeon, and the data regarding the LND template was limited. We also did not account for other treatment modalities such as radiation, systemic chemotherapy, or further management for distant metastasis, which could have an effect on patient survival. To generalize the results to the UTUC population, a larger scale multi-center prospective study should be conducted to add weight to these findings.

Conclusions

The 5-year overall survival rate of UTUC patients was 62.2%. TNM stage, pathological T stage, pathological N stage, and lymph node dissection status were associated with the overall survival. Further study with a higher population number may be conducted to confirm this association.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Soria F, Shariat SF, Lerner SP, Fritsche H-M, Rink M, Kassouf W, et al. Epidemiology, diagnosis, preoperative evaluation and prognostic assessment of upper-tract urothelial carcinoma (UTUC). World J Urol 2017;35:379-87.
2. Colin P, Koenig P, Ouzzane A, Berthon N, Villers A, Biserte J, et al. Environmental factors involved in carcinogenesis of urothelial cell carcinomas of the upper urinary tract. BJU Int 2009;104:1436-40.
3. Margulis V, Shariat SF, Matin SF, Kamat AM, Zigeuner R, Kikuchi E, et al. Outcomes of radical nephroureterectomy: a series from the Upper Tract Urothelial Carcinoma Collaboration. Cancer 2009; 115:1224-33.
4. Rouprêt M, Babjuk M, Compérat E, Zigeuner R, Sylvester RJ, Burger M, et al. European Association of Urology Guidelines on Upper Urinary Tract Urothelial Carcinoma: 2017 update. Eur Urol 2018; 73:111-22.
5. Shariat SF, Favaretto RL, Gupta A, Fritsche HM, Matsumoto K, Kassouf W, et al. Gender differences in radical nephroureterectomy for upper tract urothelial carcinoma. World J Urol 2011;29:481-6.
6. Wheat JC, Weizer AZ, Wolf JS, Lotan Y, Remzi M, Margulis V, et al. Concomitant carcinoma in situ is a feature of aggressive disease in patients with organ confined urothelial carcinoma following radical nephroureterectomy. Urol Oncol-Semin Ori 2012;30:252-8.

7. Raman JD, Messer J, Sielatycki JA, Hollenbeak CS. Incidence and survival of patients with carcinoma of the ureter and renal pelvis in the USA, 1973-2005. BJU Int 2011;107:1059-64.
8. Rimthephathip K WN. Nephroureterectomy for upper urinary tract transitional cell carcinoma in Rajavithi Hospital: Experience in the last 8 years. Thai J Urol 2017;38:31-8.
9. Wang Q, Zhang T, Wu J, Wen J, Tao D, Wan T, et al. Prognosis and risk factors of patients with upper urinary tract urothelial carcinoma and postoperative recurrence of bladder cancer in central China. BMC Urol 2019;19:24.
10. Favaretto RL, Shariat SF, Chade DC, Godoy G, Adamy A, Kaag M, et al. The effect of tumor location on prognosis in patients treated with radical nephroureterectomy at Memorial Sloan-Kettering Cancer Center. Eur Urol 2010;58:574-80.
11. Munoz JJ, Ellison LM. Upper tract urothelial neoplasms: incidence and survival during the last 2 decades. J Urol 2000;164:1523-5.
12. Taweemonkongsap T, Nualyong C, Amornvesukit T, Leewansangtong S, Srinualnad S, Chaiyaprasithi B, et al. Outcomes of surgical treatment for upper urinary tract transitional cell carcinoma: comparison of retroperitoneoscopic and open nephroureterectomy. World J Surg Oncol 2008;6:1-7.

Original Article

Treatment outcomes and factors affecting the success of extracorporeal shockwave lithotripsy in urinary stone treatment: a study of ten years of data from Mahasarakham Hospital

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Keywords:
Extracorporeal shock wave lithotripsy, factors affecting success, MK ESWL Score

Abstract

Objective: To explore the outcomes and factors affecting the success of extracorporeal shockwave lithotripsy (ESWL) in upper urinary stone treatment.

Materials and Methods: A retrospective review of 4,293 patients with renal or ureteric stones treated with ESWL using Siemens Modularis Vario lithotripter at Mahasarakham Hospital between October 2011 and September 2020. Non-contrast computed tomography or intravenous urography were used to determine stone characteristics. All patients were followed up at week 12 after treatment to evaluate treatment outcome. Success was defined by the presence of clinically insignificant residual ≤ 4 mm or complete clearance of the stones. Data were tested with multivariate logistic regression analysis to determine the predictors of ESWL success.

Results: The overall success rate was 70.1 %. The success rate of patients aged ≤ 40 years was 78.2% The lowest success rate was associated with lower calyceal stones with 54.6%, for stones ≤ 10 mm the success rate was 76.3% and the success rate of stones with a surface area ≤ 50 mm^2 was 77.0%. The complication rate was 5.2%, and auxiliary procedures were 4%. The mean number of ESWL sessions was 2.1. Multivariable logistic regression analysis demonstrated that age, stone size, stone surface area and stone location were significant predictors of ESWL success.

Conclusions: Treatment of renal and ureteric stones with ESWL showed good results. MK ESWL Scoring is a good predictive system for the success of ESWL treatment.

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Introduction

Since its introduction in the 1980s, extracorporeal shock wave lithotripsy (ESWL), a convenient noninvasive standard outpatient procedure, has been used for the treatment of renal and proximal ureteric calculi.[1] Since its introduction it has become a preferred treatment modality for uncomplicated renal and ureteral stone of < 20 mm in diameter as it was found to be safe and non-invasive.[2-5] The success rate of ESWL has a wide variation ranging from 46% to 91%.[6-11] The results of ESWL are measured with regard to stone fragmentation and clearance, which have been found to be influenced by some predicting factors such as stone size, stone location, skin-to-stone distance (SSD), stone composition, severity of obstruction, urinary tract anatomy, obesity, and ESWL machine type.[12-20] ESWL had been one of the mainstays in the management of renal and ureteric calculi since its inception in 1984, and it is currently one of the most recommended treatment options for small- and medium-sized stones. The use of ESWL increased up until 2006 but then started to decline because many urologists switched to endoscopic surgical treatments especially ureteroscopy and laser fragmentation.[21]

Nevertheless, ESWL was shown to be a cost-effective treatment for small- and medium-sized stones. It was recommended as the preferred treatment for various types of stones in many countries. In the recent coronavirus disease 2019 (COVID-19) outbreak there was a new increase in ESWL use as it avoided the need for a general anesthetic (GA) and its potential complications in patients with COVID-19 infection.[22-26] Therefore, during the pandemic period, many hospitals tended to avoid the use of GA in less urgent cases.

This retrospective review aimed to explore the outcome and factors affecting the success of Extracorporeal Shockwave Lithotripsy in upper urinary stone treatment.

Materials and Methods

This retrospective review was conducted in adult patients with renal or ureteric stones, treated with ESWL between October 2011 and September 2020 at Mahasarakham Hospital, Thailand. The research protocol was approved by the Ethical Committee of Mahasarakham Hospital (Protocol Number: MSKH_REC 64-01-049). The inclusion criteria were radiopaque stone size of > 4 mm on a pretreatment plain abdominal x-ray of the kidney, ureter, and bladder (KUB). Pregnant women and patients with uncontrolled coagulopathy, ongoing urinary tract infection, uncontrolled hypertension, and stone with distal obstruction were excluded from the study. The case summary, hematological, biochemical, radiological investigations, and follow-up data were analyzed. All patients underwent X-ray KUB and ultrasound, non-contrast computed tomography (NCCT) or intravenous urography for initial diagnosis. Patient data, and treatment data were collected from Mahasarakham Hospital Information System (MKHIS). The radiological findings were evaluated by radiologists from the Picture Archiving Communication System (PACs) at the hospital.

Out of the 4,484 patients being treated, 191 were excluded from the study due to non-availability of patient electronic medical data, radiologic data or failed follow-ups. Therefore, the final analysis, results, and conclusions were based on 4,293 patients. NCCT or intravenous urography (IVU) were used to determine stone characteristics; namely, size, surface area, location and laterality. The largest dimension of the stone with soft tissue window in coronal view was used to represent the stone size. The stone surface area (SA) was estimated from the length (L) and width (W) of the stone by using the formula: $SA = (L) \times (W) \times \pi \times 0.25$ (π=3.14159).[9]

The patients in the study were subjected to ESWL. The Siemens Modularis Vario lithotripter, a third generation of lithotripter with electromagnetic shockwave source, was implemented after collection of written informed consent. All treatments were carried out using intravenous analgesia in the form of Fentanyl IV (1 μg/kg/dose) and Midazolam IV (0.05-0.1 mg/kg) when needed. The procedure was performed under intermittent fluoroscopic guidance. The targeted stone was struck by a maximum of 4,000 shocks per session for renal stones and 4,500 shocks per session for ureteric stones; all of which were at the rate of 60-90 shocks per minute with gradually increasing energy level to maximal level of 3, or 4 for renal stones; and 4 for ureteric stones. Stone localization was achieved by fluoroscopy or a combination of ultrasound and fluoroscopy. Patients were followed up at the outpatient department at week 4 and 12 after ESWL with a

plain film KUB. ESWL was repeated if no stone fragmentation occurred, or if the residual stone fragments were larger or equal to 5 mm in size. A maximum of 4 sessions of ESWL were carried out with a time lag of 4 weeks between sessions.

After the ESWL sessions, patients were followed-up for three months for the outcome of stone clearance. At the endpoint, patients were evaluated with X-ray plain KUB. Stone clearance, stone fragmentation, stone surface area, number of ESWL sessions, requirement of auxiliary procedure, and complications were recorded. Treatment was defined as being successful in cases of complete clearance (stone free) or the presence of asymptomatic, non-infectious, and non-obstructive fragments of ≤ 4 mm Treatment failure was considered in cases with no fragmentation, or residual stone fragments of > 4 mm after four sessions of ESWL; or if the patient required other modes of treatment.

At the end-point evaluation, patients were categorized into success and failure groups. Data were described using frequency, percentage, mean and standard deviation. To test the statistical significance of the relationship between ESWL outcome and the factors affecting it, data were analyzed using chi-squared test, independent samples t-test, and correlation. Thereafter, the significant associated variables were tested with multivariate logistic regression analysis to identify the independent predictors of treatment failure. The level of significance for the two-tailed test was set at 0.05. All statistical analysis was carried out using SPSS Statistics (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.).

Results

Data from a total of 4,293 patients: 2,628 males and 1,665 females; with renal or ureteric stones (3,470 RC and 823 UC) who received ESWL treatment from October 2011 to September 2020 were analyzed. Out of all patients, ESWL was 70.1% successful with therefore a 29.9% failure rate. The baseline demographic characteristics are presented in Table 1. The multivariate analysis showed there was no statistically significant difference between the two groups as regards patient gender, BMI and stone laterality. However, differences in age, stone size, stone location and stone surface area were statistically significant.

Table 1. Demographic characteristics (N = 4,484)

Parameters	
Patients n	4,293
Gender n (%)	
Male	2,628 (61.2)
Female	1,665 (38.8)
Age (years)	
Mean±SD	55.4±11.7
Range	18-94
BMI (kg/m^2)	
Mean±SD	24.5±4.9
Range	11.8-47.6
Stone laterality n (%)	
Right	2,292 (532.4)
Left	2,001 (46.6)
Stone location n (%)	
Renal calculi	3,470 (80.8)
Ureteric calculi	823 (19.2)
Size (mm)	
Mean±SD	11.9±6.3
Range	6-70
ESWL session (episode)	2.1±1.6

SD = standard deviationl, BMI = body mass index, ESWL = extracorporeal shockwave lithotripsy

The success rate of ESWL for lower calyceal stones was the lowest (54.6%) compared to stones in the upper, middle calyx and pelvis (86.0, 75.2, and 75.3%). Patients with lower calyceal stones of ≤ 10 mm in size had a success rate of 60.0% in comparison to stones of > 10 mm in size where the success rate was noted to be 46.7%.

The overall rate of significant complications was 5.2%. This included 2.7% of severe pain that required inpatient care for pain control, 0.2% of gross hematuria with required blood transfusion, 0.3% of sepsis with a requirement of parenteral antibiotics, 1.9% of stein Strasse with failed conservative treatment and 0.1% of perirenal hematoma. Post-interventional auxiliary procedures were required in 4.0% of the patients.

In the multivariate logistic regression analysis, four variables were found to be statistically significant in predicting the success of ESWL, specifically age, stone size, stone location, and stone surface area as shown in Table 2.

Discussion

Since the introduction of ESWL in 1980, it had become an established and preferred treatment for uncomplicated renal and ureteral

Table 2. Multivariate analysis of the factors affecting outcome of ESWL

Variables	Success (n = 3,009) n (%)	Failure (n = 1,284) n (%)	OR	95% CI	P-value
Gender					
Male	1,842 (70.1)	786 (29.9)	Ref		
Female	1,167 (70.1)	498 (29.9)	0.959	0.831-1.107	0.566
Age (years)					
≤ 40	338 (78.2)	94 (21.8)	1.475	1.113-1.954	0.007*
41-60	1,712 (71.2)	692 (28.8)	1.228	1.056-1.428	0.007*
> 60	959 (65.8)	498 (34.2)	Ref		
BMI (kg/m^2)					
< 18.5	280 (71.3)	113 (28.7)	Ref		
18.5-22.9	953 (72.0)	371 (28.0)	1.037	0.808-1.330	0.777
23-24.9	562 (70.4)	236 (29.6)	0.961	0.736-1.254	0.770
≥ 25	1,214 (68.3)	564 (31.7)	0.869	0.683-1.105	0.251
Stone laterality					
Right	1,591 (69.4)	701 (30.6)	1.037	0.901-1.192	0.614
Left	1,418 (70.9)	583 (29.1)	Ref		
Stone size (mm)					
≤ 10	1,922 (76.3)	596 (23.7)	Ref		
11-20	842 (60.7)	545 (39.3)	0.540	0.434-0.673	< 0.001*
> 20	245 (63.1)	143 (36.9)	0.584	0.434-0.785	< 0.001*
Stone location					
Upper calyx	745 (86.0)	121 (14.0)	Ref		
Middle calyx	487 (75.2)	161 (24.8)	0.488	0.372-0.640	< 0.001*
Lower calyx	705 (54.6)	587 (45.4)	0.176	0.139-0.221	< 0.001*
Pelvis	500 (75.3)	164 (24.7)	0.568	0.433-0.746	< 0.001*
Upper ureter	356 (72.2)	137 (27.8)	0.285	0.212-0.382	< 0.001*
Middle ureter	58 (59.8)	39 (40.2)	0.153	0.096-0.246	< 0.001*
Lower ureter	158 (67.8)	75 (32.2)	0.225	0.158-0.321	< 0.001*
Stone surface area (mm2)					
≤ 50	1,562 (77.0)	467 (23.0)	Ref		
> 50	1,447 (63.9)	817 (36.1)	0.634	0.509-0.789	< 0.001*
Mean ± SD	91.2±86.9	140.6±194			

*Statistically significant
SD = standard deviation, OR = odds ratio, 95% CI = 95% confidence interval of the difference, Ref = reference, BMI = body mass index, ESWL = extracorporeal shockwave lithotripsy

stone (< 20 mm in diameter) as it was safe and non-invasive.[1-5] The success rate of ESWL varied from 46% to 91% and was measured in terms of stone fragmentation and clearance.[6,7] Previous studies had demonstrated that predicting factors such as stone size, stone location, stone density, severity of obstruction, urinary tract anatomy, obesity, SSD, type of ESWL machine and use of diuretics could have an influence on the success rate of ESWL.[13-19]

Many studies discussed factors affecting outcome of ESWL, but only a few considered age as being a significant factor. One study of 3,023 patients with renal and ureteric calculi treated with ESWL revealed that older patients had a significant poorer stone-free rate.[6] Another multivariate analysis of 2,954 patients with renal stones treated with ESWL revealed that patients aged > 40 years a had significant poorer stone-free rate.[11] However, another study was conducted on patients with ureteric stones within the same age range but found that age did not affect outcome of ESWL.[23]

In our study, age was found to be a significant factor affecting the outcome of ESWL. Success rate of the treatment in patients in the age group of ≤ 40 years was 78.2% (338/432) compared to that of only 71.2% (1712/2404) in those aged between 41-60 years and 65.8% (959/1457) in those aged > 60 years. Multivariate logistic regression

Table 3. Point system for MK ESWL Score

Factors	Point
Age (years)	
≤ 40	1
> 40	0
Size (mm)	1
≤ 10	0
> 10	
Surface area (mm^2)	1
≤ 50	0
> 50	
Stone location	
Upper calyx	2
Middle calyx	1
Lower calyx	0
Pelvic	2
Upper ureter	1
Middle ureter	0
Lower ureter	1

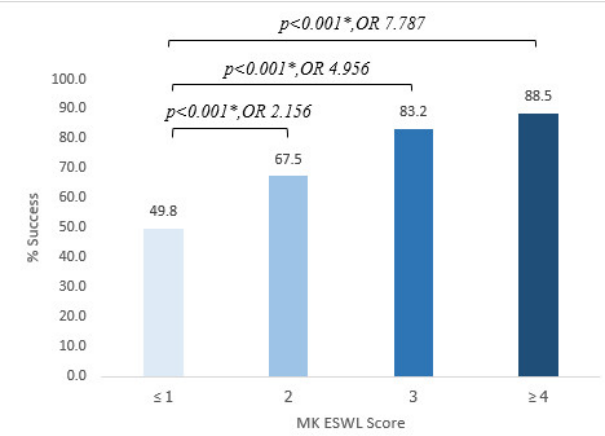

Figure 1. Success rate of ESWL treatment in each area of MK ESWL Score

analysis revealed that age was an independent predictor of failure of ESWL. The success rate in the age group of > 60 years was significantly lower when compared to the age group of ≤ 40 years. (OR = 1.475; 95% C.I.: 1.113-1.954; p = 0.007) and age group of 41-60 years. (OR = 1.228; 95% C.I.: 1.056-1.428; p = 0.007). The reason for the possible poorer stone-free rate of renal calculi in elderly patients is unknown. However, age-related sclerosis of the kidney may affect the acoustic impedance and lower the efficacy of ESWL. Many studies have shown that gender is not a significant predictor of ESWL outcome.[24] This was found to be similar, in our study, as the success rate of ESWL in males was 70.1% which was equal to a 70.1% rate of success in females. This result was not statistically significant.

Additionally, previous studies have shown that stone size was a significant predictor of ESWL treatment success. The larger the size of stone, the higher the risk of ESWL failure became. In a study of 2,954 patients with renal stones, the authors observed a success rate of 89.7% for stones of < 15 mm and of 78% for stones of >15 mm (p < 0.001).[11] In another study of 427 patients with renal stones, the success rate of ESWL for stones of ≤ 10 mm was 90% and 70% for stones of > 10 mm (p < 0.050).[12,24] Similarly, in our study, stone size was one of the most important factors determining ESWL success. Success rate of treatment in stones of ≤ 10 mm was 76.3% (1922/2518) compared to that of only 60.7% (842/1387) in stones of 11-20 mm and 63.1% in stones of > 20 mm. Multivariate analysis revealed that stone size was an independent predictor of failure of ESWL in each group when compared to stone size of ≤ 10 mm (stone size 11-20 mm; OR = 0.540; 95% CI: 0.434-0.673; p < 0.001; stone size > 20 mm; OR = 0.584; 95% CI: 0.434-0.785; p < 0.001).

Next, stone location was a significant predictor of ESWL outcome. Various studies had observed a lower success rate in treating lower calyceal stones other than stones in other sites. One study showed that the success of ESWL treatment was only 47% in the treatment of lower calyceal stones compared to that of 79% for stones in other sites (chi-squared = 6.3, df = 1, p = 0.012).[17] A recent study revealed a stone-free rate of 75% for treatment of lower calyceal stone (size ranging from 10-20 mm) with ESWL.[25] In our study, we found that the stone location was a significant predictor of ESWL outcome in the univariate analysis. We compared the success rate of lower calyceal stones with stones from other sites. The success rate of ESWL for lower calyceal stones was 54.6% compared to 86.0, 75.2, 75.3% for stones located in the upper, middle calyx and pelvis (chi-squared value = 276.517, df = 6, p < 0.001)

The multivariate analysis revealed that stone location was a strong independent predictor of ESWL failure. In each location, in comparison to upper calyceal stones, the result from the logistic regression analysis showed significant differences in comparison to other locations: middle calyceal stone: OR = 0.586; 95% CI: 0.448-0.767; p < 0.001; lower calyceal stone: OR = 0.196; 95% CI: 0.156-

0.246; p < 0.001; pelvic stone: OR = 0.738; 95% CI: 0.557-0.977; p = 0.034; upper ureteric stone: OR = 0.340; 95% CI: 0.256-0.452; p < 0.001; middle ureteric stone: OR = 0.205; 95% CI: 0.130-0.324; p < 0.001; and lower ureteric stone: OR = 0.284; 95% CI: 0.202-0.401; p < 0.001. There was a success rate of 60% in patients with lower calyceal stones of ≤ 10 mm in size in comparison to stones of > 10 mm in size, the success rate of which was 46.7% (OR 1.712; 95% CI: 1.369-2.143; p < 0.001). The stone free rate of patients with lower calyceal stones of ≤ 10 mm in size was 38.9% in comparison to stones of > 10 mm in size of which the stone free rate was 8.2% (OR 7.122; 95% CI: 5.049-10.047; p < 0.001). The clearance of the fragments was lower due to the unfavorable spatial anatomy of the lower pole collecting system. Another study of 66 patients revealed that none of the anatomic factors had a statistically significant effect in predicting the success of ESWL in patients with lower pole stones.[28] As ESWL is a non-invasive modality, it could be offered for lower calyceal stones with low burden and favorable anatomy.

One study of 109 patients with renal stone disease who underwent ESWL had shown that stone surface area was a significant predictor of ESWL treatment success. A univariate logistic regression analysis revealed the high prognostic power of stone surface area for ESWL treatment failure (OR = 1.03, 95% CI: 1.01-1.06, p = 0.02).[27] Similarly, in our study, we found from the multivariate logistic regression analysis that stone surface area was one of the significant predictors of ESWL treatment success (OR = 0.991, 95% CI: 0.989-0.993, p < 0.001). The larger the surface area of the stone, the higher the risk of ESWL failure became. A group-variate logistic regression analysis also revealed that the stone surface area was a strong significant predictor of ESWL outcome. The success rate of ESWL for stones of ≤ 50 mm^2 in surface area was 77.0% compared to 63.9% for stones of > 50 mm^2 in surface area (OR = 0.634, 95% CI: 0.509-0.789, p < 0.001).

A series of minor complications can occur after ESWL.[25,26] In this study, the overall complication rate was 5.2%. However, all complications were managed successfully with conservative treatment. Among 4.0% of the patients, post-interventional auxiliary procedures were necessary.

Finally, we developed a predictive system for the success of ESWL treatment, specifically "MK ESWL Scoring". We defined the cut-off points from four predictive factors and summarized them into an overall MK ESWL score (Table 3). The score was group and analyzed using logistic regression. We found that the MK ESWL score shows a strong correlation to the probability of ESWL treatment success (Figure 1).

This study had several limitations. It was conducted as a retrospective review which introduces variation into the various data sets. Also plain radiography was used instead of NCCT for the follow-up protocol to confirm treatment success. Stone composition, stone density and stone to skin distance which had significant influence on outcome of ESWL were not evaluated and also analysis of the retrieved fragments was not completed. However, the study provides strong evidence that patient age, stone size, stone location and stone surface area affected the ESWL outcome. In additional, the MK ESWL score could be extremely useful informing patient selection for the improvement of ESWL outcomes to save time and treatment costs.

Conclusion

This single institution study showed good results of treatment of renal and ureteric stones with ESWL. Greater success of ESWL was observed in cases of patients aged ≤ 40 years, with a stone size of ≤ 10 mm, a stone surface area of ≤ 50 mm^2 and a location in the upper calyx. MK ESWL Scoring is a good predictive system for the success of ESWL treatment.

Acknowledgement

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Conflict of Interest

The authors declare no conflict of interest.

References

1. Chaussy C, Brendel W, Schmiedt E. Extracorporeally induced destruction of kidney stones by shock waves. Lancet 1980;2:1265-8.
2. Bach C, Buchholz N. Shock wave lithotripsy for renal and ureteric stones. Eur Urol Suppl 2011;10:423-32.

3. Akal HR. The role of extracorporeal shock wave lithotripsy in the treatment of upper ureteral stone disease. Thi-Qar Med J 2011;5:16-27.
4. Labanaris AP, Kühn R, Schott GE, Zugor V. Perirenal hematomas induced by extracorporeal shock wave lithotripsy (ESWL). Therapeutic management. ScientificWorldJournal 2007;7:1563-6.
5. Preminger GM, Tiselius HG, Assimos DG, Alken P, Buck AC, Gallucci M, et al. American Urological Association Education and Research, Inc. and European Association of Urology. Guideline for the management of ureteric calculi. Eur Urol 2007;52: 1610-31.
6. Abe T, Akakura K, Kawaguchi M, Ueda T, Ichikawa T, Ito H, et al. Outcomes of shockwave lithotripsy for upper urinary-tract stones: a large-scale study at a single institution. J Endourol 2005;19:768-73.
7. Al-Dabbagh AA Extracorporeal shock wave lithotripsy for the treatment of urolithiasis. Med J Babylon 2009;6:263-7.
8. Albala DM, Assimos DG, Clayman RV, Denstedt JD, Grasso M, Gutierrez-Aceves J, et al. Lower pole I: a prospective randomized trial of extracorporeal shock wave lithotripsy and percutaneous nephrostolithotomy for lower pole nephrolithiasis-initial results. J Urol 2001;166:2072-80.
9. Turk CH, Knoll T.Petrik A, Sarica K, Seitz, Straub M, et al. Guidelines on urolithiasis: J Urol 2007;178: 2418-34.
10. Perks AE, Schuler TD, Lee J, Ghiculete D, Chung DG, D'A Honey RJ, et al. Stone attenuation and skin-to-stone distance on computed tomography predicts for stone fragmentation by shock wave lithotripsy. Urology 2008;72:765-9.
11. Abdel-Khalek M, Sheir KZ, Mokhtar AA, Eraky I, Kenawy M, Bazeed M. Prediction of success rate after extracorporeal shock-wave lithotripsy of renal stones–a multivariate analysis model. Scand J Urol Nephrol 2004;38:161-7.
12. Al-Ansari A, As-Sadiq K, Al-Said S, Younis N, Jaleel OA, Shokeir AA. Prognostic factors of success of extracorporeal shock wave lithotripsy (ESWL) in the treatment of renal stones. Int Urol Nephrol 2006;38:63-7.
13. Choi JW, Song PH, Kim HT. Predictive factors of the outcome of extracorporeal shockwave lithotripsy for ureteral stones. Korean J Urol 2012;53:424-30.
14. Tarawneh E, Awad Z, Hani A, Haroun AA, Hadidy A, Mahafza W, et al. Factors affecting urinary calculi treatment by extracorporeal shock wave lithotripsy. Saudi J Kidney Dis Transpl 2010;21:660-5.
15. Takahara K, Ibuki N, Inamoto T, Nomi H, Ubai T, Azuma H. Predictors of success for stone fragmentation and stone-free rate after extracorporeal shockwave lithotripsy in the treatment of upper urinary tract stones. Urol J 2012;9:549-52.
16. Shinde S, Balushi Y A,Hossny M, Jose S, Busaidy. Factor affecting the outcome of extracorporeal shockwave lithotripsy in urinary stone treatment. Oman Med J 2018;33:209-217
17. Cheewaisrakul P. A comparison of stone free rate between a diuretic and a control group of patients undergoing extracorporeal shock wave lithotripsy: a prospective, randomized, double-blind, placebo-controlled trial. Insight Urol 2021;42:138-43.
18. Tiselius HG, Ackermann D, Alken P, Buck C, Conort P, Gallucci M, Working party on lithiasis, European Association of Urology Guidelines on urolithiasis. Eur Urol 2001;40:362-71.
19. Patel T, Kozakowski K, Hruby G, Gupta M. Skin to stone distance is an independent predictor of stone-free status following schockwave lithotripsy. J Endourol 2009;23:1383-5.
20. Jeong US, Lee S, Kang J, Han DH, Park KH, Baek M. Factors affecting the outcome of extracorporeal shock wave lithotripsy for unilateral urinary stones in children: a 17-year single-institute experience. Korean J Urol 2013;54:460-6.
21. Matlaga B, Lingeman JE. Surgical management of urinary lithiasis. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA, editors. Campbell-Walsh Urology. 10th ed. Philadelphia: Saunders; 2012. p. 1357-410.
22. COVID Surg Collaborative. Mortality and pulmonary complications in patients undergoing surgery with perioperative SARS-CoV-2 infection: an international cohort study. Lancet 2020;396:27-38.
23. Gomha MA, Sheir KZ, Showky S, Abdel-Khalek M, Mokhtar AA, Madbouly K. Can we improve the prediction of stone-free status after extracorporeal shock wave lithotripsy for ureteral stones? A neural network or a statistical model? J Urol 2004;172:175-9.
24. Sanjay S, Younis AB, Medhat H, Sachin J, Salma AU. Factors affecting the outcome of extracorporeal shockwave lithotripsy in urinary stone treatment. Oman J 2018;33:209-17.
25. Al-Marhoon MS, Shareef O, Al-Habsi IS, Al-Balushi AS, Mathew JK, Venkiteswaran KP. Extracorporeal shockwave lithotripsy success rate and complications: initial experience at Sultan Qaboos University Hospital. Oman Med J 2013;28:255-9.
26. Salem S, Mehrsai A, Zartab H, Shahdadi N, Pourmand G. Complications and outcomes following extracorporeal shock wave lithotripsy: a prospective study of 3,241 patients. Urol Res 2010;38:135-42.
27. Snicorius M, Bakavicius A, Cekauskas A, Miglinus

M,Platkevicius G, Zesvys A. Factors influencing extracorporeal shock wave lithotripsy efficiency for optimal patient selection. Wideochir Inne Tech Maloinwazyjne 2021;16:409-16.

28. Thanakhon C, Choonhaklai V. Association of Infundibulopelvic Angle, Infundibuum Width, Infundibulum Length and Lower Pole Ratio on Stone Clearance after Shock Wave Lithotripsy. Insight Urol 2016;37:19-28.

Original Article

Radical cystectomy with a Y-shaped orthotopic ileal neobladder, early uretero-neobladder anastomosis outcomes at Khon Kaen Hospital

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Keywords:
Bladder cancer, radical cystectomy, neobladder, uretero-neobladder anastomosis

Abstract

Objective: To evaluate the clinical complications and functional outcomes associated with the modified Y-pouch neobladder technique, in particularly those related to the prevention of anastomosis stricture.

Materials and Methods: Functional outcomes and associated complications were evaluated in 25 patients (23 men, 2 women) who underwent radical cystectomy with Y-pouch neobladder by isolating 50 cm of the ileum between October 2010 and December 2020. Clinical complications included anastomosis stricture formation, hydronephrosis, pyelonephritis, vesical stone formation, and renal deterioration.

Results: No cases exhibited uretero-neobladder anastomosis stricture, urethro-neobladder anastomosis stricture, or vesical stones. In addition, no complications were observed in relation to metabolic acidosis. One year after surgery, daytime and nighttime continence rates among patients were 88% and 72%, respectively, with almost every case exhibiting near-normal voiding frequency. The average maximal neobladder capacity was 425.60±20.83 ml with a mean follow-up period of 2.8 years. There was a no statistically significant increase in creatinine with values of 1.45 mg/dl, 1.14 mg/dl, 1.21 mg/dl, and 1.35 ml/dl being recorded at preoperative baseline, 3, 6 and 12 months, respectively.

Conclusions: The Y-pouch neobladder created by isolating 50 cm of the ileum showed a low incidence of uretero-neobladder anastomosis and urethra-anastomosis stricture rate. In addition it was a straightforward procedure with a quickly reconstructed reservoir, had good functional outcomes which were comparable to most popular orthotopic neobladders, had no significant increase in postoperative creatinine levels and improved quality of life for patients.

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Introduction

In the Urology Department, radical cystectomy is performed on patients with muscle-invasive carcinoma of the bladder and in the case of some patients with recurrent T1 disease or CIS that has been unresponsive to intravesical chemotherapy.[1] Orthotopic neobladder in patients with radical cystectomy is recognized as the gold standard type of diversion[1] for improving the quality of life.[2,3] Several techniques for orthotopic neobladder surgery exist, including the Hautmann pouch3, Studer pouch[4], and T-Pouch.[5] One complication that can be encountered is ureteroneobladder anastomosis, which is caused by aggressive mobilization of the native ureter[6,7], and urethro-neobladder anastomosis, which is caused by tension on the neobladder by the native urethra.[6,7] A Y-pouch neobladder was first described by Dario Fontana with the bilateral chimney and vertical neobladder technique, which would permit minimal mobilization of the ureter with a consequential decrease in the occurrence of stricture uretero-neobladder anastomosis and free tension urethro-neobladder anastomosis with a consequent decrease in the rate of stricture of the urethra.[6-12]

Dario Fontana used Nesbit's technique (refluxing anastomosis) for uretero-neobladder anastomosis and a detubularized bowel segment with a non-absorbable mechanical stapler, which showed some incidence of stricture rate and development of a neobladder stone. In our research, we modified a Y-pouch neobladder by increasing the length of the chimney on both sides by 10 cm each, thus reducing ureter mobilization as well as reducing tension anastomosis between the native urethra and ileal reservoir. Using suture materials for the reconstruction of the ileal neobladder enabled assessment of the outcomes and complications in terms of any discernable differences.

Materials and Methods

A total of 25 patients (23 men, 2 women) who had undergone radical cystectomy with a Y-pouch neobladder at Khon Kaen Hospital from October 2010 to December 2020 were included in the study. All surgery was carried out by a single surgeon. The protocol of the study was approved by the Institute Review Board in Human Research of Khon Kaen Hospital (Study Number KEXP64042).

Inclusion criteria

1. Invasive bladder carcinoma or recurrent T1 disease or CIS
2. The intra-operative frozen-section analysis was performed at the urethral margin and bilateral ureter margin with negative tumor incidence
3. No bladder neck involvement in women
4. A serum creatinine < 2 mg/dl or an estimated creatinine clearance of ≥ 50 ml/min
5. The patients were informed in detail about the procedure they would undergo. The description included the associated risks, and all patients provided written informed consent.

Exclusion criteria

1. The patient had an underlying medical condition or could not undergo an operation under general anesthesia.
2. The patient had problems with the small intestine and was unable to manage the intestines for the neobladder.

Our research studies were divided into a primary outcome and secondary outcomes, as indicated by the information below.

