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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 tenth issue of *Insight Urology* (ISU) was published online in June 2025. It comprises eight original articles, two review articles, and one case report. It covers several fields of urology, such as oncologic urology, endourology, kidney transplantation, and functional urology.

One review article was submitted by a renowned international author, namely **"Parenchymal volume analysis and functional recovery after partial and radical nephrectomy for renal cell carcinoma."** We are confident that you will enjoy reading and applying the knowledge in these articles to your present urological work, especially when treating renal cell carcinoma patients, and performing partial and radical nephrectomy.

The front cover of this issue features photographs of the 36th Thai Urological Association (TUA) Under the Royal Patronage Annual Scientific Meeting 2025 in conjunction with Federation of ASEAN Urological Association (FAUA) Meeting 2025 in the main theme of **"Urology Beyond Borders: Together Towards a Brighter Future Across ASEAN"** during April 3-5, 2025 in Dusit Thani Hotel Pattaya, Thailand. The meeting was very successful and warmly welcomed many participants from ASEAN countries.

The FAUA was formed by the Urological Association of ASEAN countries on 31st October 1993, which also made the first The First Memorandum of Understanding (MOU). The founding members of FAUA consisted of Indonesia, Malaysia, the Philippines, Singapore, and Thailand. In July 6th 2023, the founding members and the new members, Cambodia, Myanmar, and Vietnam, amended the first MOU. Currently, the FAUA has 8 member associations and welcomes the rest of ASEAN countries to join.

The Editorial Board of ISU hopes that the cover of this issue represents the importance of international collaboration with our regional urological colleagues and societies to promote our communities in terms of clinical practice, education, and research, following the wise African proverb **"If you want to go fast, go alone. If you want to go far, go together."**

No reserve. No retreat. No regret.

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

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Original Article

Oncological outcomes of neoadjuvant chemotherapy in muscle-invasive bladder cancer in Rajavithi Hospital

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Keywords:
Neoadjuvant chemotherapy, radical cystectomy, urothelial bladder cancer, muscle-invasive bladder cancer, pathological response

Abstract

Objective: Neoadjuvant chemotherapy (NAC) can provide better survival benefits than radical cystectomy (RC) alone in patients with muscle-invasive bladder cancer (MIBC). At Rajavithi Hospital neoadjuvant chemotherapy has been used with some patients diagnosed with MIBC and in this study the oncologic outcomes have been evaluated. The precise objectives of this study are to assess the outcomes, overall survival, and factors which show a correlation with a downstaging of neoadjuvant chemotherapy in patients with muscle-invasive bladder cancer before radical cystectomy at Rajavithi Hospital.

Materials and Methods: This is a single-center, retrospective case control study conducted at this large public hospital in Thailand. Forty patients (31 males, 9 females) were enrolled onto the study and had been diagnosed with MIBC. All had received neoadjuvant chemotherapy before undergoing radical cystectomy from January 2012 to December 2020. The primary endpoint was to assess the pathologic complete response (pCR) rate in MIBC after treatment with neoadjuvant chemotherapy. The secondary endpoints were overall survival (OS), tumor downstaging, and factors correlated with downstaging following NAC.

Results: The overall complete response rate for all patients was 7.50%. Tumor downstaging occurred in 47.50% of patients, upstaging in 22.50%, and no change in 30.00%. At a median follow-up period of 35 months, the overall survival (OS) rate was 52.80%.

Conclusion: The complete response rate and overall survival were lower than those reported in previous studies. This may be due to the primary regimen being gemcitabine and carboplatin rather than one of the other pharmaceutical combinations, and also patients not completing the full course of neoadjuvant chemotherapy. We found a correlation between non-response and chronic kidney disease (CKD), positive lymphovascular invasion (LVI), and positive pelvic lymph nodes. A correlation between non-response and mortality was also found.

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Introduction

Radical cystectomy (RC) is the standard treatment for muscle-invasive bladder cancer (MIBC). However, surgery alone is associated with suboptimal disease control and survival, partly due to micrometastases. Approximately 30.00% of patients treated with surgery alone experience disease recurrence. Due to the positive improvement in overall survival in randomized trials, cisplatin-based combination chemotherapy administered before cystectomy is recommended for patients with MIBC who are eligible to receive cisplatin.[1,2]

The European Association of Urology (EAU) and the National Comprehensive Cancer Network (NCCN) have published guidelines recommending the use of neoadjuvant chemotherapy (NAC) before RC. These guidelines are rooted in meta-analyses which indicated a significant 5.00% absolute survival benefit in favor of NAC with cisplatin-based combination chemotherapy.[3-5]

Although cisplatin-based chemotherapy is effective, its nephrotoxic properties make it unsuitable for patients with renal dysfunction. It has been reported that carboplatin-containing chemotherapy has a potential role in advanced bladder cancer patients with renal impairment as carboplatin is an alkylating anti-cancer agent which is less nephrotoxic than cisplatin.[6-8] Despite these promising results, NAC remains underused worldwide. The reasons most frequently reported for this underuse include a potential delay to definitive surgery and associated toxicity.[9-10]

A previous study in Thailand showed that a group of patients treated with neoadjuvant chemotherapy had longer survival than those treated with adjuvant chemotherapy.[11]

This study analyzed patients at Rajavithi Hospital diagnosed with MIBC and treated with NAC followed by RC. At this center the neoadjuvant treatment regimen consists of three options: gemcitabine/carboplatin, gemcitabine/cisplatin, and paclitaxel. The primary objective of this study was to describe the oncologic outcomes of NAC in a neoadjuvant setting for MIBC at Rajavithi Hospital.

Materials and Methods

This is a single-center, retrospective case-controlled study. Patients included in the study had measurable and histologically proven, predominantly urothelial, muscle-invasive bladder cancer (cT2-T4, N any, M0) and had received neoadjuvant chemotherapy (regimens: gemcitabine/carboplatin, gemcitabine/cisplatin, or paclitaxel) followed by RC at Rajavithi Hospital between January 1, 2012, and December 31, 2020.

Institutional research ethics board approval was obtained prior to data collection (IRB number: 64254). Patients were excluded from the study if the pathology was not urothelial carcinoma or if there was missing data.

The primary endpoint of the study was the pathologic complete response rate (tumor downstaging to pT0 from any cT stage) after neoadjuvant chemotherapy at the time of cystectomy. The initial clinical stage and nodal status at diagnosis were assessed using computerized tomography (CT) scans and pathology after transurethral resection of the bladder tumor (TURBT). Data pertinent to the pathological stage at the time of cystectomy was also collected. The protocol for neoadjuvant chemotherapy was determined based on the advice from the medical oncologist after the urologist decided to transfer patients for NAC.

Secondary endpoints included tumor downstaging (downstage from initial clinical stage), tumor downstaging <T2, tumor non-response (tumor upstage from initial clinical stage or no change in stage), overall survival, and factors related to tumor downstaging (age, underlying conditions such as diabetes mellitus (DM), Hypertension (HT), chronic kidney disease (CKD), regimen, number of NAC cycles, body mass index (BMI), nodal status, performance status (ECOG), smoking history, and lymphovascular invasion (LVI).

Tumor downstaging was defined as a pathological T stage (ypT) at the time of cystectomy that was lower than the initial clinical T stage (cT. Tumor non-response was defined as a more invasive stage of disease or no change in the clinical T stage. Pathologic N stage (ypN) positive at the time of cystectomy was considered non-response for patients with an initial clinical stage of N0. Overall survival was assessed based on the updated patient data available in the medical records at the conclusion of the study.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences v.26.0

(SPSS Inc, Chicago, IL, USA). The percentage, mean, mode, and standard deviation (SD) were used for descriptive data. Comparisons between the two groups were carried out using the Student's T-test, Mann-Whitney U test, Chi-square test, and Fisher's Exact test. Overall survival (OS) was analyzed using the log-rank test to compare OS. For all statistical tests, a p-value of less than 0.05 was considered to indicate a significant difference.

Results

A total of 484 patients underwent radical cystectomy. Of these, 42 patients received neoadjuvant chemotherapy before the procedure. Two patients were excluded due to pathology that was not urothelial carcinoma: one had adenocarcinoma, and one had small cell carcinoma (Fig. 1).

Of the 40 patients included, 30 received NAC at Rajavithi Hospital, and 10 received it from other hospitals. The mean age was 65 years (range: 50 to 85), and 77.50% were male. Sixty percent of the patients received fewer than 3 cycles of NAC and did not complete the full course because surgery was scheduled. Baseline characteristics are listed in Table 1.

Overall, the pathological complete response rate to pT0 was 7.50% (n = 3). Tumor downstaging occurred in 47.50% of patients (n = 19). Tumor downstaging to < pT2 was 22.50%. Tumor upstaging at cystectomy compared to before NAC occurred in 22.50% of patients (n = 9). Twelve patients (30.00%) had no change in their staging following chemotherapy at the time of cystectomy. Overall, the non-response rate was 52.50% (n = 21), (Table 2).

The secondary endpoint, overall patient survival rates were 87.20%, 52.80%, and 39.60% at 12, 35, and 49 months, respectively (Fig. 2).

When the subgroup analysis was performed, overall survival was compared between the downstaging and non-response groups. The overall survival rates at 17 months were 88.90% for the downstaging group and 57.10% for the non-response group. A statistically significant difference was found in the survival curves (Fig. 3).

The overall median follow-up time was 27.6 months. The median follow-up times were 30.47 months in the downstaging group and 25 months in the non-response group.

The comparisons between the downstaging group and non-response group with regard to other factors (age, DM, HT, CKD, regimen, number of cycles of NAC, BMI, ECOG, and smoking history) did not show any statistically significant differences. However, we found that CKD, nodal status, and LVI were significantly associated with the non-response group and showed a correlation with a higher mortality rate (Table 3.).

Complications occurred during NAC in two patients: one had neutropenia and the other had anemia. Both patients had received the gemcitabine and carboplatin regimen.

A total of 18 patients died in this study, with the majority of deaths (15 patients) attributed to bladder cancer.

After neoadjuvant chemotherapy followed by radical cystectomy, most patients received

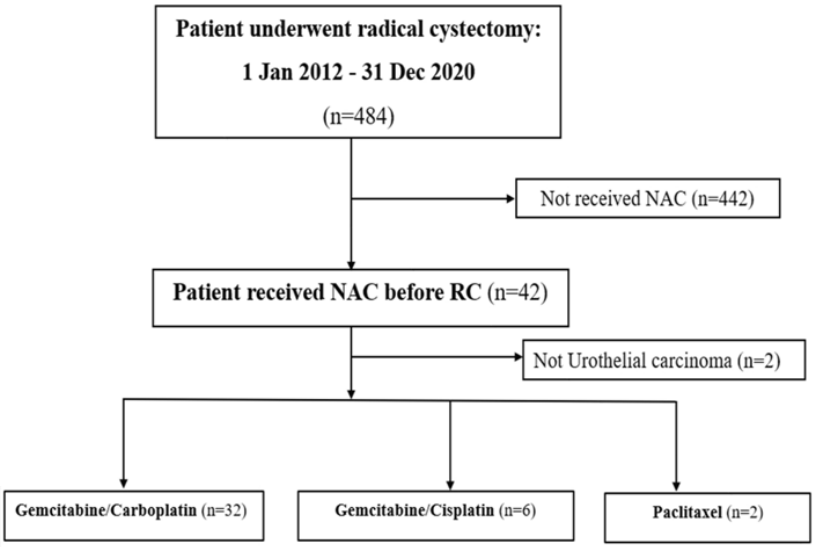

Figure 1. Study cohort selection process

Table 1. Baseline characteristics

Factors	n (%)
Age (years) Mean±SD	65.30±8.71
BMI (kg/m^2) Mean±SD	22.83±5.33
GFR (120 ml/min/1.73m^2) Mean±SD	67.60±26.19
Gender	
Male	
Female	
Smoking history	31 (77.50)
ECOG	
0	
1	
2	
Diabetes mellitus	12 (30.00)
Chronic kidney disease (GFR <40 ml/min/1.73m^2)	17 (42.50)
Hypertension	18 (45.00)
Clinical T stage	
T2	13 (32.50)
T3	20 (50.00)
T4	7 (17.50)
M stage	
M0	40 (100.00)
High grade of pathology	37 (92.50)
Lymphovascular invasion (positive)	21 (52.50)
Positive pelvic nodes at time of surgery	11 (27.50)
Place patients received NAC	
Rajavithi Hospital	30 (75.00)
Other hospitals	10 (25.00)
Regimen NAC	
Gemcitabine/carboplatin	32 (80.00)
Gemcitabine/cisplatin	6 (15.00)
Paclitaxel	2 (5.00)
Cycles of NAC	
≤3	24 (60.00)
>3	16 (40.00)

SD = standard deviation, GFR = glomerular filtration rate, ECOG = Eastern Cooperative Oncology Group, NAC = neoadjuvant chemotherapy, BMI = body mass index

adjuvant chemotherapy, while others received chemoradiotherapy or no adjuvant treatment. Distributions are shown in Figure 2.

Discussion

The results of this retrospective analysis pertinent to neoadjuvant chemotherapy at Rajavithi Hospital showed an overall pathological complete response (pCR) rate to pT0 of 7.50%, which is lower than that reported in previous studies. Meleis et al[12] reported a pCR rate of 14.00% in

Table 2. Tumor upstaging, downstaging and nonresponse

Factors	n (%)
Overall tumor downstaging	19 (47.50)
Pathologic complete response rate	3 (7.50)
Gemcitabine/carboplatin	1 (2.50)
Gemcitabine/cisplatin	2 (5.00)
Paclitaxel	0 (0.00)
Down staging < pT2	9 (22.50)
Gemcitabine/carboplatin	8 (20.00)
Gemcitabine/cisplatin	1 (2.50)
Paclitaxel	0 (0.00)
Tumor downstaging to T2 (cT3-4 to pT2)	7 (17.50)
Overall tumor non-response	21 (52.50)
No change	12 (30.00)
Upstaging	9 (22.50)
- cT2 to pT3-4	3 (7.50)
- cT3 to pT4	6 (15.00)

MIBC patients who received four cycles of neoadjuvant gemcitabine and cisplatin. Peyton et al[13] reported a pCR of 9.40% in MIBC patients who received a mean regimen of 4.4 cycles of gemcitabine and carboplatin.

However, the pCR in this study was higher than the pCR observed in patients who underwent radical cystectomy alone (2.70%), similar results to those reported by Murasawa et al[14]

There was a comparable response rate between our analysis and prior studies using gemcitabine and carboplatin for NAC. Murasawa et al[14] reported a downstaging to <pT2 after the completion of 2 cycles of NAC of 24.50%. In our study, downstaging to <pT2 was 22.50%.

As is practice at our hospital, patients received various regimens and cycles of NAC before surgery. The main regimen in this study was gemcitabine and carboplatin, which showed a lower outcome compared to cisplatin-based NAC. Additionally, the majority of the population in previous studies had tumors at pT2, whereas in this study, most patients had tumors classified as pT3. Therefore, the pCR and downstaging rates in this study are lower than those reported in other studies.

Regarding overall survival, Lee et al[15] reported a 3 year overall survival (OS) of 89.00% of patients who had received 3 complete cycles of gemcitabine and cisplatin before radical cystectomy. Koie et al[16] reported a 41-month OS of 89.70% in patients who received gemcitabine and

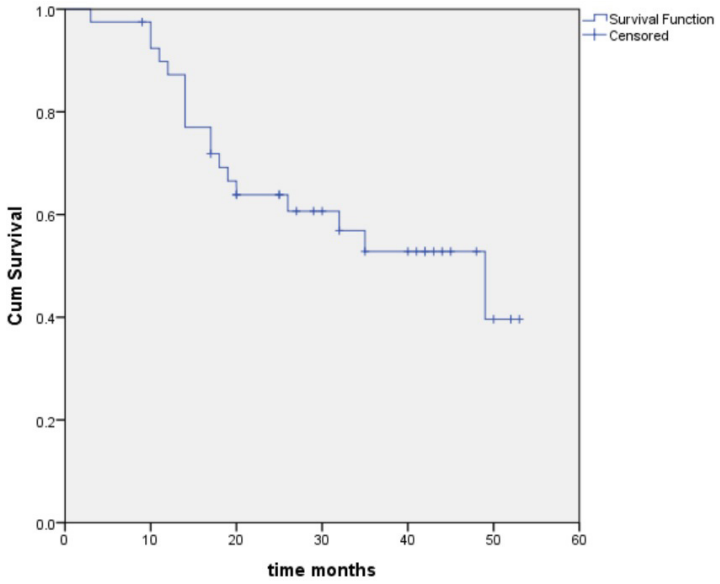

Figure 2. Overall survival

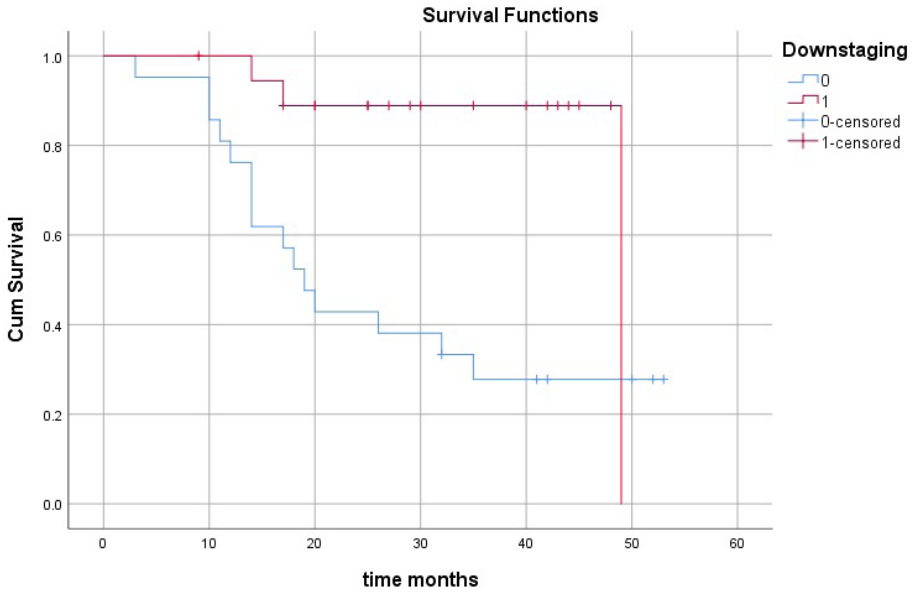

Figure 3. Overall survival between the response group (red) and non-response (blue)

carboplatin. In this study, the overall survival rates were 87.20%, 52.80%, and 39.60% at 12, 35, and 49 months, respectively. These rates are lower than those reported in previous studies[1,14,16,18]. The results could potentially be due to disease staging, regimen, and the number cycles of NAC. However, the overall survival in this study does not solely reflect the effect of NAC, as 60.00% of patients received adjuvant therapy.

When comparing patients between the response and non-response groups, we found that CKD, LVI, and nodal status showed a statistically significant correlation with the non-response group, and non-response was associated with a higher death rate. These findings are similar to those in previous studies.[16,17]

Our study has several limitations. The retrospective nature, the lack of randomization, and the absence of centralized radiology and pathology reviews may affect our results, and the rate of complete TUR-BT was not recorded. The use of clinical staging could be associated with understaging or overstaging. In future studies information regarding the rationale behind the choice of NAC regimen, and more detailed data regarding NAC administered to patients who received it at another hospital before being referred to our hospital for surgery could be included to add

Table 3. Correlation between factors and downstaging of tumor

	Down Staging n	Non-Response (no change + upstaging) n	OR (95%CI)	P-value
Age (years) Mean±SD	63.79±9.914	66.67±7.432	0.99 (0.91-1.08)	0.303
BMI (kg/m^2) Mean±SD	21.63±6.020	23.90±4.482	0.91 (0.78-1.06)	0.892
Smoking history	15	16	1.26 (0.22-7.22)	0.698
ECOG			0.23 (0.06-0.84)	0.051
0	11	5		
1	8	15		
2	0	1		
Diabetes mellitus	7	5	1.37 (0.29-7.26)	0.369
Hypertension	8	10	0.70 (0.16-3.16)	0.726
Chronic kidney disease (GFR <40 ml/min/ 1.73m^2)	5	12	0.38 (0.09-1.59)	0.049*
LVI	5	16	0.11 (0.02-0.78)	0.002*
Regimen NAC			7.39 (0.47-115.39)	0.075
Gemcitabine/carboplatin	14	18		
Gemcitabine/cisplatin	5	1		
Paclitaxel	0	2		
Cycle of NAC			3.38 (0.40-28.81)	0.366
≤3	24			
>3	16			
Grade of pathology (high grade)	16	21	-	0.098
Nodal status (positive pelvic lymph node)	0	11	-	<0.001*

SD = standard deviation, GFR = glomerular filtration rate, ECOG = Eastern Cooperative Oncology Group, NAC = neoadjuvant chemotherapy, OR = odd ratio, BMI = body mass index, LVI = lymphovascular invasion

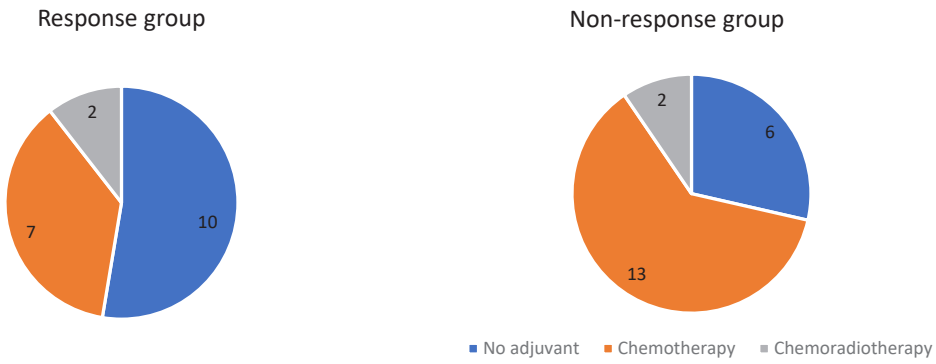

Figure 4. Adjuvant treatment

to the findings. Although treatment allocation was mostly driven by institutional preferences, selection bias cannot be confidently excluded. We were unable to assess the outcomes of patients who received NAC but did not undergo radical cystectomy due to disease progression. The relatively small number of patients enrolled in our study and the short follow-up period are additional limitations.

Conclusion

In this study, the complete response rate, response rate, and overall survival were lower than those in previous studies but higher than those observed associated with radical cystectomy alone. This may be due to the main regimen being gemcitabine and carboplatin, rather than the cisplatin-based NAC included in previous studies. Some patients did not complete the full

program of cycles of neoadjuvant chemotherapy which may have impacted response rate. Correlations between non-response and CKD, positive LVI, and positive pelvic lymph nodes were also found. There was also a correlation between non-response and a higher mortality rate. Further studies should be prospective, include the rate of complete TURBT, have longer follow-up periods, and protocols should be put in place for the completion of the full number of cycles of NAC before surgery.

Conflict of Interest

The authors declare no conflict of interest.

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Original Article

Accuracy of detecting recurrent rate of NMIBC by NBI and WLC: the prospective study

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Keywords:
Narrow-band imaging cystoscopy, white light cystoscopy, non-muscle invasive bladder cancer, transurethral resection of bladder tumors

Abstract

Objective: The aim of this study was to investigate the accuracy of narrow-band imaging cystoscopy (NBI) in cases of recurrent non-muscle invasive bladder cancer (NMIBC) compared to standard white light cystoscopy (WLC).

Materials and Methods: All NMIBC patients at Rajavithi Hospital, Thailand were enrolled onto this single-center prospective cohort study. The patients were diagnosed by transurethral resection of bladder tumor (TURBT) then underwent both WLC and NBI carried out by the same two urologists. Cold cup biopsy was performed for all visible lesions.

Results: A total of 67 NMIBC patients were enrolled onto the study. The male to female ratio was 3.5 : 1, the mean age was 69.2±10.7 years, and stage Ta and T1 were 56.7% and 43.3% respectively. Papillary urothelial neoplasm of low malignant potential (PUNLMP), low and high grade were 3.0%, 37.3%, and 59.7% respectively. The NBI significantly improved the detection rate of NMIBC and carcinoma in situ (CIS) in comparison to standard WLC (100.0% versus 80.0% and 100.0% versus 0.0% respectively). Also, NBI cystoscopy resulted in significantly superior detection rates for CIS and overall tumors. However, specificity was lower (84.0% versus 93.0%) and the false positive rates of NBI were higher than WLC (15.7% versus 7.01%).

Conclusion: NBI cystoscopy is an alternative procedure for patients with recurrent NMIBC, with significant levels of improvement regarding tumor detection. This technique may lead to better outcomes from early treatment.

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Introduction

Bladder cancer is the 11th most common malignancy worldwide[1] and the 6th most common cancer in Thailand.[2] Bladder cancer is divided into two types: non-muscle invasive bladder cancer (NMIBC) (75%) and muscle-invasive bladder cancer (MIBC) (25%).[1]

The current standard technique for diagnosis is white light cystoscopy (WLC) and urine cytology. Transurethral resection of bladder tumor (TURBT) is the key to confirmation of the diagnosis and pathological staging.[3] However

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WLC has limitations, and has a high recurrence rate. A small and flat lesion that was a tumor or carcinoma in situ (CIS) which had been overlooked at the initial investigation and also during the intra-operative phase can result in tumor recurrence.[4] EAU guidelines recommended biopsy of any abnormal looking urothelium, or even random biopsy of normal mucosa in case of potential positive cytology.[5]

Therefore, better detection methods have been established to reduce the impact of these lesions.[6] More recently narrow-band imaging (NBI) has been playing a significant role. The wavelength of the NBI which resulted in peak absorption by hemoglobin and allowed greater visual clarity of the microvessels than WLC was 390-445 nm. NBI can detect small lesions or CIS that are difficult to find.[7] NBI is useful in the detection of early-stage cancer in gastrointestinal endoscopy and is therefore expected to play an important role in detection of NMIBC.[8] However, to date, this technique is not routinely used for diagnosis.[6] This prospective, experimental trial will compare the sensitivity of the detection of NMIBC between NBI and WLC in a 1 year period.

Materials and Methods

Study population and procedures

This study was approved by the ethics committee at Rajavithi Hospital, Thailand (Study Number: 045/2021). All patients were informed about the trial and gave consent prior to the procedure. A total of 67 patients with a preliminary diagnosis of superficial bladder cancer were enrolled; 52 patients were male, 15 were female, and the age range was from 35 to 95. Each patient underwent both WLC and NBI in sequence by two different experienced urologists. After the patient was placed in the lithotomy position, the first urologist used WLC and then the second one performed NBI within 5 minutes of the first technique. Both urologists were blinded to the result's of the other to prevent bias. Rigid cystoscope's (Model EXERA II CV-180, Olympus Medical systems, Tokyo, Japan) that can be switched from WLC to NBI were used in this study. After each urologist completed the cystoscopy and recorded the suspected area under WLC and NBI in a mapped form, biopsies were conducted in accordance with the record form (1 biopsy from each lesion). The specimens were put in tagged containers and transferred to a pathologist who was blinded to the collection method. The sensitivity and specificity of WLC and NBI cystoscopy was compared from the results of biopsies.

Study design

Prospective controlled trial

Study population

1. Inclusion criteria: Patients with a preliminary diagnosis of non-muscle invasive bladder cancer by TURBT
2. Exclusion criteria: No tumor lesions found in cystoscopy

Outcome measures and statistics

The primary outcome was to compare the sensitivity and specificity of NBI cystoscopy and WLC cystoscopy for detection of recurrent NMIBC or CIS. The secondary outcome was to compare the differences in the positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio. The data were analyzed using SPSS Statistics Version 22.0. (IBM Corp., Chicago, IL, USA). Data were presented as mean and standard deviation (SD) unless otherwise noted. Measure of agreement was calculated by Kappa.

Results

The demographic data in the study are detailed in Table 1. A total of 67 patients were enrolled onto this study. Positive and negative results were based on pathological results. The Kappa statistic (0.71 $p < 0.001$) indicates that there was substantially significant agreement between the findings of the WLC and NBI techniques. According to the WLC results, number of diagnoses by directional cystoscopic examination with biopsy positive were 12 and 8, respectively. The number of diagnoses by directional cystoscopic examination and biopsy positive were 19 and 10, respectively from NBI.

A total 10 patients from 67 patients were confirmed as having recurrent bladder cancer by pathological report. A total of 2 patients were detected using NBI only, whereas 8 patients was detected using both WLC and NBI (Table 2). Regarding the pathological stage in 10 patients; 5 patients were pTa, 3 patients were pT1, and 2 patients pTis.

The diagnostic efficiency of WLC and NBI cystoscopy was calculated by the sensitivity, specificity, positive predictive values, negative predictive values, positive likelihood ratio, and negative likelihood ratio (Table 3). In these 67 patients, the sensitivities of NBI and WLC were 100.0% and 80.0%, respectively, the specificities of NBI and WLC were 84.0% and 93.0%, respectively; the false positive rates of NBI and WLC were 15.7% and 7.0%, respectively; the positive predictive values of NBI and WLC were 52.6% and 66.7%, respectively; the negative predictive values of NBI and WLC were 100.0% and 96.4%, respectively; the positive likelihood ratio of NBI and WLC were 6.33 and 11.44, respectively; and the negative likelihood ratio of NBI and WLC were 0 and 0.22 respectively.

Pathological grading in 10 patients; 1 patient was papillary urothelial neoplasm of low malignant potential (PUNLMP) (10.0%), 1 patient was low grade (10.0%), 2 patients were CIS (20.0%) and 6 patients were high grade (60.0%). The overall detection rates for patients with CIS was significantly improved as a result of NBI in comparison with WLC (100.0% versus 0.0%) (Figure 1)

After intravesical BCG therapy, NBI was positive in 4 patients; 1 patient (25.0%) had a positive biopsy. Intravesical BCG may increase false positive rates of NBI, but these findings were not significant.

Table 1. Demographic and clinical characteristics of the study patients

Characteristics	Total (N=67)
Gender, n (%)	
Male	52 (77.6)
Female	15 (22.4)
Age (years)	
Mean±SD	69±10.7
Co-morbidity, n (%)	35 (52.2)
Diabetes Meletus	10 (28.6)
Dyslipidemia	8 (22.9)
Hypertension	27 (77.1)
Other	15 (42.9)
Smoker, n (%)	19 (28.4)
Alcohol drinker, n (%)	11 (16.4)
Tumor staging, n (%)	
Ta	38 (56.7)
T1	29 (43.3)
Tumor grading, n (%)	
PUNLMP	2 (3.0)
Low grade	25 (37.3)
High grade	40 (59.7)

SD = standard deviation, PUNLMP = papillary urothelial neoplasm of low malignant potential

Discussion

Non-muscle invasive bladder cancer has a high rate of recurrence. Incomplete tumor removal is one of the reasons for early recurrence. Therefore, new technology such as narrow band imaging has been developed to improve the detection rate of NMIBC

NBI uses the light at wavelengths of 390 - 445 nm that absorbed by hemoglobin and more clearly seen the microvessels than with WLC. NBI can improve the detection of small lesions

Table 2. Cystoscopy results

Cystoscopy results	Number of cases of biopsy, n	Tumor n (%)	No tumor n (%)
WLC+, NBI+	12	8 (66.7)	4 (33.3)
WLC-, NBI+	7	2 (28.6)	5 (71.4)
WLC+, NBI-	0	0 (0.0)	0 (0.0)

WLC = white light cystoscopy, NBI = narrow band imaging cystoscopy

Table 3. Results of the multivariate analysis

Characteristics	Sensitivity (%)	Specificity (%)	95%CI	PPV	NPV	+LH	-LH
WLC	80.0	92.98	44.39-97.48	66.67	96.36	11.44	0.22
NBI	100.0	84.21	69.15-100	52.63	100.0	6.33	0.00

WLC = white light cystoscopy, NBI = narrow band imaging cystoscopy

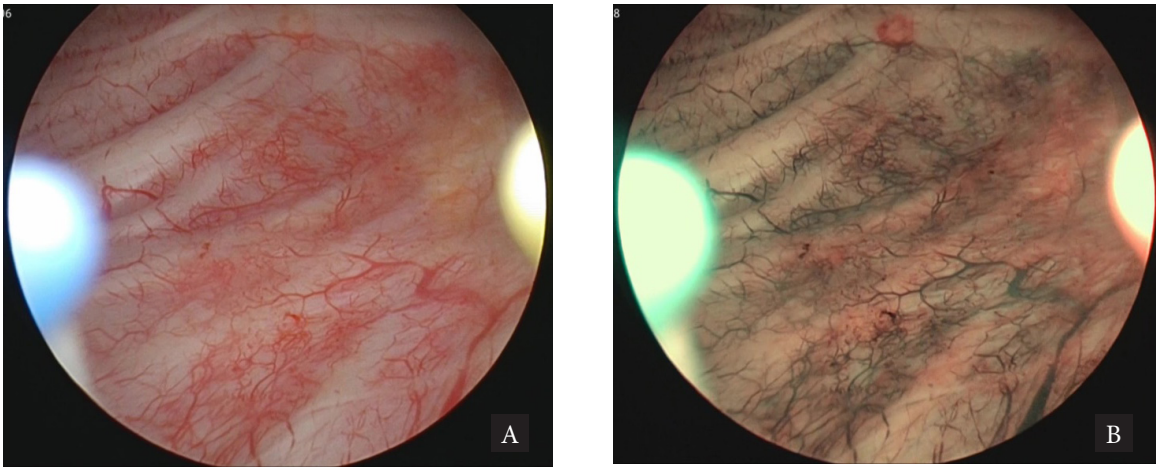

Figure 1. Carcinoma in situ lesion visible in narrow-band imaging (B) not seen in white light cystoscopy (A)

or CIS that are not easily seen with WLC. The main advantages of NBI are that there are no contraindications for the patient. Moreover, this technique is simple and does not increase the cost of therapy.[9]

Recent reports have indicated that NBI cystoscopy is more effective than WLC for the detection of the recurrence of bladder cancer. In a study by Zhangqun et al, 124 of 167 (74.3%) recurrent bladder cancer samples were diagnosed using both WLC and NBI. Forty one (24.5%) were detected using only NBI and 2 (1.2%) were detected using only WLC.[10] Zhangqun et al. reported that NBI could improve the sensitivity of the diagnosis of recurrent bladder cancer. Li et al calculated that NBI facilitated the detection of recurrence in an additional 17.0% of patients (95% confidence interval [CI], 10.0–25.0%) and an additional 24.0% of tumors (95% CI, 17.0–31.0%).[11] The disease recurrence shows that the use of NBI versus WLC improves the detection of recurrence by 15.0-32.0%, with time to recurrence of 29 and 13 months, respectively. In addition, a significantly greater rate of tumor detection was achieved with NBI cystoscopy than with WLC in a study by Geavlete et al. (94.9% vs. 84.3%, respectively).[12]

In our study, the primary outcome is a comparison of the sensitivity and specificity between NBI and WLC. The order of the WLC or NBI inspections was conducted by two urologists. After each urologist completed the cystoscopy and mapped the suspected area identified under WLC and NBI, biopsies were conducted according to their findings (1 biopsy in each lesion). Both urologists were blinded from perception of the other's results to prevent bias.

The findings of our study indicate that NBI cystoscopy could be used to improve the detection of non-muscle invasive bladder cancer. In particular, early stage tumors or carcinomas in situ could be more clearly observed under NBI cystoscopy. However, although NBI significantly improved the sensitivity of diagnosis, the procedure resulted in a lower specificity and higher false positive rate than WLC. Intravesical BCG may increase the false positive rate of NBI, but the results were not significant.

Although NBI cystoscopy has a high sensitivity, a few limitations of this study merit consideration. The accuracy of NBI and WLC were operator dependent with regard to the detection of tumors as well as to other subjective factors. The number of patients of this study was lower than expected, future research studies could enroll more patients.

Conclusions

NBI cystoscopy showed significantly improved detection rates of NMIBC and CIS in comparison to WLC. However, the rate of false-positive results was higher for NBI.

In conclusion, NBI cystoscopy is an alternative procedure for the treatment of NMIBC patients, in order to improve tumor detection. This approach also provides a substantial improvement in postoperative therapeutic management of bladder cancer.

Conflicts of Interest

The authors declare no conflicts of interest.

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Original Article

Prostate cancer detection rate of 16-core TRUS-guided prostate biopsy in Rajavithi Hospital

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Keywords:
Biopsy, prostate, prostate cancer, 16-cores, transrectal ultrasound prostate biopsy

Abstract

Objective: Prostate cancer is one of the most prevalent malignancies in the male Thai population. Early detection of prostate cancer increases the chance of organ confined and potentially curable disease. To date, the grayscale transrectal ultrasound (TRUS) is a common modality for prostate diagnosis and the extended 12-core biopsy is considered adequate for cancer detection. With the aim of increasing the peripheral zone of prostate biopsy sampling, Rajavithi Hospital performed a 16-core TRUS-guided prostate biopsy instead. The objectives of this study are to evaluate the rate of prostate cancer detection and to review the factors associated in 16-core TRUS-guided prostate biopsy in Rajavithi Hospital.

Materials and Methods: TRUS-guided prostate biopsy was performed in 243 patients between October 2019 and September 2021 in Rajavithi Hospital. Using retrospective methods, 200 patients were included in this study. The factors associated with prostate cancer detection were analyzed by independent sample t-test, Mann-Whitney U test, Chi-square test and Fisher's exact test, and Multiple logistic regression methods.

Results: The average age of TRUS-guided prostate biopsy patient in Rajavithi Hospital was 69.28 ± 8.41 years. Prostate cancer was detected in 70 patients (35.0%). Factors significantly associated with a positive diagnosis were: abnormal digital rectal exam (DRE) (74.3%, $p < 0.001$), PSA level > 10 ng/ml (mean 9.87 ng/ml, $p < 0.001$), and PSAD ≥ 15 ng/ml/g (94.3%, $p < 0.001$). Among prostate cancer patients, in the majority of cases the positive tissue was found at lateral core (31.0%), followed by the apical core (28.5%), medial core (27.5%) and anterior core (23.5%). No factors were found to be related to increasing prostate cancer detection tissue in the lateral core with the exception of abnormal DRE.