Primary outcome

1. Uretero-neobladder anastomosis stricture

Secondary outcomes

1. Urethro-neobladder anastomosis stricture
2. Vesical stone
3. Daytime and nighttime continence
4. Bladder capacity
5. Renal function outcome

Criteria for Uretero-neobladder anastomosis stricture

1. Clinical flank pain
2. Persistent and or progressive hydronephrosis identified from ultrasound, IVP or CT scan
3. Approved for surgery by diuretic renal scan

Criteria for Urethro-neobladder anastomosis stricture

1. Poor stream of urine
2. A 22 Fr cystoscope could not be passed through the anastomosis. Classification of the degree of stricture is either grade I (> 17 Fr but < 22 Fr), grade II (< 17 Fr) and grade III (pinhole).[14]

Criteria for laparoscopic radical cystectomy

1. Clinical T1, T2, no bulky mass, without lymphadenopathy
2. No obesity
3. No previous surgery

Radical cystectomy was performed in male patients. Intra operative cystoscopy with 22 Fr cystoscope was performed before surgery for evaluation of urethra diameter for the pre op baseline measurement. Anterior pelvic exenteration was performed in women using the technique proposed by Campbell-Walsh Urology (10th ed). Laparoscopic radical cystectomy was carried out with an open small incision 5 cm at the lower umbilicus midline for extracorporeal ileal neobladder with uretero-neobladder anastomosis reconstruction. The skin was then closed with intracorporeal suturing and knot-tying urethro-vesical anastomosis was performed (Figure 1). In the case of females, we utilized an omental flap to sew to the vaginal stump by placing it behind the neobladder to support the back of the pouch and to prevent acute angulation of the posterior pouch-urethral junction and pouch-urethral fistula.[4]

The Y-pouch neobladder was constructed by isolating 50 cm of the ileum, 15 to 20 cm proximal to the ileocecal valve. The isolated intestinal segment was arranged in a Y shape with two central segments of 15 cm and two chimney limbs of 10 cm. The two central segments were brought together and detubularized, and the continuous unlock single-layer technique was used with Vicryl® 2-0 for neobladder reconstruction. The uretero-neobladder anastomosis was then performed at the dorsolateral aspect of the two limbs with simple Monocryl® 4-0 sutures using the Bricker technique (refluxing technique)[8,9] (Figure 2). Ureteral stents were positioned and brought out through the dorsal aspect neobladder and then through the anterior abdominal wall. The two limbs were then fixed to the psoas muscles and then recovered with posterior peritoneum for the prevention of internal bowel hernia. The next step for urethro-neobladder anastomosis was performed with four to five sutures in Vicryl®, Taper Point, UR-6, which remained sutured to the urethra immediately after bladder removal to prevent native urethral mucosa retraction. The everted mucosa was fixed with CCG 4-0 at the urethral opening of ileal neobladder, which assists in the prevention of urethro-neobladder anastomosis stricture and the retaining 20 Fr Foley catheter (Figure 3). Suprapubic cystostomy catheters were placed in the first 2 cases. The Jackson-Pratt drain was fitted. The abdominal wall was closed; layer closure being used as the sequential closure of each fascial layer to prevent postoperative incisional hernias. Any fascial defects will reduce efficiency in completely evacuating the neobladder so need to be minimized.[10,11]

The ureteral stents were removed 14 days after surgery by removing them on successive days to prevent urosepsis. The bladder catheter was retained for 21 days. All patients were enrolled onto a perineal rehabilitation program to improve the early continence rate. A periodic evaluation of post-void residual volume was carried out. Renal ultrasonography was performed pre-operatively and postoperatively at 1 3, 6, 12 months for the evaluation of persistent or progressive hydronephrosis, with follow up every year, with CT scan or IVP if there was persistent hydronephrosis. Cystoscopy was carried out every year for the evaluation of the recurrence of tumor, vesical stone, and urethral stricture, and VCUG for the evaluation of neobladder capacity and vesicoureteral reflux. A voiding chart was filled out at 12 months and then every subsequent year (Figure 4).

The following parameters were investigated in the study: Intraoperative and postoperative complications (classified as early and delayed), uretero-neobladder anastomosis, stricture, urethro-neobladder anastomosis stricture, neobladder stone, daytime and nighttime continence, and urinary frequency. Continence was evaluated using a detailed patient questionnaire. The degree of continence was classified as good (completely dry), satisfactory (using no more than one pad per day or night), and poor (using more than one pad per day or night).[7] Renal function was evaluated using serum creatinine values pre-operative and post-operative at 3, 6, 12 months. Change in creatinine from preoperative baseline value was compared as a continuous variable using the paired- simple T-test. A $p \leq 0.05$ was used to denote statistical significance.

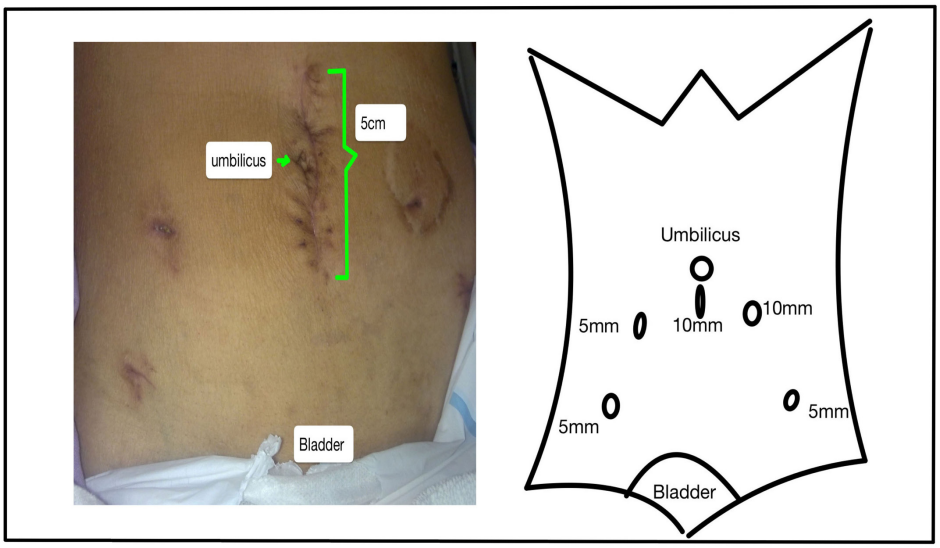

Figure 1. A laparoscopic radical cystectomy with a 5 cm small open incision on the lower umbilicus midline for an extracorporeal ileal neobladder with uretero-neobladder anastomosis reconstruction and intracorporeal suturing and knot-tying urethro-vesical anastomosis

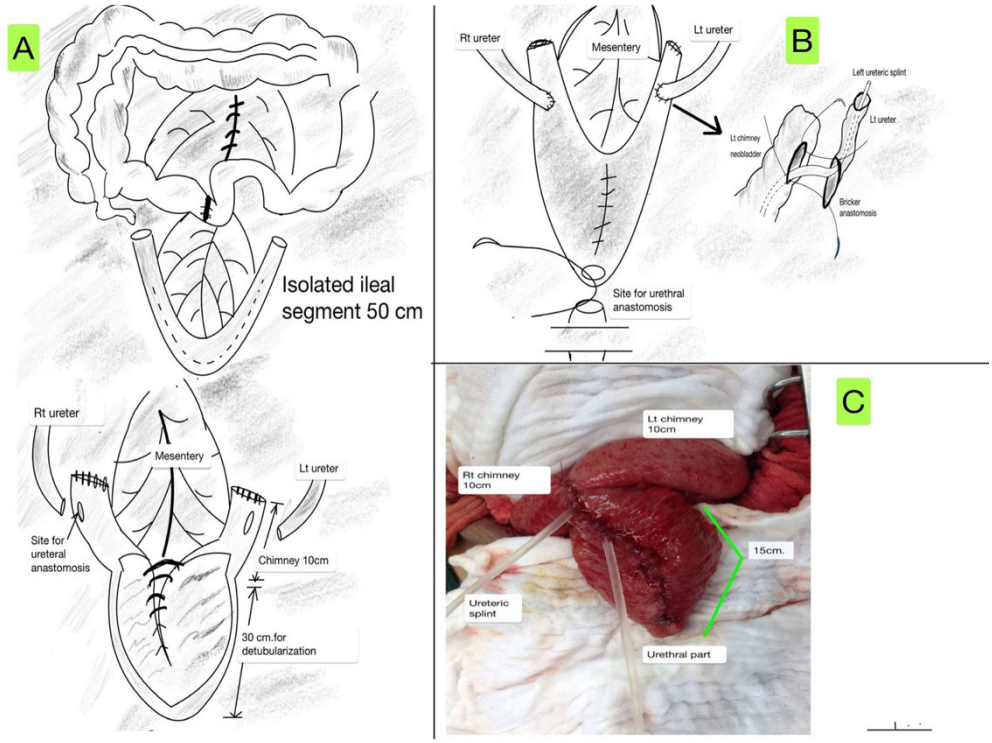

Figure 2. A: Shows the Y shape with isolated ileal segment 50 cm, two central segments of 15 cm and two chimney limbs of 10 cm. B and C, show the uretero-neobladder anastomosis as performed with the Bricker technique (refluxing technique) and the urethral part of the neobladder with everted mucosa for prevention of anastomosis stricture

Results

All 25 patients (23 men, 2 women) were considered eligible for the study, and the mean follow-up postoperative was 2.8 years (range 1.5-7 years). Two patients underwent laparoscopic radical cystectomy with intracorporeal suturing and knot-tying urethra-vesical anastomosis. Their mean age was 61.9 years (range 43-72) (Figure 5). The primary outcome in the study showed zero (0%) cases of uretero-neobladder anastomosis stricture, and the secondary outcome showed zero (0%) cases of urethro-neobladder anastomosis stricture. There were zero (0%) cases of neobladder stone, however bowel ileus occurred

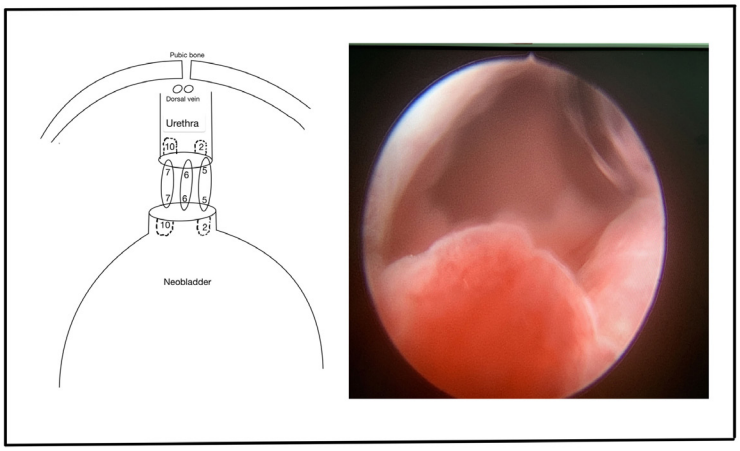

Figure 3. Shows an urethro-neobladder anastomosis which was performed with 2, 5, 6, 7, 10 o' clock simple sutures. Also showing a post operative cystoscopy with 22 Fr sheath with no urethro-neobladder stricture

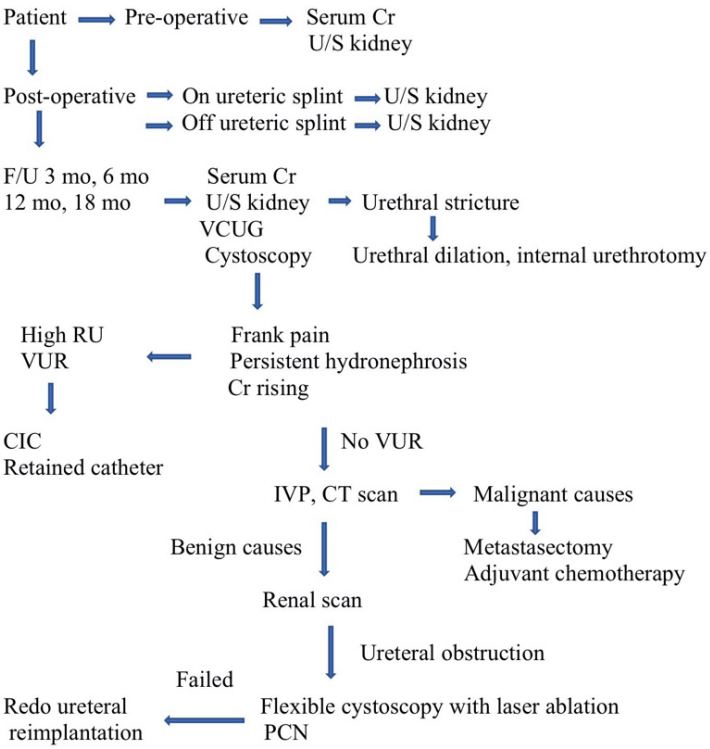

Figure 4. Showing the algorithm for investigation and management in patient follow up

in 3 cases involving conservative management. 2 cases had vesico-cutaneous fistula via the supra-pubic cystostomy tract after mucous obstruction in the first 2 cases in our study. These were managed conservatively with an increased amount of manual bladder irrigation, 1 case pT2 with neoadjuvant chemotherapy had a small bowel obstruction at the 1 year follow up. In our study, 1case pT3b cancer died 2 months after surgery therefore was excluded from the study. At the 2 year follow up it was also found that two patients had died due to the progression of the pT3b cancer. In our research, we assessed cystoscopy evaluation concerning recurrent tumors, vesical stones, and urethro-neobladder anastomosis strictures, which revealed no stones, and no urethro-neobladder anastomosis stricture. One patient with stage pT1 was found to have a recurrent tumor in the penile urethra. VCUG was assessed for bladder capacity and vesico-ureteral reflux, which found 1 female case with underlying DM and HT with high residual urine and bilateral hydronephrosis identified in the ultrasound follow up, but there was no hydronephrosis after retention of the Foley catheter, and bladder capacity at 425.60 (SD±20.83) ml in a range between 390.00-460.00 ml. One case who was treated with neoadjuvant chemotherapy had had a small bowel obstruction which was identified at the 1 year follow up (Figure 6).

Table 1. Patient characteristics

Comorbid conditions	N
Hypertension	4
Diabetes mellitus	1
Gout	1

Table 2. Demographic data and post-operative complications and outcomes

Data	N
Number of patients	25
Sex	
Male	23
Female	2
Age (years)	61.88±7.091
X±SD	43-72
Postoperative follow-up	
X±SD	2.84±1.25
Range	1.50-7.00
Primary outcome complication n (%)	
Uretero-neobladder anastomosis	0 (0)
Secondary outcome complications n (%)	
Urethro-neobladder anastomosis stricture	0 (0)
Neobladder stone	0 (0)
Bowel ileus	3 (12)
Wound infection	1 (4)
Vesico-cutaneous fistular	2 (8)
Small bowel obstruction	1 (4)
Bladder capacity (ml)	
X±SD	425.60±20.83
Range	390.00-460.00

Table 3. Mean preoperative creatinine, 3 months, 6 months, and 12 months

Time	mean	SD	P-value
Pre op	1.45	0.75	
3 months	1.15	0.59	0.010*
6 months	1.21	0.36	0.042*
12 months	1.35	0.47	0.250

*Denotes statistical significance

Mean preoperative creatinine was 1.45 mg/dl (SD 0.75). Creatinine measurements showed a statistically significant decrease from preoperative baseline at 3 months and 6 months and but was not statistically significant at 12 months.

Table 4. Showing daytime urination and nighttime urination 12 months after surgery

	Good	Satisfactory	Poor
Daytime	23	2	0
Nighttime	18	7	0

Discussion

Quality-of-life issues are becoming increasingly important when selecting the type of urinary diversion in patients and are likely to play a larger role in the future management of those undergoing lower urinary tract reconstruction after cystectomy. One of the perceived advantages of the various forms of continent urinary diversion (particularly orthotopic diversion) is the presumptive improvement in quality of life compared with a conduit form of diversion.[10,11] Orthotopic neobladder reconstructions are technically more challenging and time-consuming for the surgical team but it has been shown that early morbidity and mortality associated with cystectomy and orthotopic diversion are not increased compared with an ileal conduit.

Complications in radical cystectomy and diversion are common, and many are severe and potentially life threatening.[4,12] Most complications include bleeding, infection, and cardiovascular and pulmonary events, as well as uretero-neobladder anastomosis stricture, urethro-neobladder anastomosis stricture, neobladder stone, and bowel dysfunction (diarrhea and vitamin B1 malabsorption).

Uretero-neobladder anastomosis stricture is among the major causes of renal damage and

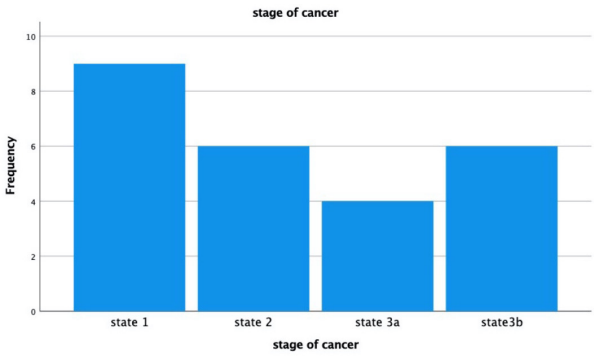

Figure 5. Showing post-operative pathological states of cancer

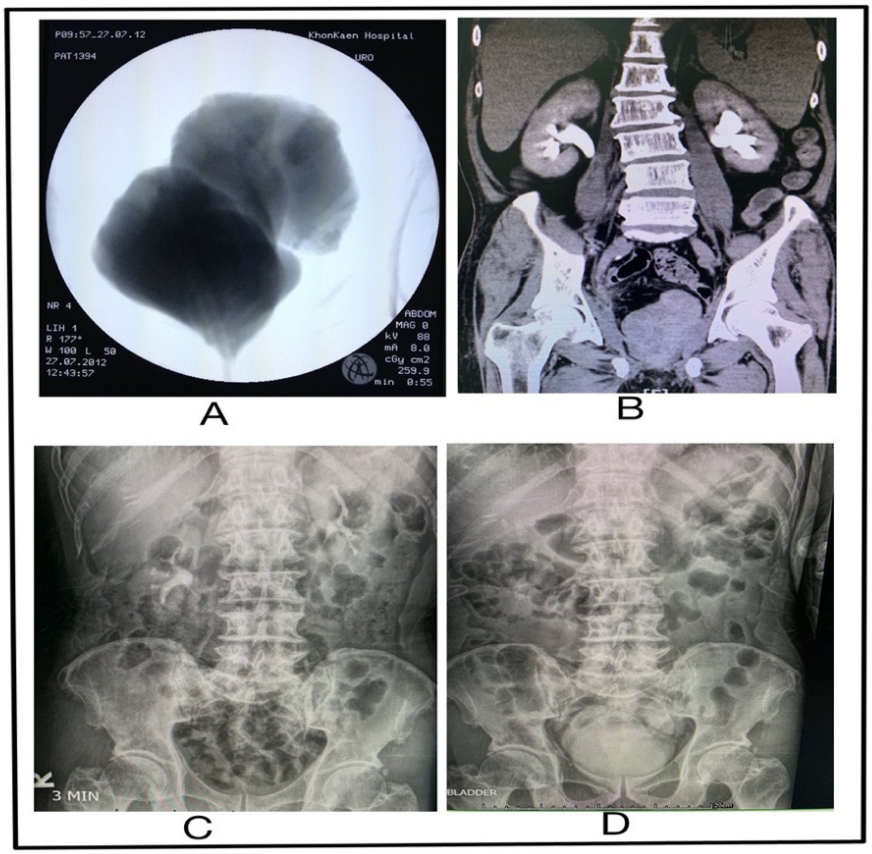

Figure 6. A: VCUG showing evaluation of VUR and bladder capacity at 12 months. B: CT scan showing kidney function 6 months after surgery. C and D, IVP showing kidney function and y pouch neobladder shape

morbidity. It is usually difficult to treat, whether endoscopically or surgically.[13] The most frequent causes are the use of a non-refluxing technique, tension on the anastomosis, kinking of the ureter, and excessive mobilization with consequent devascularization, as well as periureteral fibrosis due to urinary perianastomotic leakage.13 Strictures can also occur in ureters that have been brought under the sigmoid with extensive mobilization.[10] Pantuck et al.[13] reported a statistically significant increase in the rate of strictures for ureteral-neobladder anastomosis when a non-refluxing technique was performed (13% for non-refluxing anastomoses versus 1.7% for refluxing anastomoses). This study also confirmed that the presence of ureteral reflux with a large volume, low-pressure neobladder does not cause an increase in pyelonephritis, urolithiasis, or renal failure. Similar to the non-refluxing method, it is technically easier to perform and poses less risk of stricture.[13] Urethro-neobladder anastomosis stricture has a reported incidence of 2.7% to 8.8%. The frequent causes are tension on the anastomosis between the ileal neobladder with native urethra and short mesentery ileal neobladder. Failure due to apposition in the bladder neck mucosa to the urethral mucosa[14] is a problem that may be solved with a Y-pouch neobladder.

The ileal vertical (Y-pouch) neobladder described by Fontana et al. (2004)[6,7] was performed by isolating 40 cm of the ileum. The isolated intestinal segment was arranged in a Y shape with two central segments of 14 cm and two limbs of 6 cm. It is easy to perform and requires significantly shorter operative times (mean 90 minutes) using a non-absorbable mechanical stapler. Therefore, ureteral neobladder anastomosis can be easily performed on the posterior wall of each ileal limb without the need to mobilize the ureter. The vertical neobladder reduces the tension between the ileal neobladder and the native urethra compared with other orthotopic neobladders that provide two limbs. The Y-neobladder does not have any statistically significant urodynamic differences compared with the other mainly used neobladder.[3,6,7,15,16] In this study one (2%) case of stricture of the right ureteral-neobladder anastomosis occurred, three patients (6%) developed

neobladder stones, and two (4%) cases developed stricture of the urethro-neobladder anastomosis. Based on these findings it can be stated that late complications persist, including anastomosis stricture and vesical stones.

In our research, we constructed a modified Y-pouch neobladder performed by isolating 50 cm of the ileum and increasing the length of the chimney on two sides to 10 cm each using the reconstruction of the ileal neobladder with absorbable suture materials using the Bricker technique (refluxing technique). The results showed low occurrence uretero-neobladder anastomosis, urethro-neobladder anastomosis stricture, or vesical stone formation. Increasing the length of the chimney reduced ureter mobilization as well as tension on both anastomoses between the ileal neobladder with the native ureter, and the native urethra to improve the apposition of the bladder neck mucosa to the urethral mucosa.[14] Placing temporary ureteral stents for 14 days helped decrease early urinary leak and stricture at anastomotic sites.[17-19] This reduced the incidence of anastomosis stricture as a result.

Vesical stones have been found to form in 4 to 6% of cases[20-24], with the most likely cause to be chronic acidosis and strictures of the pouch and accumulation of mucus.14 The use of non-absorbable metal staple materials for the construction of the neobladder[7,17,18] in our study resulted in zero cases probably because of the lack of vesico-urethral anastomosis stricture and the use of absorbable suture materials.

One year after the procedure, the average bladder capacity was 425.60 ml, with good capacity of the Y-ileal neobladder, and effective voiding at suitable intervals, enabling the achievement of good daytime and nighttime continence for the vast majority of our patients. These functional outcomes are similar to those of other ileal neobladder types.[3,4,5,7] Only one female case had a high residual urine issue requiring intermittent catheterization, which improved after 1 year of bladder training. One case had penile urethral recurrence; a procedure using a transurethral endoscopic laser was effective in rectifying this issue.

Renal function, and urinary diversion following cystectomy must be effective for the maintenance of the upper urinary tract. Storage of urine in the bowel has not been shown to be inherently damaging to the kidneys; renal deterioration is often due to identifiable and reversible causes, such as ureterointestinal stricture, high pressure storage and chronic infection with associated renal scarring.[25,26]

Lantz et al. reported a statistically significant rise in serum creatinine from preoperative baseline following cystectomy and Studer neobladder reconstruction with ureteric stricture rate was 17.9%.[25] In our study we found no statistically significant rise in serum creatinine during the 12 months follow up checks with no occurrence of anastomosis stricture. However, there is a tendency for it to increase as observed during a longer follow up period, an increase in the rise of serum creatinine being influenced by patient age, sex and lean body mass. There is also evidence that intestinal segments used for urinary diversion might absorb creatinine from the urine.

Advantages of a Y-pouch neobladder

1. A vertical neobladder can be modified to increase the length of the ileal bowel segment to 40-60 cm without causing short bowel syndrome.

- Chimney length can be modified depending on native ureter length and free tension between anastomoses.
- Tension can be freed between the ileal reservoir and native ureter, resulting in the apposition of the bladder neck mucosa to the urethral mucosa, and thus reducing the incidence of urethro-neobladder anastomosis stricture.
- Crossing can be eliminated of the left ureter as in the Studer ileal neobladder
- The minimal dissected native ureter will preserve the blood supply to the ureter and prevent the occurrence of uretero-neobladder anastomosis

2. The use of Bricker (refluxing) uretero-vesical anastomosis, separate left-right site chimney and temporary ureteric stent decreased evidence of uretero-neobladder anastomotic stricture and facilitating endoscopic management of anastomosis stricture but must be closely followed up with CIC or retain the Foley catheter if there is a high residual urine to prevent upper tract deterioration

3. Laparoscopic radical cystectomy is easier and faster with intracorporeal suturing and knot-tying urethra-vesical anastomosis

4. Sutures made of absorbable materials can be used for the construction of the neobladder, thus decreasing the risk of vesical stone formation

5. Free tension between ileal neobladder mesentery with native urethra and everted mucosal urethral part of neobladder may prevent occurrence of urethro-neobladder anastomosis stricture

Conclusion

The orthotopic neobladder in patients undergoing radical cystectomy for bladder carcinoma is a presumed improvement in terms of quality-of-life compared with a conduit form of diversion. The procedure to implement a y-pouch ileal neobladder is straightforward, the reconstruction of the reservoir takes a relatively short time and the functional outcomes are similar to those of other ileal neobladder types. Although additional follow-up is necessary, our preliminary results have been very encouraging.

Conflicts of Interest

The author declares that there were no conflicts of interest.

References

1. Stein JP, Lieskovsky G, Cote R, Groshen S, Feng AC, Boyd S, et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. J Clin Oncol 2001; 19:666-75.
2. Cerruto MA, D' Elia C, Siracussano S, Gedeshi X, Mariotto A, Niero M, et al. Systematic review and meta-analysis of non RCTs on health related quality of life after radical cystectomy using validated questionnaires: better results with orthotopic neobladder versus ileal conduit. Eur J Surg Oncol 2016;42:343-60.
3. Hautmann RE, de Petriconi R, Gottfried HW, Kleinschmidt K, Mattes R, Paiss T, et al. The ileal neobladder: complications and functional results in 363 patients after 11 years of follow-up. J Urol 1999; 161:422-7.
4. Abol-Enein H, Ghoneim MA. Functional results of orthotopic ileal neobladder with serous-lined extramural ureteral reimplantation: experience with 450 patients. J Urol 2001;165:1427-32.
5. Studer UE, Burckard FC, Schumacher M, Kessler TM, Thoeny H, Fleischmann A, et al. Twenty years' experience with an ileal orthotopic low-pressure bladder substitute lesson to be learned. J Urol 2006; 176:161-6.
6. Fontana D, Bellina M, Fasolis G, Frea B, Scarpa RM, Mari M, et al. Y-neobladder: an easy, fast, and reliable procedure. Urology 2004;63:699-703.
7. Stenzl A, Colleselli K, Poisel S, Feichtinger H, Pontasch H, Bartsch G. Rationale and technique of nerve-sparing radical cystectomy prior to an orthotopic neobladder in the female. J Urol 1995;154:2044-9.
8. Davis NF, Burke JP, McDermott T, Flynn R, Maneckshа RP, Thornhill JA. Bricker versus Wallace anastomosis: a meta-analysis of ureteroenteric stricture rates after ileal conduit urinary diversion. Can Urol Assoc J 2015;9:E284-90.
9. Benson MC, Olsson CA. Continent urinary diversion. Urol Clin North Am 1999;26:125-47.
10. Skinner EC, Skinner DG, Stein JP. Orthotopic urinary diversion. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peter CA, editors. Campbell-Walsh Urology. 10th ed. Philadelphia: Elsevier Saunders; 2012. p. 2446-94.
11. Konety BR, Allareddy V, Herr H. Complications after radical cystectomy: analysis of population-based data. J Urol 2006;68:58-64.
12. Pantuck AJ, Han KR, Perrotti M, Weiss RE, Cummings KB. Ureteroenteric anastomosis in continent urinary diversion: long-term results and complications of direct versus non-refluxing techniques. J Urol 2000;163:450-5.
13. Kim BK, Song MH, Du SH, Yang WJ, Song YS. Neovesical-urethral anastomotic stricture successfully treated by ureteral dilation balloon catheter. Korean J Urol 2010;51:660-2.
14. Madersbacher S, Mohrle K, Burkhard F, Studer UE. Long- term voiding pattern of patients with ileal orthotopic bladder substitutes. J Urol 2002;167:2052-7.
15. Studer UE, Danuser H, Merz VW, Springer JP, Zingg EJ. Experience in 100 patients with an ileal low pressure bladder substitute combined with an afferent tubular isoperistaltic segment. J Urol 1995; 154:49-56.
16. Suriano F, Daneshmand S, Buscarini M. Use of non-absorbable staples for urinary diversion: a step in the wrong direction. Urol Int 2013;90:125-9.
17. Abreu SC, Fonseca GN, Cerqueira JBC, Nobrega MS, Costa MR, Machado PC. Laparoscopic radical cystectomy with intracorporeally constructed Y-shaped orthotopic ileal neobladder using non-absorbable titanium staples exclusively. Urology 2005;66:657.
18. Mattei A, Birkhaeuser FD, Baermann C, Warncke SH, Studer UE. To stent or not to stent perioperatively the ureteroileal anastomosis of ileal orthotopic bladder substitutes and ileal conduits? Results of a prospective randomized trial. J Urol 2008;179:582-6.
19. Almassi N, Cha EK, Vertosick EA, Huang C, Wong N, Dason S, et al. Trends in Management and Outcomes Among Patients with Urothelial Carcinoma Undergoing Radical Cystectomy from 1995 to 2015: The Memorial Sloan Kettering Experience. J Urol

2020;204:677-84.
20. Stein JP, Skinner DG. Orthotopic Urinary Diversion. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peter CA, editors. Campbell Urology. 9th ed. Philadelphia: Elsevier Saunders; 2007. p. 2613-48.
21. Berglund RK, Herr HW. Surgery for Bladder Cancer. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peter CA, editors. Campbell-Walsh Urology. 10th ed. Philadelphia: Elsevier Saunders; 2012. p. 2375-85.
22. Skinner EC, Skinner DG, Stein JP. Orthotopic Urinary Diversion. In: Kavoussi LR, Wein AJ, Novick AC, Partin AW, Peter CA, editors, Campbell-Walsh Urology. 10th ed. Philadelphia: Elsevier Saunders; 2012. p. 2497-506.
23. Tanaka T, Kitamura H, Takahashi A, Masumori N, Itoh N, Tsukamoto T. Long-term functional outcome and late complications of Studer's ileal neobladder. Jpn J Clin Oncol 2005; 35:391-4.
24. Lantz AG, Saltel ME, Cagianos I. Renal and functional outcomes following cystectomy and neobladder reconstruction. Can Urol Assoc J 2010;4:328-31.
25. Sirikul T, Sriplakich S, Amantakul A. Comparison of open and laparoscopic radical cystectomy as regards long-term oncological outcomes for bladder cancer. Insight Urol 2021;42:123-30.
26. Ramart P, Chaiyaprasithi B, Pradniwat K, Ratanarapee S, Amornvesukit T, Taweemonkongsap T, et al. Outcome of open radical cystectomy with pelvic lymph node dissection for bladder urothelial cancer in Siriraj hospital between 1998-2003. Thai J Urol 2010;31:27-39.

Original Article

Renal calyx access does not affect intraoperative blood loss in percutaneous nephrolithotomy: a single-center retrospective study

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Keywords: Nephrolithotomy, percutaneous, urinary calculi, blood loss, surgical

Abstract

Objective: Percutaneous nephrolithotomy (PCNL) is one of the most effective ways of dealing with large renal calculi but also comes with a risk of intraoperative blood loss. Previous evidence is contradictory as regards the difference in blood loss between different renal calyx access. We conducted this study to compare intraoperative blood loss between different renal access calyx.

Materials and Methods: We conducted a retrospective study analyzing 132 cases of single access PCNL, dividing them into an upper pole group (n = 93) and a non-upper pole group (n = 39). Intraoperative blood loss was calculated from pre-and post-operative hematocrit level, gender, body surface area, and amount of blood transfusion. Blood loss was compared between the two groups using univariable and multivariable analysis.

Results: Overall blood loss was 500 ml (IQR 200-814 ml) with a median blood loss of 461 ml (IQR 158-738 ml) in the upper pole group and 650 ml (IQR 332-1233 ml) in non-upper pole group. Median hematocrit change was 2.9% and 3.9% in the upper and non-upper pole groups, respectively. The blood transfusion rate was 4.5% in the upper pole group and 8.3% in the non-upper pole group. The multivariable analysis did not demonstrate any statistically significant difference in average blood loss, hematocrit change or blood transfusion rate.

Conclusions: Our study did not find any significant difference in intraoperative blood loss between different renal access routes in PCNL.

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Introduction

Percutaneous nephrolithotomy (PCNL) is one of the most common urologic procedures and is the cornerstone for the treatment of large renal calculi. PCNL has an advantage over other renal calculi treatments, including extracorporeal lithotripsy (ESWL) and retrograde intrarenal surgery (RIRS), owing to its close and direct contact with the calculi and the large size of the access tract. These factors allow for a more comprehensive selection of lithotripters and more aggressive irrigation, which results in a better stone clearance. Nevertheless, its superiority comes with a price. Large renal parenchymal damage, in conjunction with the highly vascularized nature of the kidney tissue, can pose a much higher risk of intraoperative and post-operative blood loss than other alternatives.[1]

A study using fluoroscope-guided renal access with 3D polyester corrosion endocast of the collecting system, arteries, and veins in cadavers revealed that renal access through the upper infundibulum had a much higher risk of arterial injury, mostly to the interlobar artery than its middle or lower counterpart.[2] However, a more recent retrospective clinical study reported a higher risk of severe blood loss in lower pole renal access PCNL compared to middle and upper pole.[3] Another retrospective study also reported a higher transfusion rate in association with renal access in the lower pole.[4,5] These authors provided hypotheses explaining their findings which were either that the lower pole kidney may be richer in arterioles or that the difficulty in the placement of a guidewire in the lower pole may require more tract manipulation. Another case series reported no significant difference in blood transfusion between different routes of renal access.[6]

A conflict of evidence from basic science and clinical research have led us to conduct this study to determine if there is a difference in intraoperative blood loss between upper pole and non-upper pole renal access sites.

Materials and Methods

Patients and population

This study was initiated after approval from the institutional review board of our institution (Protocol number MTU-EC-SU-0-127/62). A retrospective review was performed on all patients undergoing PCNL between 2012-2019. Data were collected from electronic medical records, including laboratory results, and from radiology information systems.

Patients aged more than 18 years who had undergone single tract standard PCNL with telescopic dilatation were included in this study. Exclusion criteria were a tendency of bleeding, abnormal renal anatomy, performance of the surgery in a non-prone position, and cases with insufficient data regarding hematocrit and renal access site. Cases with an unintentional infundibular injury during operation that resulted in early termination of the procedure were also excluded to prevent outliers. Abnormal renal anatomy included a horseshoe kidney, transplanted kidney, and any other anatomical abnormalities that could affect the difficulty of renal access.

Baseline patient data collected were age, height, body weight, American Association of Anesthesiology (ASA) classification, and the presence of hypertension and diabetes. Stone burden was collected as maximum stone diameter and estimated stone surface area obtained from anteroposterior plain radiograph or coronal view of computerized tomography, with or without intravenous contrast media injection. Stone surface area was calculated using a formula recommended by the European Association of Urology.[7] Operative data collected was presence of hydronephrosis of renal access tract, renal access site, size of access tract, preoperative hematocrit, post-operative hematocrit, and operative time. The presence of hydronephrosis was defined in accordance with the SFU classification.[8] Outcome data included stone clearance, blood transfusion between pre/post-operative hematocrit and post-operative complications. The Clavien-Dindo classification system for PCNL was used to grade post-operative complications.[9]

Estimated intraoperative blood loss was calculated using a formula described in a study by Syahputra et al., 2016, which uses gender, body surface area, pre-and post-operative hematocrit level, and blood transfusion during that period.[10]

Sample size (N) was calculated through a pilot study of 10 cases of upper pole access PCNL with an average intraoperative blood loss of 733±160 ml. As previous data is contradictory and there may not be any difference in blood loss, an equivalent trial may be ideal but would require a much larger sample size than available at our

institution. We, therefore, computed sample size as a non-inferiority trial with a hypothesis that blood loss in the non-upper pole access group would exceed no more than 15% of that in the upper pole access group. Sample size was then calculated with STATA version 15.1 (StataCorp LLC, Texas, United States) using a two-sample means test, a $p < 0.05$ and power of 0.8. At our institution, upper pole access is performed approximately three times more frequently than non-upper pole access therefore we calculated a sample size based on this ratio, which resulted in a sample size of 92 cases in the upper pole access group (group 1) and 31 patients in the non-upper pole access group (group 2).

Surgical technique

Prophylactic antibiotics were given to all patients in accordance with their previous urine culture and sensitivity. All procedures were performed by two experienced urologists under general anesthesia. A rigid cystoscope was used to insert a ureteral catheter into the renal pelvis of the target kidney. The patient was then turned into a prone position. Contrast media was then injected into the renal pelvis, and localization was achieved using a fluoroscope. After localization, the access tract was dilated using metallic telescopic dilators, an Amplatz sheath of 30F was then inserted into the renal pelvis. Lithotripsy was achieved by ShockPulse (Olympus corp., Tokyo, Japan), Swiss LithoClast (Boston Scientific, Mass., United States), or holmium laser. Stone fragments were extracted by stone forceps, stone baskets, and fluid irrigation. Operative time was recorded from the first needle puncture to skin closure.