Conclusion: A 16-core TRUS-guided prostate biopsy may be useful for the detection of prostate cancer in patients with abnormal DRE, high PSA, and high PSAD.

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Introduction

Prostate cancer is the most frequent malignancy in males worldwide [1], a prevalence which is reflectec in the Thai population, accounting for approximately 7.1 new diagnoses in 100,000 male patients.[2] Early prostate cancer detection increases the chance for organ confined[3] and potentially curable disease.[4] Transrectal ultrasound (TRUS) remains a common modality for prostate diagnosis and Grey-scale imaging is frequently used.[5] Originally, TRUS-guided prostate biopsy involved the collection of 6 samples from each anterior/base zone, mid-gland, and apex both sides (sextant biopsy).[6] However, the 6-core biopsy was considered inadequate for cancer detection, and the more lateral zone prostate biopsy was developed[7](extended prostate biopsy). Today the 12-core or double sextant biopsy is recommended as a routine procedure by AUA.[8]

Some studies found that 85.0% of prostate tumors presented on the posterior section of the peripheral zone[9-11] With the aim of improving the efficacy of the detection of prostate cancer from peripheral sampling, Rajavithi Hospital has been carrying out 16-core TRUS-guided prostate biopsies instead (Figure 1). This study was carried out to evaluate any changes in the detection rate of prostate cancer and to review the factors associated with efficacious detection following the introduction of 16-core TRUS-guided prostate biopsy in Rajavithi Hospital.

Materials and Methods

Study population

Between October 2019 and September 2021, 243 patients who had no history of MRI prostate underwent these procedures. 43 patients were excluded from this study because of not attending the TRUS-guided prostate biopsy with 16 core sampling, having a history of prostate cancer or treatment for prostate cancer, having received TRUS-guided prostate biopsy before, and having incomplete data. The remaining 200 patients were included in the analysis (Table 1).

Patient evaluation

TRUS-guided prostate biopsies in Rajavithi Hospital were performed under local anesthesia (1% xylocaine). Before the biopsy, a cleansing enema was administered, and the prostate volume was estimated. Core biopsies were obtained using an 18-gauge needle with a spring-loaded biopsy gun from anterior core, medial core, lateral cores, and apex core both sides. Despite the variation in prostate size, asymmetrical shape or abnormal DRE, the 16-cores were still taken as shown in Figure 1 and the lesions were collected from their site. All specimens were labeled by biopsy site and transported, separately in formalin-filled containers to the pathology department.

The Data was retrospectively collected from medical records and analyzed including demographic data, laboratory results, operative record, and pathologic report. Approval was obtained

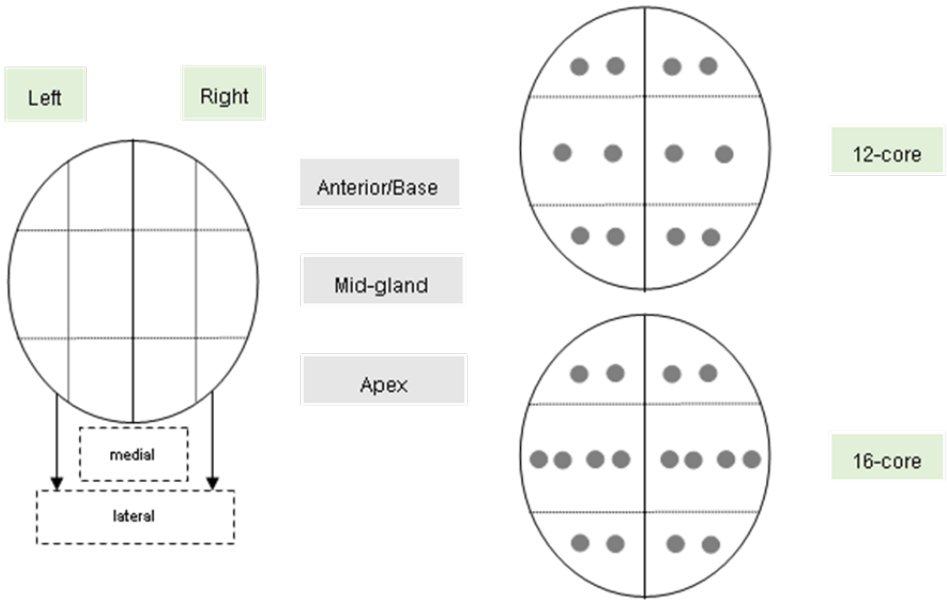

Figure 1. Sampling sites in 12- and 16-core prostate biopsy

Table 1. Demographic and clinical characteristics of participants

Variables	n (%)
Age (years), mean±SD	69.28±8.41
<60	21 (10.5)
60-69	78 (39.0)
70-79	82 (41.0)
>80	19 (9.5)
Family history CA prostate	198 (99.0)
No	2 (1.0)
Yes	
History 5-ARI used ≥ 1 year	
No	176 (88.0)
Yes	24 (12.0)
Abnormal DRE	
No	128 (64.0)
Yes	72 (36.0)
Bilateral	31 (15.5)
Right sided	22 (11.0)
Left sided	18 (9.0)
PSA (ng/ml), (range)	11.92 (7.82-21.96)
≤10	76 (38.0)
>10	124 (62.0)
Size (g), mean±SD	49.96±21.17
<40	66 (33.0)
≥40	134 (67.0)
PSAD (ng/ml/g), (range)	0.27 (0.16-0.67)
<0.15	37 (18.5)
≥0.15	163 (81.5)

DRE = digital rectal examination, PSA = prostate specific antigen, PSAD = prostate specific antigen density, CA = cancer

from the Ethical Review Board, Rajavithi Hospital (Study Number: 65170).

Outcomes

The primary outcomes were the detection rates of prostate using 16-core TRUS-guided prostate biopsy and the associated factors using data from all positive result patients (Figure 2).

Statistical analysis

The demographic and clinical characteristics of the patients were presented as numeric and interquartile range. The associated factors with prostate cancer detection were analyzed by Crude analysis with independent samples t-test, Mann-Whitney U test, Chi-square test and Fisher's exact test.

Any confounders of associated factors data was evaluated with Univariable analysis by simple logistic regression analysis and multivariable analysis by multiple logistic regression.

The demographic and clinical characteristics of patients with prostate cancer in the peripheral zones were presented as numeric and interquartile range and analyzed with independent samples t-test, Mann-Whitney U test, Chi-square test and Fisher's exact test.

Hazard ratios (HRs) with 95% confidence intervals (CIs) were used to assess the strength of the individual variables. Statistical analysis was performed using Stata v.17, and statistical significance was accepted as $p < 0.05$.

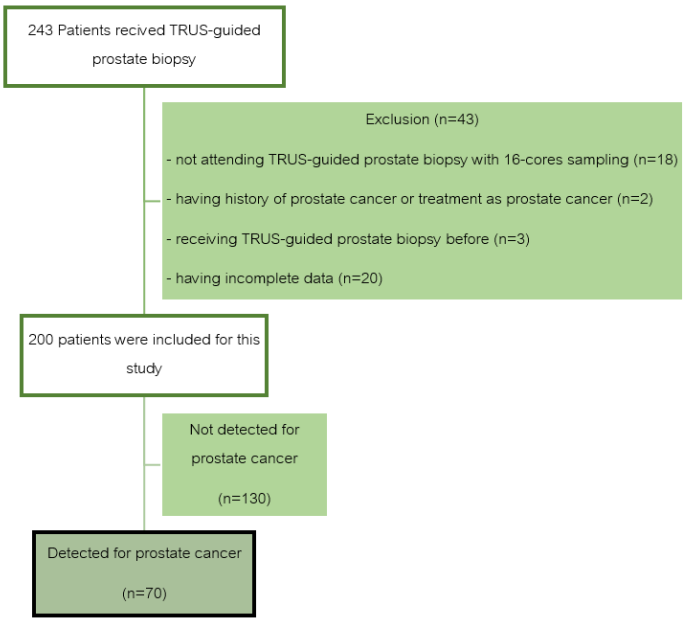

Figure 2. Participants included for the analysis

Results

Between October 2019 and September 2021, Rajavithi Hospital performed 16-core TRUS-guided prostate biopsy on 200 patients with 70 (35.0%) having a positive result for prostate cancer with 62 (31.0%), 57 (28.5%), 55 (27.5%), and 47 (23.5%) positive results being found in the lateral core, apical core, medial core, and anterior core, respectively (Table 2).

Compared with prostate cancer negative patients, patients with prostate cancer had higher average age (67.85 ± 8.03 years vs 71.74 ± 8.60 years) and the majority were likely to have abnormal DRE (74.0% vs 15.4%, $p < 0.001$), PSA > 10 ng/ml (88.6% vs 47.7%, $p < 0.001$), PSAD ≥ 15 ng/ml/g (94.3% vs 74.6%, $p < 0.001$) (Table 3).

Multivariable logistic regression analysis showed that detection of prostate cancer was associated with abnormal DRE (odds ratio [OR] 12.04, 95%Cl 5.42 to 26.73, $p < 0.001$), PSA > 10 ng/ml (OR 5.63, 95%Cl 1.98 to 15.97, $p = 0.001$), and PSAD ≥ 15 ng/ml/g (OR 1.68, 95%Cl 0.40 to 7.04, $p = 0.046$); Table 4.

Among 70 patients diagnosed with prostate cancer 62 had lateral cores positive for cancer. Their average age was 71.95 ± 8.84 years. With the exception of abnormal DRE (80.6% vs 25.4%, $p = 0.003$), our data showed that other factors (a family history of prostate cancer, history 5-ARI use ≥ 1 year, PSA level, prostate size, PSAD level) were not significantly associated with cancer detection using the lateral cores (Table 5).

Discussion

Although there have been many theories about the optimum number of cores for effective cancer diagnosis from prostate biopsy, many studies have supported that the double sextant or 12-core biopsy is optimal for TRUS-guided prostate biopsy.[8] McNeal et al.[9] in 1988 evaluated 88 from 104 prostate glands obtained from radical prostatectomy and reported a positive outcome with regard to the identification of the origin of adenocarcinoma. The pathological results showed 68.0% of tumors arose in the peripheral zone, 24.0% arose in the transitional zone, and 8.0% arose in the central zone. Some studies demonstrated that 85.0% of prostate tumors presented on the posterior portion of peripheral zone.[10-12] In 1998, Chang et al.[13] evaluated the usefulness of adding 4 lateral biopsies from the peripheral zone to routine sextant biopsy of prostate cancer.

Table 2. Pathological characteristics in tissue positive for prostate cancer

	Anterior core	Medial core	Lateral core	Apical core
Total (%)	47 (23.5)	55 (27.5)	62 (31.0)	57 (28.5)
Grade (IQR)	60 (40-80)	50 (30-72.5)	60 (30 -80)	60 (32.5-80)
Grade group (%)				
1	3 (4.3)	7 (10.0)	11 (15.7)	10 (14.3)
2	10 (14.3)	7 (10.0)	11 (15.7)	8 (11.4)
3	3 (4.3)	9 (12.9)	8 (11.4)	7 (10.0)
4	18 (25.7)	18 (25.7)	16 (22.9)	16 (22.9)
5	13 (18.6)	14 (20.0)	16 (22.9)	16 (22.9)
Right sided (IQR)	70 (40-85)	50 (30-80)	70 (50-80)	70 (45-85)
Grade group (%)				
1	3 (4.3)	5 (7.1)	8 (11.4)	9 (12.9)
2	8 (11.4)	7 (10)	8 (11.4)	6 (8.6)
3	5 (7.1)	6 (8.6)	6 (8.6)	6 (8.6)
4	7 (10.0)	11 (15.7)	10 (14.3)	8 (11.4)
5	14 (20.0)	14 (20.0)	15 (21.4)	16 (22.9)
Left sided (IQR)	60 (45-80)	60 (30-80)	60 (30-80)	70 (35-80)
Grade group (%)				
1	1 (1.4)	4 (5.7)	5 (7.1)	3 (4.3)
2	6 (8.6)	6 (8.6)	9 (12.9)	7 (10.0)
3	2 (2.9)	6 (8.6)	5 (7.1)	5 (7.1)
4	15 (21.4)	16 (22.9)	14 (20.0)	14 (20.0)
5	10 (14.3)	12 (17.1)	13 (18.6)	13 (18.6)

IQR = interquartile range

Table 3. Factors associated with prostate cancer detection

Variables	Prostate cancer		P-value
	Yes (n = 70)	No (n = 130)	
Age (years) mean±SD	71.74±8.60	67.95±8.03	0.002
<60	4 (5.7)	17 (13.1)	0.016
60-69	23 (32.9)	55 (42.3)	
70-79	31 (44.3)	51 (39.2)	
>80	12 (17.1)	7 (5.4)	
Family history CA prostate			
No	70 (100)	128 (98.5)	0.543
Yes	0 (0.0)	2 (1.5)	
History 5-ARI used ≥ 1 year			
No	65 (92.9)	111 (85.4)	0.121
Yes	5 (7.1)	19 (14.6)	
Abnormal DRE			
No	18 (25.7)	110 (84.6)	<0.001
Yes	52 (74.3)	20 (15.4)	
PSA (ng/ml) (range)	9.87 (6.99-14.24)	40.40 (13.07-93.84)	<0.001
≤10	8 (11.4)	68 (52.3)	<0.001
>10	62 (88.6)	62 (47.7)	
Size (g) mean±SD	49.74±23.82	50.08±19.67	0.918
<40	27 (38.6)	39 (30.0)	0.219
≥40	43 (61.4)	91 (70.0)	
PSAD (ng/ml/g) (range)	0.22 (0.15-0.31)	0.93 (0.33-1.98)	<0.001
<0.15	4 (5.7)	33 (25.4)	0.001
≥0.15	66 (94.3)	97 (74.6)	

IQR = interquartile range, CA = cancer, PSA = prostate specific antigen, PSAD = prostate specific antigen density

Table 4. Multiple logistic regression analysis for factors associated with detection of prostate cancer

Variables	Univariable analysis			Multivariable analysis		
	OR	95%CI	P-value	OR	95%CI	P-value
Age (years)						
<60	1.00	Reference		1.00	Reference	
60-69	1.78	(0.54-5.86)	0.345	1.52	(0.35-6.52)	0.575
70-79	2.58	(0.80-8.38)	0.114	2.70	(0.63-11.59)	0.181
>80	7.29	(1.74-30.56)	0.007	3.21	(0.51-20.16)	0.214
History 5-ARI used ≥ 1 year						
No	1.00	Reference		1.00	Reference	
Yes	0.45	(0.16-1.26)	0.129	0.49	(0.14-1.72)	0.267
Abnormal DRE						
No	1.00	Reference		1.00	Reference	
Yes	15.89	(7.76-32.55)	<0.001	12.04	(5.42-26.73)	<0.001
PSA (ng/ml)						
≤10	1.00	Reference		1.00	Reference	
>10	8.50	(3.77-19.16)	<0.001	5.63	(1.98-15.97)	0.001
Size (g)						
<40	1.00	Reference		1.00	Reference	
≥40	0.68	(0.37-1.26)	0.220	0.40	(0.17-0.98)	0.046
PSAD (ng/ml/g)						
<0.15	1.00	Reference		1.00	Reference	
≥0.15	5.61	(1.90-16.59)	0.002	1.68	(0.40-7.04)	0.476

DRE = digital rectal examination, PSA = prostate specific antigen, PSAD = prostate specific antigen density

Table 5. Demographic and clinical characteristics of patients diagnosed with prostate cancer by detection in the peripheral zone

Variables	Peripheral		P-value
	Yes (n = 62)	No (n = 8)	
Age (years) mean±SD	71.95±8.84	70.13±6.71	
<60	3 (4.8)	1 (12.5)	0.567
60-69	22 (35.5)	1 (12.5)	0.156
70-79	25 (40.3)	6 (75.0)	
>80	12 (19.4)	0 (0.0)	
History CA prostate			
No	62 (100.0)	8 (100.0)	NA
History 5-ARI			
No	58 (93.5)	7 (87.5)	0.465
Yes	4 (6.5)	1 (12.5)	
Abnormal DRE			
No	12 (19.4)	6 (75.0)	0.003
Yes	50 (80.6)	2 (25.0)	
Area (n = 51)			
Bilateral	23 (46.9)	0 (0.0)	0.296
Right sided	13 (26.5)	1 (50.0)	
Left sided	13 (26.5)	1 (50.0)	
PSA (ng/ml) (range)	45.75 (13.41-105)	19.82 (11.07-21.86)	
≤10	7 (11.3)	1 (12.5)	0.078
>10	55 (88.7)	7 (87.5)	1.000
Size (g) mean±SD	51.27±24.10	37.84±18.73	0.134
<40	22 (35.5)	5 (62.5)	0.246
≥40	40 (64.5)	3 (37.5)	
PSAD (ng/ml/g) (range)	1.06 (0.37-2.19)	0.55 (0.29-0.94)	0.104
<0.15	4 (6.5)	0 (0.0)	1.000
≥0.15	58 (93.5)	8 (100.0)	

DRE = digital rectal examination, PSA = prostate specific antigen, PSAD = prostate specific antigen density, CA = cancer

Their study found that the cancer was missed in 77.0% of prostate cancer patients from the sextant biopsies procedure, but detection was successful from lateral biopsies. They concluded that additional lateral biopsies increased the sensitivity for cancer detection.

Miyoshi et al[14] in 2013 compared 12- with 16-core biopsies in patients with PSA levels 4.0 - 20.0 ng/ml. and reported that prostate cancer detection rate was higher in the 16-core biopsy group, especially in patients with a prostate volume > 30 g and a PSAD < 0.2 ng/ml/g without any significant complication rate between these two groups. With the aim of collecting more tissue from the lateral site of the prostate gland in PSA ≥ 4 ng/ml patients as a screening procedure or confirmation of prostate cancer, 16-core biopsies were carried out in our Hospital to extend peripheral zone sampling. The aim of this retrospective study was to demonstrate an improvement in prostate cancer detection rate using 16-core TRUS-guided prostate biopsy in Rajavithi Hospital.

Between October 2019 and September 2021, our department performed 16 core TRUS-guided prostate biopsy on 200 patients. The prostate cancer detection rate was 70 out of 200 patients (35.0%). The age range was 71.74 ± 8.60 years and those who presented with an abnormal DRE (74.0%, $p < 0.001$), PSA > 10 ng/ml (88.6%, $p < 0.001$), or PSAD ≥ 15 ng/ml/g (94.3%, $p < 0.001$) were found to have a significantly higher chance of having prostate cancer. This study showed that the prostate sampling site that tested positively the most frequently was the lateral core (31.0%) followed by the apical core (28.5%), medial core

(27.5%) and anterior core (23.5%). Our data didn't indicate any factors increased the possibility of prostate cancer detection in the lateral core significantly with the exception of abnormal DRE.

A PSA > 3 ng/dl is an indication for prostate cancer screening in either a male 55 to 69 years old (AUA 2018)[15] or 45 to 75 years old (NCCN 2019).[16] Additional indications for initial prostate biopsy are patient specific risk factors, suspicious DRE findings/prostate nodules (5.0%-30.0% cancer risk), symptoms suggestive of prostate cancer, or having suggestive findings of metastasis prostate cancer.[17] Our results demonstrate that positive samples for prostate cancer at the lateral core (31.0%) were the most frequent so 16-core TRUS-guided prostate biopsy, which collects more tissue from the lateral site of the prostate gland, may be more effective over 12-core in terms of detecting prostate cancer. This is especially true in patients with abnormal DRE, high PSA (> 10 ng/ml), and high PSAD (≥ 15 ng/dl). Other factors which may have a bearing such as age and prostate size, were found to be insignificant in this study but this may be due to the small sample size. This could also be said about the relationship between abnormal DRE and prostate cancer detection at lateral core.

In addition to the possibility of increasing the detection of prostate cancer by TRUS-guided prostate biopsy, the risk benefits to the patient should also be considered, a limitation to this study as we didn't capture the risks or complications associated with prostate cancer biopsy. A second limitation was there was no comparative method with different cores from TRUS-guided prostate biopsy in this study. Third, the sample size and the patient population with prostate cancer were insufficient to stratify some possible characteristics.

Conclusion

From our data, we can conclude that 16-core TRUS-guided prostate biopsy is a potential procedure for the detection of prostate cancer in patients with abnormal DRE, high PSA (> 10 ng/ml), and high PSAD (≥ 15 ng/dl). Further studies with a larger sample size and also randomized clinical trials are warranted to add weight to this conclusion.

Conflicts of Interest

The authors declare no conflicts of interest.

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Original Article

The role of prostate MRI in clinical staging of prostate cancer before radical prostatectomy

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Keywords:
MRI, clinical, staging, prostate, cancer, radical prostatectomy

Abstract

Objective: Transrectal ultrasonography (TRUS) guided biopsy is the main method used for the diagnosis of prostate cancer. However, it may be challenging to determine the extraprostatic extension (EPE) and seminal vesicle invasion (SVI) based solely on pathology alone. Newer imaging techniques may have the potential to improve differentiation between localized and locally advanced diseases. The objective of this study is to evaluate the accuracy of mpMRI in the determination of extraprostatic extension EPE and SVI of prostate cancer with regard to the final pathology, and to predict lymph node (LN) involvement.

Materials and Methods: This retrospective study evaluated the data from the medical records of male patients with prostate cancer who underwent preoperative mpMRI (at either 3.0 Tesla or 1.5 Tesla) followed by either robotic-assisted laparoscopic radical prostatectomy or laparoscopic radical prostatectomy, between January 2017 and October 2022. The area under the receiver operating characteristic curve (AUC) value was used in multivariable analysis to compare the performance of mpMRI and clinical data (prostate-specific antigen, ISUP category) in predicting pathologic EPE or SVI.

Results: The study looked at the data pertinent to 98 men with prostate cancer who underwent an MRI scan (mpMRI) before surgery (radical prostatectomy). The average age was 67 and the average PSA level was 19.81 ng/ml. The final pathology was reviewed to see if the cancer had spread outside the prostate (extracapsular extension, EPE) or into the SVI. These are signs of a more advanced cancer. At radical prostatectomy a total of 56 out of 98 (57.14%) patients had pathologic EPE, and 22 out of 98 (22.45%) patients had pathologic SVI. To determine the relationship between mpMRI staging and pathological staging, univariate analysis was conducted. EPE and SVI were combined to characterize them as locally progressed diseases and to enhance effective prediction. The data indicated 50.88%, 95.12%, 93.55%, and 58.21% of cases, for specificity, sensitivity, positive predictive value, and negative predictive value respectively. In summary, the mpMRI has a strong ability to inform the treatment of locally advanced disease due to its ability to determine the EPE and SVI on the final pathology. The limited level of sensitivity is currently limiting and warrants further research.

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Conclusion: This study suggests that mpMRI can be a valuable tool for the identification of prostate cancer in patients who are unlikely to have advanced stages of the disease (EPE or SVI). However, due to its limited sensitivity, it may limit the diagnosis of cases of advanced cancer. Therefore, a negative mpMRI result should not completely rule out the possibility of advanced disease, and additional evaluation may be necessary.

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Introduction

The most recent data indicates that prostate cancer is currently the fifth most frequent cancer in men in Thailand.1 The incidence of prostate cancer has been declining during the previous few years.[2] and in the period 1993 to 2017, the age-adjusted death rate from prostate cancer has also steadily decreased. However, a more recent study has found that the death rate has remained constant in more recently.[3]

The diagnosis of prostate cancer typically involves a two-pronged approach: initial tests to see if further evaluation is needed, followed by a biopsy if the initial tests raise suspicion. The initial tests consist of a digital rectal examination (DRE) and measurement of prostate-specific antigen (PSA) levels. If the initial tests suggest a possibility of prostate cancer, a biopsy will likely be recommended. This biopsy is performed using a thin needle to extract a small sample of prostate tissue, often guided by transrectal ultrasonography (TRUS). Pathology reports are based on the Gleason scoring system for biopsied specimens. The clinical staging of prostate cancer is based on the TNM classification system from the AJCC Staging Manual, Eighth Edition.[4]

Treatment of prostate cancer patients is primarily guided by a risk stratification system, which includes clinical staging, Gleason grade, and PSA levels for the categorization of patients into risk groups.[5] This allows for selection of the most appropriate treatment to effectively reduce the risk of recurrence and disease progression.

In recent years, multiparametric MRI (mpMRI) has significantly improved the processes of prostate cancer staging and characterization. For the most accurate diagnosis, a 3-Tesla MRI scanner is recommended for mpMRI. While lower magnetic field strengths (1.5-Tesla) can be used with additional equipment to enhance image quality[6], mpMRI should not be considered a replacement for TRUS biopsy. It is not yet the gold standard for the detection of prostate cancer itself.

Treatment decisions are heavily influenced by the distinction between organ-confined disease (T2) and extraprostatic disease (T3).[7] The presence of extraprostatic extension (EPE) and seminal vesicle invasion (SVI) are accepted as accurate independent predictors of biochemical failure and metastasis.[8]

Any patient with prostate cancer who exhibits clinical signs of clinical localization may receive a radical prostatectomy (RP) as their initial course of treatment. Both robot-assisted laparoscopic radical prostatectomy (RALRP) and laparoscopic radical prostatectomy (LRP) are frequently performed and are believed to be comparable to conventional methods.[9]

The purpose of this study is to investigate whether mpMRI can result in the ability to distinguish between organ-confined (T2) and extraprostatic (T3) prostate cancer based on the final pathology, and to assess the potential for lymph node involvement. The objective of this study is to assess the ability for pre-operative mpMRI to predict EPE and SVI in the final prostatic specimen, and to assess potential lymph node involvement.

Materials and Methods

Study design

Retrospective diagnostic study.

Ethical approval given by the Ethics Committee Chiang Mai University (Study Code: SUR-2564-08177)

Population

Data was retrieved from the medical records of patients at Maharaj Nakorn Chiang Mai Hospital between January 2017 and October 2022. Informed consent was not obtained due to the retrospective nature of the study.

Inclusion criteria

- Male patients aged ≥ 45 years old.
- Had undergone RP due to prostate cancer.

• Underwent mpMRI prior to radical prostatectomy.

Exclusion criteria

• Has a pathological diagnosis of locally advanced disease or metastatic disease.

• Underwent external beam radiation therapy before undergoing radical prostatectomy.

Sample size

Formula used for calculation as described by Daniel, 1999 using data from a previous study: Sensitivity = 0.81, 1-Sensitivity = 0.19, Prevalence = 0.37, $d^2 = 0.08^2 = 0.0064$

$$n_{Se} = \frac{Z^2_{\frac{\alpha}{2}} \widehat{Se}(1 - \widehat{Se})}{d^2 \times Prev}$$

Calculated sample size = 127.38 = 128 patients

Study protocol

Patients who have been diagnosed with prostate cancer via TRUS biopsy based on abnormal DRE or high PSA levels are offered either a CT scan of the abdomen and pelvis or the mpMRI of the prostate for imaging investigations. If imaging shows no signs of locally advanced or metastatic disease, patients will be offered treatment options for prostate cancer. Patients choosing RP are advised further on surgical technique choices.

All patients undergo a pelvic phased-array 3-Tesla or 1.5-Tesla mpMRI using an endorectal coil (ERC). Three standard imaging sequences are used during mpMRI exams: T2-weighted imaging (TWI), diffusion-weighted imaging (DWI), and dynamic contrast enhancement imaging (DCE). MRI-derived prostate volume (PV) is calculated using the ellipsoid formula: 0.52 x (D1 x D2 x D3).[10] Results are then reported based on PI-RADS grading criteria.[11] Current practice is for two radiologists to independently identify and report the presence of EPE and SVI based on the mpMRI.

The preoperative variables are recorded as follows: age, underlying medical condition, serum PSA level, symptoms at presentation, prostate volume measured by mpMRI, date of mpMRI, mpMRI PI-RADS score, and biopsy Gleason grade group according to the ISUP classification.

The postoperative variables are recorded as follows: final specimen pathological stage and ISUP grade group, types of surgical technique used, and number of days between mpMRI and RP (Fig. 1).

Data analysis

Using a Fisher's two-tailed exact test, the categorical data have been presented as frequency and percentage. Using a Mann-Whitney U test the mean and standard deviation of the continuous variables have been reported.

Sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and area under the receiver operating characteristic curve (AuROC) calculations were performed. Data analysis was done using STATA version 16.0.

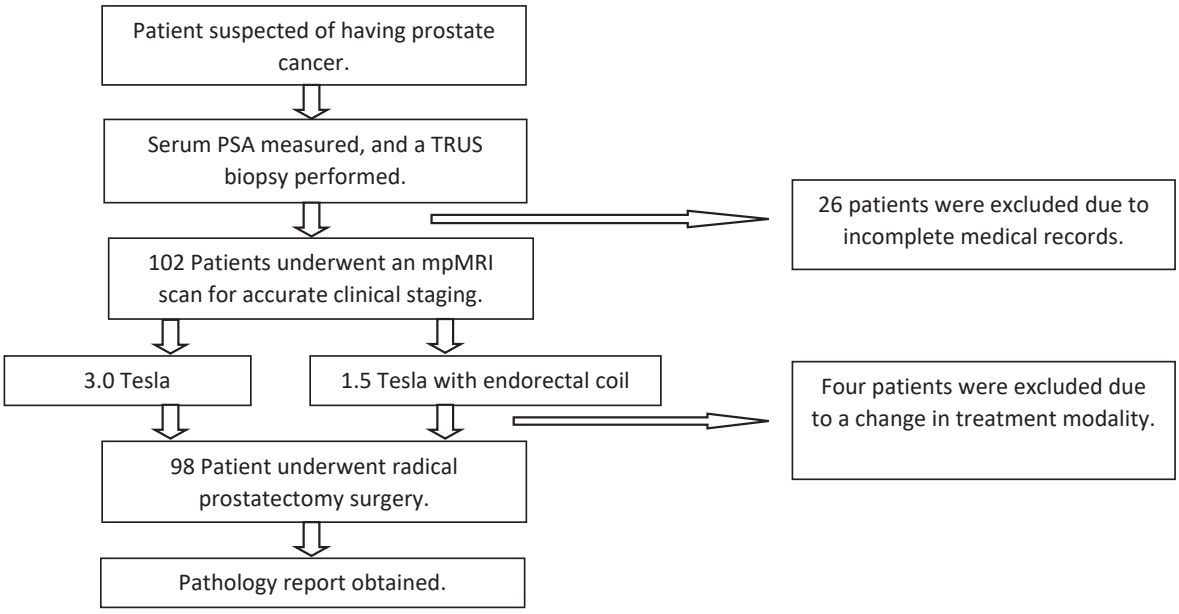

Figure 1. Study design diagram

Results

The study included data on 128 patients in total. Due to inadequate data records, patient had received other local treatments, a salvage RP performed, and not undergoing mpMRI before surgery, 30 patients were removed. 98 patients in all had data gathered for analysis.

Baseline characteristics of patients are shown in Table 1.

98 patients in all met the criteria for selection. Table 1 includes the demographics and clinical data. The mean age was 66.69 years old. The mean PSA was 19.81 ng/ml. Most prostate biopsies, 43 patients, were classified as ISUP category 2 (43.88%), followed by 22 patients classified as category 5 (22.45%), 15 patients classified as category 3 (15.31%), and 9 patients classified equally as categories 1 and 4 (18.36%). In the table, patient characteristics are displayed. In the preoperative imaging, the mpMRI enabled the identification of 31 patients with EPE (31.63%), and 13 patients with SVI (13.26%). In the RP samples, EPE was detected in 56 patients overall (57.14%), whereas SVI was detected in 22 patients (22.45%).

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the mpMRI in the identification of EPE or SVI are shown in Table 2.

The sensitivity, specificity, positive predictive value, and negative predictive value of the mpMRI in the detection of lymph node metastatic status is shown in Table 3.

The ROC curve for the detection of EPE or SVI using mpMRI are shown in Figure 2.

The ROC curve for the detection of lymph node metastatic status using mpMRI is shown in Figure 3.

Our analysis showed a statistically significant correlation ($p < 0.05$) between mpMRI staging and the final pathological staging of prostate cancer. In other words, mpMRI results compared well to the findings from tissue examination after surgery. The breakdown of mpMRI performance is as follows:

• EPE and SVI Detection: mpMRI demonstrated a high specificity (95.12%) for the identification of EPE or SVI suggesting the use of mpMRI is highly effective in correctly ruling out these conditions (low false positive rate). However, the sensitivity was moderate (50.88%), indicating mpMRI may miss some cases of EPE/SVI (false negative rate). Overall accuracy for EPE/SVI detection was 69.39%.

• Lymph Node Prediction: mpMRI showed as being a very promising technique for the prediction of lymph node involvement with very high specificity (97.50%) suggesting mpMRI is highly effective in identifying patients in whom there is no lymph node involvement. However, the sensitivity was lower (38.89%), suggesting the use of mpMRI may miss some patients with positive lymph nodes. The overall accuracy for lymph node prediction was 86.73%.

Discussion

RP is the current gold standard treatment for localized prostate cancer, offering similar oncological outcomes to external beam radiotherapy.[12] However, this surgery can cause side effects, specifically erectile dysfunction (up to 74.70%) and urine incontinence (up to 21.30%) within a year of the procedure.[13]

Current clinical staging and diagnosis of prostate cancer primarily rely on PSA levels and DRE. However, these methods have limitations in comparison with mpMRI with regard to detecting whether the disease has spread beyond the prostate gland.[14] Additionally, mpMRI also more effective than a pelvis and abdominal CT scan in terms of the detection of EPE.[15] As a result, it has been suggested that mpMRI be used as a technique to determine whether there is locally advanced disease before the actual surgery.

This study evaluated the ability of the use of mpMRI to predict EPE and SVI, as well as lymph node involvement, in patients diagnosed with prostate cancer in whom RP was being considered. Patients underwent mpMRI scans prior to surgery, and their mpMRI results were compared to the final pathology after RP.

This study found high mpMRI specificity (95.12%) for the identification of the presence of EPE or SVI confirmed by final pathology. This suggests that mpMRI can help reduce unnecessary exclusions from curative treatments by minimizing false-positive results. However, the sensitivity for EPE/SVI detection was moderate (50.88%). These results are in alignment with other studies, for example a study by Jeong et al reported moderate sensitivity for EPE (43.00%) and SVI (34.90%) but high specificity for both (84.20% and 93.80%, respectively).[16,17] These

Table 1. Baseline characteristics data of prostate cancer patients (N=98)

Parameters	n (%) [Range]
Underlying disease	
Hypertension	46 (46.94)
Dyslipidemia	29 (29.59)
Diabetes mellitus	17 (17.35)
Kidney disease	6 (6.12)
Heart disease	12 (12.24)
Symptoms at presentation	
Gross hematuria	2 (2.04)
Lower urinary tract symptoms	65 (66.33)
No symptoms	32 (32.65)
Prostate-specific antigen (ng/ml)	19.82 (21.03) [4.58-154.00]
Prostate volume at MRI (ml)	39.83 (20.19) [14.6-135.00]
Time period between MRI and radical prostatectomy (days)	132.75 (157.41) [5-1,127]
Surgical modality	
Laparoscopic radical prostatectomy	33 (33.67)
Robot-assisted laparoscopic radical prostatectomy	65 (66.33)
ISUP category and Gleason score on prostate biopsy	
1 (3+3)	9 (9.18)
2 (3+4)	43 (43.88)
3 (4+3)	15 (15.31)
4 (4+4, 3+5, 5+3)	9 (9.18)
5 (4+5, 5+4, 5+5)	22 (22.45)
Extraprostatic extension cases from mpMRI	31 (31.63)
Seminal vesicle invasion cases from mpMRI	13 (13.26)
Pathologic extraprostatic extension cases	56 (57.14)
Pathologic seminal vesicle invasion cases	22 (22.45)
mpMRI modality	
1.5 Tesla with endorectal coil	27 (27.55)
3.0 Tesla	71 (72.44)
MRI PIRADS	
3	10 (10.20)
4	33 (33.67)
5	55 (56.12)
Surgical margin	
Negative	42 (42.86)
Positive	56 (57.14)
Perineural invasion	
Negative	18 (18.37)
Positive	80 (81.63)
Lymphovascular invasion	
Negative	61 (62.24)
Positive	37 (37.76)
Lymph node(s)	
Negative	80 (81.63)
Positive	18 (18.37)
Tumor%*, Mean (SD)	37.25 (25.28) [5-100]

SD = standard deviation

*Percentage of prostate involved in the tumor

Table 2. Diagnostic accuracy of mpMRI in the identification of extraprostatic extension (EPE) or seminal vesicle invasion (SVI)

Parameters	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Surgical modality				
LRP	35.71	89.47	71.43	65.38
RALRP	55.81	100.00	100.00	53.66
ISUP category and Gleason score on radical prostatectomy				
1 (3+3)	-	-	-	88.89
2 (3+4)	45.45	90.48	83.33	83.33
3 (4+3)	50.00	100.00	100.00	50.00
4 (4+4, 3+5, 5+3)	50.00	100.00	100.00	71.43
5 (4+5, 5+4, 5+5)	60.00	100.00	100.00	20.00
mpMRI modality				
1.5 Tesla with endorectal coil	27.78	100.00	100.00	40.91
3.0 Tesla	61.54	93.75	92.31	66.67
MRI PIRADS				
3	33.33	100.00	100.00	77.78
4	23.53	87.50	66.67	51.85
5	64.86	100.00	100.00	58.06
Surgical margin				
Negative	27.27	93.55	60.00	78.38
Positive	56.52	100.00	100.00	33.33
Perineural invasion				
Negative	50.00	93.75	50.00	93.75
Positive	50.91	96.00	96.55	47.06
Lymphovascular invasion				
Negative	42.31	94.29	84.62	68.75
Positive	58.06	100.00	100.00	31.58
Lymph node (s)				
Negative	55.81	94.59	92.31	64.81
Positive	35.71	100.00	100.00	30.77

PPV = positive predictive value, NPV = negative predictive value, LRP = laparoscopic radical prostatectomy, RALRP = robot-assisted laparoscopic radical prostatectomy

findings collectively highlight that mpMRI alone may not be sufficient for definitive local staging of prostate cancer.