Statistical analysis

Statistical analysis was performed using STATA version 15.1 (StataCorp LLC, Texas, United States). Categorical data are presented as numbers and percentage and analyzed using the Fisher-exact test. Continuous data are presented as mean (SD) (for data with a normal distribution) or median (IQR) (for data with an abnormal distribution) and analyzed with a t-test or Mann-Whitney U test. After exploring our data, the primary outcomes (total blood loss and Hct change) were non-parametric; thus, we decided to use quantile regression analysis for total blood loss, post-operative hematocrit change, and risk of blood transfusion using risk regression analysis. Factors included in the multivariable analysis were factors known to affect blood loss, including age, sex, BMI, hypertension, diabetes, hydronephrosis, stone surface area, operative time, operation side, and ASA Classification.[11-15] A $p < 0.05$ was considered statistically significant.

Results

Data collection from March 16, 2012, to June 31, 2019, yielded 179 PCNL cases with single tract renal access. Forty operations were excluded due to insufficient data, and seven others were excluded in accordance with the exclusion criteria, resulting in a total of 132 operations for inclusion in the analysis. Ninety-three operations were classified as upper pole renal access (group 1) and 39 as non-upper pole (group 2). The apparent difference in the number of cases in groups 1 and 2 was most likely due to a high prevalence of staghorn stones and those with large stone burdens at our institution, which are more likely to be managed with upper pole access.

Overall baseline patient characteristics were similar between the two groups (Table 1). The average ages were 55 and 52 years in groups 1 and 2, respectively. With regard to the operative data, the median stone surface area was 710 mm^2 and 532 mm^2 in groups 1 and 2, respectively, with an average stone diameter of 33 mm in both groups. Operative time was an average of 87 minutes in group 1 and 81 minutes in the other. Hydronephrosis at the access site was present in 70% and 71% in groups 1 and 2. None of these parameters showed any statistical difference. There was also no difference in the side, operative time, preoperative hydronephrosis of renal calyx access, or preoperative hematocrit between the two groups.

The median hematocrit drop was 2.9% in group 1 and 3.9% in group 2 ($p = 0.035$). Estimated intraoperative blood losses were 461 ml and 650 ml in group 1 and group 2, respectively ($p = 0.005$). Transfusion rate between the two groups which were 4.5% in group 1 and 8.3% in group 2 ($p = 0.421$) (Table 2).

Further multivariable analysis between various factors and hematocrit change, intraoperative blood loss, and risk of blood transfusion revealed no statistically significant difference between the two groups (Table 3).

Table 1. Baseline patient characteristics, stone characteristics and operative data

	Upper pole (group 1) (n = 93)	Non-upper pole (group 2) (n = 39)	P-value
Patient characteristics			
Age, years, mean (SD)	55 (13)	52 (12)	0.321
Sex, n (%)			0.564
Male	54 (58)	25 (64)	
Female	39 (42)	14 (36)	
BMI, kg/m^2, mean (SD)	25.66 (4.8)	26.37 (4.37)	0.428
ASA Classification, n (%)			0.655
I	23 (25)	8 (21)	
II	50 (54)	22 (56)	
III	20 (21)	9 (23)	
Hypertension, n (%)			0.184
Yes	53 (57)	17 (44)	
No	40 (43)	22 (56)	
Diabetes, n (%)			0.054
Yes	14 (15)	12 (31)	
No	79 (85)	27 (69)	
Stone characteristics			
Maximum stone diameter, mm, mean (SD)	33 (13)	33 (18)	0.888
Cumulative stone surface area, mm^2, median (IQR)	710 (338-1140)	532 (276 -1067)	0.440
Operative characteristics			
Side, n (%)			0.568
Right	49 (53)	23 (59)	
Left	44 (47)	16 (41)	
Operative time, min, mean (SD)	87 (37)	81 (37)	0.346
Hydronephrosis of access site, n (%)	63 (70)	24 (71)	0.999
Preoperative hematocrit, % (SD)	38 (5.6)	39 (6.0)	0.399

SD = standard deviation, BMI = body mass index, ASA = American Society of Anesthesiology, IQR = interquartile range

Table 2. Operative outcomes

	Upper pole (n = 93)	Non-upper pole (n = 39)	P-value
Hematocrit change, %, median (IQR)	2.9 (0.6-5.4)	3.9(1.6-7.4)	0.035
Total blood loss, ml, median (IQR)	461 (158-738)	650 (332-1233)	0.005
Transfusion, n (%)			0.421
Yes	4 (4.5)	3 (8.3)	
No	89 (95.5)	36 (91.7)	

IQR = interquartile range

Table 3. Regression analyses comparing non-upper pole access to upper pole access

	Difference	95% CI	P-value
Median Hematocrit change difference[a], %	1.28	-0.63 - 3.2	0.187
Total blood loss difference[a], ml	191	-47 - 429	0.115
Relative Risk Ratio of Blood transfusion[b]	1.5	0.64 - 3.52	0.345

[a]Quantile regression analysis adjusted with age, sex, BMI, presence of hypertension, diabetes, hydronephrosis, stone surface area, operative time, operation side, and ASA classification

[b]Binary regression analysis adjusted with age, sex, BMI, presence of hypertension, diabetes, hydronephrosis, stone surface area, operative time, operation side, and ASA classification

Table 4. Post-operative complications; Modified Clavien Classification

		Upper pole	Non-upper pole	Total	P-value
Grade	n (%)				0.173
	0	18 (20)	14 (37)	32 (25)	
	1 (Fever)	37 (40)	13 (34)	50 (38)	
	2 (Transfusion, IV antibiotics)	23 (25)	10 (26)	33 (25)	
	3a (Intercostal drainage, ureteral stenting, embolization)	12 (13)	1 (3)	13 (10)	
	3b (VATS)	1 (1)	0 (0)	1 (1)	
	4a	1 (1)	0 (0)	1 (1)	

Complications, as classified by the modified Clavien system, were found to be similar between the two groups. Fifty patients were found to have a postoperative fever without the need for any interventions, 37 from group 1 and 13 from group 2 (Table 4). With regard to grade 2 complications, 25% of group 1 and 26% of group 2 required transfusion or a change in intravenous antibiotics. Thirteen percent of group 1 and three percent of group 2 were classified as grade 3a complications. Interventions required in this group included intercostal drainage, ureteral stenting, and angioembolization. Thoracic complications were observed in 7 cases in group 1 and 1 case in group 2, all of which required intercostal drainage. No colonic injury occurred in this study. One patient from group 1 was classified as grade 3b complications due to the requirement of video-assisted thoracoscopy (VATS) from empyema thoracis. Another patient from group 1 had postoperative sepsis requiring monitoring in intensive care, which was classified as grade IVa. No patients in group 2 presented with grade IIIb or IV complications.

Discussion

Previous studies regarding intraoperative blood loss in percutaneous nephrolithotomy all shared a common problem in quantifying the amount of blood loss due to the nature of any urologic procedure with continuous fluid irrigation, which renders a conventional methods of gauze counting and intraoperative suction measurement virtually useless. Many studies have shifted to measuring the difference between pre/postoperative hematocrit or hemoglobin levels which could be easily confounded by intraoperative blood transfusion.[5,16,17] Others have shifted entirely to recording blood transfusion or angioembolization rate[3,4,18], which would usually only detect a large amount of blood loss, and a clinical decision for transfusion or embolisation could be affected by various confounders. Hurle et al. proposed a more sophisticated method of estimating blood loss that takes body surface area, sex, and amount of blood transfusion into account[19], which was later adopted by Syahputra et al. in 2016.[10] Therefore, we adopted this method of blood loss estimation, believing that this method could give a more accurate estimate of blood loss.

The upper pole renal access tract has advantage over other poles as it allows the rigid nephroscope to access other calyces, the renal pelvis, and the proximal ureter in a straight line, which results in better access for complex stones than either middle or lower pole access tracts.[20] Upper pole access also provides better access for staghorn stones and those with associated ureteropelvic junction obstruction.[21] Nevertheless, the upper pole access tract also comes with a higher risk of pleural injury, with potential manifestation into a more serious complication such as empyema thoracis. While posing a relatively low risk of pleural complication, lower pole access has a slightly higher risk of colon injury. The selection of renal access tract is dependent on numerous factors, including stone burden, stone geometry, stone location, adjacent organ location, and surgeon preference, thus, not every access tract is suitable for every patient. However, the difference in blood loss between each access tract, if any, may allow the surgeon to be better prepared for the operation.

The total blood loss in non-upper pole access was statistically significantly slightly higher than in upper pole access. A median hematocrit change of 2.9% and 3.9% in the upper and non-upper pole groups, respectively, were consistent with previous reports.[12,22] Hematocrit change was also

significantly higher in the non-upper pole group. However, the amount of blood loss could be influenced by various factors. The adjusted analysis with factors previously known to affect blood loss revealed no significant difference between the two groups in terms of blood loss, hematocrit change and risk of blood transfusion. These results helped confirm previous data published by Singh et al. in a prospective study of 82 patients, which reported no significant difference in hemoglobin loss between groups.[21]

Previous existing data from a cross-sectional study in 131 cases of PCNL demonstrated no difference in transfusion rate between different renal calyx access and an overall transfusion rate of 18%.[23] Other studies also demonstrated similar results with an overall transfusion rate at 9.3-9.4%.[6,24] Our results confirmed these data, showing no statistically significant difference between upper and non-upper calyx renal access.

This study reports overall complications of 75 %, but 63% were only minor complications, similar findings to a previous large study.[25] Both groups showed no statistically significant difference in complication rates for overall complications. However, thoracic complications were higher in group 1 (7 in group 1 vs. 1 in group 2). This observation is consistent with previous data, which reported an overall thoracic complication rate of between 3-16%[26,27] with higher frequency in the upper pole renal access group.[28]

The main points of the study are:

- Intraoperative blood loss is one of the major concerns of most surgeons when performing PCNL, but data regarding blood loss between different renal calyx access is scarce.
- We conducted a retrospective analysis using a previously verified reliable intraoperative blood loss calculation, and the data did not demonstrate a correlation between renal calyx access and intraoperative blood loss.
- The incidence of complications was similar between different renal calyx access.

A further prospective trial is still needed to confirm or refute the lack of correlation and be used in clinical practice.

This study harbors some limitations that might affect the validity of the results. In a large number of cases data was incomplete, 40 cases from a total of 179 cases, a proportion which could affect the reliability of the results due to small sample size. This study also excluded cases with other methods of tract dilatation than metallic telescopic dilators, such as fascial dilator and balloon dilator, which might also affect the amount of intraoperative blood loss.[11]

Conclusion

There was no demonstrable significant difference in the amount of intraoperative blood loss, hematocrit change, and blood transfusion between different renal access routes in this study. The frequency of complications was also similar between different renal access routes.

References

1. Krambeck BRMAE. Surgical management for upper urinary tract calculi. In: Partin AW, Dmochowski RR, Kavoussi LR, Peters CA, editors. Campbell-Walsh-Wein Urology. 12th ed. Philadelphia: Elsevier; 2021. p. 2094-113.
2. Sampaio FJB. surgical anatomy of the kidney in the prone, oblique, and supine positions. In: Smith AD, Badlani GH, Preminger GM, Kavoussi LR, editors. Smith's textbook of endourology. 3rd ed. New Jersey: Wiley; 2012. p. 63-94.
3. Tan J, Chen B, He L, Yin G, Jiang Z, Yao K, et al. Renal access through the inferior calyx is associated with higher risk of severe bleeding after percutaneous nephrolithotomy. Arch Med Sci 2015;11:340-5.
4. Oner S, Okumus MM, Demirbas M, Onen E, Aydos MM, Ustun MH, et al. Factors influencing complications of percutaneous nephrolithotomy: a single-center study. Urol J 2015;12:2317-23.
5. Oner S, Karagozlu Akgul A, Demirbas M, Onen E, Aydos M, Erdogan A. Upper pole access is safe and effective for pediatric percutaneous nephrolithotomy. J Pediatr Urol 2018;14:183.e1-8.
6. Ketsuwan C, Pimpanit N, Phengsalae Y, Leenanupunth C, Kongchareonsombat W, Sangkum P. Peri-operative factors affecting blood transfusion requirements during PCNL: a retrospective non-randomized study. Res Rep Urol 2020;12:279-85.
7. Türk C, Knoll T, Petrik A, Sarica K, Straub M, Seitz C. Guidelines on urolithiasis. European Association of Urology 2011.
8. Fernbach S, Maizels M, Conway J. Ultrasound grading of hydronephrosis: introduction to the system used by the society for fetal urology. Pediatr Radidol 1993;23:478-80.
9. de la Rosette JJ, Opondo D, Daels FP, Giusti G, Serrano A, Kandasami SV, et al. Categorisation of complications and validation of the Clavien

score for percutaneous nephrolithotomy. Eur Urol 2012;62:246-55.
10. Syahputra FA, Birowo P, Rasyid N, Matondang FA, Noviandrini E, Huseini MH. Blood loss predictive factors and transfusion practice during percutaneous nephrolithotomy of kidney stones: a prospective study. F1000Res 2016;5:1550.
11. Kukreja R, Desai M, Patel S, Bapat S, Desai M. Factors affecting blood loss during percutaneous nephrolithotomy: prospective study. J Endourol 2004;18:715-22.
12. Turna B, Nazli O, Demiryoguran S, Mammadov R, Cal C. Percutaneous nephrolithotomy: variables that influence hemorrhage. Urology 2007;69:603-7.
13. Amri M, Naouar S, Ben Khalifa B, Hmidi N, Braiek S, ElKamel R. Predictive factors of bleeding and fever after percutaneous nephrolithotomy. Tunis Med 2019;97:667-74.
14. Kim HY, Choe HS, Lee DS, Yoo JM, Lee SJ. Is Absence of hydronephrosis a risk factor for bleeding in conventional percutaneous nephrolithotomy. Urol J 2020;17:8-13.
15. Ketsuwan C, Kongchareonsombat W, Sangkum P, Kijvikai K, Sananmuang T, Leenanupunth C. Perioperative renal calculus factors affecting percutaneous nephrolithotomy outcomes. Thai J Urol 2019;40:01-8.
16. Yamaguchi A, Skolarikos A, Buchholz NP, Chomon GB, Grasso M, Saba P, et al. Operating times and bleeding complications in percutaneous nephrolithotomy: a comparison of tract dilation methods in 5,537 patients in the Clinical Research Office of the Endourological Society Percutaneous Nephrolithotomy Global Study. J Endourol 2011;25:933-9.
17. Haghighi R, Zeraati H, Ghorban Zade M. Ultra-mini-percutaneous nephrolithotomy (PCNL) versus standard PCNL: a randomised clinical trial. Arab J Urol 2017;15:294-8.
18. Munver R, Delvecchio FC, Newman GE, Preminger GM. Critical analysis of supracostal access for percutaneous renal surgery. J Urol 2001;166:1242-6.
19. Hurle R, Poma R, Maffezzini M, Manzetti A, Piccinelli A, Taverna G, et al. A simple mathematical approach to calculate blood loss in radical prostatectomy. Urol Int 2004;72:135-9.
20. Viprakasit DP, Miller NL. Upper calyx access for percutaneous nephrolithotomy. In: Smith AD, Badlani GH, Preminger GM, Kavoussi LR, editors. Smith's Textbook of Endourology. 3rd ed. New Jersey: Wiley; 2012. p. 206-13.
21. Singh R, Kankalia SP, Sabale V, Satav V, Mane D, Mulay A, et al. Comparative evaluation of upper versus lower calyceal approach in percutaneous nephrolithotomy for managing complex renal calculi. Urol Ann 2015;7:31-5.
22. Akman T, Binbay M, Sari E, Yuruk E, Tepeler A, Akcay M, et al. Factors affecting bleeding during percutaneous nephrolithotomy: single surgeon experience. J Endourol 2011;25:327-33.
23. Ullah S, Ali S, Karimi S, Farooque U, Hussain M, Qureshi F, et al. Frequency of blood transfusion in percutaneous nephrolithotomy. Cureus 2020;12: e11086.
24. Phaijitwichian S. One-shot dilation versus metallic dilation technique for access in percutaneous nephrolithotomy: comparison of efficacy, access time and fluoroscopic time. Insight Urol 2021;42:154-9.
25. Labate G, Modi P, Timoney A, Cormio L, Zhang X, Louie M, et al. The percutaneous nephrolithotomy global study: classification of complications. J Endourol 2011;25:1275-80.
26. Lojanapiwat B, Prasopsuk S. Upper-pole access for percutaneous nephrolithotomy: comparison of supracostal and infracostal approaches. J Endourol 2006;20:491-4.
27. Sukumar S, Nair B, Ginil KP, Sanjeevan KV, Sanjay BH. Supracostal access for percutaneous nephrolithotomy: less morbid, more effective. Int Urol Nephrol 2008;40:263-7.
28. Shilo Y, Kleinmann J, Zisman A, Peer A, Lindner A, Siegel YI. Comparative morbidity for different accesses in percutaneous nephrolithotripsy. Harefuah 2006;145:107-10, 166.

Original Article

Long term complications associated with the ureteric stump in patients with double collecting system who underwent upper pole heminephrectomy

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Keywords:
Double collecting system, duplex kidney, hemi-nephrectomy, ureteric stump

Abstract

Objective: To assess the long-term ureteric-stump outcomes and complications among patients who had undergone upper-pole heminephrectomies of double collecting systems.

Materials and Methods: The medical records of patients who had undergone upper-pole heminephrectomies for non-functioning upper moiety between January 2007 and December 2018 were retrospectively reviewed. Data regarding clinical presentations, age during surgery, operative details, and complications were recorded.

Results: Ten patients were included in the study, nine were children and one was an adult. Double collecting systems with ureteroceles were found in four patients, ectopic ureters being found in six. Nine patients had undergone open heminephrectomies, whereas one patient had undergone robot-assisted surgery. Median age at heminephrectomy was one year old (range: 0.58 to 74 years). Median follow-up time was 81.1 months (range: 40.6 to 140.1 months). Median length of hospital stay was seven days (range: 5 to 22 days). Three patients (30%) had stump complications, including stump abscess in one patient, persistent vaginal discharge in another, and a prolapsed ureterocele in the third. Additional interventions were required in two patients, comprising percutaneous drainage of a stump abscess and the excision of a prolapsed ureterocele.

Conclusions: Our study found three-cases of long-term complications, with only a single patient requiring distal ureteric stump excision. These findings were similar to another study which also showed that the majority of patients did not require stump excision. Other complications were minor and could be treated by local anesthetic intervention for stump abscess and oral antibiotic for UTI. Therefore, upper pole heminephrectomy with subtotal ureterectomy was the appropriate option for in-patients with double collecting system and non-functioning upper moiety.

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Introduction

Duplication of the collecting system of the upper urinary tract, or duplex kidney, is a congenital anomaly among children, with a childhood incidence of 0.8%.[1,2] Duplication of the ureter and renal pelvis can be either complete or incomplete. A ureterocele or an ectopic ureter commonly originates from upper moiety, whereas vesicoureteral reflux frequently occurs in the lower moiety ureter.[3] In the case of ectopic ureters with a functioning upper moiety, common treatments are common sheath reimplantation or ureteroureterostomy. For ureteroceles with a functioning upper moiety, treatment options are transurethral-incision ureterocele or common sheath reimplantation with excision ureterocele or ureteroureterostomy. For a nonfunctioning upper moiety, due to obstructive nephropathy, the standard treatment is upper-pole heminephrectomy.[4] Subtotal ureterectomy is considered to remove the ureter as distally as possible at the same exposure and incision of a heminephrectomy.[5] However, the remaining distal ureteric stump after such procedures may cause a febrile urinary tract infection (UTI), lower-quadrant pain, and/or hematuria.[6] Recently, laparoscopic ureteral clipping has been used to treat non-functioning or poorly functioning renal moieties with ectopic ureters or obstructive ureteroceles; no long-term data are available on this treatment.[7] This study aimed to review the long-term outcomes and complications of ureteric stumps in patients who had undergone heminephrectomies for double collecting systems with non-functioning upper moieties.

Materials and Methods

After receiving ethical approval from the Committee on Human Rights Related to Research involving Human Subjects at the Faculty of Medicine of Ramathibodi Hospital (MURA2018/472), we conducted a retrospective review of patients with double collecting systems who had undergone upper-pole heminephrectomies for non-functioning upper moieties at Ramathibodi Hospital between January 2007 and December 2018. Data including sex, presenting symptoms, preoperative imaging, diagnosis, affected side, surgical procedure, ureter-management details, age at the time of operation, pathology, follow-up time, and intraoperative, early postoperative, and late postoperative complications were collected. Patient baseline characteristics and details of the procedures were reported as frequency with percentage of mean with standard deviation (SDs) or median with range.

Results

Ten patients with double collecting systems were included in this study. Among these 10 patients, nine were children (eight girls and one boy) and one patient was an adult. Clinical presentations included febrile UTIs for nine patients, prenatal hydronephrosis for one patient, vaginal discharge for two patients, and a protruding vaginal mass for one patient. The adult patient had presented with flank pain. The details of patient disease characteristics are shown in Table 1. We defined the non-functioning upper moiety by a finding from ultrasound that showed a paper-thin cortex or by renal scan that showed no radio nucleotide uptake in the upper moiety.

For radiological evaluation, genitourinary tract ultrasound scans were performed in all patients. Five patients underwent intravenous pyelogram (IVP), computed tomography (CT), or

Table 1. Baseline characteristics of patients

Ureteric stump (N = 10)	n (%)
Gender	
Male	1 (10)
Female	9 (90)
Age (years), median (range)	1 (0.58, 74)
Presenting symptoms	
Febrile UTI	5 (50)
Febrile UTI with vaginal discharge	2 (20)
Febrile UTI with protruding vaginal mass	1 (10)
Prenatal diagnosis with febrile UTI	1 (10)
Flank pain	1 (10)
Diagnosis	4 (40)
Double collecting system with ureterocele	
- Extravesical ureterocele 3 cases	
- Intravesical ureterocele 1 case	
Double collecting system with ectopic ureter	6 (60)
- Opening to vagina 2 cases	
- Opening to bladder 2 cases	
- Opening to urethra 1 case	
- Opening to bladder neck 1 case	
Side	
Left	8 (80)
Right	2 (20)

UTI = urinary tract infection

magnetic resonance imaging (MRI) in addition to ultrasonography as their anatomy and pathology could not be clearly identified using ultrasonography alone. Voiding cystourethrography (VCUG) was performed in seven patients in an attempt to evaluate vesicoureteral reflux (VUR). Renal scans using mercaptoacetyltriglycine (MAG3), diethylenetriamine pentaacetic acid (DTPA), or dimercaptosuccinic acid (DMSA) were performed in six patients.

All patients had double collecting systems with a non-functional upper moiety. Ureteroceles were found in four patients, and one patient had a previous transurethral incision (TUI) ureterocele due to protrusion from their vagina. VUR grades 3-4 at the upper moiety were found in the patient who had a previous TUI ureterocele. Ectopic ureters were found in six patients. VUR grades 4-5 at the lower moiety were found in three patients and all VUR were decreased to grades 3 postoperatively.

Median age of the patients at the time of heminephrectomies was one year (range: 0.58 to 74 years). Median operation time was 120 minutes (range: 95 to 180 minutes). Left-side heminephrectomies had been performed in eight patients, and right-side heminephrectomies had been performed in two patients. A robot-assisted heminephrectomy had been performed in one adult patient. Three patients had clip or ligated distal ureteric stumps, six patients had left open distal ureteric stumps, and one patient had no record regarding a distal ureteric stump. Median length of related hospital stay was seven days (range: 5 to 22 days). Median follow-up time was 81.1 months (range: 40.6 to 140.1 months). The details of patients' perioperative and postoperative outcomes are shown in Table 2.

Intraoperative complications comprised collecting-system injuries of the lower moiety in two patients (repaired with chromic catgut) and renal-vessel injury of the lower moiety in one patient (repaired with Prolene®). Early postoperative complications were found in three patients, two of whom had experienced turbid urine intraoperatively. One of these three patients had experienced febrile UTI, while another patient had experienced febrile UTI with surgical-site infection that required stitch removal, dressing, and re-suturing of the surgical wound. The other patient had experienced febrile UTI. Late postoperative complications were found among five patients, three of whom had stump complications. A summary of the details of surgical complication are shown in Table 3.

Discussion

Duplex kidney or double collecting systems are usually associated with an ectopic ureter or a ureterocele. Upper-pole heminephrectomy is an appropriate treatment for a non-functioning upper moiety of a duplex kidney.[2,4] The appropriate management of a distal ureter, such as a total or subtotal ureterectomy, remains under debate in the literature. In the case of a subtotal ureterectomy the ureter is divided as low as possible through an upper-pole heminephrectomy incision. The remaining distal ureteric stump may cause problems, such as febrile UTI, lower-quadrant pain, or hematuria.[8] These complications may be as a consequence of urine stasis in the distal ureteric stump, which acts as a reservoir.[9,10] This study aimed to evaluate long-term complications of the distal ureteric stump after an upper-pole heminephrectomy as few data have been available with regard to this area.

Plaire et al.[10] reported that four out of 32 patients required a secondary operation for distal ureteric stump excision. Three patients had febrile UTIs, and another patient had flank pain with voiding.[10]

Table 2. Perioperative and postoperative outcomes

Ureteric stump (N = 10)	n (%)
Surgical operation	
Open	9 (90)
Robot	1 (10)
Distal ureter	
Clip or ligated stump	3 (30)
Opened stumps	6 (60)
Not recorded	1 (10)
Operative time (minutes), median (range)	120 (95, 180)
Length of stay (days), median (range)	7 (5, 22)
Follow-up time (months), median (range)	81.1 (40.6, 140.1)
Pathology	
Chronic inflammation or infection	6 (60)
Oligonephric hypoplasia	1 (10)
Not recorded	3 (30)

UTI = urinary tract infection

Table 3. Surgical complications

No.	Presenting symptoms	Sex	Background disorder	Surgery before heminephrectomy	Age during heminephrectomy	Intraoperative and early complications	Late complications	Treatment	Time to additional intervention
1	Febrile UTI	F	Lt double collecting system with ureterocele	–	7 months	UTI	Single episode of UTI	Oral ATB	–
2	Febrile UTI with vaginal discharge	F	Lt double collecting system with ectopic ureter	–	2 years	Renal-vessel injury of the lower moiety (repaired with Prolene®); UTI	Persistent vaginal discharge;declining lower-moiety function	Supportive treatment	–
3	Febrile UTI with protruding vaginal mass	F	Rt double collecting system with prolapsed ureterocele	Endoscopic puncture of the Rt ureterocele	2 years	–	Prolapsed ureterocele	Excision ureterocele and distal ureteric stump	11 months
4	Febrile UTI with vaginal discharge	F	Lt double collecting system with ectopic ureter	–	1 year	UTI; surgical-site infection	Ureteric stump abscess	Percutaneous abscess drainage	2 months
5	Febrile UTI with prenatal HN	F	Lt double collecting system with ectopic ureter	–	1 year	–	UTI	On Bactrim® prophylaxis until 5 years old	–

UTI = urinary tract infection, F = female, Lt = left, Rt = right, ATB = antibiotic, HN = hydronephrosis

Meanwhile, De Caluwe et al.[4] evaluated long-term ureteric-stump complications. Five of their patients (10%) had recurrent UTIs and were treated with distal ureteric stump excisions. Four out of five of their patients experienced ureteroceles before their upper-pole heminephrectomies. Two patients in this group were treated with an endoscopic puncture before their upper-pole heminephrectomy, while the other patients were not.[4] From this we could assume that an endoscopic puncture before an upper-pole heminephrectomy is not associated with late distal-ureteric-stump complications, further research would clarify this.

Androulakakis et al.[8] reported that three of their 89 patients required a ureteric stump excision. One patient experienced recurrent hematuria and bacteriuria despite antibiotic treatment, whilst the other two patients were referred from other hospitals. Both of these two patients required stump excisions, and Androulakakis et al. found that the stumps in these patients had been left extended above the iliac crest. One patient had a refluxing stump, and the other patient had a non-refluxing stump which converted into a refluxing stump as a result of dysfunctional voiding. A long stump could be a potential risk factor in the pathogenesis of ureteric stump syndrome.[8] Some studies[11,12] have suggested total ureterectomies to treat high-grade refluxing stumps, but this procedure carries a risk of injury to the healthy lower-moiety ureter. Thus, an upper-pole-moiety ureter should be excised as far as possible to prevent stump complications.

Tonvichien et al. reported that 7/25 (28%) ureterocele cases underwent upper-pole heminephrectomy alone and 1 needed excision of the ureterocele and common sheath reimplantation due to high grade reflux of the lower moiety ureter. They concluded that transurethral incision of ureterocele is the treatment of choice for decompression of the obstructed hydroureter but a second operation is needed in complicated cases especially in patients who have multiple lower tract anomalies.[13]

In our study, five out of ten patients had experienced late complications. Resection of the ureteric stump and ureterocele was required in one patient (10%) due to a prolapsed ureterocele. The incidence rate for secondary procedures in our study was similar to the corresponding rates in previous studies (1-13%).[8,11,14,15] One patient had a stump abscess and underwent percutaneous drainage (PCD); she experienced good results and did not require stump excision. Another patient experienced intermittent vaginal discharge, this symptom being relieved after a five-year follow-up. Meanwhile, another patient experienced a single UTI episode that was treated with an oral antibiotic.

Ureteric stump abscesses have been reported in 0.8%-1% of cases of upper pole heminephrectomy[16] The traditional treatment is ureteric stump excision[17,18], but minimally invasive techniques are available for drainage without a stump excision, for example transurethral fulgulation or transgluteal percutaneous drainage.[15] In this study we performed percutaneous retroperitoneal drainage for a ureteric stump abscess and were able to forego the need for a ureteric stump excision.

Robot-assisted upper-pole heminephrectomies can present as an interesting choice for heminephrectomies because of their good surgical fields, small surgical scars, and removal of more of the ureter than an open approach. Our patient who underwent this robot-assisted treatment option experienced less postoperative pain and a quicker recovery.[14] In our institution, robotic surgery is most often used in prostate and kidney surgery. We performed the institution's first case of robot-assisted laparoscopic upper-pole heminephrectomy, and the outcome was promising, as is suggested in related literature.[11,14]

Conclusions

Our study results showed five-cases in which there were long-term complications. Only one of these patients required a distal ureteric stump excision, this result being similar to another study in which the majority of patients did not require stump excision. The other complications in patients in this study were minor, and could be treated with local anesthetic intervention for stump abscesses and oral antibiotics for UTIs. Therefore, upper pole heminephrectomy with subtotal ureterectomy was the appropriate option for in-patients with double collecting system and non-functioning upper moiety.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Vates TS, Bukowski T, Triest J, Freedman A, Smith C, Perlmutter A, et al. Is there a best alternative to treating the obstructed upper pole? J Urol 1996;156: 744-6.
2. Jednak R, Kryger JV, Barthold JS, González R. A simplified technique of upper pole heminephrectomy for duplex kidney. J Urol 2000;164:1326-8.
3. Chacko JK, Koyle MA, Mingin GC, Furness PD, 3rd. Ipsilateral ureteroureterostomy in the surgical management of the severely dilated ureter in ureteral duplication. J Urol 2007;178:1689-92.
4. De Caluwe D, Chertin B, Puri P. Fate of the retained ureteral stump after upper pole heminephrectomy in duplex kidneys. J Urol 2002;168:679-80.
5. Belman AB, Filmer RB, King LR. Surgical management of duplication of the collecting system. J Urol 1974;112:316-21.
6. Persad R, Kamineni S, Mouriquand PD. Recurrent symptoms of urinary tract infection in eight patients with refluxing ureteric stumps. British J Urol 1994; 74:720-2.
7. Romao RL, Figueroa V, Salle JL, Koyle MA, Bägli DJ, Lorenzo AJ. Laparoscopic ureteral ligation (clipping): a novel, simple procedure for pediatric urinary incontinence due to ectopic ureters associated with non-functioning upper pole renal moieties. J Pediatr Urol 2014;10:1089-94.
8. Androulakakis PA, Stephanidis A, Antoniou A, Christophoridis C. Outcome of the distal ureteric stump after (hemi)nephrectomy and subtotal ureterectomy for reflux or obstruction. BJU Int 2001; 88:586-9.
9. Cain MP, Pope JC, Casale AJ, Adams MC, Keating MA, Rink RC. Natural history of refluxing distal ureteral stumps after nephrectomy and partial ureterectomy for vesicoureteral reflux. J Urol 1998; 160:1026-7.
10. Plaire JC, Pope JCt, Kropp BP, Adams MC, Keating MA, Rink RC, et al. Management of ectopic ureters: experience with the upper tract approach. J Urol 1997;158:1245-7.
11. Malik RD, Pariser JJ, Gundeti MS. Outcomes in pediatric robot-assisted laparoscopic heminephrectomy compared with contemporary open and laparoscopic series. J Endourol 2015;29:1346-52.
12. You D, Bang JK, Shim M, Ryu DS, Kim KS. Analysis of the late outcome of laparoscopic heminephrectomy in children with duplex kidneys. BJU Int 2010; 106:250-4.
13. Jitkarnka U, Tonvichien L. The outcome of ureterocele management at Queen Sirikit National Institue of Child Health. Thai J Urol 2005;26:12-8.
14. Olsen LH, Jørgensen TM. Robotically assisted retroperitoneoscopic heminephrectomy in children: initial clinical results. J Pediatr Urol 2005;1:101-4.
15. Escolino M, Riccipetitoni G, Yamataka A, Mushtaq I, Miyano G, Caione P, et al. Retroperitoneoscopic partial nephrectomy in children: a multicentric international comparative study between lateral versus prone approach. Surg Endos 2019;33:832-9.
16. Singhal S, Yadav B, Bayne C, Vellody R. Percutaneous transgluteal ureteral stump access: a novel approach to hybrid management of ureteral stump syndrome. Urology 2020;138:156-9.
17. Pereira J, Reis A, Castro R. [Ureteral stump empyema after heminephrectomy]. Acta medica portuguesa 2014;27:404.
18. Dénes FT, Danilovic A, Srougi M. Outcome of laparoscopic upper-pole nephrectomy in children with duplex systems. J Endourol 2007;21:162-8.

Original Article

Predictors of pathologic response to neoadjuvant chemotherapy in muscle-invasive bladder cancer

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Keywords:
Muscle-invasive bladder cancer, neoadjuvant chemotherapy, pathologic response, predictors, carboplatin

Abstract

Objective: To identify factors that could predict pathologic response to neoadjuvant (NAC) therapy in muscle invasive bladder cancer (MIBC) patients and report the impact of NAC on the risk of perioperative complications after radical cystectomy at our institution.

Materials and Methods: We reviewed the hospital database from January 2014 to March 2021 for MIBC patients who received NAC prior to radical cystectomy (RC). All patients were divided into a responder (pT ≤ T1) or non-responder group (> pT2). Data was analyzed to determine the factors associated with pathologic response to NAC. A subgroup analysis of the gemcitabine and carboplatin (GCb) regimens was also carried out.

Results: Out of the 50 patients who met the inclusion criteria, 13 (26%) were categorized as responders and 37 (74%) as non-responders. With regard to NAC variables, 12 patients (24%) received cisplatin-based NAC, and 38 patients (74%) received GCb. From the multivariate analysis, pretreatment hemoglobin (Hb) > 12 g/dl (OR 16.42, 95% CI 1.78-151.86, p = 0.01) and neutrophil-to-lymphocyte ratio (NLR) < 3 (OR 12.81, 95% CI 1.36-120.9, p = 0.03) were associated with significantly increased odds of pathologic response, while tumor size < 4 cm (OR 12, 95% CI 1.92-75.05, p = 0.008) was associated with significantly increased odds of pathologic response in the subgroup analysis.

Conclusions: Pretreatment Hb and NLR were independently associated with pathologic response to NAC. For MIBC patients who are cisplatin ineligible, GCb followed by RC may be the recommended treatment, particularly in those with tumors less than 4 cm in size. In addition, administering NAC prior to RC does not increase the risk of perioperative complications.

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Introduction

Muscle-invasive bladder cancer (MIBC) is an aggressive disease that has mortality rates far higher than non-muscle-invasive bladder cancer (NMIBC); approximately 85% of untreated MIBC patients died within 2 years.[1] Radical cystectomy (RC) and pelvic lymphadenectomy (PLND) were formerly the mainstay of treatment for MIBC patients but subsequently, the use of neoadjuvant chemotherapy (NAC) followed by RC and PLND has been supported by numerous randomized clinical trials and meta-analyses, which have found a 6% survival benefit at 10 years.[2-5] For this reason, the current treatment guidelines recommend NAC as a standard treatment for nonmetastatic MIBC.[6-8]

As a result of the Southwest Oncology Group (SWOG) 8710 trial, Grossmann et al. demonstrated significant improvement in pathologic complete response (pCR) (38% vs 15%; $p < 0.001$) and median overall survival (77 vs 46 months; $p = 0.05$) in patients treated with NAC compared to those treated with cystectomy alone.[2] The survival benefit of NAC was shown to be strongly associated with downstaging of the tumor to pCR.[2,9-13] Interestingly, patients treated with NAC which resulted in residual non-muscle invasive cancer including carcinoma in situ (CIS), pTa, and pT1 disease also showed no statistically significant difference in overall survival, compared to pCR patients.[10,11,13-15] Recently, there have been efforts to develop prognostic tools that allow the selection of patients likely to respond to NAC. Many predictive factors have been investigated, but none have been validated for routine use in clinical practice.[16]

Several chemotherapy regimens have been used for treatment of MIBC, most of which included a cisplatin-based regimen due to evidence of better outcome. Despite the effectiveness of cisplatin-based chemotherapy, its toxicity profile, especially severe renal toxicity, makes it unsuitable for patients with renal dysfunction. In addition, patients with TCC are often elderly, with frequent concomitant diseases, in particular, clinical or subclinical renal function impairment. A gemcitabine and carboplatin (GCb) combination regimen, which has a considerably lower toxicity profile, has been reported to play a potential role in cisplatin ineligible advanced bladder cancer patients in many studies.[17-23] However, in the neoadjuvant setting, there is only limited evidence from a few centers that supports the use of the GCb regimen in MIBC patients in whom cisplatin is unsuitable.[20,24-26] Our institution, King Chulalongkorn Memorial Hospital (KCMH), is one of the centers that also commonly uses GCb as alternative treatment in cisplatin-unsuitable patients. To date, there is no clear evidence to support the inferiority of a carboplatin-based regimen against a cisplatin-based one in a neoadjuvant setting.

Therefore, the objective of this study was to determine the clinicopathologic factors that could predict the pathologic response to NAC in order to improve the selection of patients who would benefit from chemotherapy prior to cystectomy and to evaluate a subgroup analysis of GCb regimen from our institution. Additionally, we aimed to report the impact of NAC on the risk of perioperative complications after RC at our institution.

Materials and Methods

Patients

The study was retrospective in design and we reviewed the records of all 60 consecutive patients treated with neoadjuvant chemotherapy before undergoing RC and bilateral pelvic lymphadenectomy at King Chulalongkorn Memorial Hospital from January 2014 to March 2021. Patients were included if they had MIBC (> T2) that was feasible for RC and were excluded if they had not completed at least two cycles of NAC, received preoperative radiotherapy for MIBC, or had predominant squamous or adenocarcinoma components or any small cell components. The study protocol was approved by the Institutional Review Board of Faculty of Medicine, Chulalongkorn University (IRB number 089/64)

Study measures, definitions, and outcomes

Demographic data including age, gender, body mass index (BMI), and underlying medical conditions were collected. Clinical data and parameters including smoking and alcohol drinking status, hemoglobin (Hb) and serum creatinine at first visit, radiological evidence of hydronephrosis, size of bladder tumor and neutrophil-to-lymphocyte ratio (NLR) were also collected. Histopathologic reviews of the transurethral resection of bladder tumor (TURBT) specimens and cystecto-

my specimens were completed by the pathologists at our institution. Clinical staging was based on TURBT and preoperative cross-sectional imaging including computed tomography (CT) imaging and magnetic resonance imaging (MRI).

At our institution, the main cisplatin-based NAC regimens that have been used for treating MIBC patients included gemcitabine and cisplatin (GCp), and cisplatin, methotrexate, and vinblastine (CMV). In addition to standard regimens, we also used gemcitabine and carboplatin (GCb) as a first-line treatment regimen in the patients who were unfit for cisplatin-based chemotherapy. The decision regarding NAC regimens was made solely by our oncologists in accordance with the need determined by the patient's clinical status. During NAC administration, chemotherapy toxicities were routinely monitored in the oncology outpatient clinic. Presence of any adverse events associated with the chemotherapy would usually lead to individual regimen adjustment, ranging from a decrease in NAC dosage to a change of regimen. The NAC variables included types of regimens, number of cycles, time from TURBT to NAC, and time from end of NAC to RC.

After the full therapeutic course, the chemotherapy response was evaluated with cross-sectional imaging, and subsequently, resectable cases underwent surgery. Intra- and post-operative variables were collected, specifically operative time, estimated blood loss (EBL), total blood transfusion, and anesthetic record. Perioperative complications were recorded for the first 30 days after surgery. All perioperative complications were classified in accordance with Clavien-Dindo system as either minor (grade < 2) or major (grade > 3A).[27]

All patients were divided into 2 groups based on final histopathologic findings at cystectomy: a responder group including those with a pathologically noninvasive downstaging or a pathologic partial response (pPR), defined as pTis/pTa/pT1 and those with pathologic complete response (pCR), defined as no residual tumor in cystectomy specimen (pT0) and a non-responder group, defined as > pT2. The primary outcome of interest was identification of predictive factors associated with pathologic downstaging and pathologic complete response to NAC. In addition, specific interpretation of the subgroup analysis of GCb regimen was carried out. Secondary outcome was focused on perioperative complications associated with RC after receiving NAC, as defined in accordance with the Clavien-Dindo system as described above.

Statistical analyses

Demographic and clinical data were collected and described for all included patients. Continuous variables are expressed as median (interquartile range: IQR) and percentage for categorical variables. Differences in continuous and categorical variables between two groups were assessed using a Wilcoxon rank sum test and Chi-square test or Fisher's exact test, respectively. Logistic regression was used to determine the factors associated with pathologic response to NAC. Multivariate models were developed by adjusting for covariates with $p < 0.1$ in univariate models and a stepwise backward LR to select the final model. All p-values reported are two-sided. Statistical significance was defined as $p < 0.05$. Stata version 15.1 (Stata Corp., College Station, Texas) was used for analysis.

Results

Patient demographics and clinical characteristics

During the study period, a total of 60 patients who received neoadjuvant chemotherapy before undergoing RC at our institution were included in the study. Of these, 50 patients (83.3%) fulfilled the inclusion and exclusion criteria of the study.

Baseline characteristics and pathologic features between the responder and non-responder groups are summarized in Table 1. The median age of the population was 69 years (IQR, 44-87 years), with the number of males predominating (64%). Of the 50 patients, 14 (28%) were cT2 disease, 25 (50%) had cT3 disease, and 11 (22%) had cT4 disease. Lymph node involvement (cN+) was found in 11 (22%) patients, and M1a disease in 4 (8%).

Of all 50 patients who received NAC prior to RC, 13 patients (26%) were grouped into responders and 37 patients (74%) were non-responders. In the responder group, 5 (10%) were pCR (pT0), and 8 (16%) were non-invasive downstaging or pPR (pTis/pTa/pT1). There were no significant differences in age, gender, ECOG performance status, clinical T stage, and histologic type between two groups. Conversely, there was a statistically significant difference in the presence of lymphovascular invasion (LVI) between the two groups, with none of the responder patients having LVI.

Table 1. Clinical characteristics and pathologic features stratified by treatment response

Characteristics	Total (N = 50)	Non-responder (N = 37)	Responder (N = 13)	P-value
Male, n (%)	32 (64)	24 (64.9)	8 (61.5)	0.83
Age, years mean (SD)	67.4 (9.8)	68.6 (9.5)	64 (10.2)	0.15
BMI (kg/m^2), mean (SD)	24 (4)	23.4 (3.9)	25.5 (4.3)	0.11
Smoker, n (%)	25 (50)	17 (46)	8 (61.5)	0.33
Alcohol drinking status, n (%)	22 (44)	15 (40.5)	7 (53.9)	0.41
Diabetes mellitus (DM), n (%)	12 (24)	10 (27)	2 (15.4)	0.40
Hypertension (HT), n (%)	35 (70)	26 (70.3)	9 (69.2)	0.94
Hb at first visit (g/dl, mean (SD)	10.7 (1.4)	10.6 (1.4)	11 (1.6)	0.36
ECOG performance status, n (%)				0.06
- 0	11 (22)	6 (16.2)	5 (38.5)	
- 1	38 (76)	31 (83.8)	7 (53.9)	
- 2	1 (2)	0(0)	1 (7.7)	
eGFR at first visit (ml/min/1.73 m^2), median (IQR)	66.6 (54-81.2)	65 (50.7-80)	77.4 (60.5-87.1)	0.21
Presence of hydronephrosis, n (%)	25 (50)	22 (59.5)	3 (23.1)	0.02
Histologic type (TURBT), n (%)				0.026
- Pure TCC	41 (82)	29 (78.4)	12 (92.3)	
- Others	9 (18)	8 (21.6)	1. (7.7)	
Clinical T stage at diagnosis, n (%)				0.37
- T2	14 (28)	9 (24.3)	5 (38.5)	
- T3	25 (50)	18 (48.7)	7 (53.9)	
- T4	11 (22)	10 (27)	1 (7.7)	
Tumor size (cm), median (IQR)	4.2 (3.5-5)	4.6 (3.9-5.7)	2.9 (2-3.8)	0.001
Grossly complete resection	12 (29.3)	5 (16.7)	7 (63.6)	0.003
NAC Regimens				0.16
- Gemcitabine / Carboplatin (GCb)	38 (74)	30 (81.1)	8 (61.5)	
- Cisplatin-based NAC (CMV, and GCp)	12 (24)	7 (18.9)	5 (38.5)	
Number of NAC cycles, mean (SD)	3.6 (1.1)	3.8 (1.1)	3.3 (0.9)	0.19
Time from TURBT to NAC (day), median (IQR)	34 (23-72)	31.5 (21-50)	50 (30-81)	0.10
Time from TURBT to RC (day), median (IQR)	165 (128-211)	154 (122-208)	168 (145-229)	0.57
Time from end of NAC to RC (day), median (IQR)	42 (32-61)	42.5 (32-62)	41 (32-58)	0.72
Presence of LVI, n (%)	22 (44)	22 (59.5)	0 (0)	<0.001
Positive surgical margin from RC specimen, n (%)	4 (8)	4 (10.8)	0 (0)	0.59
Neutrophil to lymphocyte ratio (NLR), median (IQR)	2.84 (2.04-3.68)	3.15 (2.11-4.6)	2.07 (2-2.6)	0.01
Operative time (min), median (IQR)	353 (307-417)	350 (300-410)	415 (322-450)	0.12
Total estimated blood loss (ml), median (IQR)	950 (700-1600)	900 (700-1600)	1100 (800-1350)	0.83

N = patient number, BMI = body mass index, Hb = hemoglobin, ECOG = Eastern Cooperative Oncology Group, NAC = neoadjuvant chemotherapy, RC = radical cystectomy, SD = standard deviation, IQR = interquartile range, TURBT = transurethral resection of bladder tumor, LVI = lymphovascular invasion

Regarding NAC variables, 12 patients (24%) received cisplatin-based NAC (GCp and CMV), and 38 patients (74%) received GCb. There were no significant differences in NAC regimens, number of NAC cycles, time from TURBT to NAC, and time from end of NAC to RC between two groups.

The pCR rates for the cisplatin-based NAC were 25% (3 of 12 patients) which were higher than GCb regimen (5.26%, 2 of 38 patients). The pPR rates for the cisplatin-based regimens and GCb regimen were 16.67% (2 of 12 patients) and 15.79% (6 of 38 patients), respectively. Positive surgical margins were reported in 4 patients (8%)

Table 2. Factor associated with pathologic response

	Univariate		Multivariate	
	OR (95% CI)	P-value	aOR (95% CI)	P-value
Male sex	0.87 (0.23-3.2)	0.83		
Age < 60 years	4 (0.93-17.25)	0.06		
Smoker, n (%)	1.88 (0.52-6.84)	0.34		
Alcoholic drinking status	1.71 (0.48-6.11)	0.41		
Presence of DM	0.49 (0.09-2.61)	0.4		
Presence of HT	0.95 (0.24-3.76)	0.94		
Histologic type: pure TCC	0.3 (0.03-2.69)	0.28		
Grossly complete resection	8.75 (1.84-41.61)	0.01		
Hb at first visit >12 g/dl	22.15 (2.58-189.95)	0.01	16.42 (1.78-151.86)	0.01
eGFR at baseline > 60 ml/min/1.73 m^2	2.03 (0.48-8.66)	0.34		
Absence of hydronephrosis	4.89 (1.15-20.79)	0.03		
Tumor size < 4 cm	4.98 (1.3-19.13)	0.02		
cT stage				
2	Ref			
3	0.7 (0.17-2.83)	0.62		
4	0.18 (0.02-1.84)	0.15		
GCb vs Cisplatin-based regimens	2.27 (0.58-8.86)	0.24		
Number of NAC cycle > 3	1.88 (0.52-6.84)	0.34		
Neutrophil to lymphocyte ratio (NLR) < 3	15.75 (1.85-134.02)	0.01	12.81 (1.36-120.9)	0.03

DM = diabetic mellitus, HT = hypertension, Hb = hemoglobin, eGFR = estimated glomerular filtration rate, GCb = gemcitabine and carboplatin, NAC = neoadjuvant chemotherapy, CI = confidence interval, OR = odds ratio, aOR = adjusted odds ratio

which were found only in GCb regimen group. Then, the rate of positive surgical margins in GCb regimen group was 10.53% (4 of 38 patients).

Factors associated with NAC response

We demonstrated factors associated with pathologic response to NAC on table 2, and noticed that grossly complete resection (OR 8.75, 95% CI 1.84-41.61, p = 0.01), absence of hydronephrosis (OR 4.89, 95% CI1.15-20.79, p = 0.03), tumor size < 4 cm (OR 4.98, 95% CI 1.3-19.13, p = 0.02), NLR < 3 (OR 15.75, 95% CI1.1.85-134.02, p = 0.01) as well as hemoglobin (Hb) at first visit > 12 g/dl (OR 22.15, 95% CI 2.58-189.95, p = 0.01) were associated with significantly increased odds of pathologic response (< pT2). These factors were submitted to the multivariate analysis which we found that Hb at first visit > 12 g/dl (OR 16.42, 95% CI 1.78-151.86, p = 0.01) and NLR < 3 (OR 12.81, 95% CI 1.36-120.9, p = 0.03) were the independent variables in the pathologic downstaging and complete response to NAC.

In subgroup analysis, the total number of patients who received GCb regimen were 38. Eight patients (21.1%) were responders, while 30 (78.9%) were non-responders. Table 3 summarizes the baseline characteristics and pathologic aspects of the subgroup population. Contrast to the first analysis, we found that tumor size less than 4 cm (OR 12, 95% CI 1.92-75.05, p = 0.008) was the only parameter that associated with significantly increased odds of pathologic response (< pT2) on multivariate analysis (Table 4).

Perioperative complications

Data of perioperative complications in patients treated with NAC followed by RC are shown in table 5 and table 6. Seventy-five perioperative complications occurred in 42 patients (84%). Most of perioperative complications were minor (74%). There were only 5 major complications (10%), none of which were classified as grade 4 or 5. Anemia requiring blood transfusion (n = 32) and renal insufficiency (n = 14) were the most common minor complications. The median operative

Table 3. Clinical characteristics and pathologic features of patients receiving GCb regimen

Characteristics	Total (N = 38)	Non-responder (N = 30)	Responder (N = 8)	P-value
Male, n (%)	24 (63.2)	19 (63.3)	5 (62.5)	0.97
Age, years mean (SD)	68.4 (9.5)	69.3 (9.6)	64.8 (8.6)	0.23
Smoker, n (%)	21 (55.3)	15 (50)	6 (75)	0.26
Alcoholic drinking status, n (%)	17 (44.7)	12 (40)	5 (62.5)	0.43
Diabetes mellitus, n (%)	10 (26.3)	9 (30)	1 (12.5)	0.65
Hypertension, n (%)	27 (71.1)	22 (73.3)	5 (62.5)	0.67
BMI, mean (SD)	23.9 (3.8)	23.5 (4.2)	25.2 (1.2)	0.25
Hb at first visit, mean (SD)	11.7 (2)	11.4 (2.1)	12.9 (0.9)	0.04
ECOG performance status, n (%)				0.20
- 0	8 (21.1)	5 (16.7)	3 (37.5)	
- 1	30 (79)	25 (83.3)	5 (62.5)	
- 2	0 (0)	0 (0)	0 (0)	
eGFR at first visit (ml/min/1.73 m^2), median (IQR)	68 (25.2)	66.6 (27)	73.5 (17)	0.50
Presence of hydronephrosis, n (%)	21 (55.3)	19 (63.3)	2 (25)	0.11
Histologic type (TURBT), n (%)				0.31
- Pure TCC	31 (81.6)	23 (76.7)	8 (100)	
- Others	7 (18.4)	7 (23.3)	0 (0)	
Clinical T stage at diagnosis, n (%)				0.23
- cT2	11 (29)	8 (26.7)	3 (37.5)	
- cT3	18 (47.4)	13 (43.3)	5 (62.5)	
- cT4	9 (23.7)	9 (30)	0 (0)	
Tumor size (cm), median (IQR)	4.4 (3.65-5.45)	4.7 (4-5.8)	2.6 (1.7-3.8)	0.004
Grossly complete resection, n (%)	7 (24.1)	4 (17.4)	3 (50)	0.13
Number of NAC cycles, mean (SD)	3.8 (1.1)	3.9 (1.2)	3.5 (0.9)	0.43
Time from TURBT to NAC (day), median (IQR)	34.5 (23.5-80)	31.5 (22.5-81.5)	53.5 (29.5-76.5)	0.35
Time from TURBT to RC (day), median (IQR)	169 (132-229)	169 (128-229)	169 (138.5-200)	0.72
Time from end of NAC to RC (day), median (IQR)	41 (28-56)	41 (28-62)	40.5 (30-49)	0.83
Presence of LVI, n (%)	20 (52.6)	20 (66.7)	0 (0)	0.001
Positive surgical margin from RC specimen, n (%)	4 (10.5)	4 (13.3)	0 (0)	0.64
Neutrophil to lymphocyte ratio (NLR), median (IQR)	2.9 (2.1-3.78)	3.1 (2.1-4.6)	2.3 (2-2.62)	0.12

N = patient number, BMI = body mass index, Hb = hemoglobin, ECOG = Eastern Cooperative Oncology Group, NAC = neoadjuvant chemotherapy, RC = radical cystectomy, SD = standard deviation, IQR = interquartile range, TURBT = transurethral resection of bladder tumor, LVI = lymphovascular invasion

time (IQR), median estimated blood loss (IQR), median time to start soft diet (IQR), and median length of postoperative hospital stay (IQR) were 353 (307-411) minutes, 950 (700-1,600) ml, 7 (6-8) days, and 9 (8-12) days respectively.

Discussion

The use of neoadjuvant cisplatin-based chemotherapy has been advocated for more than a decade since several prospective trials showed significant improvement in survival among MIBC patients compared with cystectomy alone.[2-5] Patients who meet a pCR after receiving NAC have excellent long-term overall survival as well as a pPR.[2,9-14] The results from our seven-year experiences revealed that pCR (25%) and pPR rates (16.67%) following cisplatin-based NAC were comparable to recent systematic reviews and meta-analyses.[28-30] For instance, according to the most recent meta-analysis, pCR was achieved in 16.6% (95% CI : 7.4-25.9%, I2 = 89.7%) patients and pPR was achieved in 14.6% (95% CI : 0.8-28.5%, I2 = 89.7%) patients.[28] Conversely, there was no systematic review or meta-analysis, but

Table 4. Factor associated with pathologic response in subgroup GCb regimen (N = 38)

Characteristics	Total (N=38)	Non-responder (N = 30)	Responder (N = 8)	P-value
Male sex	0.96 (0.19-4.84)	0.97		
Age < 60 years	5.4 (0.84-34.8)	0.08		
Smoker	3 (0.52-17.32)	0.22		
Alcoholic drinking status	2.5 (0.5-12.47)	0.26		
Presence of DM	0.33 (0.04-3.12)	0.34		
Presence of HT	0.61 (0.12-3.14)	0.55		
eGFR at baseline > 60 ml/min/1.73 m^2	4.67 (0.51-42.92)	0.17		
Absence of hydronephrosis	5.18 (0.89-30.25)	0.07		
Tumor size < 4 cm	19 (1.89-190.92)	0.004	12 (1.92-75.05)	0.008
Number of NAC cycle > 3	1.5 (0.31-7.19)	0.61		
Neutrophil to lymphocyte ratio (NLR) < 3	8 (0.87-73.26)	0.12		

GCb = gemcitabine and carboplatin, DM = diabetic mellitus, HT = hypertension, eGFR = estimated glomerular filtration rate, NAC = neoadjuvant chemotherapy, CI = confidence interval, OR = odds ratio, aOR = adjusted odds ratio

Table 5. Perioperative complications classified by Clavien Classification (N = 50*)

Clavien-Dindo classification	N (%)
No complication	8 (16)
Complication	42 (84)
- Grade 1	6 (12)
- Grade 2	31 (62)
- Grade 3a	2 (4)
- Grade 3b	3 (6)
- Grade 4a	0 (0)
- Grade 4b	0 (0)
- Grade 5	0 (0)

*Highest grade of complication was used in patient who had more than one complication

only a few studies, that reported efficacies of carboplatin-based NAC. We found that our patients receiving GCb regimen had lower pCR (5.26%) and pPR rates (15.79%) compared to previously published studies[24-26], which revealed pCR and pPR rates ranging from 15-24.1% and 23.3-38%, respectively.[24-26] The difference could be caused by many reasons. Firstly, the proportion of locally advanced disease, including 72% of high T-stage (cT3-4), 22% of node involvement (cN+), and 8% of M1a disease, in our study was slightly higher than other published series. These might be the result of our early practice that most patients with organ-confined disease (cT2) tended to undergo immediate cystectomy rather than NAC prior to RC. Secondly, in this study, there was no specific criterion for determining who was cisplatin-unfit. In fact, renal insufficiency is a major issue that prevents many patients from receiving cisplatin therapy. However, considering our patients' mean creatinine clearance of 66.59 ml/min in the carboplatin group, it seemed that some of them would be better suited to cisplatin-based regimens. Thirdly, due to the small number of trials conducted so far, the response rates from previous studies that we compared may be a bit imprecise. Finally, we noticed that our patients in the carboplatin group had a slightly longer mean interval time from the last cycle of NAC to RC (47.4 days) when compared to the Murasawa et al trial[26] (< 30 days). However, the optimal time for RC following NAC that impacts NAC responsiveness is still unknown.

Recently, the literatures on predictive factors of NAC response in MIBC patients were thoroughly reviewed by European Association of Urology (EAU).[16] All aspects including disease-related factors, patient-related factors, and pathological factors were explored. Data from some literatures showed a significant association between pathologic response and specific parameters. For example, small series by Pokuri et al. demonstrated a positive correlation between pCR and the presence of pure urothelial carcinoma[31]; and Boeri at al. found that cigarette smoking was significantly associated with adverse pathological response to cisplatin-based NAC.[32] However, they finally concluded that there are currently no established tools in clinical practice for predicting pathologic

Table 6. Detail of perioperative complications

Perioperative complications, no. (%)	Minor complication (Clavien-Dindo grade < 2)	Major complication (Clavien-Dindo grade > 3A)
Wound complications	2 (2.7)	1 (1.3)
Pulmonary complications	2 (2.7)	0 (0)
Renal insufficiency	14 (18.7)	0 (0)
Urinary leakage	2 (2.7)	0 (0)
Neurological complications	3 (4)	0 (0)
Anemia	32 (42.7)	1 (1.3)
Deep vein thrombosis	0 (0)	0 (0)
Infection	4 (5.3)	0 (0)
Prolong bowel ileus	4 (5.3)	0 (0)
Bowel injury	4 (5.3)	1 (1.3)
Gut obstruction	1 (1.3)	0 (0)
Lymphocele	2 (2.7)	2 (2.7)

*Highest grade of complication was used in patient who had more than one complication

response to NAC. In our study, although, we discovered four parameters linked to pathologic downstaging in univariable analysis, there were only two after multivariable adjustment, which were Hb at first visit > 12 g/dl (OR 16.42, 95%CI 1.78-151.86, p = 0.01) and NLR < 3 (OR 12.81, 95%CI 1.36-120.9, p = 0.03).

NLR is the basic blood-based marker that has been thought to represent both systemic inflammation and antitumor immune response. An elevated NLR may indicate that the host is unable to develop a targeted immune response against tumor cells, and is related to a poor prognosis.[33] Our findings on the pre-neoadjuvant chemotherapy NLR were perfectly comparable to those from a larger retrospective study recently published by Black et al.[34] which showed that NLR > 3 was the only significant risk factor associated with a reduced response to NAC in multivariable analysis (OR 0.43, 95% CI 0.22-0.82, p = 0.01). Meanwhile, anemia and low hemoglobin (Hb) levels are highly typical in patients with malignant tumors. Furthermore, anemia has been linked to a poor outcome in a variety of malignancies.[35] According to a recent meta-analysis, preoperative anemia and low Hb levels in MIBC patients undergoing RC are significantly associated with earlier recurrence and even shorter survival.[36] Our study not only supports these findings but it's also the first one to show a correlation between Hb and pathologic response. Tumor hypoxia, which promotes tumor growth by stimulating angiogenesis and has been linked with resistance to chemotherapy, is one of the hypotheses that could explain this relevance.[35,36] Another interesting result from our study was that NAC regimens had no effect on the pathologic response, regardless of whether they were cisplatin-based or not (Table 2). This result may be caused by many limitations which are discussed later.

Although a few cohort studies reported the utility of GCb in its role as NAC prior to RC, the predicting factors for NAC response have yet to be thoroughly investigated. In our subgroup analysis focusing on GCb regimen, it appeared that tumor size smaller than 4 cm (OR 12, 95%CI 1.92-75.05, p = 0.008) was the only factor related to pathological response. Our median tumor size was 4.4 cm, which was comparable to the larger study from Murasawa et al (4.3 cm). According to the American Urological Association (AUA) guideline[37], tumor size is an essential determinant in the risk stratification to select subsequent management and a follow-up strategy in NMIBC. On the other hand, the usefulness of tumor size in MIBC was questionable. It's likely to be used only in bladder-sparing treatments such as trimodal therapy. We wish that our results could be adapted for use in MIBC patients who are cisplatin-ineligible, and that tumor size will be a promising predictive factor in the future for selecting patients who should be treated with chemotherapy before RC.

Earlier, Boonnam et al. has published a single-center retrospective study of perioperative outcomes in bladder cancer underwent RC at KCMH between 2003 and 2013.[38] Almost all of the 144 patients in their study underwent immediate RC except one patient who had NAC and three who received radiotherapy before RC. Their rates of major complications were slightly higher than ours (17.4% vs 10%). Operative outcome variables including median operative time, median estimated blood loss, and time to start soft diet from their study were 340 minutes, 1,700 ml, and 8 days, respectively. In comparison to our results, it appears to be superior to theirs. Despite the fact that the two trials differ in many aspects, we may presume that administering NAC before RC does not increase perioperative complications.

Our study has several limitations. The fact that it is a single-institution cohort with a retrospective design puts it at a high risk of bias. In addition, our study's sample size was relatively modest, and the population in our series with a high proportion of locally advanced disease, as described earlier, might not represent ideal candidates for NAC treatment prior to RC. Furthermore, many factors such as the patients' age, renal function, performance status, comorbidities, and oncologist's experience may all impact the decision to use the NAC regimen, which is solely determined by our oncologists. As a result, it appears that selection bias is unavoidable. Despite these limitations, the strength of our study is that we reported a real-world practice series that differed from the typically enrolled patients in the clinical trials. Moreover, it is worth noting that our series is one of a few published studies of carboplatin-base NAC in MIBC patients that have been reported so far.

Conclusion

Pretreatment Hb and NLR were independently associated with pathologic response to NAC. For this reason, they have been determined as a prognostic marker in MIBC patient receiving NAC prior to RC. Furthermore, GCb followed by RC may be the standard treatment for MIBC patients who are unfit for cisplatin-based chemotherapy, particularly in those with tumors less than 4 cm in size. Finally, administering NAC prior to RC does not increase the risk of perioperative complications.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Prout GR, Marshall VF. The prognosis with untreated bladder tumors. Cancer 1956;9:551-8.
2. Grossman HB, Natale RB, Tangen CM, Speights VO, Vogelzang NJ, Trump DL, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med 2003;349:859-66.
3. Winquist E, Kirchner TS, Segal R, Chin J, Lukka H. Neoadjuvant chemotherapy for transitional cell carcinoma of the bladder: a systematic review and meta-analysis. J Urol 2004;171:561-9.
4. Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data advanced bladder cancer (ABC) meta-analysis collaboration. Eur Urol 2005;48:202-5;discussion 5-6.
5. Griffiths G, Hall R, Sylvester R, Raghavan D, Parmar MK. International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: long-term results of the BA06 30894 trial. J Clin Oncol 2011;29:2171-7.
6. Chang SS, Bochner BH, Chou R, Dreicer R, Kamat AM, Lerner SP, et al. Treatment of Non-Metastatic Muscle-Invasive Bladder Cancer: AUA/ASCO/ASTRO/SUO Guideline. J Urol 2017;198:552-9.
7. Witjes JA, Bruins HM, Cathomas R, Compérat EM, Cowan NC, Gakis G, et al. European Association of Urology Guidelines on muscle-invasive and metastatic bladder cancer: summary of the 2020 guidelines. Eur Urol 2021;79:82-104.
8. Network NCC. NCCN clinical practice guidelines in oncology: bladder cancer, version 4.2021. 2021.
9. Splinter TA, Scher HI, Denis L, Bukowski R, Simon S, Klimberg I, et al. The prognostic value of the pathological response to combination chemotherapy before cystectomy in patients with invasive bladder cancer. European Organization for Research on Treatment of Cancer--Genitourinary Group. J Urol 1992;147:606-8.
10. Sonpavde G, Goldman BH, Speights VO, Lerner SP, Wood DP, Vogelzang NJ, et al. Quality of pathologic response and surgery correlate with survival for patients with completely resected bladder cancer after neoadjuvant chemotherapy. Cancer 2009;115:4104-9.
11. Rosenblatt R, Sherif A, Rintala E, Wahlqvist R, Ullén A, Nilsson S, et al. Pathologic downstaging is a surrogate marker for efficacy and increased survival following neoadjuvant chemotherapy and

radical cystectomy for muscle-invasive urothelial bladder cancer. Eur Urol 2012;61:1229-38.
12. Petrelli F, Coinu A, Cabiddu M, Ghilardi M, Vavassori I, Barni S. Correlation of pathologic complete response with survival after neoadjuvant chemotherapy in bladder cancer treated with cystectomy: a meta-analysis. Eur Urol 2014;65:350-7.
13. Waingankar N, Jia R, Marqueen KE, Audenet F, Sfakianos JP, Mehrazin R, et al. The impact of pathologic response to neoadjuvant chemotherapy on conditional survival among patients with muscle-invasive bladder cancer. Urol Oncol 2019;37:572.e21-8.
14. Pearce SM, Ashrafi A, Winter M, Ghodoussipour S, Zainfeld D, Gill I, et al. Predictors of pathologic response after radical cystectomy for muscle invasive bladder cancer: A population-based analysis. J Clin Oncol 2018;36:503.
15. Martini A, Jia R, Ferket BS, Waingankar N, Plimack ER, Crabb SJ, et al. Tumor downstaging as an intermediate endpoint to assess the activity of neoadjuvant systemic therapy in patients with muscle-invasive bladder cancer. Cancer 2019;125:3155-63.
16. Motterle G, Andrews JR, Morlacco A, Karnes RJ. Predicting response to neoadjuvant chemotherapy in bladder cancer. Eur Urol Focus 2020;6:642-9.
17. Shannon C, Crombie C, Brooks A, Lau H, Drummond M, Gurney H. Carboplatin and gemcitabine in metastatic transitional cell carcinoma of the urothelium: effective treatment of patients with poor prognostic features. Ann Oncol 2001;12:947-52.
18. Nogué-Aliguer M, Carles J, Arrivi A, Juan O, Alonso L, Font A, et al. Gemcitabine and carboplatin in advanced transitional cell carcinoma of the urinary tract: an alternative therapy. Cancer 2003;97:2180-6.
19. Park JH, Lee SW, Kim HS, Kang SG, Ko YH, Kim ST, et al. Combination of gemcitabine and carboplatin as first line treatment in elderly patients or those unfit for cisplatin-based chemotherapy with advanced transitional cell carcinoma of the urinary tract. Cancer Chemother Pharmacol 2013;71:1033-9.
20. Dogliotti L, Cartenì G, Siena S, Bertetto O, Martoni A, Bono A, et al. Gemcitabine plus cisplatin versus gemcitabine plus carboplatin as first-line chemotherapy in advanced transitional cell carcinoma of the urothelium: results of a randomized phase 2 trial. Eur Urol 2007;52:134-41.
21. Bellmunt J, de Wit R, Albanell J, Baselga J. A feasibility study of carboplatin with fixed dose of gemcitabine in "unfit" patients with advanced bladder cancer. Eur J Cancer 2001;37:2212-5.
22. Linardou H, Aravantinos G, Efstathiou E, Kalofonos C, Anagnostopoulos A, Deliveliotis C, et al. Gemcitabine and carboplatin combination as first-line treatment in elderly patients and those unfit for cisplatin-based chemotherapy with advanced bladder carcinoma: phase II study of the Hellenic Co-operative Oncology Group. Urology 2004;64:479-84.
23. Ryan Pritchard E, Waddell JA, Solimando DA, Jr. Gemcitabine and carboplatin (renally dosed) regimen for bladder cancer. Hosp Pharm 2015;50:103-7.
24. Iwasaki K, Obara W, Kato Y, Takata R, Tanji S, Fujioka T. Neoadjuvant gemcitabine plus carboplatin for locally advanced bladder cancer. Jpn J Clin Oncol 2013;43:193-9.
25. Koie T, Ohyama C, Hashimoto Y, Hatakeyama S, Yamamoto H, Yoneyama T, et al. Efficacies and safety of neoadjuvant gemcitabine plus carboplatin followed by immediate cystectomy in patients with muscle-invasive bladder cancer, including those unfit for cisplatin: a prospective single-arm study. Int J Clin Oncol 2013;18:724-30.
26. Murasawa H, Koie T, Ohyama C, Yamamoto H, Imai A, Hatakeyama S, et al. The utility of neoadjuvant gemcitabine plus carboplatin followed by immediate radical cystectomy in patients with muscle-invasive bladder cancer who are ineligible for cisplatin-based chemotherapy. Int J Clin Oncol 2017;22:159-65.
27. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205-13.
28. Liu W, Tian J, Zhang S, Yang E, Shen H, Li F, et al. The utilization status of neoadjuvant chemotherapy in muscle-invasive bladder cancer: a systematic review and meta-analysis. Minerva Urol Nephrol 2021;7:144-53.
29. Pignot G, Houédé N, Roumiguié M, Audenet F, Brunelle S, Colin P, et al. [ypT0N0 after neoadjuvant chemotherapy and cystectomy for muscle-invasive bladder cancer: Incidence and prognosis. A review from the Bladder group of the French Committee of Oncology]. Prog Urol 2018;28:567-74.
30. Yin M, Joshi M, Meijer RP, Glantz M, Holder S, Harvey HA, et al. Neoadjuvant chemotherapy for muscle-invasive bladder cancer: a systematic review and two-step meta-analysis. Oncologist 2016;21:708-15.
31. Pokuri VK, Syed JR, Yang Z, Field EP, Cyriac S, Pili R, et al. Predictors of complete pathologic response (pt0) to neoadjuvant chemotherapy in muscle-invasive bladder carcinoma. Clin Genitourin Cancer 2016;14:e59-65.
32. Boeri L, Soligo M, Frank I, Boorjian SA, Thompson RH, Tollefson M, et al. Cigarette smoking is associated with adverse pathological response and

increased disease recurrence amongst patients with muscle-invasive bladder cancer treated with cisplatin-based neoadjuvant chemotherapy and radical cystectomy: a single-centre experience. BJU Int 2019;123:1011-9.
33. Buisan O, Orsola A, Areal J, Font A, Oliveira M, Martinez R, et al. Low pretreatment neutrophil-to-lymphocyte ratio predicts for good outcomes in patients receiving neoadjuvant chemotherapy before radical cystectomy for muscle invasive bladder cancer. Clin Genitourin Cancer 2017;15:145-51.e2.
34. Black AJ, Zargar H, Zargar-Shoshtari K, Fairey AS, Mertens LS, Dinney CP, et al. The prognostic value of the neutrophil-to-lymphocyte ratio in patients with muscle-invasive bladder cancer treated with neoadjuvant chemotherapy and radical cystectomy. Urol Oncol 2020;38:3.e17-3.e27.
35. Knight K, Wade S, Balducci L. Prevalence and outcomes of anemia in cancer: a systematic review of the literature. Am J Med 2004;116:11-26s.
36. Xia L, Guzzo TJ. Preoperative anemia and low hemoglobin level are associated with worse clinical outcomes in patients with bladder cancer undergoing radical cystectomy: a meta-analysis. Clin Genitourin Cancer 2017;15:263-72.e4.
37. Chang SS, Boorjian SA, Chou R, Clark PE, Daneshmand S, Konety BR, et al. Diagnosis and treatment of non-muscle invasive bladder cancer: AUA/SUO Guideline. J Urol 2016;196:1021-9.
38. Boonnam S, Panumatrassamee K, Opanuraks J, Santi-ngamkun A, Tantiwongse K, Ratchanon S, et al. Perioperative outcomes of open radical cystectomy in bladder carcinoma: King Chulalongkorn Memorial Hospital experiences. Chula Med J 2016;60:1-12.