However, mpMRI offers significant advantages as a non-invasive diagnostic tool. It does not require hospitalization or antibiotic prophylaxis, unlike some procedures. This study also showed that both 1.5-Tesla and 3.0-Tesla MRI scanners with ERC achieved similar accuracy and specificity in the detection of EPE/SVI and lymph node involvement. However, the sensitivity was lower in the case of the 1.5-Tesla scanner in comparison to the 3.0-Tesla scanner.

The limited sensitivity of mpMRI for the detection of EPE or SVI can be attributed to several factors. These include host factors such as prostate inflammation or recent biopsy, as well as the limitations of the technique itself. For instance, mpMRI may be unclear with the identification of the periprostatic fat plane or when the seminal vesicle plane is obliterated.[18]

While mpMRI shows promise in the other areas of prostate cancer diagnosis, its accuracy with regard to the prediction of lymph node involvement remains under investigation. Some studies suggest the procedure has potential, but more research is needed. However, the established strengths of the use of mpMRI in the detection of EPE and SVI can still benefit prostate cancer patients. By accurately identifying these factors, mpMRI can help select patients who are more likely to benefit from pelvic lymph node dissection during RP, potentially improving patient selection for this procedure.

Table 3. Diagnostic accuracy of mpMRI in the detection of lymph node metastatic status

Parameters	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Surgical modality				
LRP	-	-	-	96.67
RALRP	41.18	95.83	77.78	82.14
ISUP category and Gleason score on radical prostatectomy				
1(3+3)	-	-	-	88.89
2(3+4)	-	-	-	90.70
3(4+3)	50.00	90.91	66.67	83.33
4(4+4, 3+5, 5+3)	-	-	-	88.89
5(4+5, 5+4, 5+5)	62.50	92.86	83.33	81.25
mpMRI modality				
≥ 1.5 Tesla with endorectal coil	50.00	100.00	100.00	87.50
≥ 3.0 Tesla	96.61	96.61	66.67	87.69
MRI PIRADS				
≥ 3	-	-	-	-
≥ 4	50.00	96.55	66.67	93.33
≥ 5	35.71	97.56	83.33	81.63
Surgical margin				
Negative	0	97.50	-	95.12
Positive	43.75	97.50	87.50	81.25
Perineural invasion				
Negative	-	-	-	94.44
Positive	41.18	96.83	77.78	85.92
Lymphovascular invasion				
Negative	0	98.18	0	90.00
Positive	58.33	96.00	87.50	82.76
Lymph node (s)				
Negative	-	97.50	-	-
Positive	-	61.11	-	-

PPV = positive predictive value, NPV = negative predictive value, LRP = laparoscopic radical prostatectomy, RALRP = robot-assisted laparoscopic radical prostatectomy

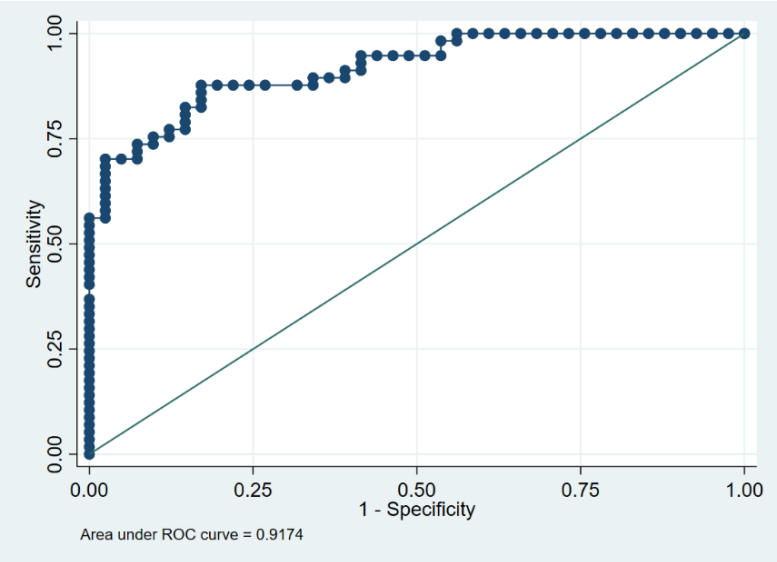

Figure 2. ROC curve for detection of EPE or SVI by mpMRI
Area Under Receiver Operating Characteristic curve (AuROC) = 0.9174

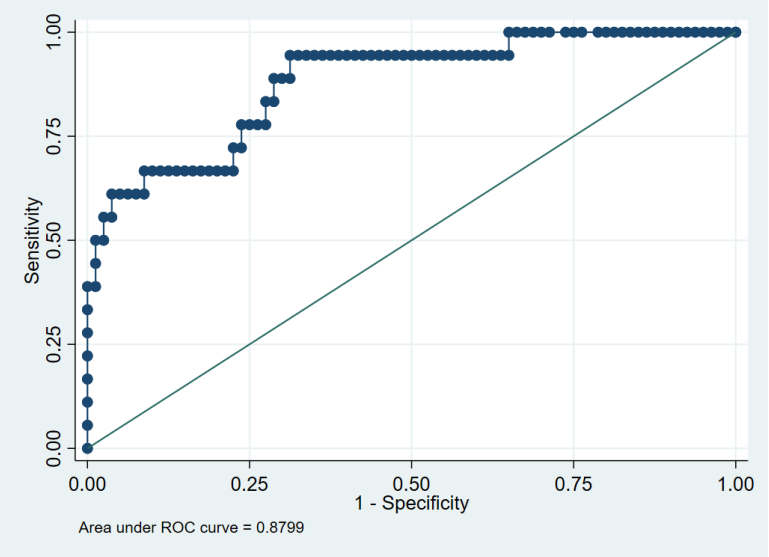

Figure 3. ROC curve for detection of lymph node metastatic status
Area Under Receiver Operating Characteristic curve (AuROC) = 0.8799

This study has both strengths and limitations. While its retrospective nature is a drawback, a key strength is that the radiologists evaluated all images prior to surgery, eliminating the possibility of selection bias. However, due to the non-uniform use of mpMRI, we were unable to determine the time interval between biopsy and mpMRI for all patients. This is important because the average time between mpMRI and surgery in this study was quite extended at132 days, which could be a relevant factor in influencing disease progression and potentially affecting the pathological staging of cancer.

Conclusion

mpMRI is a promising tool for prostate cancer diagnosis, particularly with regard to the identification of EPE/SVI and potentially reducing unnecessary exclusions from curative treatments. However, the limitations surrounding its sensitivity necessitate further research, especially with regard to predictions pertinent to lymph node involvement. Future studies are warranted and should aim for a more uniform time interval between mpMRI and surgery to minimize potential confounding factors.

Conflict of Interest

The authors declare no conflict of interest.

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Original Article

Incidence of nocturia in post kidney transplant patients at Chiang Mai University Hospital: a descriptive study

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Keywords:
Incidence, nocturia, post renal transplant, patients

Abstract

Objective: Kidney transplantation is the most effective long term treatment for ESRD patients one reason being the decrease in complications related to hemodialysis/ peritoneal dialysis. However, the transplantation is associated with high urine volume which makes ESRD patients experience increased nocturia affecting quality of life. The objective of this study is to investigate incidence and frequency of nocturia at different periods of time after kidney transplantation and the percentage of increase in bladder capacity.

Materials and Methods: This descriptive and ambispective study was carried out using data from medical records and self-frequency voiding charts recorded after transplantation at 1, 3 and 6 months. Data used was pertinent to kidney transplant patients at Chiang Mai University Hospital from June 2018 to February 2020 and August 2020 to December 2021.

Results: Data from a total of 132 patients fitted the criteria, 68 patients from prior study and 64 patients who were enrolled onto a prospective study. Virtually 100% of patients (131/132) have nocturia (nighttime voiding ≥ 2) at 1 month after surgery, the frequency decreasing in incidence at 3 and 6 months (96.21 & 87.88% respectively). The mean frequency of nighttime voiding is also decreasing at 1, 3, and 6 months (5.72, 4.24, 3.29 respectively). Meanwhile, the mean post-operative bladder capacity(ml) is increasing, at 360, 449, and 486 ml at 1, 3, and 6 months respectively. These results may show a correlation between increase in bladder capacity and decrease in frequency of nighttime voiding

Conclusion: Post-kidney transplant patients will face nocturia, but in most cases this will improve in time because of the increase of bladder capacity. Further research into this area needs to include a longer follow up period to enable the identification of the timing of the plateau phase when nighttime voiding and bladder capacity are stable. This will enable both patients and health professionals to plan and advise regarding any idiosyncracies in recovery after kidney transplantation.

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Introduction

Due to the development and improvement in medical treatment and technologies, Thailand is becoming an elderly population. Chronic kidney disease affects health, well-being and national expenditure. The prevalence of therapies associated with chronic kidney disease and kidney failure such as peritoneal dialysis and hemodialysis are also increasing. However, those techniques have many complications such as cardiovascular and infectious complications and poor quality of life (QoL).

Kidney transplant (KT) has become the gold standard treatment for end-stage renal disease (ESRD) due to fewer complications and better QoL in comparison to the various therapeutic procedures. Preoperative anuria/oliguria in end-stage renal disease and post-operative polyuria after transplantation[2] can cause lower urinary tract symptoms (LUTs) such as frequency and nocturia.[1,3,4]

Nocturia, nighttime voiding ≥2, is one symptom that affects QoL.[5-9] This study investigates the incidence, correlation between bladder capacity and nocturia, and frequency of night-time voiding at different periods of time after transplant.10

The Primary outcome is the incidence of nocturia in post KT patients

Secondary outcomes are the frequency of nocturia and volume of bladder capacity at different periods of time post-transplant, with a view to application of the data to be able to inform patients before surgery and collect data for more studies in the future.

Materials and Methods

This study is an ambispective study. Earlier data from a prior study at our institute was used. In the cohort of that study 68 patients from June 2018 to July 2020 fitted the criteria for this study. We also collected prospective data from patients who underwent kidney transplant at Chiang Mai University Hospital from August 2020 to May 2022

The inclusion criteria were patients who underwent kidney transplantation at our institute, of ≥ 20 years of age and could follow up at our out-patient department for at least 6 months.

The exclusion criteria were patients who did not consent to inclusion in the study, had an indwelling catheter postoperatively, urinary diversion patients and who had urine output per day less than 1.5 l/day.

Data collected included patient characteristics such as age, sex, body mass index (BMI), underlying disease and voiding volume or duration of anuria before transplantation.

Bladder capacity was measured by bladder filling intraoperatively, a routine procedure before kidney transplant surgery.

At the time of discharge, patients were provided with a bladder diary and were instructed to complete a voiding diary diligently. The diary was to be presented to our physicians during their follow-up appointments. We also recorded creatinine levels both prior to discharge and during subsequent follow-up assessments.

This study is a descriptive study and the results are shown as the mean of each parameter.

Ethical approval was given by the Ethical Committee of Chiang Mai University (Study Number: 125/2023) (Fig. 1)

Results

Data was collected from 68 patients from a prior study and all 83 patients that fitted the inclusion criteria were initially enrolled Nineteen patients were excluded from the study due to a delay in graft function necessitating hemodialysis (5), death (3), lost to follow up (3), urine volume less than 1.5 L/day (3), graft failure (2), ureteric stricture that need diversion (1) and language problems (2). Therefore, data from a total 132 patients were included in the study.

The majority of patients were aged 31 to 60 years, with males outnumbering females by nearly two to one (85 males compared to 47 females).

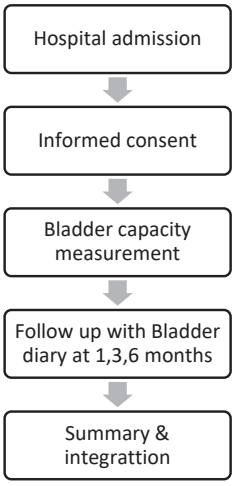

Figure 1. Diagram to show how the data was collected and integrated

Table 1. Demographic data of post kidney transplant patients (N=132)

Parameters	n (%)
Age (years), mean (SD)	42.80 (12.15)
Age (years)	
≤ 20	3 (2.27)
21-30	19 (14.39)
31-40	35 (26.52)
41-50	32 (24.24)
1-60	35 (26.52)
> 60	8 (6.06)
Sex	
Male	85 (64.39)
Female	47 (35.61)
BMI (kg/m^2), mean (SD)	20.87 (3.02)
BMI (kg/m^2)	
≤ 17	19 (14.39)
18-23	93 (70.45)
24-30	20 (15.15)
Co-morbidity	
HT	59 (44.70)
DM	19 (14.39)
HBV	6 (4.55)
SLE	8 (6.06)
Others	25 (18.94)
None	28 (21.21)
RRT before KT	
None	2 (1.52)
HD	104 (78.79)
CAPD	23 (17.42)
HD+CAPD	2 (1.52)
Pre-emptive	1 (0.76)
Cause of ESRD	
DM	11 (8.33)
IgA nephropathy	9 (6.82)
Chronic glomerulonephritis	13 (9.85)
ADPKD	4 (3.03)
Stone	8 (6.06)
Lupus nephritis	9 (6.82)
Others	19 (14.39)
Unknown	59 (44.70)

RRT = Renal replacement therapy, CAPD = continuous ambulatory peritoneal dialysis, HD = hemodialysis, BMI = body mass index, HT = hypertension, DM = diabetes mellitus, HBV = hepatitis B viral infection, SLE = systemic lupus erythematosus, ADPKD = autosomal dominant polycystic kidney disease

Over 70.00% of the patients exhibited a normal BMI and presented with comorbidities. Characteristics of patients are shown in Table 1.

The vast majority of the patients had nocturia after surgery, nearly 100% (99.24%) had nocturia at 1st month numbers decreasing to 88.00% in six months (Table 2).

Table 2. Incidence of nocturia in post kidney transplant patients at 1, 3, 6 months

Parameters	n (%)
1st month nocturia frequency	
< 2	1 (0.76)
≥ 2	131 (99.24)
3rd month nocturia frequency	
< 2	5 (3.79)
≥ 2	127 (96.21)
6th month nocturia frequency	
< 2	16 (12.12)
≥ 2	116 (87.88)

Table 3. Mean of nighttime voiding and bladder capacity in post kidney transplant patients at 1, 3, and 6 months

Parameters	Mean (SD)
1st month nighttime voiding	5.72 (2.54)
3rd month nighttime voiding	4.24 (2.09)
6th month nighttime voiding	3.29 (1.73)
1st month bladder capacity	360.07 (138.90)
3rd month bladder capacity	449.17 (162.92)
6th month bladder capacity	486.10 (160.84)

SD = standard deviation

Table 4. Mean percentage difference of bladder capacity and nighttime voiding between 1st vs 3rd and 6th months

Parameters	Mean (SD)
% Increase of bladder capacity at 1 & 3 months	30.50 (42.19)
% Increase of bladder capacity at 1 & 6 months	43.45 (49.50)
% Decrease of nighttime voiding at 1 & 3 months	22.43 (33.07)
% Decrease of nighttime voiding at 1 & 6 months	37.69 (34.38)

SD = standard deviation

The mean numbers of patients experiencing nighttime voiding also decreased with time after surgery; a frequency of 5.72, 4.24, 3.29 at 1st, 3rd,6th months respectively (Table 3).

Mean percentage decrease of nighttime voiding was calculated at 1st vs 3rd month and 1st vs 6th month, the results were 22.43 and 37.69 respectively (Table 4).

The mean bladder capacity that we inferred from functional bladder capacity from maximal voiding volume recorded in the bladder diary was increasing in line with time after surgery from 360 ml to 486 ml over the 6 months (Table 3).

Average percentage increase in bladder capacity at 1st vs 3rd month and 1st vs 6th month were 30.5 and 43.45 respectively (Table 4).

Discussion

A prior study carried out by der Weide et al in 20081, investigated lower urinary tract symptoms in post kidney transplant patients with a sample size of 52 patients. They found that the incidence of nocturia was 60.00% and they used subgroup analysis with structural equation modelling to find risk factors. Results showed that factors associated with nocturnal polyuria were small bladder capacity and dysfunctional voiding.

Our study showed that nearly 100% of post kidney transplantation patients encountered nocturia which decreased by around 12.00% in 6 months. In study risk factors were not investigated but the results indicate an inverse correlation between bladder capacity and nighttime voiding.

The mean numbers of nighttime voiding decreased over the six month period by approximately twice and the mean percentage of decrease of nighttime voiding was more than 33.00% in 6 months. The mean bladder capacity increased by around 150 ml and the mean percentage of increase in bladder capacity was nearly 50.00% by the 6 month follow up.

From this prospective data, we found that the incidence of nocturnal polyuria was 100% but the data from the retrospective patients was insufficient to draw any conclusions.

The limitations of this study are that the research team could not measure bladder capacity by the same interventions in the patients who were not under anesthetic due to the invasiveness nature of the bladder filling. In addition the ESRD patients who had anuria/oliguria pre-operatively could not provide the detailed bladder diary.

This study investigated only nocturia and bladder capacity in association with kidney transplant, however, nocturia and other LUTs can also be caused by urinary tract infections, benign prostate hypertrophy, bladder disease, and dysfunctional voiding, all of which could have impacted on our results. The short period of follow-up and the reliability of the bladder diary are also limitations of this investigation which would need to be addressed in future studies.

Conclusion

Post-kidney transplant patients will face nocturia, but this will improve over time largely because of the increase in bladder capacity. A longer follow up period is essential for future studies in order to identify the plateau phase following surgery to document the time that nighttime voiding and bladder capacity are stable. This will enable both patients and health professionals to plan and advise regarding any idiosyncracies in recovery after kidney transplantation.

Conflict of Interest

The authors declare no conflict of interest.

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Original Article

Identification of somatic mutations and their effects in a Thai population with both non-muscle invasive and muscle invasive bladder cancer using whole exome sequencing analysis

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Keywords:
Urothelial carcinoma, non-muscle invasive bladder cancer, muscle invasive bladder cancer, somatic mutation, whole exome sequencing

Abstract

Objective: Whole exome sequencing is a new technology which enables the detection of genetic mutation in cancer. Genetic alterations in urothelial carcinoma have been identified and studies are being carried out with regard to clinical applications. Proposals have been made pertinent to molecular classifications for the prediction of treatment response and prognosis. To date, there is a paucity of data regarding somatic mutation of bladder cancer in Thailand, therefore, the aim of this study is to identify specific somatic mutations associated with different types of bladder cancer in Thailand.

Materials and Methods: Fourteen patients were enrolled onto this study, 7 with non-muscle invasive (NMIBC) and 7 with muscle invasive bladder cancer (MIBC). DNA was isolated from peripheral blood mononuclear cells and tumor tissue for whole exome sequencing to identify any tumor somatic mutations and the mutation burden in each patient. The results were analyzed and correlated with the clinical status of the patients after treatment.

Results: In the NMIBC group, the most common mutated genes were found to be HLA-F, KDM6A, and TTN. In the MIBC group, the most common mutated genes were TP53, TTN, and KMT2D. Patients with urothelial carcinoma with small cell variant show TP53 and RB1 mutation. This is the same as the current consensus on molecular classification. The disease has usually metastasized after 1 year. This supports the evidence that Neuroendocrine-like groups have poorer prognosis.