Original Article

Progression time of de novo metastases in relation to castration resistant prostate cancer at a tertiary care hospital in Southern Thailand

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Keywords:
Metastasis prostate cancer, androgen deprivation therapy, orchiectomy, castration-resistant prostate cancer, high volume metastatic prostate cancer

Abstract

Objective: Androgen deprivation therapy (ADT) is often the treatment of choice in metastatic prostate cancer patients. However, there is currently an insufficiency of biomarker-related data that can be used in order to predict how the disease would respond to ADT. In this study we evaluated the clinical response to ADT, including factors which are affecting the progression of the disease into castration-resistant prostate cancer (CRPC) in patients with de novo metastatic prostate cancer.

Materials and Methods: This retrospective study incorporated patients with metastatic prostate cancer who received ADT at our center from January 2008 to December 2019. Baseline characteristics, mode of ADT, prostate-specific antigen (PSA), blood chemistry, Gleason score (GS) grade group, location, and the number of metastases were analyzed. The risk factors affecting the progression of the disease were identified.

Results: Data from 125 patients were included in the study. One hundred patients (80%) were classified as suffering from high volume metastatic prostate cancer and six patients (6%) with visceral metastasis. Baseline PSA in high volume and low volume metastatic prostate cancer were defined as 500 ng/ml and 215.1 ng/ml respectively. Eighty-one patients (64.8%) received a gonadotrophin-releasing hormone (GnRH) agonist while 42 patients (33.6%) underwent bilateral orchiectomy. Time to CRPC in high and low volume metastasis was 12 months and 23 months respectively. Patients with Alkaline Phosphatase (ALP) ≥350 U/L had 8.5 months to CRPC while patients with ALP <350 U/L had 15 months. High GS grade group (3-5), short time to PSA nadir (<6 months), PSA nadir level (≥ 2 ng/ml), and serum ALP ≥350 U/L were independent factors associated with shorter time to CRPC.

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Conclusion: The clinical management of metastatic prostate cancer is challenging; the main aims of treatment are to prolong overall survival whilst maintaining quality of life. Patients with aggressive tumors, high volume metastasis, short time to nadir (TTN), high PSA nadir level, and high ALP level were independent factors associated with shorter time to CRPC.

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Introduction

Prostate cancer is the most common urologic cancer. The estimated incidence of prostate cancer in Thailand is 7.2 per 100,000 population and the mortality rate is 3.7 per 100 000 with a 5-year prevalence of 14.9%.[1] The most common organ metastasis is to the bones.[2] Patients with de novo metastatic disease at presentation have a poorer prognosis compared with patients who relapse after local therapy. The main treatment for patients with de novo metastatic prostate cancer is androgen deprivation therapy (ADT). Treatment aims to inhibit and delay disease progression into Castration-resistant Prostate Cancer (CRPC); a condition that is resistant to hormone inhibition therapy and is associated with poor prognosis and survival rates.[3] Currently, upfront treatment with chemotherapy and novel androgen receptor agents is approved for high volume/risks metastatic prostate cancer.[4-6] However, upfront treatment is not reimbursable in some countries and monotherapy with ADT is the mainstay treatment for those patients. There are several risk factors for the progression to CRPC that have been identified including: serum hemoglobin (Hb) levels, serum alkaline phosphatase (ALP), Gleason grade group, the prostate-specific antigen (PSA) nadir level, the time to PSA nadir (TTN), the neutrophil to lymphocyte ratio (NLR) and the platelet to lymphocyte ratio (PLR) ≥150.[7-12]

Therefore, the primary goal of this study is to explore the time duration of disease progression into CRPC, in de novo metastatic prostate cancer patients, post ADT treatment. A secondary aim of this study is to identify risk factors affecting such progression.

Materials and Methods

Study population

This is a retrospective observational study. The patients who were diagnosed with de novo metastatic prostate cancer in our center from January 2008 to December 2019, who received ADT, were retrieved from computer-based medical records. Patient baseline characteristics included: age, body mass index (BMI), and Eastern Cooperative Oncology Group (ECOG) score, mode of ADT, serum PSA level, time to PSA nadir, location and number of bone metastases, pathological report and Gleason (GS) grade group, serum hemoglobin, serum ALP, serum albumin, neutrophil count, lymphocyte count, and platelet count. High-volume disease was defined as the presence of visceral metastases or ≥ 4 bone lesions with ≥ 1 beyond the vertebral bodies and pelvis in accordance with CHAARTED Trials.[4]

The exclusion criteria were: patients who underwent local controlling treatment, both radical prostatectomy and radiation therapy or had previous treatment with the chemotherapeutic agents Enzalutamide, and Abiraterone. In addition, patients with no observational investigation evidence including bone scan and/or computed tomography (CT) scan and/or magnetic resonance imaging (MRI) abdomen and pelvis and/or chest radiographic results were excluded. The patients who received chemo-hormonal therapy, ADT plus docetaxel, were also excluded from the study.

Time to CRPC was defined as the time until documented clinical progression or serologic progression with a testosterone level of less than 50 ng/dl.[6] The time to clinical progression was defined as the time lapse until progression to bone metastases and progression according to RECIST, version 1.0.[12] Serologic progression was defined as an increase in the PSA level of more than 50% above the nadir, reached after the initiation of ADT, with two consecutive increases at least 2 weeks apart. The date of a first recorded increase of more than 50% above the nadir was deemed the date of progression. If the nadir level was less than 2 ng/ml, then a minimum increase of more than 2 ng/ml was required.[6]

The institution ethics committee approved the observation protocol and the collection of clinical data for research purposes (Project Number REC.63-193-10-1).

Statistical analyses

Continuous variables are reported as mean±SD or Median (IQR). Discrete variables are presented as number (percentage). The primary endpoint was the time to CRPC of de novo metastatic prostate cancer patients and the secondary endpoint was the risk factors affecting the progression.

CRPC timing was analyzed using the Kaplan-Meier curve and a comparison between the two groups by log-rank test. Finding of risk factors was examined using the Cox proportional hazards model.

Cox proportional hazards regression was used to estimate hazard ratios (HRs) with a 95% confidence interval (CI). Variables associated with $p < 0.2$ in univariate analysis were selected for multivariate analysis. $P < 0.05$ were considered statistically significant. Analyses were performed using the R program version 3.6.1.

Results

Demographic data

Patient characteristics are shown in Table 1, with a total of 125 cases of de novo metastatic prostate cancer patients who received monotherapy treatment with ADT being included in the analysis. The mean age was 69.7 years. Twenty-five patients (20%) were classified as having low volume metastasis while 100 patients (80%) had high volume metastasis. PSA levels in the high and low volume metastasis groups were 500 ng/ml and 215.1 ng/ml respectively. In low volume metastasis patients, 7 (28%) had a GS grade group 1-2, and 18 (72%) a GS grade group 3-5. In the high volume metastasis patients, there were 19 patients (19%) and 81 patients (81%) in GS grade groups 1-2 and 3-5 respectively. Eighty-one patients (64.8%) received a Gonadotrophin-releasing hormone (GnRH) agonist while 42 patients (33.6%) underwent bilateral orchiectomy. Six patients (6%) had visceral metastasis. Twenty-three patients received chemo-hormonal therapy.

Outcomes

The factors related to duration to CRPC are shown in Table 2. Patients in the high-volume cohort had time to CRPC of 12 months compared to 23 months in the low volume cohort ($p < 0.001$)

Table 1. Patient characteristics

	Total N = 125	High volume n = 100	Low volume n = 25	P-value
Age at diagnosis years (SD)	69.7±8.9	69.3±9.0	71.5±8.3	0.255
Body weight (kg) (IQR)	61 (52.0,67.0)	61 (50.0,67.0)	60 (55.0,67.0)	0.491
Height (cm) (SD)	163.7±6.8	163.6±6.9	164±6.6	0.820
BMI (kg/m^2) (IQR)	22.5±3.7	22.3±3.9	22.9±3.0	0.510
ECOG n (%)				0.209
0	83 (66.4)	63 (63.0)	20 (80.0)	
1	32 (25.6)	29 (29.0)	3 (12.0)	
2	10 (8.0)	8 (8.0)	2 (8.0)	
Initial PSA (ng/ml) (IQR)	500 (208.5, 625.0)	500 (304.6, 737.4)	215.1 (78.8, 377.1)	< 0.001
GS grade group n (%)				0.474
1-2	8 (6.4)	19 (19.0)	7 (28.0)	
3-5	18 (14.4)	81 (81.0)	18 (72.0)	
Mode of ADT n (%)				
GnRH agonist	81 (64.8)	63 (63.0)	18 (72.0)	0.543
GnRH antagonist	2 (1.6)	2 (2.0)	0 (0)	1.000
Orchiectomy	42 (33.6)	35 (35.0)	7 (28.0)	0.652
Visceral metastasis n (%)				0.727
Lungs	5 (4.0)	5 (5.0)	0	
Liver	1 (0.8)	1 (1.0)	0	

SD = standard deviation, BMI = body mass index, IQR = interquartile range, ECOG = Eastern Cooperative Oncology Group performance status, GS = Gleason scores, ADT = androgen deprivation therapy, GnRH = Gonadotrophin-releasing hormone

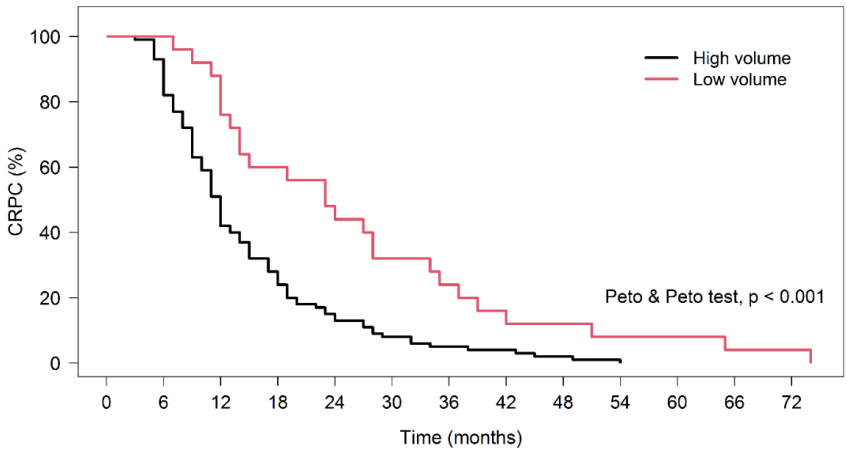

Figure 1. Kaplan-Meier curve of castration-resistant prostate cancer by disease burden

Table 2. Time to CRPC (months) in de novo metastatic prostate cancer patients

Factors	n	Time to CRPC Median (IQR)	P-value
Disease burden			< 0.001
High volume	100	12 (8.0,18.)	
Low volume	25	23 (13.0,35.0)	
GS grade group			0.026
1-2	26	17 (11.2,28.0)	
3-5	99	12 (8.0,19.0)	
Time to PSA nadir			< 0.001
< 6 months	69	7 (6.0,9.0)	
≥ 6 months	86	17 (12.0,27.0)	
Serum Hb			0.549
≥ 12 g/dl	71	12 (8.5,21.5)	
> 12 g/dl	54	12.5 (9.0,21.5)	
PSA nadir level			0.024
< 0.2 ng/ml	8	19.5 (14.2,39.8)	
≥ 0.2 ng/ml	117	12 (9.2,20.0)	
Serum Alb			0.174
≥ 4 g/dl	40	12 (7.0,20.8)	
> 4 g/dl	30	15 (10.2,31.0)	
Serum ALP			0.002
< 350 U/L	45	15 (11.0,32.0)	
≥ 350 U/L	18	8.5 (6.2,12.8)	
NLR			0.584
< 3	68	12 (8.8,22.2)	
≥ 3	57	12 (9.0,19.0)	
PLR			0.885
< 150	56	12 (9.0,19.2)	
≥ 150	69	12 (9.0,23.0)	

GS = Gleason score, PSA = prostate-specific antigen, Hb = hemoglobin, Alb = albumin, ALP = alkaline phosphatase

(Figure 1). The duration in which PSA declined to nadir level was 7 months in the high-volume metastasis group in comparison to 11 months in the low volume metastasis group (p-value =0.011) (Figure 2). Patients with a low GS grade group score (1-2), low serum ALP (< 350 U/L), and/or lower PSA nadir level (< 0.2 ng/ml) had longer time to CRPC. The factors that did not affect the progression of the disease were serum albumin, NLR, and PLR. Time to PSA nadir and time to CRPC in the chemohormanal group were 7 months and 12 months respectively (Figure 5).

The univariate analysis indicated that factors affecting the progression to CRPC were TTN < 6 months (HR 0.15(95% CI 0.09, 0.23), p < 0.001), PSA nadir level ≥ 0.2 ng/ml (HR 2.14 (95% CI 1.02, 4.48), p = 0.025), serum albumin (Alb) level > 4 g/dl (HR 0.74 (95% CI 0.46, 1.2), p = 0.219), and ALP level ≥ 350 U/L (HR 2.83 (95% CI 1.56, 5.1), p = 0.001).

In multivariate analysis, patients with time to PSA nadir < 6 months, high-grade group score (3-4), PSA nadir < 0.2 ng/ml, and high serum ALP ≥ 350 U/L were the independent factors associated with short time progression into CRPC status (Table 3).

When considering factors affecting the progression to CRPC, it was found that the patients with high volume metastatic disease with TTN < 6 months had the shortest time duration with regard to the development of CRPC. This was followed by the patients in the high volume metastatic disease group, with time to PSA nadir level ≥ 6 months and low volume metastatic disease with TTN ≥ 6 months, as shown in Figure 3.

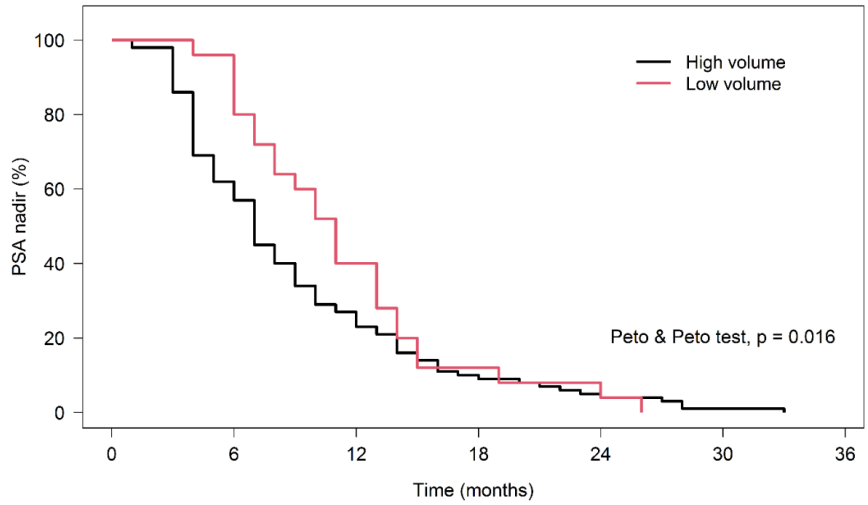

Figure 2. Kaplan-Meier curve of time to Prostatic specific antigen nadir level by disease burden

Table 3. Univariate and multivariate analysis of risk factors affecting the progression to CRPC

	Univariate analysis		Multivariate analysis	
	HR (95% Cl)	P-value	HR (95%Cl)	P-value
GS grade group	1	0.075	1	0.038
1-2	1.47		2.013	
3-5	0.95-2.27		1.04-3.90	
Time to PSA nadir	1	< 0.001	1	< 0.001
< 6 months	0.15		0.053	
≥ 6 months	0.09-0.23		0.02-0.13	
PSA nadir level	1	0.025	1	0.02
< 0.2 ng/ml	2.14		4.487	
≥ 0.2 ng/ml	1.02-4.48		1.27-15.85	
Serum Alb	1	0.219	-	-
≥ 4 g/dl	0.74			
> 4 g/dl	0.46-1.20			
Serum ALP	1	0.001	1	0.002
< 350 U/L	2.83		2.646	
≥ 350 U/L	1.56-5.10		1.42-4.93	

GS = Gleason score, PSA = prostate-specific antigen, Hb = hemoglobin, Alb = albumin, ALP = alkaline phosphatase

However, due to the demographic data of the low volume metastasis disease with TTN < 6 months group, there is only 1 person, therefore it is not possible to find a relationship in the graph. Furthermore, when considering the factors of the GS grade group together with disease burden (Figure 4), it was found that high volume metastatic disease with GS grade group 3-5 resulted in the shortest time to development of CRPC, followed by the high-volume metastatic group with GS grade group 1-2, low volume metastatic disease with Gleason grade group 3-5, and low volume metastatic disease with Gleason grade group 1-2.

Time to CRPC in the low volume, high volume, and high-volume metastasis groups that received chemohormonal therapy was 25, 12, and 12 months respectively (Figure 5). The median time from ADT to chemotherapy was 2.78 weeks.

Discussion

Prostate cancer is one of the most common malignancies in males. Treatment in metastatic prostate cancer aims to prolong overall survival whilst preserving quality of life. For decades, the standard of care (SOC) for metastatic hormone-sensitive prostate cancer (mHSPC) was ADT.[7]

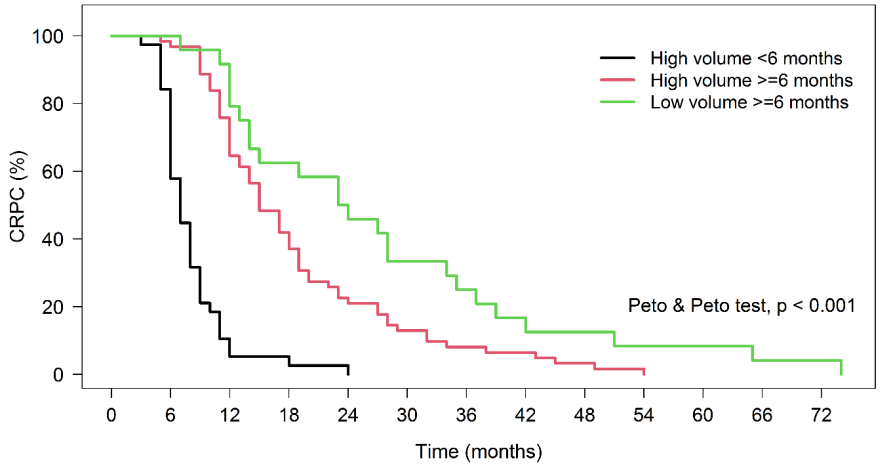

Figure 3. Kaplan-Meier curve of castration-resistant prostate cancer by disease burden and time to prostatic specific antigen nadir level

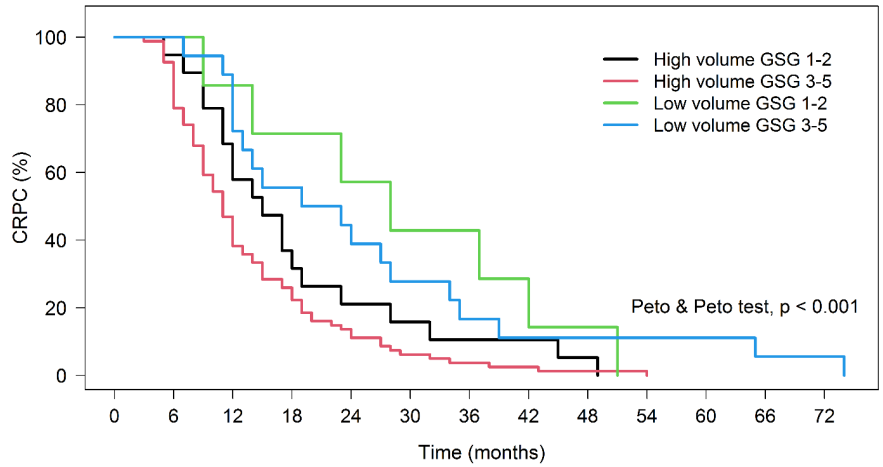

Figure 4. Kaplan-Meier curve of castration-resistant prostate cancer by disease burden and Gleason grade groups

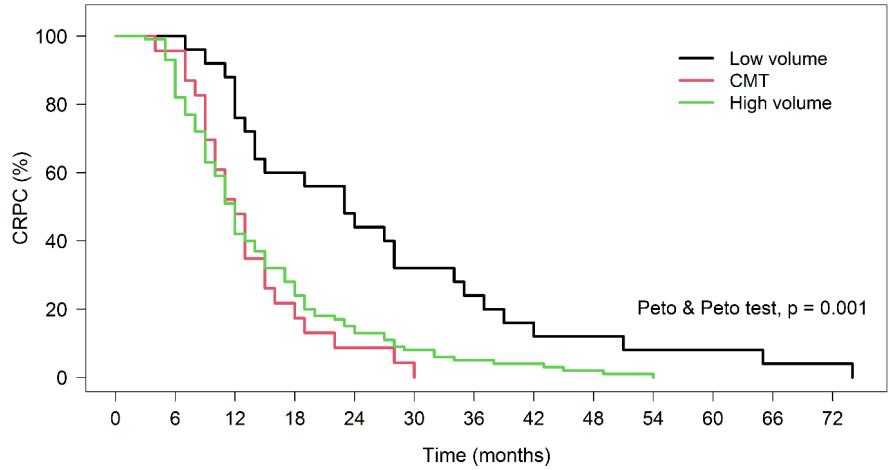

Figure 5. Kaplan-Meier curve of castration-resistant prostate cancer by disease burden and chemohormonal therapy

Over the last 5 years, the treatment landscape has changed dramatically with the addition of systemic agents that have previously been beneficial in the castrate-resistant setting[4]; specifically, docetaxe[8], abiraterone[9], enzalutamide[10,11], and apalutamide.[12] Since that time, many changes have occurred in the treatment of mHSPC. Nevertheless, at some point, all patients will progress to CRPC.

The time duration until CRPC may be a useful tool for the prediction of OS and tumor behavior.[13-18] The main focus of this article is to explore the factors associated with a short duration of disease progression to CRPC.

The time to CRPC, in a study about the combination treatment of Docetaxel plus ADT versus ADT alone in high volume metastatic hormone-sensitive prostate cancer, was reported to be 20.2 months VS 11.7 months,[6] Nevertheless, in Songklanagarind Hospital, the time to CRPC in both groups was 12 months. This is possibly due to the small study population in the combination therapy group (23 patients).

The demographic of high-volume metastatic status in our center looked higher than the previous study, as 80% of patients had high volume metastatic disease.[6,19] Most of the patients developed skeleton-related events or lethal urinary complications during their 1st visit. Forty-two patients (33.6%) received bilateral orchiectomy as their primary ADT. The mode of ADT treatment depended on the patients' health insurance.

PSA is widely used for prostate cancer detection, evaluation of therapeutic outcomes, and predicting prognosis.[20,21] Faster decline in PSA might be associated with cancer related death or transcriptional outcomes from ADT.[22,23] Recent studies demonstrated that a rapid decline in PSA during ADT treatment was a risk factor for the early progression into CRPC.[24,25] Choueiri et al. reported TTN < 6 months and PSA nadir > 0.2 ng/ml had shorter overall survival. Hamano et al. also found that short TTN (< 7 months) and high levels of PSA nadir (> 0.64 ng/ml) were associated with a worse overall survival. Our findings were in agreement with those studies.

Pathology was a strong predictor for OS and time to CRPC. Patients in the higher grade group had a poorer prognosis of progression to CRPC.[26,27] Kongseang et al. revealed that the median time to progression in mHSPC patients treated with ADT, was 37.5, 18.1 and 12.5 months in patients with Gleason scores ≤ 6, 7 and ≥ 8 respectively. In our study, we found a patient with a high GS grade group score (3-5) had a 1.47-fold high risk of progression when compared with a lower GS grade group score (1-2), a finding which was in agreement with a prior study.[10]

ALP is an enzyme primarily found in the liver, bone, intestine, and kidney. It has been associated with bone turnover markers and it has also been used to evaluate the efficacy of treatment in mCRPC.[28] Mikah et al. reported that the dynamic changes in ALP during treatment were associated with better OS in bone metastatic CRPC.[29] Recently, evidence associated with ALP and the prediction of outcomes with regard to mHSPC has been lacking. Our findings suggest that ALP ≥ 350 U/L is associated with poor outcomes.

There was a significantly shorter duration of progression to CRPC after ADT in patients in the high-volume metastasis group. The reason for this may be that the majority of these patients had severe prostate biopsy pathology. The group with a Gleason grade of more than 3, constituted 80% of the patients in this study. Hence, they had a statistically significant shorter duration of PSA reduction to nadir level than the low volume metastasis group. This is thought to be explained by the high expression of androgen receptors in the more severe prostate biopsy pathological group.[14] Nevertheless, the response to ADT treatment was lower.[15]

There are two limitations of this study. The first is due to its 10-year retrospective design, it is dependent on the data collection of several modalities, for example hand-written notes and electronic medical recording (EMR). In addition, there was no standard follow-up or imaging protocol and serum testosterone and blood chemistry were not routinely monitored in our cohort. Furthermore, upfront treatment is not available in Thailand. We believe our data could serve as a guide in making decisions about the proper treatment for patients with metastatic prostate cancer. The second limitation is as all the data is from a single institution the transferability of the findings may be limited. However, the significant nature of the findings warrants a multi-center, larger sample size study in the near future.

Conclusion

Management in metastatic prostate cancer is challenging. Prolonging overall survival and maintaining quality of life are the main clinical aims. Gleason grade group 3-5, time to PSA nadir < 6 months, PSA nadir level ≥ 0.2 ng/ml, and ALP level ≥ 350 U/L were all independent factors found to be associated with poorer outcomes. Thus, close follow-up and upfront treatment is essential in this group of patients.

References

1. Lojanapiwat B. Urologic cancer in Thailand. Jpn J Clin Oncol 2015;45:1007e15.
2. Tantiwong A, Soontrapa S, Sujijantrarat P, Vanprapar N, Sawangsak L. The prevalence of prostate cancer screening in Thai elderly. J Med Assoc Thai 2002; 85:502e8.
3. Cattrini C, Castro E, Lozano R, Zanardi E, Rubagotti A, Boccardo F, et al. Current Treatment Options for Metastatic Hormone-Sensitive Prostate Cancer. Cancers (Basel) 2019;11:1355.
4. Kyriakopoulos CE, Chen YH, Carducci MA, Liu G, Jarrard DF, Hahn NM, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer: long-term survival analysis of the randomized phase III E3805 CHAARTED trial. J Clin Oncol 2018;36:1080-87.
5. Tamada S, Iguchi T, Kato M, Asakawa J, Kita K, Yasuda S, et al. Time to progression to castrationresistant prostate cancer after commencing combined androgen blockade for advanced hormonesensitive prostate cancer. Oncotarget 2018;9:36966-74.
6. Sweeney CJ, Chen YH, Carducci M, Liu G, Jarrard DF, Eisenberger M, et al. Chemohormonal Therapy in Metastatic HormoneSensitive Prostate Cancer. N Engl J Med 2015;373:737-46.
7. Narita S, Nomura K, Hatakeyama S, Takahashi M, Sakurai T, Kawamura S, et al. Prognostic significance of early changes in serum biomarker levels in patients with newly diagnosed metastatic prostate cancer. Sci Rep 2019;9:12071:48600-8.
8. Watanabe M, Kanao K, Sugie M, Morinaga S, Muramatsu H, Kobayashi I et al. Prognostic and predictive clinical factors for progression to castration refractory prostate cancer in patients with hormone sensitive prostate cancer. Ann Oncol 2018;29:IX73.
9. Lin T, Chen YH, Wu YP, Chen SZ, Li XD, Lin YZ, et al. Risk factors for progression to castration-resistant prostate cancer in metastatic prostate cancer patients. J Cancer 2019;10:5608-13.
10. Kongseang C, Attawettayanon W, Kanchanawanichkul W, Pripatnanont C. Predictive factor of androgen deprivation therapy for patients with advanced stage prostate cancer. Prostate Int 2017;35-38.
11. Yin X, Xiao Y, Li F, Qi S, Yin Z, Gao J. Prognostic role of neutrophil-to-lymphocyte ratio in prostate cancer: a systematic review and meta-analysis. Medicine (Baltimore) 2016;95:e2544.
12. Wang J, Zhou X, He Y, Chen X, Liu N, Ding Z, et al. Prognostic role of platelet to lymphocyte ratio in prostate cancer: A meta-analysis. Medicine (Baltimore) 2018;97:e12504.
13. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors, special article. J Nat Cancer Inst 2000;92:205-16.
14. Hashmi AA, Mudassir G, Irfan M, Hussain ZF, Hashmi SK, Asif H, et al. Prognostic significance of high androgen receptor expression in prostate acinar adenocarcinoma. Asian Pac J Cancer Prev 2019;20:893-6.
15. Yang DD, Mahal BA, Muralidhar V, Martin NE, Orio PF, Mouw KW, et al. Androgen deprivation therapy and overall survival for Gleason 8 versus Gleason 9-10 prostate cancer. Eur Urol 2019;75:35-41.
16. Fizazi K, Tran N, Fein L, Matsubara N, Rodriguez-Antolin A, Alekseev BY, et al. Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (LATITUDE): final overall survival analysis of a randomised, double-blind, phase 3 trial. Lancet Oncol 2019;20:686-700.
17. Armstrong AJ, Szmulewitz RZ, Petrylak DP, Holzbeierlein J, Villers A, Azad A, et al. ARCHES: A Randomized, Phase III Study of Androgen Deprivation Therapy With Enzalutamide or Placebo in Men With Metastatic Hormone-Sensitive Prostate Cancer. J Clin Oncol 2019;37:2974-86.
18. Wenzel M, Preisser F, Hoeh B, Schroeder M, Würnschimmel C, Steuber T, et al. Impact of time to castration resistance on survival in metastatic hormone sensitive prostate cancer patients in the era of combination therapies. Front Oncol 2021; 11:659135.
19. Narita T, Hatakeyama S, Narita S, Takahashi M, Sakurai T, Kawamura S, et al. Therapeutic effects of the combined androgen blockade therapy versus luteinizing hormone-releasing hormone analog monotherapy in patients with hormone naïve metastatic prostate cancer: a multi-institutional comparative analysis. Transl Androl Urol 2021;10:417-25.
20. Filella X, Fernandez-Galan E, Fernandez Bonifacio R, Foj L. Emerging biomarkers in the diagnosis of prostate cancer. Pharmgenomics Pers Med 2018;11: 83-94.

21. Hendriks RJ, van Oort IM, Schalken JA. Blood-based and urinary prostate cancer biomarkers: a review and comparison of novel biomarkers for detection and treatment decisions. Prostate Cancer Prostatic Dis 2017; 20: 12-9.
22. Choueiri TK, Xie W, D'Amico AV, Ross RW, Hu JC, Pomerantz M, et al. Time to prostate-specific antigen nadir independently predicts overall survival in patients who have metastatic hormone-sensitive prostate cancer treated with androgen-deprivation therapy. Cancer 2009;115: 981-7.
23. Hamano I, Hatakeyama S, Narita S, Takahashi M, Sakurai T, Kawamura S, et al. Impact of nadir PSA level and time to nadir during initial androgen deprivation therapy on prognosis in patients with metastatic castration-resistant prostate cancer. World J Urol 2019;37:2365-73.
24. Sasaki T, Onishi T, and Hoshina A. Nadir PSA level and time to PSA nadir following primary androgen deprivation therapy are the early survival predictors for prostate cancer patients with bone metastasis. Prostate Cancer Prostatic Dis 2011;14:248-52.
25. Lin YC, Lin PH, Shao IH, Chu YC, Kan HC, Liu CY, et al. Prostate-specific antigen kinetics effects on outcomes of low-volume metastatic prostate cancer patients receiving androgen deprivation therapy. J Oncol 2021;2021:9648579.
26. Lin TT, Chen YH, Wu YP, Chen SZ, Li XD, Lin YZ, et al. Risk factors for progression to castration-resistant prostate cancer in metastatic prostate cancer patients. J Cancer 2019;10:5608-13.
27. Tamada S, Iguchi T, Kato M, Asakawa J, Kita K, Yasuda S, et al. Time to progression to castration-resistant prostate cancer after commencing combined androgen blockade for advanced hormone-sensitive prostate cancer. Oncotarget 2018;9:36966-74.
28. Hammerich KH, Donahue TF, Rosner IL, Cullen J, Kuo HC, Hurwitz L, et al. Alkaline phosphatase velocity predicts overall survival and bone metastasis in patients with castration-resistant prostate cancer. Urol Oncol 2017;35:460.e21-8.
29. Mikah P, Krabbe LM, Eminaga O, Herrmann E, Papavassilis P, Hinkelammert R, et al. Dynamic changes of alkaline phosphatase are strongly associated with PSA-decline and predict best clinical benefit earlier than PSA-changes under therapy with abiraterone acetate in bone metastatic castration resistant prostate cancer. BMC Cancer 2016;16:214.

Review Article

Kidney health for all: bridging the gap in kidney health education and literacy

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Educational gap, empowerment, health literacy, health policy, information technology, kidney health

Abstract

The high burden of kidney disease, global disparities in kidney care, and poor outcomes of kidney failure bring a concomitant growing burden to persons affected, their families, and careers, and the community at large. Health literacy is the degree to which persons and organizations have or equitably enable individuals to have the ability to find, understand, and use information and services to make informed health-related decisions and actions for themselves and others. Rather than viewing health literacy as a patient deficit, improving health literacy largely rests with health care providers communicating and educating effectively in codesigned partnership with those with kidney disease. For kidney policy makers, health literacy provides the imperative to shift organizations to a culture that places the person at the center of health care. The growing capability of and access to technology provides new opportunities to enhance education and awareness of kidney disease for all stakeholders. Advances in telecommunication, including social media platforms, can be leveraged to enhance persons' and providers' education; The World Kidney Day declares 2022 as the year of "Kidney Health for

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All" to promote global teamwork in advancing strategies in bridging the gap in kidney health education and literacy. Kidney organizations should work toward shifting the patient-deficit health literacy narrative to that of being the responsibility of health care providers and health policy makers. By engaging in and supporting kidney health–centered policy making, community health planning, and health literacy approaches for all, the kidney communities strive to prevent kidney diseases and enable living well with kidney disease.

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Introduction

Given the high burden of kidney disease and global disparities related to kidney care, in carrying forward our mission of advocating Kidney Health for All, the challenging issue of bridging the well-identified gap in the global understanding of kidney disease and its health literacy is the theme for World Kidney Day (WKD) 2022. Health literacy is defined as the degree to which persons and organizations have-or equitably enable individuals to have-the ability to find, understand, and use information and services to inform health-related decisions and actions for themselves and others.[1] Not only is there is growing recognition of the role that health literacy has in determining outcomes for persons affected by kidney disease and the community in general, but there is an emergent imperative for policy makers worldwide to be informed and cognizant of opportunities and real measurable outcomes that can be achieved through kidney-specific preventative strategies.

The global community of people with kidney disease

Most people are not aware of what kidneys are for or even where their kidneys are. For those afflicted by disease and the subsequent effects on overall health, an effective health care provider communication is required to support individuals to be able to understand what to do, to make decisions, and to take action. Health literacy involves more than functional abilities of an individual; it is also the cognitive and social skills needed to gain access to, understand, and use information to manage health condition.[2] It is also contextual[3] in that as health needs change, so too does the level of understanding and ability to problem solve alter. Health literacy is, therefore, an interaction between individuals, health care providers, and health policy makers.[4] This why the imperatives around health literacy are now recognized as indicators for the quality of local and national health care systems and health care professionals within it.[5] For chronic kidney disease (CKD), as the disease progresses alongside other health changes and increasing treatment complexities, it becomes more difficult for individuals to manage.[6] Promoted in health policy for around a decade involving care partnerships between health-centered policy, community health planning, and health literacy,[7] current approaches need to be shifted forward (Table 1).

Assessing health literacy necessitates the use of appropriate multidimensional patient-reported measures, such as the World Health Organization–recommended Health Literacy Questionnaire (available in over 30 languages) rather than tools measuring only functional health literacy (e.g., Rapid Estimate of Adult Literacy in Medicine or Short Test of Functional Health Literacy in Adults).[8] It is therefore not surprising that studies of low health literacy (LHL) abilities in people with CKD have been demonstrated to be associated with poor CKD knowledge, self-management behaviors, and health-related quality of life and in those with greater comorbidity severity.[7] Unfortunately, most CKD studies have measured only functional health literacy, so the evidence that LHL results in poorer outcomes, particularly that it increases health care utilization and mortality,[9] and reduces access to transplantation,[10] is weak.

Recently, health literacy is now considered to be an important bridge between lower socioeconomic status and other social determinants of health.[4] Indeed, this is not a feature that can be measured by the gross domestic product of a country, as the effects of LHL on the extent of CKD in the community are experienced globally regardless of country income status. The lack of awareness of risk factors of kidney disease, even in those with high health literacy abilities,

Table 1. Summary characteristic of kidney health promotion, involving kidney health–centered policy, community kidney health planning, and kidney health literacy, and proposed future direction

Kidney health promotion	Definition	Stakeholders	Current status	Limitations/challenges	Suggested solutions/future research
Kidney health–centered policy	• Incorporate kidney health into policy decision making • Prioritize policies with primary prevention for CKD	• Governance • Policy makers • Insurance agencies	• Policy emphasizing treatment for CKD and kidney failure rather than kidney health prevention	• Economic-driven situation challenging CKD risk factor minimization (e.g., food policy)	• Promote implementation of public health program for primary CKD prevention • Promote sustainable treatment for CKD and dialysis - Increase kidney transplant awareness - Enhance visibility and encourage brother-sister nephrology and transplant program in LMIC • Support research funding from government - Health care cost-effectiveness for caring for CKD - Kidney failure, including maintenance dialysis and transplant - Promote surveillance programs for kidney diseases and their risk factors
Community kidney health planning	• Building up preventive strategies to promote healthy communities and primary health care facilities	• Community leadership • Kidney patient advocacy	• Belief in community leaders in LMIC	• Education and understanding kidney health promotion of community leadership and people	• Improve role model of community • Enhance kidney support networks
Kidney health literacy	• Receive knowledge, skills, and information to be healthy	• People with CKD • Care partners • Health care providers	• Lack of awareness of CKD and risk factors • Care partner burden and burnout • Inadequate health care workers • High patients-to-health care workers ratio, especially in rural areas	• Inadequate policy direction • Ineffective health care providers' communication skills	• Organizational paradigm shift toward health literacy • Improving communication between health care providers with patients and care partners • Using teach-back methods for consumer education • Adapting technologies for appropriate health literacy and sociocultural environments • Family engagement in the patient care • Incentive for community health care providers in rural areas

CKD = chronic kidney disease, LMIC = low- to middle-income country

is testament to the difficulties in understanding this disease, and why the United States, for instance, recommends that a universal precautions approach toward health literacy is undertaken.[11]

So, what does the perfect health literacy program look like for people with CKD? In several high-income countries, there are national health literacy action plans with the emphasis shifted to policy directives, organizational culture, and health care providers. In Australia, for instance, a compulsory health literacy accreditation standard makes the health care organization responsible for ensuring providers are cognizant of individual health literacy abilities.[12] Although many high-income countries, health care organizations, nongovernmental organizations, and jurisdictions are providing an array of consumer-facing web-based programs that provide detailed information and self-care training opportunities, most are largely designed for individual/family use that are unlikely to mitigate LHL. There is, however, substantial evidence that interventions improving health care provider communication are more likely to improve understanding of health problems and abilities to adhere to complex treatment regimens.[13]

Access to information that is authentic and tailored specifically to the needs of the individual and the community is the aim. The challenge is recognized acutely in more remote and low- to middle-income countries of the world, specifically the importance of culturally appropriate knowledge provision. The principals of improving health literacy are the same, but understanding how to proceed, and putting consumers in charge, with a codesign approach, is critical and may result in a different outcome in more remote parts of the world. This principal especially applies to communities that are smaller, with less access to electronic communication and health care services, where the level of health literacy is shared across the community and where what affects the individual also affects all the community. Decision support systems are different, led by elders, and in turn educational resources are best aimed at improving knowledge of the whole community.

A systematic review of the evaluation of interventions and strategies shows this area of research is still at an early stage,[14] with no studies unravelling the link between LHL and poor CKD outcomes. The best evidence is in supporting targeted programs on improving communication capabilities of health care professionals as central. One prime example is Teach-back, a cyclical, simple, low-cost education intervention, shows promise for improving communication, knowledge, and self-management in the CKD populations in low- or high-income countries.[15] Furthermore, the consumer-led voice has articulated research priorities that align closely with principals felt to be important to success of education: building new education resources, devised in partnership with consumers, and focused on the needs of vulnerable groups. Indeed, programs that address the lack of culturally safe, person-centred and holistic care, along with improving the communication skills of health professionals, are crucial for those with CKD.[16]

The networked community of kidney health care workers

Nonphysician health care workers, including nurses and advanced practice providers (physician assistants and nurse practitioners) as well as dietitians, pharmacists, social workers, technicians, physical therapists, and other allied health professionals, often spend more time with persons with kidney disease, compared with nephrologists and other physician specialists. In an ambulatory care setting at an appointment, in the emergency department, or in the inpatient setting, these health care professionals often see and relate to the patient first, last, and in between, given that physician encounters are often short and focused. Hence, the nonphysician health care workers have many opportunities to discuss kidney disease–related topics with the individuals and their care partners and to empower them.[17,18] For instance, medical assistants can help identify those with or at risk of developing CKD and can initiate educating them and their family members about the role of diet and lifestyle modification for primary, secondary, and tertiary prevention of CKD while waiting to see the physician.[19] Some health care workers provide networking and support for kidney patient advocacy groups and kidney support networks, which have been initiated or expanded via social media platforms (Figure 1).[20,21] Studies examining the efficacy of social media in kidney care and advocacy are on the way.[22,23]

Like physicians, many activities of nonphysician health care workers have been increasingly affected by the rise of electronic health recording

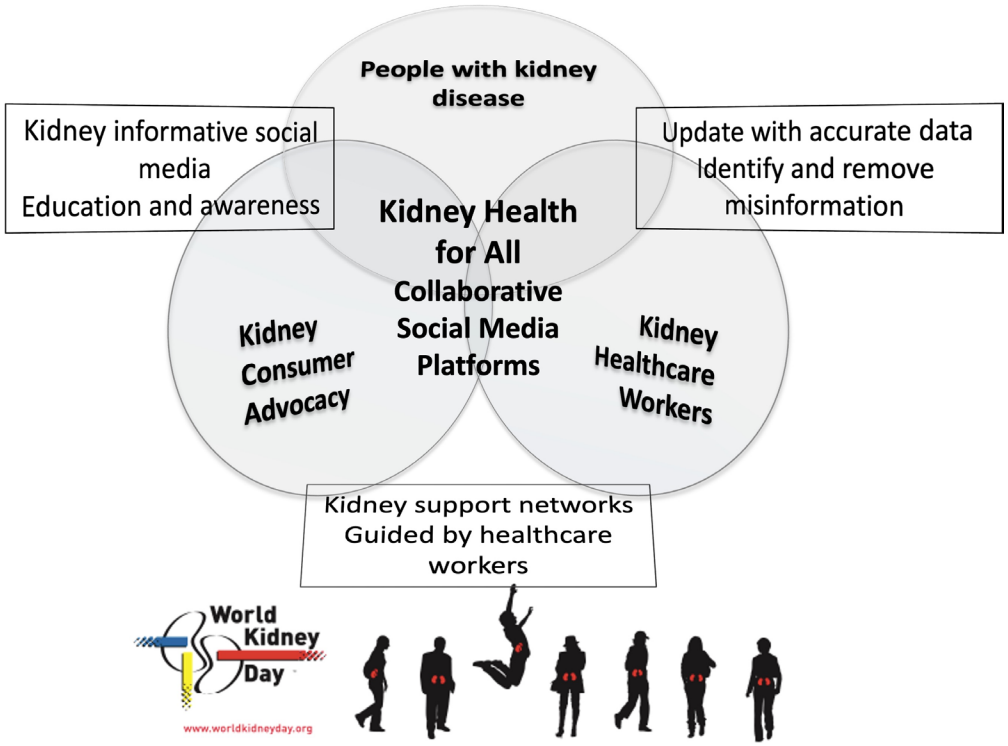

Figure 1. Schematic representation of consumer and health care professionals' collaborative advocacy using social media platforms with the goal of Kidney Health for All

and growing access to internet-based resources, including social media, that offer educational materials related to kidney health, including kidney-preserving therapies with traditional and emerging interventions.[24] These resources can be used for both self-education and for networking and advocacy on kidney disease awareness and learning. Increasingly, more health care professionals are engaged in some types of social media–based activities, as shown in Table 2. At the time of this writing, the leading social media used by many—but not all—kidney health care workers include Facebook, Instagram, Twitter, LinkedIn, and YouTube. In some regions of the world, certain social media are more frequently used than others given unique cultural or access constellations (e.g., WeChat is a platform often used by health care workers and patient groups in China). Some health care professionals, such as managers and those in leadership and advocacy organization positions, may choose to embark on social media to engage those with CKD and their care partners or other health care professionals in alliance building and marketing. To that end, effective communication strategies and outreach skills specific to responsible use of social media can provide clear advantages given that these skills and strategies are different and may need modification in those with LHL. It is imperative to ensure the needed knowledge and training for accountable approach to social media is provided to health care providers, so that these outreach strategies are utilized with the needed awareness of their unique strengths and pitfalls, as follows[25]:

(i) Consumers' and care partners' confidentiality may not be breached upon posting anything on social media, including indirect referencing to a specific individual or a particular description of a condition unique to a specific person (e.g., upon soliciting for transplant kidney donors on social media).[26,27]

(ii) Confidential information about clinics, hospitals, dialysis centers, or similar health care and advocacy entities may not be disclosed on social media without ensuring that the needed processes, including collecting authorizations to disclose, are undertaken.

(iii) Health care workers' job security and careers should remain protected with thorough review of the content of the messages and illustrations/videos before online posting.

(iv) Careless and disrespectful language and emotional tones are often counterproductive and may not be justified under the context of freedom of speech.

Table 2. Social media that are more frequently used for kidney education and advocacy

Social media	Strength	Limitations	Additional comments
Facebook	- Frequently used social media platform by many kidney patients and patient groups	- Widely used for entertaining purposes, which can dilute its professional utility	- User-friendly platform for kidney advocacy, enabling wide ranges of outreach goals
Instagram	- Photo-predominating platform	- Not frequently used by health care professionals	- Picture friendly, potentially effective for illustrative educational purposes
Twitter	- Often used by physician specialists and scientists, including nephrologists	- Less frequently used by patients and care partners	- Increasing popularity among physician and specialty circles
LinkedIn	- More often used by professionals, including in industry	- Originally designed for employment and job-seeking networking	- Mostly effective to reach out to industry and managerial professionals
YouTube	- Video-predominating platform	- Less effective with non–video-based formats	- Wide ranges of outreach and educational targets
WeChat	- Widely used in mainland China	- Access is often limited to those living in China or its diaspora	- Effective platform to reach out to patients and health care professionals in China
Pinterest	- Picture-based, often used by dietitians	- Currently limited use by some health care workers	- Useful for dietary and lifestyle education

The global kidney community of policy and advocacy

Policy and advocacy are well-recognized tools that, if properly deployed, can bring about change and paradigm shift at jurisdictional level. The essence of advocating for policy change to better address kidney disease is, in itself, an exercise in improving health literacy of the policy makers. Policy development, at its core, is a key stakeholder or stakeholder group (e.g., the kidney community, who believes that a problem exists that should be tackled through governmental action). There is an increasing recognition of the importance of formulating succinct, meaningful, and authentic information, akin to improving health literacy, to present to government for action.

Robust and efficacious policy is always underpinned by succinct and applicable information; however, the development and communication of this message, designed to bridge the gap in knowledge of relevant jurisdictions, is only part of the process of policy development. An awareness of the process is important to clinicians who are aiming to advocate for effective change in prevention or improvement of outcomes in the CKD community.

Public policies, the plans for future action accepted by governments, are articulated through a political process in response stakeholder observation, usually written as a directive, law, regulation, procedure, or circular. Policies are purpose fit and targeted to defined goals and specific societal problems and are usually a chain of actions effected to solve those societal problems.[28] Policies are an important output of political systems. Policy development can be formal, passing through rigorous lengthy processes before adoption (such as regulations), or it can be less formal and quickly adopted (such as circulars). As already mentioned, the governmental action envisaged by the key stakeholders as solution to a problem is at its core. The process enables stakeholders to air their views and bring their concerns to the fore. Authentic information that is meaningful to the government is critical. The policy development process can be stratified into 5 stages (i.e., the policy cycle), as depicted by Andersen (1994)[29] and adapted and modified by other authors[30] (Figure 2). The policy cycle constitutes an expedient framework for evaluating the key components of the process.

Subsequently, the policy moves on to implementation phase. This phase may require subsidiary policy development and adoption of new regulations or budgets (implementation). Policy evaluation is integral to the policy processes and applies evaluation principles and methods to assess the content, implementation, or impact of a

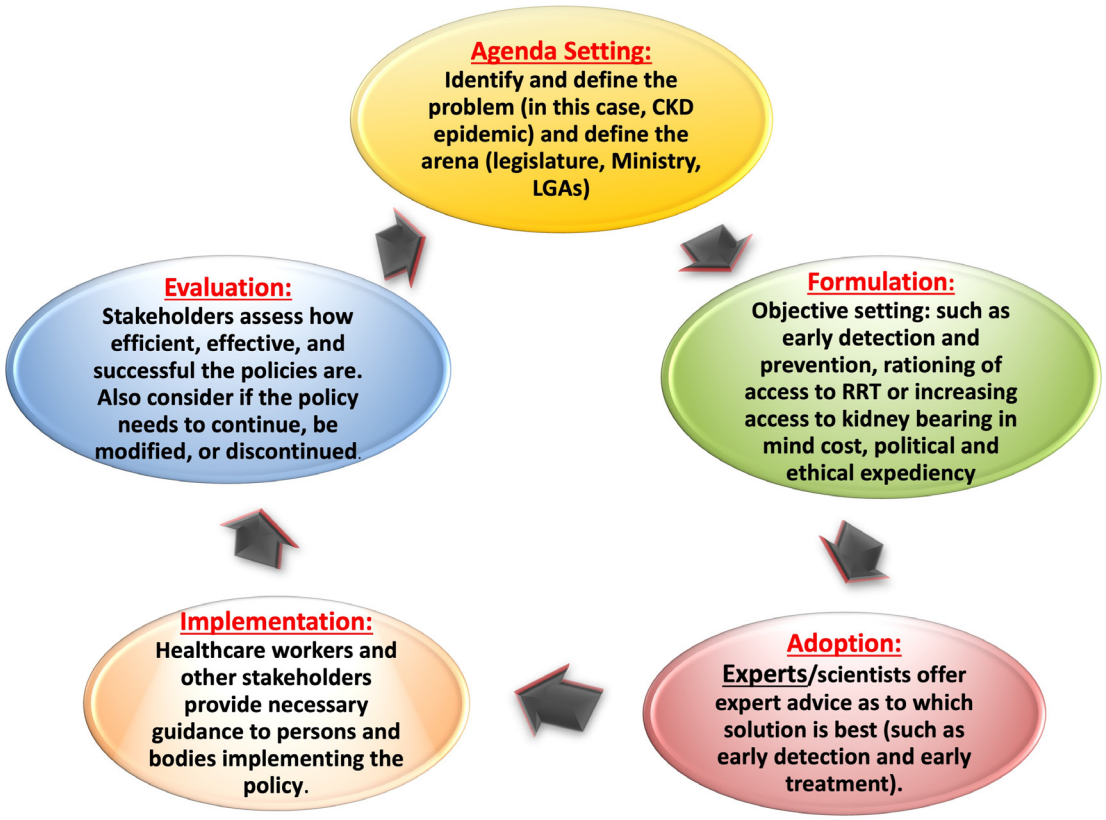

Figure 2. Policy cycle involving 5 stages of policy development. CKD = chronic kidney disease, KRT = kidney replacement therapy; LGA, local government area.

policy. Evaluation facilitates understanding and appreciation of the worth and merit of a policy as well as the need for its improvement. More important, of the 5 principles of advocacy that underline policy making,[31] the most important for clinicians engaged in this space is that of commitment, persistence, and patience. Advocacy takes time to yield the desired results.

The Advocacy Planning Framework, developed by Young and Quinn in 2002,[30] consists of overlapping circles representing 3 sets of concepts (way into the process, the messenger, and message and activities) that are key to planning any advocacy campaign:

(i) "Way into the process": discusses the best approaches to translate ideas into the target policy debate and identify the appropriate audience to target.

(ii) Messenger: talks about the image maker or face of the campaign and other support paraphernalia that are needed.

(iii) Message and activities: describe what can be said to the key target audiences that is engaging and convincing. And how best it can be communicated through appropriate communication tools.

Advocacy is defined as "an effort or campaign with a structured and sequenced plan of action which starts, directs, or prevents a specific policy change."[31] The goal being to influence decision makers through communicating directly with them or getting their commitment through secondary audiences (advisers, the media, or the public) to the end that the decision maker understands, is convinced, takes ownership of the ideas, and finally has the compulsion to act.[31] As with improving health literacy, it is the communication of ideas to policy makers for adoption and implementation as policy that is key. There is much to be done with bridging this gap in understanding of the magnitude of community burden that results from CKD. Without good communication, many good ideas and solutions do not reach communities and countries where they are needed. Again, aligned with the principles of developing resources for health literacy, the approach also needs to be nuanced according to the local need, aiming to have the many good ideas and solutions be communicated to communities and countries where they are needed.

Advocacy requires galvanizing momentum and support for the proposed policy or recommendation. The process is understandably slow as it involves discussions and negotiations for paradigms, attitudes, and positions to shift. In contemplating advocacy activities, multiple factors must be considered, interestingly not too dissimilar to that of building health literacy resources: What obstructions are disrupting the policy-making process from making progress? What resources are available to enable the process to succeed? Is the policy objective achievable considering all variables? Is the identified problem already being considered by the policy makers (government or multinational organizations)? Any interest or momentum generated around it? Understandably, if there is some level of interest and if government already has its spotlight on the issue, it is likely to succeed.

Approaches to choose from include the following[31,32]

• Advising (researchers are commissioned to produce new evidence-based proposals to assist the organization in decision making).

• Activism: involves petitions, public demonstrations, posters, fliers, and leaflet dissemination, often used by organizations to promote a certain value set.

• Media campaign: having public pressure on decision makers helps in achieving results.

• Lobbying: entails face-to-face meetings with decision makers; often used by business organizations to achieve their purpose.

Here lies the importance of effective and successful advocacy to stakeholders, including policy makers, health care professionals, communities, and key change makers in society. The WKD, since inception, has aimed at playing this role. WKD has gained people's trust by delivering relevant and accurate messaging and supporting leaders in local engagement, and it is celebrated by kidney care professionals, celebrities, those with the disease, and their care givers all over the world. To achieve the goal, an implementation framework of success in a sustainable way includes creativity, collaboration, and communication.

The ongoing challenge for the International Society of Nephrology and International Federation of Kidney Foundations–World Kidney Alliance, through the Joint Steering Committee of WKD, is to operationalize how to collate key insights from research and analysis to effectively feed the policy-making process at the local, national, and international levels, to inform or guide decision making (i.e., increasing engagement of governments and organizations, like World Health Organization, United Nations, and regional organizations, especially in low-resource settings). There is a clear need for ongoing renewal of strategies to increase efforts at closing gap in kidney health literacy, empowering those affected with kidney disease and their families, giving them a voice to be heard, and engaging with the civil society. This year, the Joint Steering Committee of WKD declares "Kidney Health for All" as the theme of the 2022 WKD to emphasize and extend collaborative efforts among people with kidney disease, their care partners, health care providers, and all involving stakeholders for elevating education and awareness on kidney health and saving lives with this disease.

Conclusions

In bridging the gap of knowledge to improve outcomes for those with kidney disease on a global basis, an in-depth understanding of the needs of the community is required. The same can be said for policy development, understanding the processes in place for engagement of governments worldwide, all underpinned by the important principal of codesign of resources and policy that meets the needs of the community for which it is intended.

For World Kidney Day 2022, kidney organizations, including the International Society of Nephrology and International Federation of Kidney Foundations–World Kidney Alliance, have a responsibility to immediately work toward shifting the patient-deficit health literacy narrative to that of being the responsibility of clinicians and health policy makers. LHL occurs in all countries regardless of income status; hence, simple, low-cost strategies are likely to be effective. Communication, universal precautions, and teach back can be implemented by all members of the kidney health care team. Through this vision, kidney organizations will lead the shift to improved patient-centered care, support for care partners, health outcomes, and the global societal burden of kidney health care.

Conflict of Interest

KK-Z reports honoraria from Abbott, Abbvie, ACI Clinical, Akebia, Alexion, Amgen, Ardelyx, AstraZeneca, 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. VL reports nonfinancial support from Genesis Pharma. GS reports personal fees from Multicare, Novartis, Sandoz, and AstraZeneca. ET reports nonfinancial support from Natera. All the other authors declared no competing interests.

Appendix

The World Kidney Day Joint Steering Committee includes coauthors Robyn G. Langham, Kamyar Kalantar-Zadeh, Alessandro Balducci, Li-Li Hsiao, Latha Kumaraswami, Paul Laffin, Vassilios Liakopoulos, Gamal Saadi, Ifeoma Ulasi, and Siu-Fai Lui.

References

1. Centers for Disease Control and Prevention. Healthy People 2030: What is health literacy? [Internet]. [cited 2022 Jan 16]. Available from: https://www.cdc.gov/healthliteracy/learn/index.html.
2. Nutbeam D. The evolving concept of health literacy. Soc Sci Med 2008;67:2072-8.
3. Lloyd A, Bonner A, Dawson-Rose C. The health information practices of people living with chronic health conditions: implications for health literacy. J Librarianship Information Science 2014;46:207-2016.
4. Sorensen K, Van den Broucke S, Fullam J, Doyle G, Pelikan J, Slonska Z, et al. Health literacy and public health: a systematic review and integration of definitions and models. BMC Public Health 2012;12:80.
5. Nutbeam D, Lloyd JE. Understanding and responding to health literacy as a social determinant of health. Annu Rev Public Health 2021;42:159-73.
6. Mathias-Shah J, Ramsbotham J, Seib C, Muir R, Bonner A. A scoping review of the role of health literacy in chronic kidney disease self-management. J Ren Care 2021;47:221-33.
7. Dinh HTT, Nguyen NT, Bonner A. Healthcare systems and professionals are key to improving health literacy in chronic kidney disease. J Ren Care 2022; 48:4-13.
8. Dobson S, Good S, Osborne R. Health literacy toolkit for low and middle-income countries: A series of information sheets to empower communities and strengthen health systems. New Delhi: World Health Organization; 2015.
9. Taylor DM, Fraser S, Dudley C, Oniscu G, Tomson C, Ravanan R, et al. Health literacy and patient outcomes in chronic kidney disease: a systematic review. Nephrol Dial Transplant 2018;33:1545-58.
10. Taylor DM, Bradley JA, Bradley C, Draper H, Dudley C, Fogarty D, et al. Limited health literacy is associated with reduced access to kidney transplantation. Kidney Int 2019;95:1244-52.
11. Brega AG, Barnard J, Mabachi NM, Wiess, BD, DeWalt DA, Brach C, et al. AHRQ health literacy universal precautions toolkit. 2nd ed. (Prepared by Colorado Health Outcomes Program, University of Colorado Anschutz Medical Campus under Contract No. HHSA290200710008, TO#10.) AHRQ Publication No. 15-0023-EF. Rockville, MD: Agency for Healthcare Research and Quality; 2015.
12. Australian Commission on Safety and Quality in Health Care. Health literacy: taking action to improve safety and quality. Sydney: ACSQHC; 2014. [Internet]. [cited 2022 Jan 17] . Available from: https://www.safetyandquality.gov.au/publications-and-resources/resource-library/health-literacy-taking-action-improve-safety-and-quality.
13. Visscher BB, Steunenberg B, Heijmans M, Hofdtede JM, Deville W, van der Heide I, et al. Evidence on the effectiveness of health literacy interventions in the EU: a systematic review. BMC Public Health 2018;18:1414.
14. Boonstra MD, Reijneveld SA, Foitzik EM, Westerhuis R, Navis G, de Winter AF. How to tackle health literacy problems in chronic kidney disease patients? A systematic review to identify promising intervention targets and strategies. Nephrol Dial Transplant 2020;36:1207-21.
15. Nguyen NT, Douglas C, Bonner A. Effectiveness of self-management programme in people with chronic kidney disease: a pragmatic randomized controlled trial. J Adv Nurs 2019;75:652-64.
16. Synnot A, Bragge P, Lowe D, Nunn J, O'Sullivan M, Horvat L, et al. Research priorities in health communication and participation: international survey of consumers and other stakeholders. BMJ Open 2018;8:e019481.
17. Kalantar-Zadeh K, Kam-Tao Li P, Tantisattamo E, Kumaraswami L, Liakopoulos V, Lui SF, et al. Living well with kidney disease by patient and care-partner empowerment: kidney health for everyone everywhere. Kidney Int 2021;99:278-84.
18. Jager KJ, Kovesdy C, Langham R, Rosenberg M, Jha V, Zoccali C. A single number for advocacy and communication-worldwide more than 850

million individuals have kidney diseases. Kidney Int 2019;96:1048-50.
19. Li PK, Garcia-Garcia G, Lui SF, Andreoli S, Fung WWS, Hradsky A, et al. Kidney health for everyone everywhere-from prevention to detection and equitable access to care. Kidney Int 2020;97:226-32.
20. Gilford S. Patients helping patients: the renal support network. Nephrol Nurs J 2007;34:76.
21. Muhammad S, Allan M, Ali F, Bonacina M, Adams M. The renal patient support group: supporting patients with chronic kidney disease through social media. J Ren Care 2014;40:216-8.
22. Li WY, Chiu FC, Zeng JK, Li YW, Huang SH, Yeh HC, et al. Mobile health app with social media to support self-management for patients with chronic kidney disease: prospective randomized controlled study. J Med Internet Res 2020;22:e19452.
23. Pase C, Mathias AD, Garcia CD, Garcia Rodrigues C. Using social media for the promotion of education and consultation in adolescents who have undergone kidney transplant: protocol for a randomized control trial. JMIR Res Protoc 2018;7:e3.
24. Kalantar-Zadeh K, Jafar TH, Nitsch D, Neuen BL, Perkovic V. Chronic kidney disease. Lancet 2021; 398:786-802.
25. Chen L, Sivaparthipan CB, Rajendiran S. Unprofessional problems and potential healthcare risks in individuals' social media use. Work 2021;68:945-53.
26. Henderson ML, Herbst L, Love AD. Social media and kidney transplant donation in the united states: clinical and ethical considerations when seeking a living donor. Am J Kidney Dis 2020;76: 583-5.
27. Henderson ML. Social media in the identification of living kidney donors: platforms, tools, and strategies. Curr Transplant Rep 2018;5:19-26.
28. van Deth JW, Newton K, editors. Foundations of Comparative Politics Democracies of the Modern World. 2nd ed. Cambridge, UK: Cambridge University Press; 2010. [Internet] [cited 2021 Dec 13]. Avaliable from: http://www.nicat-mammadli.narod.ru/b1.html/b36.pdf.
29. Anderson JE. Public Policymaking: An Introduction. 2nd ed. Boston, MA: Houghton Mifflin; 1994.
30. Young E, Quinn L, editors. Writing effective public policy papers: a guide to policy advisers in central and Eastern Europe. Budapest, Hungary: Open Society Institute; 2002. [Internet] [cited 2021 Dec 13]. Avaliable from: https://www.icpolicyadvocacy.org/sites/icpa/files/downloads/writing_effective_public_policy_papers_young_quinn.pdf.
31. Young E, Quinn L, editors. Making research evidence matter: a guide to policy advocacy in transition countries. Budapest, Hungary: Open Society Foundations; 2012. [Internet]. [cited 2021 Dec 13]. Avaliable from: https://advocacyguide.icpolicyadvocacy.org/sites/icpa-book.local/files/Policy_Advocacy_Guidebook_2012.pdf.
32. Start D, Hovland I. Tools for Policy Impact: A handbook for researchers, research and policy in development programme. London, UK: Overseas Development Institute; 2004. [Internet]. [cited 2021 Dec 13]. Avaliable from: https://www.ndi.org/sites/default/files/Tools-for-Policy-Impact-ENG.pdf.

Review Article

Concern issues around frequency-volume charts and bladder diaries

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Keywords: Frequency-volume chart, bladder diary, reliability, compliance, lower urinary tract symptoms

Abstract

Frequency-volume charts (FVC) and Bladder diaries (BD) are widely accepted as additional tools for the evaluation of urinary tract symptoms to assist in treatment. They are simple and inexpensive as well as raising awareness and providing precise information. Despite the guidelines and experts recommending a 3-day use of FVC/BD for evaluation in both men and women with lower urinary tract symptoms, the findings may not be sufficiently detailed for some specific symptoms. To avoid poor compliance and poor reliability, the appropriate duration and instructions are mandatory and standardized in each patient. However, there are some limitations and concerns which need to be recognized before interpretation. The aim of this review is to investigate and demonstrate the appropriate duration of FVC/BD to increase completion rate, compliance and reliability as well as to decrease interpretation errors of FVC/BD

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Introduction

Frequency-volume charts (FVC) and Bladder diaries (BD) are additional tools for the evaluation of urinary tract symptoms (LUTS) to assist in treatment, being particularly useful because they are simple and inexpensive. The International Continence Society (ICS) classified three types of diaries for lower urinary tract evaluation. The first is the micturition chart (MC) which is a record of the times of micturition, day and night, for at least 24 hours. Secondly, the FVC which is used to record the time of each micturition and the voided volume for at least 24 hours. Lastly, the BD is used to add information from the FVC which includes fluid intake, pad usage, incontinence episodes and the degree of incontinence.[1]

According to ICS terminology, all measurements from the FVC included daytime frequency, nighttime frequency (nocturia), 24-hour frequency, 24-hour urine production, voided volume and maximum voided volume.[1] Both polyuria and nocturnal polyuria could be diagnosed using data from the FVC. Additional information added from the BD includes daily fluid intake, time of consumption, incontinence episodes, type

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of incontinence, pad usage, urgency and degree of urgency.[2] Not all the information is necessary in some circumstances but the completion of all aspects is usually recommended.

In order to successfully analyze the voiding pattern, the patients need to record all details completely for an appropriate length of time, however, usually the longer the duration of use of the FVC/BD the more precise the record of the pattern of voiding. However, in some cases compliance by the patient to finish the FVC/BD decreased over time due to the burden.[3] As a result, the reliability may be decreased. Not only is the increase in patient burden a limitation but also the time necessary for the physicians who assign FVC/BD to analyze the data. This retrospective study was carried out in patients primarily diagnosed with nocturia over a period of 6 years in a functional urology practice. It revealed that FVC/BD was recommended in only 50% of patients after the initial visit and only 62% of these patients complied with FVC/BD.[4] Approximately 50-60% of patients successfully completed a 3-day BD and the most difficult part was the calculation of the voided volume, particularly in women.[5,6] The lowest percentage of completion and reliability was maximum voided volume during the night.[6]

The 3-day FVC/BD as a standard recommendation may not be appropriate for all lower urinary tract conditions, particularly in cases in which high accuracy is required.[7] In many studies it was found that the completion rate of FVC/BD was between 50 and 60% of participants.[4-6] However, there have been some limitations and pitfall experienced during the recording using the FVC/BD. In order to address these concerns, this review aims to discover the appropriate duration of FVC/BD to increase completion rate, compliance and reliability as well as to decrease interpretation errors of FVC/BD.

Limitation of FVC/BD

Before a physician directs a patient to record FVC/BD, any limitations need to be recognized before in order to maximize recording, analysis and interpretation. Although FVC/BD is more accurate than patient recall[7], it needs to be recognized it does not replace history taking.

The most important limitations are the level of education and cooperation of the patient. In well-educated patients, health care providers can simply teach them how to fill in and complete the FVC/BD before the first visit without compromising the accuracy of the information.[8]

In addition, the habits of the individual patients can affect recording such as convenience void and self-learning. Convenience voids were described in 2005 and defined as voiding episodes when the bladder was emptied for social reasons, before going out on a long journey and before retiring to bed at night.[9] This issue affected the analysis of the data collected from the FVC, particularly with regard to mean voided volume and mean interval between voids. A previous study demonstrated that 72% of healthy volunteers recorded at least 1 convenience void in a 7-day FVC.[9] In the case of self-learning, the longer duration of BD may influence a patient with UUI by effects of self-monitoring so that episodes of urinary incontinence (UI) would be decreased over time.[10]

FVC duration VS Reliability and Compliance

Appropriate duration of recording FVC has been debated. To increase reliability a longer duration is required but then the compliance will decrease.[11] In addition, the day-to-day variation was found to decrease over a longer duration. With regard to reliability, various studies reported on duration of recording of FVC between 1 and 14 days, all in different population and with different lower urinary tract problems.

The latest AUA/SUFU guidelines for diagnosis and treatment of a non-neurogenic overactive bladder in adults stated that information from BD may be obtained and useful to monitor efficacy and guide treatment.[12] The EAU guidelines for non-neurogenic male and female LUTS recommended using BD to assess the symptoms, especially in the case of prominent storage symptoms. The duration of BD completion was at least 3 days.[13,14]

One study proposed the terms "diary fatigue" and "diary despair" from longer duration of completion of a BD.[15] To avoid both conditions, physicians need to optimize the duration according to symptoms. Before discussing the reliability, most studies used intraclass or interclass correlation coefficients (ICC) as a tool to define reliability in each quantitative parameter. If ICC was equal to or more than 0.75, the parameter indicated good reliability. In contrast, if ICC was less than 0.5, the parameter had poor reliability.[16]

Non-specific lower urinary tract symptoms (LUTS)

Despite the greater burden from a longer duration FVC, the study comparing 2-, 3- and 7-day FVC revealed that both male and female participants significantly preferred the 7-day rather than a 2- or 3-day FVC.[3] Many studies compared less than 7-day and 7-day FVCs and found that the completion rate of a 3-day and 7-day FVC was 90% and 50%, respectively. This suggested that the 3-day FVC was superior to the 7-day in terms of data completeness.[15] Another study in women with LUTS concluded that completion of a 4-day was as adequate as a 7-day FVC with nearly a 50% reduction in burden.[17] In the case of a 1-day FVC, a study demonstrated that it might be sufficient to differentiate between high and low symptoms scores, but it could not be used to diagnose lower urinary tract dysfunction or monitor after treatment.[18] A systematic review study of the optimum duration of FVC for the assessment and monitoring of patients with LUTS revealed that 3- and 7-day FVC had higher ICC (reliability) but no statistically strong conclusions could be made due to the variety of methodologies used, the quality of the studies, sample sizes and selection bias.[19]

Urinary incontinence (UI)

Information regarding UI has been found to be accurately gained from FVC/BD. In the case of a 1-day FVC positive outcomes were that less time was needed and there was sufficient information to gain insight in women with objective urgency urinary incontinence (UUI) but the negative outcome was there was not enough detail pertinent to various activity conditions such as a leisure day and a working day.[20]

In the case of the 3-day FVC, the total number of incontinent and total number of voiding episodes were reliable following the 3 days[21] but the data was not enough in cases with a small number of UI episodes. A 7-day FVC showed enough of a pattern for an evaluation of the frequency of UI episodes10 particularly in a patient who had 3 or more UI episodes per day.[7] Longer than 7 days such as 14-day FVC may be effective in women with UUI due to self-monitoring and life-style modification.[10] Therefore, duration of FVC/BD should be considered on type and severity of UI.