Conclusion: The somatic mutations of bladder cancer in this Thai population showed greater diversity of genetic alteration in comparison with the worldwide database. The mutations in the muscle invasive bladder cancer were the same as previous findings. We also found a similar association in neuroendocrine-like genomic mutations. Despite the number of patients in this study being small, there is evidence of genetic diversity and tumor origins of mutation in our patients.

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Introduction

Bladder cancer, the tenth most-common malignancy worldwide, is a major cause of morbidity and mortality. Currently, approximately 573,000 cases of bladder cancer have been diagnosed globally, and 212,000 fatalities recorded.[1] Due to the differences in prognosis and management, urothelial carcinoma (UC), the most common type of bladder cancer, is divided into non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC).[2,3]

The rapid advancement of next-generation sequencing (NGS) technology has facilitated the investigation of molecular characterization of bladder cancer. In 2014, a group of researchers in The Cancer Genome Atlas (TCGA) project published an integrated genomic analysis of 131 MIBC samples, finding statistically significant recurrent mutations in 32 genes, including several chromatin regulators.[4] In a more recent study of 412 MIBC patients the expression of five subtypes was demonstrated which may help in treatment response stratification.[5] In 2020, a consensus molecular classification had been proposed for MIBC, the sub-types being divided into Luminal Papillary, Luminal non specified, Luminal unstable, stroma-rich, Basal/Squamous and Neuroendocrine-like.[6] This study also provided insight into the specific mutation and clinical characteristics of each subtype. The molecular characteristics of NMIBC were also studied. In 2016, Hedegaard et al.[7] published the UROMOL 2016 subtyping system that classified NMIBC into three categories (Class 1-3). Although the global trend of precision medicine has expanded by the use of modern genomic sequencing technologies, in Thailand the application of genomic knowledge for medical purposes is still relatively rare. Furthermore, there is no dataset pertinent to the association between somatic mutation and bladder cancer in a Thai population.

This is a descriptive pilot study aiming to identify the somatic mutated genes in UC of the bladder, including both NMIBC and MIBC in a Thai population. The focus was on comparing the common genetic alterations of UC of the bladder between Thai patients and large public databases to identify differences that may impact our treatment and clinical practice with regard to bladder cancer patients. We believe that our study will be the first small step toward long-term development in genomic and molecular research in our country.

Materials and Methods

Patient selection

All patients newly diagnosed with a bladder tumor that was suspected bladder cancer who underwent transurethral resection of bladder tumor (TUR-BT) in the King Chulalongkorn Memorial Hospital (KCMH) between August 2019 to March 2020 were enrolled onto this study. Patients were excluded if they had any other histological type besides UC, or if tissue specimens were limited or of too low quality for DNA extraction.

Specimen Collection

Blood was collected to isolate peripheral blood mononuclear cells (PBMCs) from the participants before the operation. Germline DNA samples were isolated from PBMCs. All tumor tissues were gathered immediately after transurethral resection to maintain the viability of tissues and to lessen DNA breakdown. Tumor tissue sampling was performed randomly from multiple areas of the tumor to ensure samples were diverse and then rapidly preserved in liquid nitrogen for transport to the laboratory. Some specimens were preserved in formalin and sent to uropathologists for subtype classification.

DNA isolation

DNA was isolated from peripheral blood mononuclear cells (germline DNA) and tumor tissue (somatic DNA) using the genUp dDNA kit (Promega, Madison, WI, USA), in accordance with the manufacturer's instructions. The quantity of extracted genomic DNA was assessed by a fluorimetric method with a Qubit device.

Whole exome sequencing of PBMC and tumor tissues

Libraries from the PBMC and the fresh tissue samples from all patients were prepared starting from 200 ng of extracted DNA by using the SureSelect All Exon v6 (Agilent Technologies, Santa Clara, USA) in accordance with the protocol described by the manufacturer. All libraries were sequenced on the MGC sequencer and 2x150 bp paired end reads were generated.

Data analysis

The short reads were aligned with the human reference genome (GRCh38) by using Burrows Wheeler Aligner (BWA). After the alignment, PCR duplicates were removed using Picard MarkDuplicates. The alignments were then recalibrated and filtered using the Genome Analysis Toolkit (GATK). Varscan was then applied to identify somatic mutations by comparing tumor against normal tissues. The oncoprint diagram was created using the Maftools software.

Results

Patient demographics, clinical and pathological characteristics of patients

During the study period, 14 patients underwent TUR-BT at our institution and were included in this study. Baseline characteristics and pathologic features of patients with NMIBC and MIBC are summarized in table 1 and 2, respectively. The mean age of the population was 72.5 years, with a male-to-female ratio of 1.3:1. The variant histology of UC may result in a negative impact on patient outcome.8 In the NMIBC group all patients had high grade UC and two patients showed mixed histologic features between UC and variant histology including micropapillary features and squamous differentiation. In the MIBC group all the patients had high grade UC, with two patients having small cell differentiation and glandular/nested variant. Among the 14 patients, there was only one patient with the carcinoma in situ (CIS) and two with lymphovascular invasion (LVI).

Summary of somatic mutations

Figure 1 shows the distribution of the mutations in our study population. The six most common genes harboring somatic mutations were TTN, NRXN1, MUC19, HYDIN, CTNNA2 and TP53. The CA-B3 sample shows the highest mutation burden followed by CA-B21 and CA-B15 respectively. In the NMIBC group the most common mutated genes are TTN, HYDIN, DMD, and ADGRV1 (Fig. 2). In comparison, in the MIBC group the most common genes are TP53, KMT2D, TTN and MUC4 (Fig. 3). Missense mutation and single nucleotide polymorphism (SNP) were the main variant class and type respectively in both NMIBC and MIBC groups. The dominant single nucleotide variation (SNV) classes were C>T in both NMIBC and MIBC.

From the TCGA database 5, from this Thai population we identified TP53 and KMT2D as among the top mutations, findings the same as published in the TCGA database. However, in the NMIBC group the top 10 mutated genes did not match the top 10 mutated genes listed in the UROMOL study.

Consideration of variant histology

Many studies have shown that the variant histology may affect the outcome of the patient.[8,9] These studies have been working to identify the genomic mutation of each subtype. It has been shown that the small cell/neuroendocrine variant is strongly associated with the TP53 and RB1 mutation.[10] One of the MIBC samples had UC with small cell variant. This sample harbored both the TP53 and RB1 mutations, the same as in the neuroendocrine-like group in the consensus molecular classification of MIBC.[6]

Nested variant histology is rare, one study has shown that this variant is associated with the TP53 and JAK3 mutations which were not found in our specimens.11 Another study shows that the most common genomic alterations in UC with squamous cell variants are TP53 (67.7%), KMT2D (48.4%) and ARIDIA (32.3%).[12] The patients with the squamous cell variant in our study did not harbor any of the aforementioned genetic mutations.

Summary of tumor mutation burden (TMB)

TMB is the total number of mutations per megabase detected in the DNA of cancer cells. The higher TMB may correlate with the response of immune checkpoint inhibitors in solid organ tumors, especially in bladder cancer.[13,14] In our study CA B3 had the highest TMB which may correlate with the high stage of the tumor in that patient.

Discussion

Genomic sequencing is now used to identify the mutations of the molecular signature in cancer. Studies are looking for potential actionable genomic alterations which could lead to clinical implications, especially with regard to new treatment. In bladder cancer, NMIBC and MIBC are two almost distinct clinicopathological conditions due to their behavior as well as their

Table 1. Characteristics of patients with non-muscle invasive bladder cancer

Sample	Age (yrs)	Sex	Presence of Histologic Subtype	Tumor Grading	TNM Stage	Presence of CIS	Presence of LVI	Multi-focality	Size (> 3 cm)	Smoking History	BCG	Ref.
CA-B4	70	M	Focal micropapillary features	High grade	pTaN0M0	No	No	Solitary	No	Yes	No	No
CA-B8	75	F	No	High grade	cTaN0M0	Yes	No	Multifocal	No	No	No	Yes
CA-B9	82	M	No	High grade	cTaN0M0	No	No	Multifocal	No	Yes	Yes	Yes
CA-B10	74	M	No	High grade	cTaN0M0	No	No	Multifocal	No	No	No	Yes
CA-B19	70	F	No	High grade	cTaN0M0	No	No	Multifocal	Yes	No	Yes	No
CA-B20	88	F	No	High grade	cT1N0M0	No	No	Multifocal	No	No	No	Yes
CA-B21	67	F	Focal squamous differentiation	High grade	cT1N0M0	No	No	Solitary	Yes	No	Yes	No

CIS = carcinoma in situ, LVI = lymphovascular invasion, BCG = Bacillus Calmette-Guérin, F = female, M = male, Ref. = references, yrs = years

Table 2. Characteristics of patients with muscle invasive bladder cancer

Sample	Age (yrs)	Sex	Presence of Histologic Subtype	Tumor Grading	TNM Stage	Presence of CIS	Presence of LVI	Multi-focality	Size (> 3 cm)	Smoking History	Neoadjuvant Chemo-therapy	Adjuvant Chemo-therapy
CA-B2	65	M	Small cell differentiation	High grade	ypT2aN0M0	No	No	Solitary	Yes	No	Yes	No
CA-B3	72	F	No	High grade	ypT3bpN1 M1a	No	Yes	Solitary	Yes	No	Yes	Yes
CA-B5	70	F	No	High grade	pT3a pN1cM0	No	Yes	Multifocal	Yes	No	No	No
CA-B14	80	M	No	High grade	cT2N0M1	No	No	Solitary	No	No	No	No
CA-B15	69	M	No	High grade	cT2N0M0, (pT1N0M0)	No	No	Multifocal	Yes	No	No	No
CA-B17	70	M	No	High grade	pT3aN0M0	No	No	Solitary	Yes	Yes	No	No
CA-B18	62	M	Glandular variant & Nested variant	High grade	ypT4aN0M0	No	No	Solitary	Yes	Yes	Yes	Yes

CIS = carcinoma in situ, LVI = lymphovascular invasion, BCG = Bacillus Calmette-Guérin, F = female, M = male, yrs = years

somatic mutations. By identifying the mutation, clinicians may be able to evaluate the risk of disease progression, response to chemotherapy, or even tailor treatment for each specific mutation.

In this study, we explored the common somatic mutations of NMIBC and MIBC in a Thai population. In the NMIBC group TTN, HYDIN, DMD, and ADGRV1 are the most common mutations in our study. However, according to the UROMOL study FGFR3, KIAA1109 and SYNE2 are the genes which most frequently mutate.[7] In the MIBC group in our study the most common mutations were in the TP53, KMT2D, TTN and MUC4 genes. In the TCGA database the genes which show the most frequent mutations are TP53, KMT2D and KDM6A.[5] Despite the study population in our study being small, the results still show that the somatic mutations may prove to be the same as in the global population.

Being able to identify somatic mutations in specimens by performing TUR-BT may benefit the prediction of the response to neoadjuvant

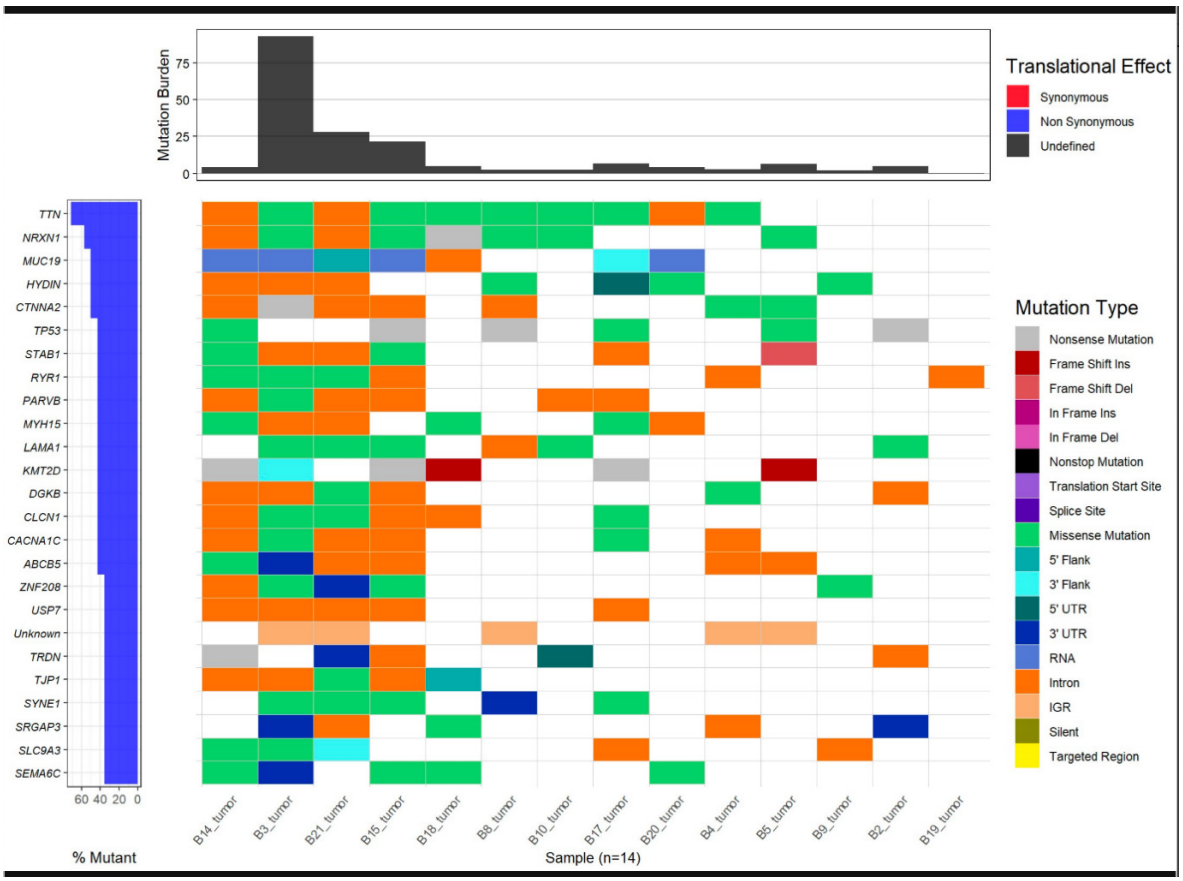

Figure 1. Somatic mutations of all study participants

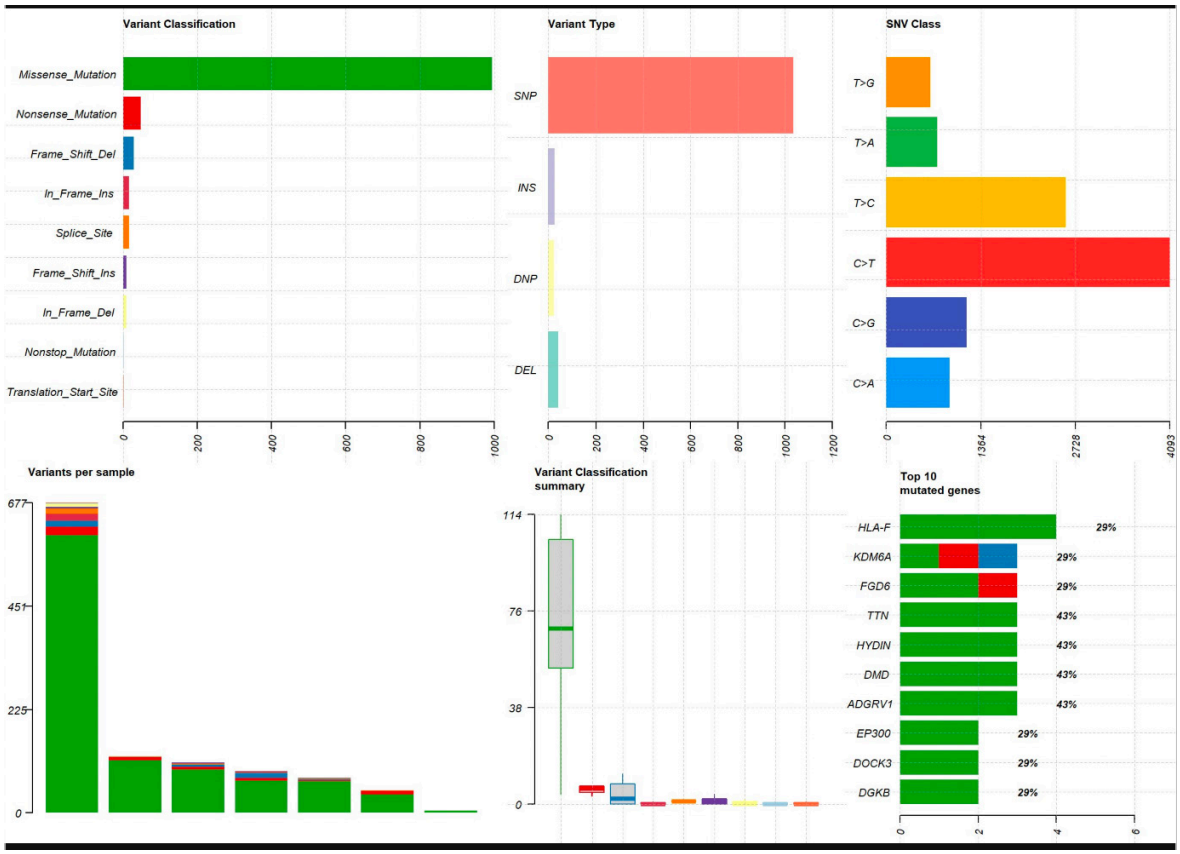

Figure 2. Somatic mutations of all study participants

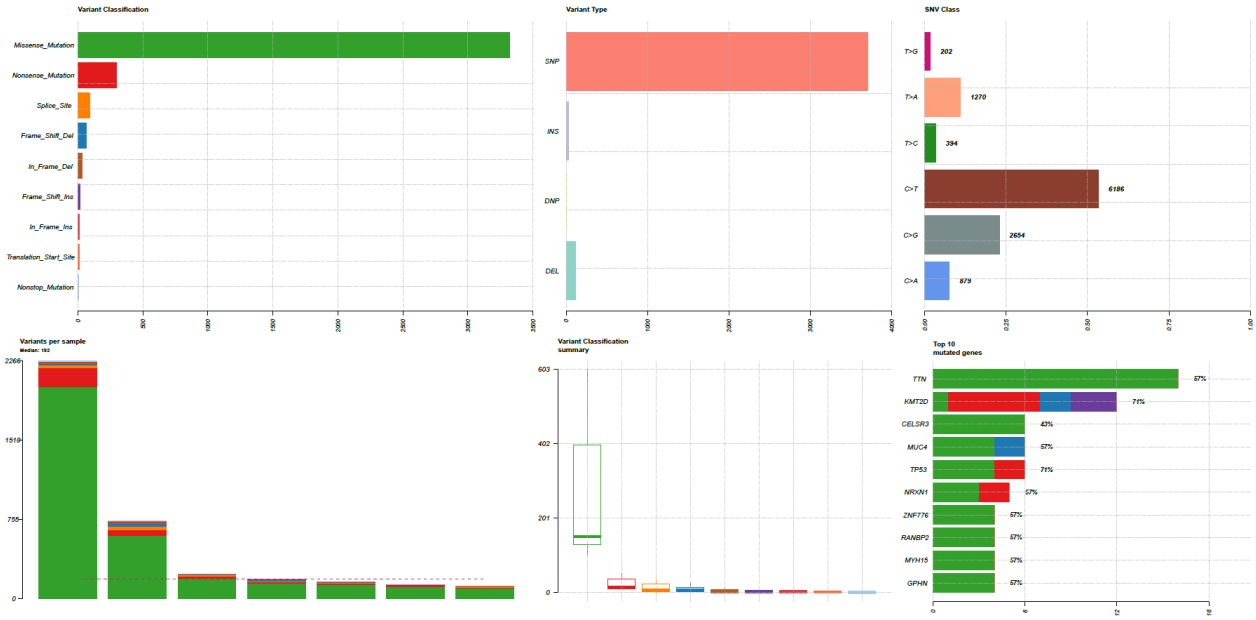

Figure 3. Bar chart of somatic mutations in the MIBC group

Cisplatin-based chemotherapy. One study has shown that luminal tumors have a lower rate of pathological up staging to non-organ-confined-disease in comparison to non-luminal tumors.[15] The TMB has now also been found to be associated with immune checkpoint inhibitor response.[16] Fibroblast growth factor receptors (FGFRs) have been a potential target for the development of cancer treatment. The FGFR3 mutation is known to facilitate the development of cancer by promoting cell proliferation, survival, migration, invasion, and angiogenesis in bladder cancer.[17] FGFR inhibitors have been recognized as a promising targeted therapy of bladder cancer with FGFR3 mutation. Studies are ongoing to verify the clinical benefits for bladder cancer patients with an FGFR mutation.[18] Erdafitinib, a tyrosine kinase inhibitor of FGFR1-4, is currently the only available treatment for locally advanced or metastatic UC with an FGFR3 mutation. It showed a 40.0% response rate and 13.8 months of median overall survival.[19] These findings highlight the potential treatment which may be developed to target a specific genetic mutation for other genes to inform the selection of candidates for chemotherapy, immunotherapy or up-front radical surgery.