Nocturia

The primary aim of using FVC in cases of nocturia is to define the etiology including global polyuria, nocturnal polyuria and/or low voided volume.[22] Generally, the FVC is considered a standard tool in the diagnosis of nocturnal polyuria and the monitoring of a treatment outcome.[23] If a reliability of more than 80% is needed, a 3-day FVC or longer is enough for nocturia and nocturnal urine production but compliance significantly decreased after day 4 therefore would not be advisable.[11] In addition to FVC, another promising method for the diagnosis of nocturnal polyuria is analysis of a single urine sample produced at the time of first nocturnal awakening.[24]

FVC and Questionnaires

There was a weak correlation and lack of agreement between a 3-day FVC and the International Prostate Symptom Score (IPSS)[25,26] indicating that the FVC could not replace the questionnaire. Moreover, the questionnaire may under- or overestimate the number of nighttime voids so therefore the FVC should be included as part of the evaluation of nocturia.[26,27] As a consequence of the lack of a standard BD, the International Consultation on Incontinence Questionnaire (ICIQ) Bladder Diary for evaluation of LUTS was developed in 2012. On phase 1a of the testing of this diary, [27] patients and 30 clinicians were enrolled onto the study. The results showed that the patients preferred a diary duration of 7 days or less without a specific format and the clinicians preferred a 3-day duration in a single format.[28] Phase 1b – content validation was carried out and then the ICIQ-BD was validated and compared with the outcomes of the questionnaire or urodynamics. Only nocturia revealed strong agreement between ICIQ-male/female LUTS questionnaires and ICIQ-BD whereas urgency had weak correlation between the questionnaires and urodynamics.[29]

FVC and Urodynamics

FVC and urodynamics need to be used for different aims. Many studies tried to use FVC as a tool to diagnose lower urinary tract dysfunction instead of urodynamics. In 1994, the Larsson FVC was proposed as a differential diagnostic tool using frequency and mean voided volumes between UUI with detrusor overactivity (DO)

and genuine stress urinary incontinence (SUI) in women instead of urodynamics.[30] At the end of the study this tool was not popularly used because the sensitivity and specificity for DO were 52% and 70%, and the sensitivity and specificity for SUI were 66% and 65%, respectively.[31] Another study in women with DO showed a low correlation between FVC and urodynamic parameters as well as concluding that FVC could not be used for diagnostic purposes.[32]

A study in 15 healthy nulliparous women, who scored a grade of fullness on FVC as a tool to measure bladder sensation during normal daily life and later were examined by urodynamics, showed that 65% of all voids was made without any desire to void. When comparing bladder sensation between FVC and urodynamics, there was no statistically significant difference in FVC with the exception of the volume at urgent desire to void after voluntarily postponing to void.[33] Therefore, bladder sensation on FVC can provide information regarding bladder sensation before a urodynamics study is performed.

Conclusion

FVC/BD is a simple, basic and useful tool to help physicians understand lower urinary tract symptoms. The greater the length of time the FVC/BD is completed by the patient, the greater the reliability of the data collected but the higher the patient burden. Lack of some information in the FVC/BD does not mean the data are useless as it depends on the focus of the physician at that time. In some cases, in which the diagnosis is doubtful, completion of the FVC/BD is encouraged not only for the monitoring a treatment outcome but also for research purposes. The FVC/BD cannot replace history taking, questionnaires and urodynamics and all are essential to support each other to help physicians to give a precise diagnosis.

Conflict of Interest

The author declares no conflict of interest.

References

1. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn 2002;21:167-78.
2. Drake MJ. Fundamentals of terminology in lower urinary tract function. Neurourol Urodyn 2018;37: S13-9.
3. Ku JH, Jeong IG, Lim DJ, Byun SS, Paick JS, Oh SJ. Voiding diary for the evaluation of urinary incontinence and lower urinary tract symptoms: prospective assessment of patient compliance and burden. Neurourol Urodyn 2004;23:331-5.
4. Drangsholt S, Ruiz MJA, Peyronnet B, Rosenblum N, Nitti V, Brucker B. Diagnosis and management of nocturia in current clinical practice: who are nocturia patients, and how do we treat them? World J Urol 2019;37:1389-94.
5. Cameron AP, Wiseman JB, Smith AR, Merion RM, Gillespie BW, Bradley CS, et al. Are three-day voiding diaries feasible and reliable? Results from the Symptoms of Lower Urinary Tract Dysfunction Research Network (LURN) cohort. Neurourol Urodyn 2019;38:2185-93.
6. Jimenez-Cidre MA, Lopez-Fando L, Esteban-Fuertes M, Prieto-Chaparro L, Llorens-Martinez FJ, Salinas-Casado J, et al. The 3-day bladder diary is a feasible, reliable and valid tool to evaluate the lower urinary tract symptoms in women. Neurourol Urodyn 2015;34:128-32.
7. Homma Y, Ando T, Yoshida M, Kageyama S, Takei M, Kimoto K, et al. Voiding and incontinence frequencies: variability of diary data and required diary length. Neurourol Urodyn 2002;21:204-9.
8. Robinson D, McClish DK, Wyman JF, Bump RC, Fanti JA. Comparison between urinary diaries completed with and without intensive patient instructions. Neurourol Urodyn 1996;15:143-8.
9. Darling R, Neilson D. Convenience voids: an important new factor in urinary frequency volume chart analysis. J Urol 2005;173:487-9.
10. Locher JL, Goode PS, Roth DL, Worrell RL, Burgio KL. Reliability assessment of the bladder diary for urinary incontinence in older women. J Gerontol A Biol Sci Med Sci 2001;56:M32-5.
11. van Haarst EP, Bosch JL. The optimal duration of frequency-volume charts related to compliance and reliability. Neurourol Urodyn 2014;33:296-301.
12. Lightner DJ, Gomelsky A, Souter L, Vasavada SP. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU Guideline Amendment 2019. J Urol 2019;202:558-63.
13. Gravas S, Cornu JN, Gacci M, Gratzke C, Herrmann TRW, Mamoulakis C, et al. EAU Guidelines on Management of Non-neurogenic Male Lower Urinary Tract Symptoms (LUTS), incl. Benigh Prostatic Obstruction (BPO) [Internet]. Arnhem, the Netherlands: EAU Guidelines Office; 2022. [cited 2022 Jan

31]. Available from: https://uroweb.org/guideline/treatment-of-non-neurogenic-male-luts/#9.
14. Harding CK, Lapitan MC, Arlandis S, Bø K, Cobussen-Boekhorst H, Costantini E, J, et al EAU Guidelines on management of non-neurogenic female lower urinary tract symptoms [Internet]. Arnhem, the Netherlands: EAU Guidelines Office; 2022. [cited 2022 Jan 31]. Available from: https://uroweb.org/guideline/non-neurogenic-female-luts/.
15. Tincello DG, Williams KS, Joshi M, Assassa RP, Abrams KR. Urinary diaries: a comparison of data collected for three days versus seven days. Obstet Gynecol 2007;109:277-80.
16. Koo TK, Li MY. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. J Chiropr Med 2016;15:155-63.
17. Schick E, Jolivet-Tremblay M, Dupont C, Bertrand PE, Tessier J. Frequency-volume chart: the minimum number of days required to obtain reliable results. Neurourol Urodyn 2003;22:92-6.
18. Yap TL, Cromwell DA, Brown C, Emberton M, van der Meulen J. The reliability of the frequency-volume chart in assessing lower urinary tract symptoms. BJU Int 2007;100:111-5.
19. Yap TL, Cromwell DC, Emberton M. A systematic review of the reliability of frequency-volume charts in urological research and its implications for the optimum chart duration. BJU Int 2007;99:9-16.
20. van Melick HH, Gisolf KW, Eckhardt MD, van Venrooij GE, Boon TA. One 24-hour frequency-volume chart in a woman with objective urinary motor urge incontinence is sufficient. Urology 2001;58:188-92.
21. Groutz A, Blaivas JG, Chaikin DC, Resnick NM, Engleman K, Anzalone D, et al. Noninvasive outcome measures of urinary incontinence and lower urinary tract symptoms: a multicenter study of micturition diary and pad tests. J Urol 2000;164:698-701.
22. Weiss JP. Nocturia: focus on etiology and consequences. Rev Urol 2012;14:48-55.
23. Lojanapiwat B, Jitpraphai S. nocturia and efficacy of desmopressin for treatment of polyuric nocturia. Thai J Urol 2007;28:7-15.
24. Monaghan TF, Verbalis JG, Haddad R, Pauwaert K, Agudelo CW, Goessaert AS, et al. Diagnosing nocturnal polyuria from a single nocturnal urine sample. Eur Urol Focus 2020;6:738-44.
25. Yap TL, Cromwell DA, Brown C, van der Meulen J, Emberton M. The relationship between objective frequency-volume chart data and the I-PSS in men with lower urinary tract symptoms. Eur Urol 2007;52:811-8.
26. Blanker MH, Bohnen AM, Groeneveld FP, Bernsen RM, Prins A, Ruud Bosch JL. Normal voiding patterns and determinants of increased diurnal and nocturnal voiding frequency in elderly men. J Urol 2000;164:1201-5.
27. Ku JH, Hong SK, Kim HH, Paick JS, Lee SE, Oh SJ. Is questionnaire enough to assess number of nocturic episodes? Prospective comparative study between data from questionnaire and frequency-volume charts. Urology 2004;64:966-9.
28. Bright E, Cotterill N, Drake M, Abrams P. Developing a validated urinary diary: phase 1. Neurourol Urodyn 2012;31:625-33.
29. Bright E, Cotterill N, Drake M, Abrams P. Developing and validating the International consultation on incontinence questionnaire bladder diary. Eur Urol 2014;66:294-300.
30. Larsson G, Blixt C, Janson G, Victor A. The frequency/volume chart as a differential diagnostic tool in female urinary incontinence. Int Urogynecol J 1994;5:273-7.
31. Tincello DG, Richmond DH. The Larsson frequency/volume chart is not a substitute for cystometry in the investigation of women with urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct 1998; 9:391-6.
32. Larsson G, Abrams P, Victor A. The frequency/volume chart in detrusor instability. Neurourol Urodyn 1991;10:533-43.
33. De Wachter S, Wyndaele JJ. Frequency-volume charts: a tool to evaluate bladder sensation. Neurourol Urodyn 2003;22:638-42.

Review Article

Active surveillance in small renal masses

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Keywords:
Renal mass, active surveillance, renal cancer

Abstract

Active surveillance is one of the options available for management of renal masses smaller than 4 cm with a suspicion of malignancy in association with nephrectomy and ablative procedures. In general, small renal masses grow slowly and have a very low metastatic potential, but exceptions occur. Active surveillance is generally offered in the elderly with high comorbidities but there is a lack of validated data in other patient demographics. Data from younger and healthier patients are gradually emerging and have shown promising results but still require further validation. Computed tomography (CT), magnetic resonance imagin (MRI), and ultrasonography (US) are all acceptable imaging modalities for surveillance of renal masses, but CT is the most commonly used. Intervals of surveillance differs from study to study, but the most common schedule is 3, 6, and 12 months after initiation, then annually. The cut off point for delayed intervention is growth > 0.5 cm/year or absolute size > 4 cm. Oncologic outcome is comparable to nephrectomy and ablation in terms of cancer-specific survival. Quality of life for patients undergoing active surveillance is also comparable but is significantly lower in those with confirmed malignant biopsy results. Cost of active surveillance is as a rule more cost effective than nephrectomy or ablation.

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Introduction

Renal cell carcinoma is the 6th most common cancer in males and 10th in females, accounting for 5% and 3% respectively of all diagnosed malignancies.[1] In the Thai population, the age-standardized rate of renal cell carcinoma is 1.2 per 100,000. The incidence of diagnosis of renal mass has been increasing over the past 20 years potentially due to the increased utilization of cross-sectional imaging for various reasons.[2] This also increases the detection of small renal masses (SRMs), defined as a solid renal mass or complex renal cyst sized < 4 cm or a T1a tumor, as the trend is that renal masses are being discovered at a smaller and smaller size.[3]

Due to its low malignancy and metastatic potential, and the fact that most patients are asymptomatic, management of SRMs remains a clinical dilemma between the risk of deterioration of renal function and surgical complications from nephrectomy, and the benefit of early removal and accurate pathologic diagnosis. Active surveillance is one of the available management options according to guidelines from the majority of in-

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stitutions and the referral of patients for periodic monitoring, usually with imaging and laboratory tests, for signs of progression or metastasis with an intention for curative intervention once progression is detected.

This aim of this review is to describe evidence which is currently available with regard to active surveillance of SRMs.

Nature of small renal masses

In contrast with larger enhancing renal masses where the diagnosis of malignancy is relatively reliable from imaging and the aim of treatment is mainly eradication, small enhancing renal masses pose slightly unique challenges for clinical decision making due to uncertainty in diagnosis and the rather indolent biological nature of these potential tumors.

SRMs are known for their low levels of both malignant potential and aggressive nature. Data from renal mass biopsy and molecular profiling have indicated that 20% are benign masses, 60% are indolent RCC and only 20% are potentially aggressive RCC.[4]

Size and growth

SRMs were found to exhibit various growth potentials ranging from no growth at all to a rapid growth, but the majority grow rather slowly. In 2012, Lane conducted a pooled retrospective analysis from 18 studies into a total of 957 SRMs with an average initial size of 2.8 cm and reported an average growth of 3.2 mm/year. The data from the included studies even indicated a proportion of 15-25% which exhibited zero growth.[5] Data from the Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) Registry, which is a large prospective multi-institutional prospective clinical study regarding outcomes of active surveillance of SRMs, demonstrated a median growth rate of 0.9 mm/year in 271 patients and also reported that 42% of tumors showed zero growth or less (size reduction).[6] Although growth rates vary from patient to patient, there has yet to be a reliable parameter to predict which tumor is more likely to grow, as many authors have failed to demonstrate any correlation between growth rates and specific parameters.[6-8] Even malignant tumors can exhibit zero growth.[9,10]

Although no parameters are predictive of tumor growth, the test of time will. Data from the DISSRM registry have demonstrated that SRMs are more likely to grow (or shrink) during the first 6 months of follow-up than after 1 year of active surveillance.[6]

Metastasis

SRMs do possess a small but non-negligible potential to metastasize. A systematic review in 2012 from a total of 880 patients reported a metastatic rate of 2% during a median follow-up time of 2 years.[10] Data from post-nephrectomy (partial or radical) patients have also demonstrated a similar metastatic rate of 1.8% during 6.9 years of follow-up.[11] A recent systematic review in 2021 collected data from 20 studies and found that 6 studies reported a 0% rate of metastasis while an overall metastatic rate was 2.2% with a median follow up time of between 21-77 months.[12]

While size does not predict growth, it appears to predict metastasis as initial tumor size was found to be larger in patients who developed metastasis than those who did not.[13] Even post-nephrectomy patients with pathologically confirmed RCC still demonstrated similar results with a metastatic rate of 0%, 1.1%, 3.3%, and 6% in tumors smaller than 1 cm, 1-2 cm, 2-3 cm, and 3-4 cm, respectively.[14]

Mortality

As SRMs carry a very low potential for metastasis, the same could be inferred in terms of mortality. McIntosh described a five-year cancer-specific mortality of 1.2%.[8] Data from the DISSRM registry which pooled patients who received any treatment or surveillance showed an even lower mortality with a seven-year cancer-specific survival of 98.8% in the partial nephrectomy group and 100% for radical nephrectomy, ablation and active surveillance group.[15] Overall survival, in contrast, was much lower in the active surveillance group, in comparison with other groups, probably due to older age and higher comorbidity rates of subjects.

Case selection

Patient status

The selection of an appropriate patient remains one of the most challenging and vital aspects of active surveillance, and a well-defined universally accepted group of criteria for eligibility of active surveillance has yet to be established. This is largely due to the paucity of evidence in young and healthy patients.[12] Fundamentally,

active surveillance is usually offered to patients with significant competing health risks that might offset the risk of death by cancer progression or renders the risk of interventions to be excessively high.[16] As there has yet to be a randomized trial and the majority of patients who chose active surveillance tend to have old age and high co-morbidities, most of the available studies have a median age between 67-83 years.[12]

In comparison, the guidelines from other major institutions including the NCCN, American Urological Association (AUA), and European Association of Urology (EAU) similarly recommend prioritization of active surveillance in elderly patients and those with significant co-morbidities. AUA and NCCN also offer active surveillance as an option for patients with a mass smaller than 2 cm.[17-19] AUA also describe multiple favorable factors for active surveillance including borderline renal function and patient preference, as well as other tumor characteristics such as size < 3 cm, cystic feature predomination, non-infiltrative features, low complexity, growth < 5 mm/year, and favorable histology.

As data supporting the safety of active surveillance in the elderly and those with significant co-morbidities are becoming more reliable, its applicability in young and healthy patients is starting to be recognized as well. Recent data in 2021 analyzing the subgroup of patients from the DISSRM registry with an age younger than 60 years have shown promising results. Of 82 patients, overall survival and cancer-specific survival at seven years were 90.8% and 100%, respectively. Intervention rate was also found to be similar to previous data at 19%. These results are not simply a representation for young patients but represent young and healthy patients as 96% of the active surveillance population has an Eastern Cooperative Oncology Group (ECOG) performance status grade 0-1 and half of the study population has a Charlson Comorbidity Index of zero.[20]

Cell types and renal mass biopsy

As SRMs can vary in nature and consist of both benign and malignant tumors. Renal cell carcinoma (RCC) can also be classified into multiple histologic subtypes including clear cell RCC, chromophobe RCC, papillary RCC, and rarely, collecting (Bellini) duct carcinoma. Different histological subtypes of RCC are known to behave differently, as collecting duct carcinoma is considered to be the most aggressive, followed by papillary RCC type II, clear cell RCC, and papillary RCC type I, respectively.[21] Different levels of aggressiveness also translate into a difference in mortality, as has been indicated in a recent meta-analysis. This study demonstrated a significantly higher mortality in patients with papillary RCC type II than clear cell RCC (HR: 1.2) and similar outcomes between clear cell RCC and papillary RCC type I.[22]

Similar behavior has also been observed in SRMs. Finelli et al. reported a predicted growth rate of 2.5 mm/year in biopsy-proven clear cell RCC and 0.17 mm/year in papillary type I RCC. Chromophobe RCC and papillary type II RCC growth fall in the range between clear cell and papillary type I RCC. It is worth noting that although the average growth is significantly different between subtypes, all subtypes demonstrate a wide heterogeneity of growth ranging from slight regression to rapid progression.[23] In addition to histologic subtype classification, multiple pathologic features such as a high nuclear grading, lymphovascular invasion, sarcomatoid differentiation, and rhabdoid differentiation can adversely affect cancer-specific survival as well.[24]

Although the accuracy and safety of renal mass biopsy is often, historically, of major concern for most clinicians, a growing body of literature may be suggesting otherwise. A systematic review of 17 studies reported a non-diagnostic rate ranging from 0-22%.[25] This number could possibly be reduced further by a repeat biopsy.[26] A more recent study also reported a similar result.[27]

Renal mass biopsy has also been found to accurately diagnose malignancy and histologic subtypes in SRMs. Marconi et al. conducted a meta-analysis which included 33 studies from 1967 to 2011, sensitivity and specificity for the diagnosis of malignancy were 99.7% and 98.2%, respectively, in those with diagnostic biopsy. The reported concordance rate of histologic subtype between biopsy and surgical pathology from multiple studies was 96%.[25,28] However, sensitivity for the detection of tumor grading and adverse pathologic features from biopsy may not be as high.[29]

Another major concern with regard to renal mass biopsy for most clinicians is its incidence of associated complications. Renal mass biopsy can potentially lead to various complications

including pain, bleeding complications including hematoma and hematuria, infection, and the area of greatest concern, biopsy tract tumor seeding. Perirenal hematoma is the most common complication of renal mass biopsy at approximately 2-7%, but hematomas that required transfusion only occurred in 0.7% of cases. Hematuria occurred in 3% which were shown to be almost entirely self-limiting.[25] There were also multiple reports of pseudoaneurysm which required angioembolization.[30,31] The risk of needle track tumor seeding is extremely low. There was a single case reporting needle tract seeding diagnosed by radiologic imaging from a mass that turned out to be urothelial carcinoma, but the tract was not confirmed pathologically.[32] Another pathological analysis of perirenal fat and peritumoral fat to specifically detect seeding in another study did not find any evidence of tumor seeding.[33]

As the benefit and safety of renal mass biopsy are becoming more established, renal mass biopsy has, therefore, become more and more utilized over the last decade, especially in SRMs.[34,35] However, as renal mass biopsy still harbors some non-diagnostic risk and demonstrable, though very low, risk of false-negative for malignancy, most guidelines from European and American institutions still regard the use of renal mass biopsy as "consider" and almost unanimously recommend against renal mass biopsy when the result may not alter clinical management (Table 1).

In summary, the selection of patients with SRMs who are eligible for active surveillance is a clinical challenge. To date, available data suggests that old age, high co-morbidity, small size, less aggressive cell types, and absence of adverse features are favorable factors for patient selection for active surveillance.

Surveillance protocols

As the purpose of active surveillance is to delay a primary intervention until a patient actually shows signs of tumor progression and to omit the intervention for those who do not, three components are of utmost importance in doing so; modality of surveillance, interval of surveillance, and triggers for intervention.

Modalities

Since radiographic imaging is used to detect the clinical progression of SRMs, the ideal imaging modality should be able to reliably provide clinicians with tumor characteristics including its size, complexity (in terms of cystic mass), invasion, and any signs of distant metastasis. At the same time there needs to be a minimizing of cost, exposure to ionizing radiation, and adverse effects of contrast media, as patients under active surveillance are deemed to potentially undergo multiple imaging procedures throughout their lifetime.

Computerized tomography (CT) with contrast media is one of the most commonly used imaging

Table 1. Institutional guidelines recommendation for renal mass biopsy (RMB) in the setting of active surveillance

AUA 2021	For patients with a solid or Bosniak 3/4 complex cystic renal mass in whom the risk/ benefit analysis for treatment is equivocal and who prefer AS, clinicians should consider renal mass biopsy (RMB) (if the mass is solid or has solid components) for further oncologic risk stratification
EAU 2021	Perform a percutaneous biopsy in select patients who are considering active surveillance. Use core needle biopsy rather than fine needle aspiration. Do not perform a renal tumor biopsy of cystic renal masses, unless areas with a solid pattern are present. Not indicated for comorbid and frail patients who can be considered only for conservative management.
NCCN 2022	Consider renal mass biopsy at initiation of active surveillance or at follow-up, as clinically indicated.
ASCO 2017	All patients with an SRM should be considered for RTB when the results may alter management. Patients who are considered for an active surveillance protocol may benefit from a biopsy to assess risk for metastasis while undergoing surveillance but not necessary for all patients who undergo surveillance.
ESMO 2019	Renal biopsy is recommended to select patients with small masses for active surveillance, especially because of the incidence of non-malignant tumors in this setting.

modalities in the diagnosis and follow-up of renal masses due to its high availability, accessibility, and accuracy.[12] Therefore, CT is ranked at 9 points in the American College of Radiology (ACR) appropriateness criteria for the diagnosis of renal mass.[36] In addition to the obvious risk of adverse reactions from contrast agents, ionizing radiation exposure is one of the major concerns of utilizing CT for surveillance. From a single triple-phase protocol of KUB system CT scan, patients are usually exposed to an average effective dose of 11.2 mSv of radiation.[37] This seemingly insignificant dose of radiation can accumulate rapidly when performed repeatedly every 3-12 months resulting in a significant amount of radiation.[38] Hence, attention to the minimization of radiation should be ensured in patients undergoing active surveillance. Omission of some phases that may not play an important role in surveillance such as a pre-contrast phase or delayed phase could potentially reduce radiation exposure in some situations. A dual-energy CT scan is also another technique that carries the potential to reduce radiation exposure. The dual-energy CT scan is an emerging imaging technique that uses different energy (kV) of radiation simultaneously, which results in two different image data sets from a single scan. The technique, when used during image acquisition after contrast media injection, creates images that can be processed using a specialized algorithm to create "virtual unenhanced (VUE) images". Thus, the virtual unenhanced images could, theoretically, replace the need to acquire a pre-contrast image and reduce the radiation exposure by up to 33%.[39] In reality, however, the technique still harbors some limitations that hinder its widespread use. In comparison with true unenhanced images, there are some increases in the attenuation value of multiple solid organs in VUE images, including the kidney, which might affect the radiologic interpretation of enhancement.[40] However, another study reported that these variations do not significantly affect the classification of renal mass.[41] In addition, there has yet to be a standardized protocol of dual-energy CT across various manufacturers.[39]

Magnetic resonance imaging (MRI) carries an equally high accuracy as CT in the diagnosis and follow-up of renal masses. It is ranked at 8 points in the ACR appropriateness criteria; one point below CT, owing to its higher cost and lower availability.[36] MRI may be superior to CT in the detection of enhancement in the internal solid part of cysts with wall calcification as the MRI signal is not interfered with by calcification.[42] In addition, MRI is also preferable to CT as it does not expose patients to ionizing radiation. Furthermore, patients with chronic kidney disease (CKD) may be more suitable for MRI as the gadolinium used does not affect renal function. Nephrogenic systemic fibrosis (NSF) is one of the major adverse reactions of gadolinium-based contrast agents (GBCA) and by far the most serious one. It is well known that CKD patients with glomerular filtration rates <30 ml/min/1.73 m^2 are at significant risk of developing NSF. Surprisingly, recent evidence indicated that the risk is only applicable to group I and III GBCAs only. Group II GBCAs are found to expose patients to an extremely low to non-existent risk of developing NSF[43,44], such that the ACR manual on contrast media recommended a routine assessment of renal function to be optional prior to group II GBCAs administration.[45] Therefore, an MRI, if available, could potentially be regarded as the modality of choice for patients with severe renal impairments in the near future.

The advantages of ultrasonography are its high availability, low cost, and lack of ionizing radiation. However, ultrasonography has its limitations due to its lower image resolution especially in patients with obese body habitus, hemorrhage in cystic mass, and cyst wall calcification. Owing to its lower resolution, its ability to detect a renal mass smaller than 2 cm is also much lower than CT.[46] The use of color Doppler imaging has been shown to further enhance the characterization of renal mass.[36] In recent years, contrast-enhanced ultrasonography (CEUS) is emerging as a new technique to improve the image quality and accuracy of ultrasound. CEUS has been demonstrated to have a similar diagnostic value to CT and can even outperform CT scan in the detection of septa, wall thickenings and wall enhancements in cystic renal masses.[47] In terms of surveillance, size measurement of renal mass is also similar to CT, Bertelli et al. demonstrating that median size did not differ between CT and CEUS at all follow-up points during a surveillance period of over 2 years.[48] CEUS is also especially useful in patients with renal impairments as the microbubble-filled contrast agent used in CEUS

is not excreted through the kidney.[39]

As the resolution of conventional ultrasound is still inferior to cross-sectional imaging and the contrast media for CEUS is only available in a few selected institutions, the diagnosis of SRM is usually determined by CT or MRI. For surveillance, however, all three modalities were found to be used in various reported surveillance protocols. CT with contrast media was the most commonly used modality for follow-up in 33 studies. The use of MRI for follow-up was reported in 14 studies to be between 6 and 34%. Ultrasonography was reported as being used for follow-up after initial cross-sectional imaging in 11 studies with 2 studies using ultrasonography for follow-up in 100% of cases.[12] This is in accordance with the recommendations from NCCN in which CT or MRI was recommended for the diagnosis and the first follow-up for active surveillance, and could be followed up by CT, MRI or ultrasonography as indicated.[19]

Surveillance intervals and triggers for intervention

While most SRMs usually grow slowly, reports have shown that a minute proportion of SRMs can still grow up to 7 mm per month and most SRMs that do exhibit changes in size do so in the early period of surveillance.[6] Therefore, most surveillance protocols use a follow-up schedule that is most frequent initially then gradually become less frequent as patients go through their surveillance years. Data from a meta-analysis reported that the most commonly used follow-up schedule was at 3, 6, 12 months after initiation of surveillance, then annually afterwards. None of the studies reported on the rationale behind their follow-up schedule nor mentioned the endpoint of surveillance.[12]

Initial data with regard to the trigger for delayed intervention stemmed from the literature on renal masses in patients with von Hippel-Lindau disease who usually develop multiple renal masses and, thus, are usually treated with surveillance until the masses were of a significant size. The cut-off size used in the study was 3 cm in which any masses below this size had shown to develop no metastasis in a median follow-up of nearly 5 years.[49] On the contrary, sporadic renal masses are usually more heterogeneous in tumor biology, therefore, the cut-off from size alone may not suffice. The growth rate of SRMs has been found to be associated with metastasis and no metastasis was found in SRMs with no growth at all.[5,13] As a result, most studies adopt a cut-off at an absolute size of > 4 cm or a growth rate of > 0.5 cm/year with some studies also included the detection of metastasis for triggering a delayed intervention[6,12] (Figure 1).

Outcomes

Oncologic outcomes

Comparison of oncologic outcomes between active surveillance and other treatment options is based on very limited data owing to the lack of prospective randomized studies and the scarcity of long-term outcome. Early data came from the Surveillance, Epidemiology, and End Results (SEER) Program urinary cancer file which enrolled 733 patients from 2000 to 2013. The results have shown a benefit of thermal ablation and cryoablation over deferred therapy, even when adjusted for age, tumor size and grade.[50] However, a more recent prospective data set from the DISSRM Registry which enrolled patients from 2009 onwards has demonstrated a comparable cancer-specific survival among nephrectomy, ablation and active surveillance when adjusted for Charlson comorbidity index, age and sex. Overall survival was lower in the active surveillance arm due to a significantly higher comorbidity but active surveillance was not independently associated with worse overall survival in an adjusted analysis.[15]

Most recent data on active surveillance in young healthy patients eventually confirmed that the lower overall survival in the active surveillance arm could be attributed to old age and high comorbidities. With a 5 year median follow-up time, there was no significant difference in seven-year overall survival between active surveillance and primary intervention; 94% vs 91%, respectively. Cancer-specific survival was 100% in both groups. Furthermore, a delayed intervention may not actually be "delayed" as the term indicates since a subgroup of patients who eventually underwent a delayed intervention, which may represent a more aggressive portion of SRMs, demonstrated a similar 5-year recurrence-free survival to primary intervention; 100% for active surveillance and 96% for primary intervention.[20]

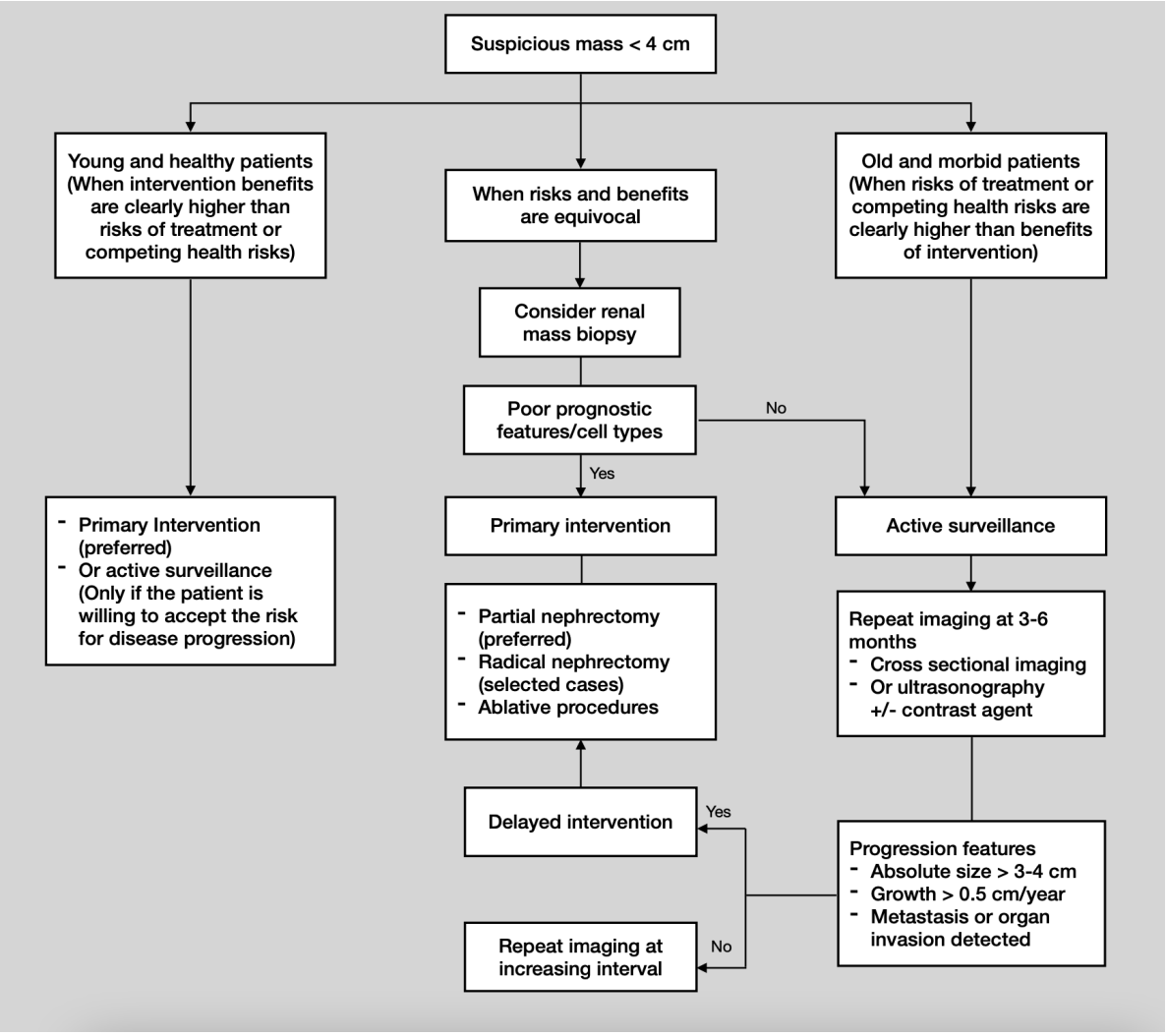

Figure 1. Suggested aigorithm for the management of renal mass smaller than 4 cm with a suspicion of malignancy

Quality of life

In terms of quality of life, active surveillance has its advantages with regard to the possibility of avoiding unnecessary procedures and recovery at the price of stress from uncertainty in relation to the diagnosis. Balancing the two sides of a coin is crucial in advising patients to choose from various treatment options. McAlpine et al. demonstrated that in the 10-year horizon, 70 years old patients would similarly benefit from partial nephrectomy or active surveillance as the gain in Quality Adjusted Life Months (QALMs) was found to be 38 months and 36 months, respectively.[51] When compared with ablative procedures, active surveillance also demonstrated a similar quality-adjusted life expectancy to cryoablation and was significantly higher than radiofrequency ablation.[52]

With regard to psychological distress, Goldberg et al. reported a similar Edmonton Symptom Assessment System - revised score (ESAS-r) and a psychological distress sub-score (PDSS) of ESAS-r between active surveillance and primary treatment. Nonetheless, the similar results between the two groups could possibly rely on the hope of the tumor being benign since a subgroup analysis of patients with biopsy-proven malignancy resulted in significantly higher ESAS-r and PDSS scores than in primary treatment.[53]

Cost

The cost of different management options is one of the factors that could affect a doctor-patient decision, especially in a low-resource setting. Cryotherapy was shown to be over 3,000 Canadian dollars more costly than active surveillance while providing the same quality-adjusted life expectancy (during the average exchange rate of CAD 1.03 to USD 1).[52] Active surveillance was also the option of choice when analysis was

carried out using the willingness to pay (WTP) threshold of USD 50,000 per QALY gain while primary treatment was the option of choice when the WTP threshold is raised to USD 75,000.[54] In Thailand, however, these numbers should be regarded cautiously since the WTP threshold in Thailand and the United States are widely different. From a random survey across all regions of Thailand, an average WTP/QALY-gain ranged between THB 59,000 to 285,000 (USD 1,843-8,906 at the exchange rate on Nov 2nd, 2020) and there were no data on the analysis of cost-effectiveness concerning SRMs at this range.[55]

It is also worth noting that most of the quality of life and cost-effectiveness analyses are based on the 60-70 year old patient demographic due to the rarity of long-term outcome data on younger patients.

Conclusion

Active surveillance is a safe, effective, and also cost-effective option for small renal masses in patients in the old age and high comorbidity demographic. Data on active surveillance in young and healthy patients is emerging and could possibly extend the utilization of the active surveillance option for SRMs in a more generalized population in the future. Renal mass biopsy is an effective method for further risk stratification of SRMs prior to the selection of treatment options. Most surveillance protocols use cross-sectional imaging at the first follow-up study which is then followed up by CT, MRI, or ultrasonography, usually over increasing intervals.