Special consideration for neuroendocrine-like group

We also investigated the incidence of mutations in UC with variant histology. We found that in the small cell variant in this study there was a consistent occurrence of TP 53 and RB1 mutation as in other study. This can be classified as a neuroendocrine-like variant.[10] The patient with small cell variant in this study received neoadjuvant chemotherapy followed by radical cystectomy. Within the 1 year follow up period the patient lung metastasis developed. One study has demonstrated that small cell carcinoma of the bladder with an ERCC2 mutation can have a complete pathologic response after neoadjuvant chemotherapy of 50.0%.[10] Our patient did not harbor the ERCC2 mutation and did not respond to neoadjuvant chemotherapy. Pembrolizumab, a PD-1 inhibitor, was initiated and the disease was stable for 1.5 years. Immunotherapy is an established option for the treatment of advance UC as a second line treatment.[20, 21] but is now emerging as a first line treatment in stage IV bladder cancer.[22,23] There are few studies into histologic variants and the response of immunotherapy, but some case reports show a good response.[24] A study combining chemotherapy with immunotherapy compared to chemotherapy alone has also shown improved median overall survival in locally advanced or metastatic small cell genitourinary cancer.[25] Hopefully in the future with more clinical data, the establishment of a specific treatment for a specific mutation will emerge.

Limitations

Our study is limited by a small population, and the lack of clinical outcomes and statistics. However, the study is of value because it is the first to provide clinical data for NMIBC and MIBC genomic variants in a Thai population. In a future study data should be collected for other types of variant histology such as sarcomatoid. We believe that the description of some of the genomic mutations found in association with the variant histology could play a role in facilitating the selection of treatment in the near future.

Conclusion

Whole exome sequencing has provided greater insight into the genomic alterations associated with UC. This will surely play a role in future treatment of UC. NMIBC, MIBC, and their variant histology have distinct mutations and oncogenic pathways which lead to the development of UC. We have identified common somatic mutations in a Thai population which have similarities with the global database for example TP53 and KMT2D. We have also shown that some common mutations are found in the cancers in this population including FGFR3, TP53, and RB1. Even though our study is limited, this is an exciting first step into the application of whole exome sequencing for the treatment of bladder cancer in a Thai population.

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Original Article

Comparison of heated topical intrarectal anesthesia and periprostatic nerve block in transrectal ultrasound-guided prostate biopsy in Chaophrayayommarat Hospital: a prospective randomized trial

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Keywords:
Prostate biopsy, intrarectal local anesthesia, lidocaine gel, periprostatic nerve block, prostate cancer, pain score

Abstract

Objective: To compare efficacy between heated intrarectal local anesthesia (HIRLA) and periprostatic nerve block (PNB) with respect to pain reduction during transrectal ultrasound-guided prostate biopsy (TRUS-Bx).

Materials and Methods: A prospective randomized trial including 60 participants scheduled for TRUS-Bx from July to December 2024. Participants were assigned to a group using heated intrarectal local anesthesia with 10 ml 40 °C 2% lidocaine gel (n=30) or PNB (n=30). Primary outcome was the level of pain as measured by pain score using a visual analog scale (VAS) during TRUS-Bx. The secondary outcome was complications which occurred during and after the procedure.

Results: The level of pain in the HIRLA group was greater in comparison to PNB (4.03±1.85 versus 2.57±1.68; p=0.002). No differences in complications were observed between the two groups.

Conclusion: PNB provides more effective pain reduction in comparison to HIRLA during TRUS-Bx.

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Introduction

Prostate cancer is one of the most common cancers in men, ranking fourth among all cancers in males. According to the Thai Cancer Registry data from the National Cancer Institute, approximately 3,700 new cases of prostate cancer are reported each year, with an incidence rate of 7.7 cases per 100,000 population. The Bureau of Strategy and Planning in the Ministry of Public Health has reported that each year approximately 1,700 people die from prostate cancer. Early detection, whether through screening for prostate-specific antigen (PSA) or other methods, can significantly improve outcomes. A digital rectal examination by a doctor involves the insertion of a finger into the rectum to feel for any abnormalities of the prostate. Early detection of the disease allows for prompt treatment, leading to better treatment outcomes and increased chance of survival from the disease.[1]

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Currently, transrectal prostate biopsy guided by ultrasound (Ultrasound-guided transrectal prostate biopsy; TRUS-Bx) remains the standard method for the diagnosis of prostate cancer.[2] The systematic biopsy was first introduced by Hodge in 1989, and involved six punctures. Later, Eichler and colleagues conducted a systematic review and found that 12 punctures significantly increased the rate of detection of prostate cancer without adding complications. This has led to the widespread adoption of this biopsy method, and is now included in the treatment guidelines published by the European Association of Urology (EAU). Although there are recommendations to perform magnetic resonance imaging (MRI) before TRUS-Bx to increase the rate of cancer detection1, these recommendations may be difficult to implement in Thailand due to limitations of the healthcare budget, a problem experienced in many other countries. Additionally, interpretation of a prostate MRI requires a radiologist who has received specialist training.

TRUS-Bx often causes pain or discomfort during the procedure, and various forms of analgesics are available. The most commonly used method is a local anesthetic due to its convenience, speed, cost, and the feasibility to be applied by the surgeon. These include intrarectal local anesthesia (IRLA), periprostatic nerve block (PNB), intraprostatic local anesthesia (IPLA), and pelvic plexus block (PPB).[3] Intravenous sedation (IVS) and spinal anesthesia (SA) can also be used.[4] The most widely used methods in practice are IRLA and PNB since they are simple and quick to perform. However, some studies indicate that the use of local anesthesia may not reduce pain during TRUS-Bx.[5-8] Subsequently, meta-analyses have revealed that the use of local anesthetics can reduce pain during TRUS-Bx.[3,9] Several studies have found that IRLA provides more effective pain relief than regular lubricants[10,11], while IRLA is less effective than PNB.[3,9,12] According to some studies, application of the two IRLA creams together reduces pain to the same extent as applying IRLA plus PNB, while others have found no difference between IRLA and PNB.[13,14] The main disadvantage associated with the use of PNB is the pain caused by the needle which is used to apply anesthesia around the nerve group near the prostate.[13-15]

The application of heat in combination with topical anesthetics has been shown to improve pain relief[16,17], pointing to a mechanism by which heat facilitates the faster and more efficient penetration of the medication into the epidermal layers. One study found that heated IRLA (Heated IRLA; HIRLA) is a more effective method of pain relief method regular IRLA.[18] Jang and colleagues compared HIRLA with PNB and found that HIRLA was no less effective than PNB.[19,20] However, research studying the efficacy of local anesthetics is still limited in Thailand in comparison to other countries. The primary objective of this study was to compare the efficacy of HIRLA with PNB in patients undergoing prostate interventions. The secondary objective was to compare post-procedural complications following prostate biopsy between the two methods.

Materials and Methods

A prospective randomized trial was performed from July to December 2024 with a 1:1 allocation ratio. The sample size was calculated based on the study by Ding et al[21] Eligibility criteria were: men aged 50 years and above with PSA≥4.0 ng/ml and/or abnormal finding on digital rectal examination. Exclusion criteria included: bleeding disorders, use of antiplatelet/anticoagulant 7 days prior to the study, use of analgesics 2 days prior to the study, no prior antibiotic prophylaxis, comorbidities including inflammatory bowel disease, anal stricture, anal fissure, hemorrhoid, colorectal cancer, urinary tract infection, prostatitis, and cognitive impairment. The study protocol was reviewed and approved by the Ethics Committee Chaophrayayommarat Hospital (YM025/2567), and written informed consent was obtained from all participants. Data was collected in the operating theater and the outpatient clinic in Chaophrayayommarat Hospital. Age, comorbidities, PSA level, and prostate size were recorded as demographic data. After having obtained informed consent and data, participants were randomly assigned to the HIRLA group and PNB group using computer-generated software.

Biopsy protocol

A prophylactic antibiotic (ciprofloxacin 500 mg), along with a cleansing enema, was started on the day of the procedure. Participants were placed in the dorsal lithotomy position. The HIRLA group received 10 ml 2% lidocaine gel, which was heated to 40°c in a temperature-controlled cabinet (Warmer solution model WS-01, Iso tech

instrument (Thailand) co. ltd.), and applied inside the anal canal 5 minutes prior to TRUS-Bx. The PNB group received 10 mL of 1%lidocaine 5 minutes prior to TRUS-Bx by injecting 5 mL on each side of the junction between the prostate and seminal vesicle where the neurovascular bundle is located. After local anesthesia was applied, an ultrasound probe (Toshiba Xario SSA-660 A, Schmidt Biomedtech (Thailand) Ltd.) was inserted transrectally and a standard 12-core prostate biopsy was performed. Pain score was evaluated using a visual analog scale (VAS) ranging from 0 (no pain) to 10 (worst pain ever experienced). The VAS board was positioned at the eye level of the participant to allow self-evaluation. The team member who recorded the pain score of the participant was blinded from the method of anesthesia used. The participant was then transferred to the recovery room, vital signs were monitored for 30 minutes and the patient was checked for signs of lidocaine toxicity.[22-24] The patient was discharged home if vital signs were stable and was directed to continue with the prophylactic dose antibiotic for 3 days. After 1 week, the patient was seen at the outpatient clinic for to discuss the pathology results and as a regular follow-up. Other members of the research team documented any problems, including significant hematuria, defined as gross hematuria lasting more than 48 hours, urinary tract infection, hematospermia, and severe rectal bleeding. Pathology results were recorded by the urologist performing TRUS-Bx.

Outcome measurement

The primary outcome was measured from the pain scores recorded during TRUS-Bx. The secondary outcome was the recording of any significant complications which were noted after the procedure. The margin of difference in VAS score was defined as 1 based on a previous randomized controlled trial.[21] Continuous variables are presented as mean and standard deviation and analyzed using either a Mann-Whitney U test or an unpaired t-test. For the categorical variables, the data are presented as number and percentage, the chi-square test or Fisher exact test were implemented. Analysis of the primary outcome was assessed using a two-sided 95% confidence interval (CI) of the mean difference. Additionally, the 95% CI for the mean difference in VAS score was estimated. Two-sided p-values for the superiority test were used for evaluation of the secondary outcome. Statistical software SPSS version 15 was used to evaluate the data by documenting age, prostate size, PSA value, pathological results, and pre-existing conditions in the data entry form, with a $p < 0.05$ considered statistically significant.

Results

Between July and December 2024, 85 patients underwent a prostate biopsy at Chaophrayayommarat Hospital, 60 of whom fulfilled the selection criteria of the study. Figure 1 shows a flow diagram of the study. Demographic data of all participants

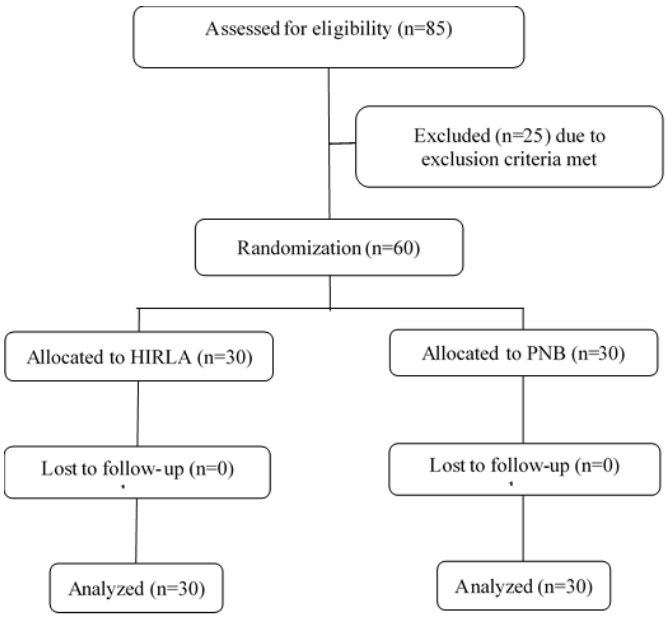

Figure 1. Flow diagram of the study according to consolidated standard of reporting trials (CONSORT)

is presented in Table 1 and shows no significant differences between two groups. Mean pain score during TRUS-Bx was 4.03 in the HIRLA group and 2.57 in the PNB group; the difference was 1.47 with a 95% CI of 0.56 to 2.38 (p = 0.002) as shown in Table 2.

Regarding post-biopsy complications, no statistically significant differences were observed between the two groups, as shown in Table 3. Overall complication rate was 13.3% in both groups. Urinary tract infections were reported in 6.7% of patients in both groups. Significant hematuria was observed in 6.7% of patients in the HIRLA group and 3.3% in the PNB group. Hematospermia persisting for more than 48 hours was recorded in 3.3% of patients in the PNB group, whereas no cases were reported in the HIRLA group. No severe rectal bleeding occurred in either group. No severe adverse events or lidocaine toxicity were noted in either group.

Discussion

TRUS-Bx is a widely performed procedure, yet pain management remains a crucial consideration.[2] While PNB has traditionally been regarded as the gold standard for local anesthesia[3,9,12,21,25], and there are studies that have demonstrated that IRLA and PNB may alleviate pain equally[14,20], HIRLA has been proposed as a potential alternative due to its ease of use.[18,19] However, the findings of this study demonstrate that PNB provides significantly more effective pain relief than HIRLA.

Jung et al introduced the use of HIRLA, showing that it demonstrated improved analgesic efficacy in comparison to standard IRLA.[18] Sub-

Table 1. Characteristic data of the patients

	HIRLA (n=30)	PNB (n=30)	P-value
Age (years) mean ± SD	69.47 ± 8.74	69.67±6.4	0.92
Comorbidities			
- Diabetes melliutus n (%)	6 (20.0)	7 (23.3)	0.754
- Hypertension n (%)	8 (26.7)	11 (36.7)	0.405
- Chronic kidney disease n (%)	3 (10.0)	3 (10.0)	1.000
Cancer present on pathologic result n (%)	10 (33.3)	9 (30.0)	0.781
Prostate volume (ml) median (IQR)	38.5 (22, 67)	42.5 (26, 56)	0.988
PSA level (ng/ml) median (IQR)	10.6 (7.8, 33)	12.4 (5.8, 39)	0.706

SD = standard deviation, PSA = prostate specific antigen, HIRLA = heated intrarectal local anesthesia, PNB = periprostatic nerve block, IQR = interquartile range

Table 2. Mean pain score between two groups

	HIRLA (n=30)	PNB (n=30)	Treatment difference (95%CI)	P-value
Pain score mean ± SD	4.03±1.85	2.57±1.68	1.47 (0.56, 2.38)	0.002*

SD = standard deviation = HIRLA = heated intrarectal lidocaine gel, PNB = periprostatic nerve block, CI = confidence interval

Table 3. Characteristic data of the patients

	HIRLA (n=30)	PNB (n=30)	P-value
Complications n (%)	4 (13.3)	4 (13.3)	1
Significant hematuria	2 (6.7)	1 (3.3)	1
Severe rectal bleeding	0 (0.0)	0 (0.0)	1
Hematospermia	0 (0.0)	1 (3.3)	1
Urinary tract infection	2 (6.7)	2 (6.7)	1

SD = standard deviation, PSA = prostate specific antigen, HIRLA = heated intrarectal local anesthesia, PNB = periprostatic nerve block, IQR = interquartile range

sequently, Jang et al reported that HIRLA was non-inferior to PNB in terms of pain control during TRUS-Bx[19], suggesting that HIRLA could be a viable alternative to PNB, especially considering its simpler technique and fewer procedural requirements.

In contrast, the present study found that PNB provided significantly more effective analgesia than HIRLA, with patients in the PNB group reporting predominantly mild pain levels, whereas those in the HIRLA group reported moderate pain levels. The mean difference in pain scores between the two groups was 1.47. Several factors may explain this discrepancy. First, the methodology differed in terms of drug dosage and timing. In this study, HIRLA was administered using 10 mL of lidocaine gel retained for 5 minutes, while Jang and Jung used 20 ml retained for 10 minutes.[18,19] It is plausible that a higher volume and longer retention time enhance mucosal absorption and analgesic depth, which could explain the lower mean pain scores reported in their studies (3.44 and 3.2) compared to ours (4.03).

Additionally, the concentration and volume of lidocaine used in PNB differed across studies. In our study, 10 ml of 1% lidocaine was used, whereas Jang et al utilized 5 ml of 2% lidocaine. Although the total amount of active drug (100 mg) was equivalent, a larger volume of a lower-concentration solution may provide broader periprostatic tissue coverage and facilitate a more effective nerve blockade. This might explain the lower mean pain score observed in our PNB group (2.57) in comparison to Jang's study (3.14).[19]

From a cost-effectiveness perspective, PNB may require more resources and operator expertise, whereas HIRLA is easier to administer and may offer logistical advantages in high-volume settings. However, the trade-off in analgesic efficacy, as shown in our study, should be carefully considered when selecting the appropriate method.

In terms of safety, both PNB and HIRLA were well tolerated. No patients developed severe allergic reactions to any local anesthetics. The overall complication rate, including urinary tract infection, hematuria, rectal bleeding, and hematospermia lasting more than 48 hours, was 13%. This is in alignment with previously reported complication rates and reinforces the safety of TRUS-Bx with local anesthesia.