References

1. Capitanio U, Bensalah K, Bex A, Boorjian SA, Bray F, Coleman J, et al. Epidemiology of renal cell carcinoma. Eur Urol 2019;75:74-84.
2. Lightfoot N, Conlon M, Kreiger N, Bissett R, Desai M, Warde P, et al. Impact of noninvasive imaging on increased incidental detection of renal cell carcinoma. Eur Urol 2000;37:521-7.
3. Nguyen MM, Gill IS, Ellison LM. The Evolving Presentation of Renal Carcinoma in the United States: Trends From the Surveillance, Epidemiology, and End Results Program. J Urol 2006;176:2397-400.
4. Campbell SC, Lane BR, Pierorazio PM. Malignant Renal Tumors. In: Partin AW, Demochowski RR, Kavoussi LR, Peters CA, editors. Campbell-Walsh-Wein Urology. 12nd ed. Philadelphia: Elsevier; 2021. p. 2164.
5. Lane BR, Tobert CM, Riedinger CB. Growth kinetics and active surveillance for small renal masses. Curr Opin in Urol 2012;22:353-9.
6. Uzosike AC, Patel HD, Alam R, Schwen ZR, Gupta M, Gorin MA, et al. Growth Kinetics of Small Renal Masses on Active Surveillance: Variability and Results from the DISSRM Registry. J Urol 2018;199:641-8.
7. Organ M, Jewett M, Basiuk J, Morash C, Pautler S, Siemens R, et al. Growth kinetics of small renal masses: A prospective analysis from the Renal Cell Carcinoma Consortium of Canada. Can Urol Assoc J 2014;8:24-7.
8. McIntosh AG, Ristau BT, Ruth K, Jennings R, Ross E, Smaldone MC, et al. Active surveillance for localized renal masses: tumor growth, delayed intervention rates, and > 5-yr clinical outcomes. Eur Urol 2018;74:157-64.
9. Jewett MAS, Mattar K, Basiuk J, Morash CG, Pautler SE, Siemens DR, et al. Active surveillance of small renal masses: progression patterns of early stage kidney cancer. Eur Urol 2011;60:39-44.
10. Smaldone MC, Kutikov A, Egleston BL, Canter DJ, Viterbo R, Chen DYT, et al. Small renal masses progressing to metastases under active surveillance. Cancer 2012;118:997-1006.
11. Umbreit EC, Shimko MS, Childs MA, Lohse CM, Cheville JC, Leibovich BC, et al. Metastatic potential of a renal mass according to original tumour size at presentation. BJU Int 2012;109:190-4.
12. Rebez G, Pavan N, Mir MC. Available active surveillance follow-up protocols for small renal mass: a systematic review. World J Urol 2021;39:2875-82.
13. Crispen PL, Viterbo R, Boorjian SA, Greenberg RE, Chen DYT, Uzzo RG. Natural history, growth kinetics, and outcomes of untreated clinically localized renal tumors under active surveillance. Cancer 2009;115:2844-52.
14. Lee H, Lee JK, Kim K, Kwak C, Kim HH, Byun S-S, et al. Risk of metastasis for T1a renal cell carcinoma. World J Urol 2016;34:553-9.
15. Alam R, Patel HD, Osumah T, Srivastava A, Gorin MA, Johnson MH, et al. Comparative effectiveness of management options for patients with small renal masses: a prospective cohort study. BJU Int 2019;123:42-50.
16. Wilcox Vanden Berg RN, Basourakos SP, LaRussa S, McClure TD. Management of the Small Renal Mass: a 2020 Update. Curr Oncol Rep 2020;22:69.
17. Ljungberg B, Albiges L, Abu-Ghanem Y, Bensalah K, Dabestani S, Fernández-Pello S, et al. European Association of Urology Guidelines on Renal Cell Carcinoma: The 2019 Update. Eur Urol 2019;75:799-810.

18. Campbell SC, Uzzo RG, Karam JA, Chang SS, Clark PE, Souter L. Renal mass and localized renal cancer: evaluation, management, and follow-up: AUA Guideline: Part II. J Urol 2021;206:209-18.
19. National Comprehensive Cancer Network. Kidney cancer (Version 2.2022) [Internet]. [cited 2021 Sep 8] Available from: https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf.
20. Metcalf MR, Cheaib JG, Biles MJ, Patel HD, Peña VN, Chang P, et al. Outcomes of active surveillance for young patients with small renal masses: prospective data from the DISSRM Registry. J Urol 2021;205:1286-93.
21. Deng FM, Melamed J. Histologic variants of renal cell carcinoma: does tumor type influence outcome? Urol Clin North Am 2012;39:119-32.
22. Deng J, Li L, Xia H, Guo J, Wu X, Yang X, et al. A comparison of the prognosis of papillary and clear cell renal cell carcinoma: Evidence from a meta-analysis. Medicine (Baltimore) 2019;98:e16309.
23. Finelli A, Cheung DC, Al-Matar A, Evans AJ, Morash CG, Pautler SE, et al. Small renal mass surveillance: histology-specific growth rates in a biopsy-characterized cohort. Eur Urol 2020;78:460-7.
24. Syed JS, Nawaf CB, Rosoff J, Bryson C, Nguyen KA, Suarez-Sarmiento A, et al. Adverse pathologic characteristics in the small renal mass: implications for active surveillance. Can J Urol 2017;24:8759-64.
25. Marconi L, Dabestani S, Lam TB, Hofmann F, Stewart F, Norrie J, et al. Systematic review and meta-analysis of diagnostic accuracy of percutaneous renal tumour biopsy. Eur Urol 2016;69:660-73.
26. Jeon HG, Seo SI, Jeong BC, Jeon SS, Lee HM, Choi H-Y, et al. Percutaneous kidney biopsy for a small renal mass: a critical appraisal of results. J Urol 2016; 195:568-73.
27. Bada M, Rapisarda S, Cicero C, Mauro MDI, Sebben M, B DEC, et al. The role of renal biopsy to improve small renal mass diagnosis and management: are there predictive factors for a higher detection rate?. The first Italian study of 100 cases. Minerva Urol Nephrol 2021;73:78-83.
28. Amaral BS, Macek P, Arora A, Pazeto CL, Zugail AS, Mombet A, et al. Renal tumor biopsy: rationale to avoid surgery in small renal masses. Curr Urol Rep 2021;22:46.
29. Kapur P, Setoodeh S, Araj E, Yan J, Malladi VS, Cadeddu JA, et al. Improving renal tumor biopsy prognostication with BAP1 analyses. Arch Pathol Lab Med 2022;146:154-65.
30. Maturen KE, Nghiem HV, Caoili EM, Higgins EG, Wolf Jr JS, Wood Jr DP. Renal mass core biopsy: Accuracy and impact on clinical management. Am J Roentgenol 2007;188:563-70.
31. Nuktong D, Sirisreetreerux P, Jenjitranant P, Viseshsindh W. Presentation and treatment of arteriovenous fistula, arteriovenous malformation, and pseudoaneurysm of the kidney in Ramathibodi Hospital. Insight Urol 2020;41:42-7.
32. Tikkakoski T, Paivansalo M, Apaja-Sarkkinen M, Ollikainen A, Lohela P, Matti K. Ultrasound-guided aspiration cytology of renal expansions. Rontgenblatter 1990;43:502-6.
33. Neuzillet Y, Lechevallier E, Andre M, Daniel L, Coulange C. Accuracy and clinical role of fine needle percutaneous biopsy with computerized tomography guidance of small (less than 4.0 Cm) Renal Masses. J Urol 2004;171:1802-5.
34. Ozambela M, Jr., Wang Y, Leow JJ, Silverman SG, Chung BI, Chang SL. Contemporary trends in percutaneous renal mass biopsy utilization in the United States. Urol Oncol 2020;38:835-43.
35. Patel DN, Ghali F, Meagher MF, Javier-Desloges J, Patel SH, Soliman S, et al. Utilization of renal mass biopsy in patients with localized renal cell carcinoma: a population-based study utilizing the National Cancer Database. Urol Oncol 2021;39:79.e1-.8.
36. Heilbrun ME, Remer EM, Casalino DD, Beland MD, Bishoff JT, Blaufox MD, et al. ACR Appropriateness criteria indeterminate renal mass. J Am Coll Radiol 2015;12:333-41.
37. Lukasiewicz A, Bhargavan-Chatfield M, Coombs L, Ghita M, Weinreb J, Gunabushanam G, et al. Radiation dose index of renal colic protocol CT studies in the United States: a report from the American College of Radiology National Radiology Data Registry. Radiology 2014;271:445-51.
38. Lopez PO, Dauer LT, Loose R, Martin CJ, Miller DL, Vano E, et al. ICRP Publication 139: occupational radiological protection in interventional procedures. Ann ICRP 2018;47:1-118.
39. Krishna S, Leckie A, Kielar A, Hartman R, Khandelwal A. Imaging of renal cancer. Semin Ultrasound CT MRI 2020;41:152-69.
40. Sahni VA, Shinagare AB, Silverman SG. Virtual unenhanced CT images acquired from dual-energy CT urography: accuracy of attenuation values and variation with contrast material phase. Clin Radiol 2013;68:264-71.
41. Neville AM, Gupta RT, Miller CM, Merkle EM, Paulson EK, Boll DT. Detection of renal lesion enhancement with dual-energy multidetector CT. Radiology 2011;259:173-83.
42. Israel GM, Bosniak MA. Calcification in cystic renal masses: is it important in diagnosis? Radiology

2003;226:47-52.
43. Bruce R, Wentland AL, Haemel AK, Garrett RW, Sadowski DR, Djamali A, et al. Incidence of nephrogenic systemic fibrosis using gadobenate dimeglumine in 1423 patients with renal insufficiency compared with gadodiamide. Invest Radiol 2016;51:701-5.
44. Michaely HJ, Aschauer M, Deutschmann H, Bongartz G, Gutberlet M, Woitek R, et al. Gadobutrol in renally impaired patients: results of the GRIP study. Invest Radiol 2017;52:55-60.
45. American College of Radiology, ACR Committee on Drugs and Contrast M. ACR Manual on Contrast Media. 2021 [Internet]. [cited 2021 Sep 8] Available from: https://www.acr.org/-/media/ACR/files/clinical-resources/contrast_media.pdf
46. Jamis-Dow CA, Choyke PL, Jennings SB, Linehan WM, Thakore KN, Walther MM. Small (< or = 3-cm) renal masses: detection with CT versus US and pathologic correlation. Radiology 1996;198:785-8.
47. Park BK, Kim B, Kim SH, Ko K, Lee HM, Choi HY. Assessment of cystic renal masses based on Bosniak classification: comparison of CT and contrast-enhanced US. Eur J Radiol 2007;61:310-4.
48. Bertelli E, Palombella A, Sessa F, Baldi I, Morelli N, Verna S, et al. Contrast-enhanced ultrasound (CEUS) imaging for active surveillance of small renal masses. World J Urol 2021;39:2853-60.
49. Duffey BG, Choyke PL, Glenn G, Grubb RL, Venzon D, Linehan WM, et al. The relationship between renal tumor size and metastases in patients with von Hippel-Lindau disease. J Urol 2004;172:63-5.
50. Uhlig A, Hahn O, Strauss A, Lotz J, Trojan L, Müller-Wille R, et al. Treatment for localized T1a clear cell renal cell carcinoma: survival benefit for cryosurgery and thermal ablation compared to deferred therapy. Cardiovasc Intervent Radiol 2018;41:277-83.
51. McAlpine K, Sud M, Finelli A, Kulkarni GS. Optimizing the management of patients with small renal masses in a Canadian context: A Markov decision-analysis model. Can Urol Assoc J 2021;16:E32-8.
52. Bhan SN, Pautler SE, Shayegan B, Voss MD, Goeree RA, You JJ. Active surveillance, radiofrequency ablation, or cryoablation for the nonsurgical management of a small renal mass: a cost-utility analysis. Ann Surg Oncol 2013;20:3675-84.
53. Goldberg H, Ajaj R, Cáceres JOH, Berlin A, Chandrasekar T, Klaassen Z, et al. Psychological distress associated with active surveillance in patients younger than 70 with a small renal mass. Urol Oncol 2020;38:603.e17-25.
54. Heilbrun ME, Yu J, Smith KJ, Dechet CB, Zagoria RJ, Roberts MS. The cost-effectiveness of immediate treatment, percutaneous biopsy and active surveillance for the diagnosis of the small solid renal mass: evidence from a Markov model. J Urol 2012;187:39-43.
55. Thavorncharoensap M, Teerawattananon Y, Natanant S, Kulpeng W, Yothasamut J, Werayingyong P. Estimating the willingness to pay for a quality-adjusted life year in Thailand: does the context of health gain matter? Clinicoecon Outcomes Res 2013;5:29-36.

Case Report

Multiple revisions of inflatable penile prosthesis: a case report

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Keywords:
Multiple revisions, inflatable, penile, prosthesis, non-infectious, malfunction

Abstract

This article presents considerations regarding dilemmas and treatment concerning the revision of inflatable penile prosthesis (IPP) after non-infectious mechanical malfunction. The aim of this report is to improve surgical planning to avoid the most common complications after revision of inflatable penile prosthesis. With greater understanding, implanters could more accurately select patients and provide increased information and advice maximizing the results.

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Introduction

Penile prosthesis is an effective option for erectile dysfunction (ED), refractory to medical and non- invasive therapy. Implants are reliable and high satisfaction rates have been recorded among patients and partners. Mechanical failure is the most common non-infectious complication. Revision rates from system failure vary between centers, with recorded failure range of 15% at 5 years and 30-40% at 10 years.[1] Failure rate was not related to surgeon expertise.[2] Mean duration to initial malfunction was 7.4 years.[3]

Infectious complications remain of significant concern in IPP revision surgery, the risk of specific device infection showing a strong correlation with increased risk being based on number of prior IPPs: 1st (6.8%; 3/44), 2nd (18.2%; 4/22), 3rd (33.3%; 4/12), 4th (50%; 4/8), and 5th (100%; 2/2) ($R2 = 0.90$, $p = 0.01$).[4]

This article presents the issues surrounding dilemmas and treatment in order to prevent infection in non- infectious revision of IPP.

Case Report

This 82-year-old Australian gentleman had his 1st implanted IPP procedure 16 years ago. He had no known etiology of ED and no history of diabetes or any potentially related disease. The 1st implant worked well for 15 years but then the malfunction occurred. A 2nd implant procedure was then carried out, also with IPP, but this was effective for only 1 year, the implant only resulting in 50% inflation. There was no sign of infection and the patient desires a 3rd implant.

The exact sites of malfunction differ between the infrapubic vs scrotal implants. Most malfunctions of the scrotal device have been shown to involve tubing fractures at the pump strain reliefs, whereas infrapubic device malfunctions typically involve the cylinders or the reservoir.[5] The dilemma is whether to only remove and replace the specific malfunction part or exchange the whole component. From a review of relevant literature the exchange of the entire component appears to be advantageous as regards low infection rate and

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future malfunction.

Another important issue is the chance of infection in revision cases. Estimates of infection rates following revision surgery have been as high as between 10.0 and 13.3% in comparison to between 0.46 and 2.00% in virgin cases.[6] Henry et al.[7] found positive bacterial cultures on 70% of clinically uninfected devices suggesting biofilms are a significant source of infection risk with revision surgery. Gross et al.[8] evaluated culture results at the time of explantation of clinically infected device or Mulcahy salvage, and found no growth in 33% of cases, gram positive isolates in 73% of cases, and gram negative isolates in 39% of cases. Candida (11.1%), anaerobes (10.5%), and MRSA (9.2%).

In the drive to prevent infection, many recommendations have proved beneficial: preoperative urine culture[9], hair removal[10], antibiotic impregnated/coated implant[11], and preoperative parenteral antibiotics.[8,9] In 1996, Mulcahy et al. described a new protocol for the immediate replacement of infected IPPs which involved complete device removal, and serial wound washout, followed by re-implantation of a new IPP (Table 1).[12] Similar results were reported in 2000 by Mulcahy[13], showing no evidence of infection in 45 out of 55 patients (82%) at a mean follow-up of 35 months.

The patient in this study took a shower with chlorhexidine solution on the day of the operation. Parenteral antibiotics were administered, specifically Vancomycin 1 gm and Amikacin 500 mg. Hair was clipped in the operating room. The operative site was scrubbed with Povidone iodine scrub for 15 minutes. A Foley catheter was inserted into the urethra to empty the bladder. An incision was made at the penoscrotal site. The former implant (AMS 700® model 20 cm length with 1 cm rear tip extender) was removed. Only 50 ml of NSS remained in the reservoir, therefore potentially the malfunction in this case was from minor leakage in the system. There was no pus or collection detected. Implant sites were vigorously irrigated following the Mulcahy protocol. Gentamicin 240 mg diluted in NSS 200 ml was used instead of Kanamycin plus Bacitracin. The surgeon and the whole team changed gowns and gloves and new cloths were draped on the patient. A 20 cm standard length Coloplast Titan® with standard cap was implanted. A new subdartos pouch was created for the pump in the scrotum to avoid infection from the Biofilm of the former pump. A 50 ml syringe filled with NSS was attached to the reservoir tube to test the prosthesis cylinders. This process was to ensure the function and quality of the erection. In preparation for reservoir placement, the contralateral side to the previous operation was selected. The external ring was identified, and a small Deaver retractor and index finger were inserted to create space in front of the transversalis fascia. The reservoir was placed and filled with NSS 60 ml, then the final connection between the pump and reservoir was completed. The system was checked by inflation and deflation several times to make sure that it was functioning properly, then the incision was closed.

On post-operative day 1 no immediate complications were detected. The catheter was removed and the patient could walk with only minor pain. An oral antibiotic was prescribed, specifically Amoxiklav® 1 gm twice daily for 2 weeks. One week after surgery there was no sign of infection. After one month, the patient started operating the implant.

Discussion

Penile prosthesis revision in a clinically uninfected patient has a higher infection rate than is found in first-time implantation. A combination of infection-retardant coated components, vigorous washout, proper preparation of skin incision site, use of perioperative antibiotics, and avoiding contact between the patient's skin and the implant lowers infection rates. Implanters should inform patients about risks associated with the procedure and carry out the operation

Table 1. Mulcahy protocol

1. Remove all prostatic parts and foreign materials
2. Irrigate wound and all compartments with 7 antiseptic solutions
2.1 Washes 1 and 7: kanamycin and bacitracin
2.2 Washes 2 and 6: half-strength hydrogen peroxide
2.3 Washes 3 and 5: half-strength povidone iodine
2.4 Wash 4: water pic pressure irrigation with vancomycin 1 g and gentamycin 80 mg in normal saline 5 L
3. Change gown, gloves, drapes, and instruments
4. Implant new prosthesis

using the strict guidelines advised in the Mulcahy protocol. Penile prosthesis infection is the most significant complication following prosthesis implant surgery leading to postoperative morbidity, increased health care costs, and psychological stress for the patient. These can all be reduced effectively following the guidelines advised in this study.

References

1. Carson CC, Mulcahy JJ, Govier FE. Efficacy, safety and patient satisfaction outcomes of the AMS 700CX inflatable penile prosthesis: results of a long-term multicenter study. J Urol 2000;164:376-80.
2. Onyaji IC, Sui W, Pagano MJ, Weinberg AC, James MB, Theofanides MC, et al. Impact of surgeon case volume on reoperation rates after inflatable penile prosthesis surgery. J Urol 2017;197:223-9.
3. Miranda E, Teloken P, Deveci S, Mulhall J. Mechanical malfunction profiles in men undergoing 3 piece inflatable penile implants. J Sex Med 2017;14:S75.
4. Montgomery BD, Lomas DJ, Zeigelmann MJ, Trost LW. Infection risk of undergoing multiple penile prostheses: an analysis of referred patient surgical histories. Int J Impot Res 2018;30:147-52.
5. Garber BB. Inflatable penile prosthesis: site-specific malfunction analysis. Int J Impot Res 2003;15:22-5.
6. Jarow JP. Risk factors for penile prosthetic infection. J Urol 1996;156:402-4.
7. Henry GD, Wilson SK, Delk JR 2nd, Carson CC, Silverstein A, Cleves MA, et al. Penile prosthesis cultures during revision surgery: a multicenter study. J Urol 2004; 172:153-6.
8. Gross MS, Phillips EA, Carrasquillo RJ, Thornton A, Greenfield JM, Levine LA, et al. Multicenter investigation of the micro-organisms involved in penile prosthesis infection: an analysis of the efficacy of the AUA and EAU Guidelines for penile prosthesis prophylaxis. J Sex Med 2017;14:455-63.
9. Wolf JS Jr, Bennett CJ, Dmochowski RR, Hollenbeck BK, Pearle MS, Schaeffer AJ, et al. Best practice policy statement on urologic surgery antimicrobial prophylaxis. J Urol 2008;179:1379-90.
10. Tanner J, Norrie P, Melen K. Preoperative hair removal to reduce surgical site infection. Cochrane Database Syst Rev 2011;11:CD004122.
11. Mandava SH, Serefoglu EC, Freier MT, Wilson SK, Hellstrom WJ. Infection retardant coated inflatable penile prostheses decrease the incidence of infection: a systematic review and meta-analysis. J Urol 2012;188:1855-60.
12. Brant MD, Ludlow JK, Mulcahy JJ. The prosthesis salvage operation: immediate replacement of the infected penile prosthesis. J Urol 1996;155:155-7.
13. Mulcahy JJ. Long-term experience with salvage of infected penile implants. J Urol 2000;163:481-2.

Invited Surgical Technique

Rotational labial and inferior pudendal artery based inner thigh flaps for vaginal defect after reconstructive surgery

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Keywords:
Vaginal reconstructive surgery, vaginal defect; cutaneous flap, rotational flap, pudendal artery-based flap

Abstract

For vaginal reconstructive surgery, the vaginal defect sometimes cannot be closed with primary intention due to poor tissue quality or loss of the vaginal wall. To cover the defect, plastic surgeons may be consulted with regard to a tissue advancement flap, a very complex procedure, and urologists may not feel familiar with it or comfortable with carrying it out. The rotational labial and inferior pudendal artery based inner thigh flap, devised by Professor Shlomo Raz, is a simple and useful procedure which urologists can perform with a short learning curve. Therefore, this article aims to demonstrate the surgical technique involved in this flap which can be widely used as an adjunct to any vaginal reconstructive procedures.

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Introduction

In vaginal reconstructive surgery for lower urinary tract problems, many flaps have been used for many purposes. To summarize, the aims of the use of the flap are to create a new urethra for luminal stricture, interposed between the urinary tract and vagina after genitourinary fistula repair and prevent further scar formation after lysis adhesion. Sometimes, a large vaginal defect is unintentionally created after reconstructive surgery or wide excision, and it cannot primarily be closed in an appropriate manner. As a consequence of the unclosed vaginal defect, urologists need to know how to perform a rotational cutaneous flap from the perineal area. Many cutaneous flap techniques have been reported[1] but the majority are complex and may not be appropriate for vaginal reconstructive surgery. This surgical illustration aims to demonstrate step by step the techniques involved in the carrying out of this simple cutaneous flap, namely the rotational labial and inferior pudendal artery based inner thigh flap. This flap is known, in brief, as the rotational labial and inner thigh flap, a procedure which was invented and disseminated by Professor Shlomo Raz.[2] In our experience, this flap is mostly used as an adjunct to transvaginal closure of irradiated vesicovaginal fistula (VVF) but is sometimes used in cases of severe labial agglutination with distal vaginal stenosis, in which simple vaginoplasty has failed.

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Materials and Methods

This is a case study in which rotational labial and inner thigh flap was performed. A 67-year-old woman presented with continuous urinary incontinence for 1 year. The patient had been diagnosed with cervical cancer and treated by hysterectomy with adjuvant external beam combined with intracavitary radiotherapy 23 years ago. After carefully evaluation, VVF was confirmed as a cause of the symptoms and was suitable for transvaginal closure.

In cases of irradiated VVF, repairs can successfully be carried out if the bladder and urethra are of good quality. The criteria for successful completion are bladder capacity more than 200 mL with low pressure after occluded fistula, no detectable telangiectasia or scarring on endoscopic examination and no luminal or extraluminal urethral stricture defined by easy passage of a larger than 22 Fr cystoscopic sheath. In addition, if hydroureteronephrosis is presented preoperatively, the surgery has a high likelihood of failure or requires supravesical diversion.

Surgical steps

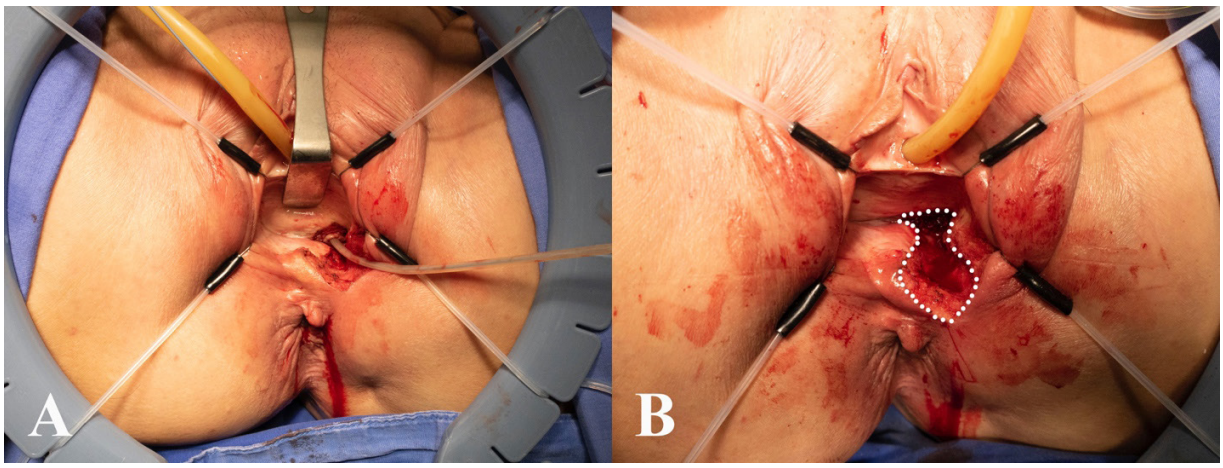

Figure 1. (A) In order to decrease tension on the bladder wall before closing the fistula, the vaginal wall needed to be dissected and released from the bladder wall. (B) After the bladder wall had been closed in a watertight fashion, the vaginal defect was revealed (area indicated by the dotted line) and it could not be repaired by primary intention because of poor tissue quality and tension.

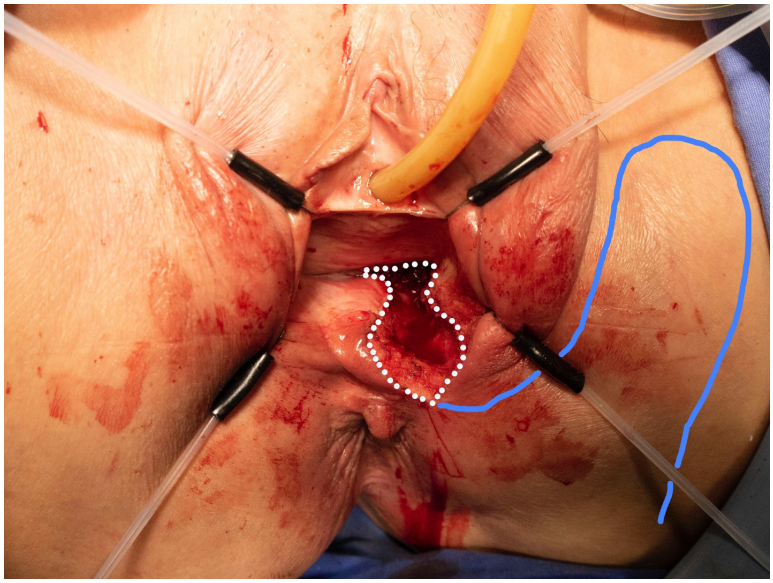

Figure 2. An extended incision (blue line) was made from the introitus as an inverted U shape. The arterial supply of inner thigh flap was based on the inferior pudendal artery. The flap length was dependent on the length of the vaginal defect which was measured from the proximal to distal end. Importantly, the flap length to base ratio needed to be 1.5-2 to 1.

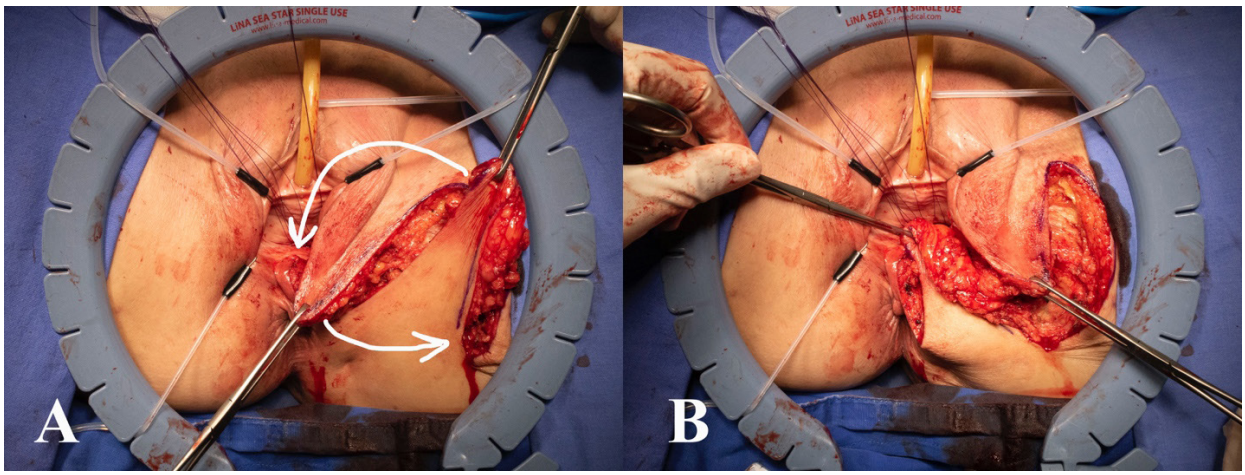

Figure 3. After completion of the incision and dissection of the subcutaneous tissue, the two flaps were detached from underlying structures including fascia and bone. The first one is known as the labial wing and the second one as the inner thigh wing. (A) The inner thigh wing was medially rotated to the vagina whereas the labial wing was laterally rotated to the inner thigh (white arrows). (B) After the flaps were rotated into the appropriate position without tension and the blood supply was not compromised, the inner thigh flap was overlaid onto the vaginal defect and sutured to the vaginal wall with interrupted absorbable suture No. 2-0. The labial flap was overlaid on the inner thigh defect and sutured layer by layer, starting from the subcutaneous layer and proceeding to the skin using interrupted absorbable suture No. 2-0 initially and subcuticular stitches for the closure of the skin.

Figure 4. After the flaps were completely fixed and all defects covered, the final appearance was as shown in this figure. The drain is not required if the dead space is completely obliterated by suturing. For postoperative care, this surgical wound could be easily cared for by the patient themselves with regular cleaning, for example with a sitz bath. In this instance, oral antibiotics, covering gram negative, aerobic and anaerobic bacteria, were prescribed for 2-4 weeks, a practice particularly important in cases involving pelvic radiation.

Results

In Siriraj Hospital, we have performed rotational labial and inner thigh flap in 12 cases between 2016 and 2021 (Table 1). All had small areas of wound dehiscence without infection. No active bleeding, abscess formation, flap necrosis or reoperation were reported.

Discussion

Sometimes, urologists need to perform vaginal reconstructive surgery to treat lower urinary tract problems such as VVF repair. In specific conditions, including those associated with pelvic radiation and multiple vaginal surgery, vaginal wall quality is poor even though topical estrogen is preoperatively applied to improve tissue quality. Therefore, tissue graft or flap may play a role in closure of the vaginal defect. Use of a tissue flap is more appropriate than a graft as it is well tolerated by the vaginal environment, a site with multiple microorganisms[3] and also avoids problems of graft contraction.

Most surgical techniques used for external genitalia reconstruction are complex[1,4] as are those for neovaginal creation.[5-9] To date few studies have reported using a flap for closure of vaginal defect after reconstruction. The flaps which have been described and reported are the gracilis myocutaneous flap[8] and the pedicled profunda artery perforator with gracilis muscle flap.[9] These techniques are reliable, but they need plastic surgeons. From our experience, the rotational labial and inferior pudendal artery based inner thigh flap, as described in this case study, is simple and is associated with low morbidity. We believe that most urologists could perform this procedure with a short learning curve so that it may be useful and helpful in real-life practice.

Table 1. Patient information and outcome of rotational labial and inferior pudendal artery based inner thigh flap

No.	Age (years)	Symptoms	Diagnosis	Outcome at follow up	Comments
1	72	Urinary incontinence	Irradiated VVF	No recurrent VVF at 21 months	-
2	45	Urinary incontinence	Irradiated VVF	No recurrent VVF at 45 months	-
3	60	Urinary incontinence	Irradiated VVF	No recurrent VVF at 30 months	After 30 months, cervical cancer had recurred and involved the bladder. Treatment: Palliative care
4	67	Urinary incontinence	Irradiated VVF	No recurrent VVF at 14 months	After 14 months, VVF has recurred due to urethral stricture. Treatment: Ileal conduit
5	61	Urinary retention	Distal vaginal stenosis Labial agglutination	Spontaneous voiding at 41 months	-
6	76	Urinary incontinence	Irradiated VVF	Failed	Treatment: Ileal conduit
7	73	Urinary retention	Distal vaginal stenosis from prolapse surgery	Failed	Long-term indwelling urethral catheter
8	75	Urinary retention	Distal vaginal stenosis from pelvic radiation	Failed	Long-term indwelling urethral catheter
9	70	Urinary retention	Distal vaginal stenosis from pelvic radiation	Failed	Treatment: transurethral incision bladder neck
10	81	Urinary incontinence	Irradiated VVF	Failed	No further treatment
11	76	Painful lesion	Extramammary Paget's disease at distal urethra and vagina	No perineal recurrence at 18 months	Tumor recurrence in other areas including bladder and ureters Treatment: Chemotherapy
12	70	Urinary retention	Distal vaginal stenosis Labial agglutination	Spontaneous voiding at 6 months	-

VVF = vesicovaginal fistula

Conclusion

The rotational labial and inferior pudendal artery based inner thigh flap is a simple and useful adjunct procedure to vaginal reconstructive surgery which may facilitate repair of a large vaginal defect which has proved difficult to treat with primary closure.

Acknowledgement

We wish to thank the innovative surgeon Professor Shlomo Raz, M.D. who taught us how to perform this simple, useful and highly effective procedure.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Sinna R, Qassemyar Q, Benhaim T, Lauzanne P, Sabbagh C, Regimbeau JM, et al. Perforator flaps: a new option in perineal reconstruction. J Plast Reconstr Aesthet Surg 2010;63:e766-74.
2. Jellison F, Ng G, Rogo-Gupta L, Nakamura L, Chow D, Kim J-H, et al. V263 Rotational labial and inferior pudendal artery based inner thigh flaps in vaginal reconstruction. J Urol 2013;189:e108.
3. Ma B, Forney LJ, Ravel J. Vaginal microbiome: rethinking health and disease. Annu Rev Microbiol 2012;66:371-89.
4. Nassar MK, Jordan DJ, Quaba O. The internal pudendal artery turnover (IPAT) flap: a new, simple and reliable technique for perineal reconstruction. J Plast Reconstr Aesthet Surg 2021;74:2104-9.
5. Ganatra MA, Ansari NU. Pudendal thigh flap for congenital absence of vagina. J Pak Med Assoc 2005; 55:143-5.
6. Prakash V. Triple flap vaginoplasty for agenesis of the vagina. J Obstet Gynaecol Res 2011;37:501-4.
7. Benson C, Soisson AP, Carlson J, Culbertson G, Hawley-Bowland C, Richards F. Neovaginal reconstruction with a rectus abdominis myocutaneous flap. Obstet Gynecol 1993;81:871-5.
8. Heath PM, Woods JE, Podratz KC, Arnold PG, Irons GB, Jr. Gracilis myocutaneous vaginal reconstruction. Mayo Clin Proc 1984;59:21-4.
9. Sharp O, Kapur S, Shaikh I, Rosich-Medina A, Haywood R. The combined use of pedicled profunda artery perforator and bilateral gracilis flaps for pelvic reconstruction: a cohort study. J Plast Reconstr Aesthet Surg 2021;74:2654-63.

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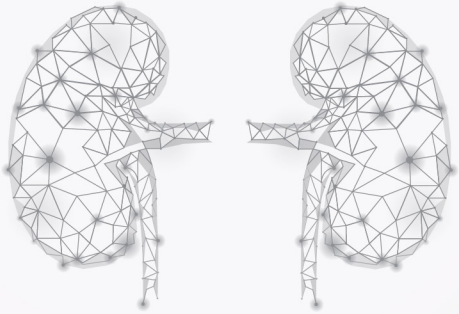

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