This study has several limitations. First, the study was conducted at a single institution, potentially introducing selection bias. Second, the pain assessment was performed during the procedure without long-term follow-up to assess delayed pain or other discomfort. Third, the study did not include plain unheated intrarectal lidocaine gel, which could potentially demonstrate the efficacy of heating the lidocaine gel. Finally, variations in operator technique and individual pain thresholds could have influenced the results. Future multicenter studies with larger sample sizes and extended follow-up periods are needed to confirm the findings of this study.

Conclusions

PNB is superior to HIRLA in reducing pain during TRUS-Bx and has an equivalent safety profile. While HIRLA may be considered when PNB is unavailable, PNB remains the preferred local anesthesia technique for optimizing patient comfort during TRUS-Bx.

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Conflict of Interest

The authors declare no conflict of interest

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Original Article

Ofloxacin prophylaxis can reduce bacteriuria in patients with sterile urine who underwent extracorporeal shockwave lithotripsy (ESWL) for treatment of upper urinary tract stone: a randomized controlled trial

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Keywords:
ESWL, antibiotic prophylaxis, ofloxacin, bacteriuria, pyuria, sterile urine

Abstract

Objective: Urinary tract infections (UTI) are a serious complication in patients undergoing extracorporeal shock wave lithotripsy (ESWL). While antibiotic prophylaxis has proven beneficial in various surgical procedures, this study aimed to evaluate its benefits in ESWL patients with sterile urine.

Materials and Methods: This double-blind, randomized clinical trial was conducted in patients with upper urinary tract stones admitted for ESWL at Sunpasitthiprasong Hospital, Thailand. Patients were randomly assigned to receive either ofloxacin (200 mg) or placebo one hour before ESWL. The incidence of UTI, bacteriuria, pyuria, and patient characteristics including gender, age, underlying conditions, and stone location were assessed in both groups.

Results: Data were collected from a total of 598 patients who were admitted for ESWL between 2008 and 2015. No cases of UTI were observed, and the incidence of pyuria did not differ significantly between the two groups (p = 0.399). However, bacteriuria was found in 11 patients, with 2 (0.60%) in the antibiotic group (n = 310) and 9 (3.10%) in the placebo group (n = 286), showing a statistically significant difference (p = 0.023).

Conclusions: Ofloxacin prophylaxis in sterile urine ESWL patients showed a benefit in reducing the incidence of bacteriuria but incidence of UTI and pyuria showed no change.

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Introduction

Extracorporeal shockwave lithotripsy (ESWL) is a minimally invasive procedure that uses shock waves to break down stones in the upper urinary tract. Compared to percutaneous nephrolithotomy (PCNL) and retrograde intrarenal surgery (RIRS), ESWL results in shorter hospital stays, quicker treatment times, and fewer complications.[1]

Standard laboratory tests for bacteriuria and pyuria are used to confirm the presence of a urinary tract infection (UTI) in patients with clinical symptoms suggestive of a UTI, such as increased urinary frequency or urgency, hematuria, dysuria, suprapubic pain, fever, chills, severe pain, or sepsis.[2,3] UTI are a significant complication following urological procedures, including ESWL. UTI involves the colonization of the urinary system by uropathogenic bacteria, leading to different degrees of inflammatory response. Common clinical symptoms of UTI can involve organs, pyuria and bacteriuria. UTIs can be present in ESWL patients who have kidney injury and vascular disruption, which may allow bacteria in the urine or stone to enter the bloodstream and also cause a significant rise in intrapelvic pressure during shockwave treatment.[4] The use of routine prophylactic antibiotics in ESWL remains a topic of debate. Several studies, including randomized controlled trials, have shown no benefit from using prophylactic antibiotics in patients who do not have a preoperative UTI or infection-related stones.[5]

Canadian Urological Association (CUA) guidelines suggest that antibiotic prophylaxis for ESWL does not significantly reduce the risk of UTI and fever in patients undergoing ESWL, but should be considered in patients at high risk of infectious complications.[6] The American Urological Association (AUA) guidelines recommend that noninvasive procedures such as shock wave lithotripsy do not require antimicrobial prophylaxis if the pre-procedural urine microscopy shows as negative for infection.[7] The European Association of Urology (EAU) guidelines on urological infections state that for patients undergoing ESWL who have no evidence of bacteriuria, no prophylaxis recommended.[8]

This study aimed to assess the benefits of antibiotic prophylaxis in patients with sterile urine undergoing ESWL. The primary objective was to determine the incidence of UTI, which included bacteriuria, pyuria, and clinically diagnosed UTI. The secondary objective focused on the identification of risk factors that may predispose patients to develop UTI after ESWL.

Material and Methods

This study was a randomized, double-blind, and parallel clinical trial with a 1:1 allocation ratio. The trial received approval from the Ethics Committee of Sunpasitthiprasong Hospital, Ubon Ratchathani, Thailand (ECSPS: 017/2551). All procedures were conducted in accordance with good clinical practice guidelines and the Declaration of Helsinki. Written informed consent was obtained from all participants before enrollment.

Between September 2008 and June 2015, patients with upper urinary tract stone diagnosed by plain film kidney, ureter and bladder (KUB) with ultrasonography of kidney, intravenous pyelography (IVP) or computer tomography (CT scan) with negative urine culture before ESWL (no growth/sterile) with planned ESWL in Sunpasitthiprasong Hospital were invited to participate in this study. Inclusion criteria were: (1) patients aged 18 years or older, and (2) patients with opaque kidney stones less than 2 cm or opaque ureteric stones less than 1 cm. Exclusion criteria were: (1) immunocompromised patients (e.g., those with liver cirrhosis, HIV, or on immunosuppressive therapy), (2) pregnant or breastfeeding women, (3) patients without a double J stent, ureteric catheter, Foley catheter, or nephrostomy tube, (4) patients with known allergies to quinolones, (5) patients who had received antibiotics within four weeks prior to ESWL, and (6) those with prosthetic devices such as valvular heart prostheses.

Patient characteristics including gender, age, underlying medical conditions, and stone location were recorded. Preoperative evaluation included a thorough assessment of clinical symptoms and signs, laboratory tests (complete blood count, blood chemistry, urinalysis, and urine culture), chest X-ray, and a plain KUB film.

All participants were admitted to the hospital one day before until one day after undergoing ESWL. Ward nurses used a random number list and sealed envelope technique to assign patients to either the experimental group (receiving ofloxacin 200 mg) or the placebo group. Ofloxacin (200

mg) or placebo was administered to patients one hour before ESWL.

All ESWL procedures were performed using the SIMENS Lithostar MODULARIS machine. For renal calculi, the energy protocol involved delivering 3,000-3,500 shockwaves at a rate of 90 per minute (maximum energy level 2.5). For ureteric calculi, 3,500-4,000 shockwaves were delivered at the same rate, but with a maximum energy level of 3.0.

One day after ESWL, urine samples were collected from patients for urinalysis and urine culture. The incidence of UTI, bacteriuria (any bacterial growth), pyuria, and clinical UTI was assessed in both groups. At the one month follow up, UTI symptoms, stone-passing history, and plain KUB imaging were evaluated. Additionally, any risk factors that predisposed patients to UTI following ESWL were explored.

The primary aim of the study was to assess the efficacy of prophylactic antibiotics in reducing post-ESWL bacteriuria, pyuria, and UTI. The sample size calculation adhered to a 1:1 allocation ratio. Based on an alpha value of 0.05 and a beta value of 0.2, with expected bacteriuria rates of 2.00% in the prophylaxis group and 7.00% in the untreated group[9], a minimum of 269 patients per group was required to detect a statistically significant difference. After application of continuity correction, the sample size was adjusted to 308 patients per group. The authors used 320 patients per group to take potential dropout into consideration.

Simple randomization was used to allocate patients to the experimental (ofloxacin 200 mg) or placebo group. A coordinating nurse then re-arranged the sequence of paper sheets and packed each into sealed envelopes to ensure blinding. Ofloxacin (200 mg) or placebo was administered in a double-blind, randomized manner, one hour before ESWL. Only the ward nurses were aware of the assignment through the sealed-envelope technique, while the authors, surgeons, scrub nurses, technicians, and participants remained blinded.

Data were analyzed using SPSS version 25th, with statistical tests including chi-square, independent t-tests, and multivariate logistic regression. A p-value of <0.05 was considered statistically significant

Results

Six hundred and forty patients were initially enrolled onto this study, with a total of 598 patients being included in the study. The cut off dates were between 2008 and 2015. Of these, 312 patients were assigned to the experimental group, and 286 patients were assigned to the control group. The demographic data are presented in Table 1, with no statistically significant differences observed between the two groups. Pyuria in the pre-ESWL urine analysis was identified in 38.10% of patients in the experimental group and 31.80% in the control group ($p = 0.106$). After ESWL, pyuria was present in 46.80% of the experimental group and 43.40% of the control group ($p = 0.655$), again showing no significant difference.

None of the patients in either group developed clinical signs of a UTI the day after ESWL or at the one-month follow-up. Post-ESWL

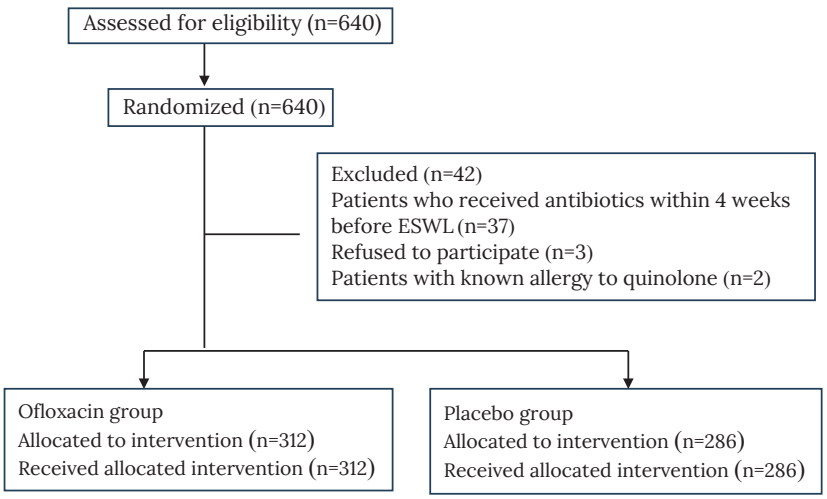

Figure 1. Participant flow

bacteriuria was detected in fewer patients in the experimental group (2 patients) compared to the control group (9 patients), and this difference was statistically significant (p = 0.023). Only one patient in the experimental group developed a hypertensive disorder. The bacteria identified in urine samples were either Escherichia coli or Proteus spp. However, there was no significant difference between the two groups in terms of bacteriuria with pyuria. Further details are shown in Table 2 and Table 3.

Table 1. Demographic data in ofloxacin and placebo group

	Ofloxacin Group (n=312)	Placebo Group (n=286)	P-value
Male gender n (%)	248 (79.50)	232 (81.10)	0.616
Age [years] mean (SD)	50.40 (12.14)	52.58 (11.37)	0.459
Underlying disease n (%)	40 (12.90)	33 (11.50)	0.099
Renal calculi n (%)	290 (93.60)	265 (92.70)	0.652
Pre-ESWL pyuria n (%)	119 (38.10)	91 (31.80)	0.106
Co-morbidity n (%)			0.099
DM	0(0.00)	4 (1.40)	
HT	10 (3.20)	17 (5.90)	
Gout	0 (0.00)	1 (0.30)	
Asthma/COPD	1 (0.30)	2 (0.70)	
≥ 2 underlying diseases	14 (4.50)	9 (3.10)	

ESWL = extracorporeal shock wave lithotripsy, DM = diabetes mellitus, HT = hypertension, COPD = chronic pulmonary obstructive disease

Table 2. Urine culture and urine analysis results on post-ESWL day 1

	Ofloxacin Group (n=312)	Placebo Group (n=286)	P-value
Bacteriuria n (%)	2(0.60)	9 (3.10)	0.023
Post-ESWL pyuria n (%)	146 (46.80)	124 (43.40)	0.712
Bacteriuria with pyuria n (%)	1 (50.00)	5 (55.60)	0.655

ESWL = extracorporeal shock wave lithotripsy, DM = diabetes mellitus, HT = hypertension, COPD = chronic pulmonary obstructive disease

Table 3. Bacteriuria on post-ESWL day 1

No	Groups	Genders	Age years	Underlying diseases	Stone location	Pre-operative pyuria	Post-operative pyuria	Type of bacteriuria
1	Placebo	Male	68	None	Kidney	No	Yes	*E. coli*
2	Ofloxacin	Male	54	None	Kidney	No	Yes	*E. coli*
3	Placebo	Female	55	None	Kidney	Yes	No	*E. coli*
4	Placebo	Male	59	None	Ureter	Yes	Yes	*E. coli*
5	Placebo	Male	68	None	Kidney	Yes	Yes	*E. coli*
6	Placebo	Female	65	None	Kidney	Yes	No	*Proteus*
7	Placebo	Male	76	None	Kidney	Yes	Yes	*E. coli*
8	Ofloxacin	Male	54	Hypertension	Kidney	No	No	*E. coli*
9	Placebo	Male	49	None	Kidney	Yes	Yes	*Proteus*
10	Placebo	Male	53	None	Kidney	No	No	*Proteus*
11	Placebo	Male	38	None	Kidney	No	No	*E. coli*

ESWL = extracorporeal shock wave lithotripsy

Discussion

Shafi et al studied the impact of antibiotic prophylaxis on the prevention of UTI in patients with sterile urine before extracorporeal shock wave lithotripsy and found that incidence of bacteriuria was 10.13% and 13.01% in the treatment and control groups, respectively. The incidence of bacteriuria after ESWL was generally low in patients and the use of antibiotic prophylaxis resulted in no significant difference with regard to the reduction of the incidence of bacteriuria after ESWL.[10] In a prospective cohort study by Moreno et al, urine culture was positive in 8.50% of patients 7 days after ESWL, 2.10% of these patients being symptomatic and the rest asymptomatic. They also found that elderly patients were more at risk of bacteriuria after ESWL, hence more at risk of possible infectious complications.[11] Therefore, it is evident that antibiotic prophylaxis before ESWL is not necessary in patients without risk factors and with negative urine culture.[12-15]

In the present study, the incident of bacteriuria was 0.60% in the ofloxacin group and 3.10% in the placebo group, the results being statistically significantly difference ($p = 0.023$). However, no significant difference was found in the incidence of UTI with regard to pyuria ($p = 0.655$). The lower incidence of bacteriuria when compared to other studies is most likely because one of the inclusion criteria was sterile urine. In some studies the term negative bacteriuria was used when the mean growth of bacteria in the urine of patients was less than 10^5 bacterial colonies per milliliter.[9-13] The cause of post-ESWL day 1 bacteriuria could be explained by some patients having an infected stone, and the reporting of the different pathogens for stone or renal pelvic urine or urinary bladder urine in the same patients could be misleading. The incidence of bacteria in the stone or renal pelvic urine or urinary bladder urine did not always show a correlation in nephrolithiasis patients.[16,17]

The focus of this study was on the short term results during the admission period, specifically bacteriuria, pyuria, and clinical UTI post-ESWL on the day after ESWL and then one month after ESWL. The authors were not able to explore any risk factors that predisposed patients to UTI following ESWL as there was no evidence of the complete pattern of UTI in any participants. There was no evidence of any UTI in this study which might be a result of the inclusion of only inclusion immune-competent individuals. Approximately 50.00% of participants with bacteriuria, also had pyuria. The tests used for bacteriuria, pyuria, and clinical UTI may not be the most sensitive tests for the detection of UTI.

In clinical practice, some urologists just give routine oral antibiotic prophylaxis in ESWL patients as results of urine culture may be delayed for at least 24 hours. However, in this study the urine samples were tested before the ESWL so there was the assurance that the antibiotic prophylaxis in ESWL was not necessary for uncomplicated patients who had sterile urine. Antibiotic prophylaxis should be considered in immunocompromised patients because bacteriuria is more likely to emerge after ESWL. All relevant evidence needs to be considered, balancing benefit and harm, to ensure the best outcome for the patient.

The authors suggest that in immunocompetent urolithiasis patients who have sterile urine who are scheduled to undergo ESWL there is no need for antibiotic prophylaxis. However, in immunocompromised urolithiasis patients, urinary catheterized patients and patients with prosthetic devices prophylaxis needs to be considered.

Conclusion

The use of ofloxacin prophylaxis in sterile urine ESWL patients showed benefits in reducing the incidence of bacteriuria but did not affect UTI or pyuria rates. In immunocompetent patients, prophylaxis is largely unnecessary.

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Conflict of Interest

The authors declare no conflict of interest.

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Review Article

Are your kidneys OK? detect early to protect kidney health

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Screening, case finding, chronic kidney disease, albuminuria, proteinuria, prevention

Abstract

Early identification of kidney disease can protect kidney health, prevent kidney disease progression and related complications, reduce cardiovascular disease risk and decrease mortality. We must ask "Are your kidneys ok?" using serum creatinine to estimate kidney function and urine albumin to assess for kidney and endothelial damage. Evaluation for causes and risk factors for chronic kidney disease (CKD) includes testing for diabetes and measurement of blood pressure and body mass index. This World Kidney Day we assert that case-finding in high-risk populations, or even population level screening, can decrease the burden of kidney disease globally. Early-stage CKD is asymptomatic, simple to test for and recent paradigm shifting CKD treatments such as sodium glucose co-transporter-2 inhibitors dramatically improve outcomes and favor the cost-benefit analysis for screening or case-finding programs. Despite this, numerous barriers exist, including resource allocation, healthcare funding, healthcare infrastructure and healthcare-professional and population awareness of kidney disease. Coordinated efforts by major kidney non-governmental organizations to prioritise the kidney health agenda for governments and aligning early detection efforts with other current programs will maximise efficiencies.

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Introduction

Timely treatment is the primary strategy to protect kidney health, prevent kidney disease progression and related complications, reduce cardiovascular disease risk and prevent premature kidney-related and cardiovascular mortality.[1-3] International population assessments show low awareness and low detection of kidney disease and substantial gaps in treatment.[2] People with kidney failure universally express the preference for having been diagnosed early in their disease trajectory to allow more time for educational, lifestyle and pharmacologic interventions.[4] Therefore, increasing knowledge and implementing sustainable solutions for early detection of kidney disease to protect kidney health are public health priorities.[2,3]

Epidemiology and complications of kidney disease

CKD (chronic kidney disease) is prevalent, affecting 10% of the world's population, or over 700 million people.[5] Almost 80% of the population with CKD reside in low-income countries (LICs) and lower middle-income countries (LMICs), with approximately 1/3 of the known affected population living in China and India alone.[5,6] Prevalence of CKD increased by 33% between 1990 and 2017.[5] Increasing prevalence of CKD is driven by population growth, aging and the obesity epidemic, resulting in higher prevalence of two major risk factors for CKD: type-2 diabetes (T2DM) and hypertension. In addition, risk factors for CKD beyond cardiometabolic conditions contribute to the rising burden of kidney disease, including social deprivation, pregnancy-related acute kidney injury (AKI), preterm birth and increasing environmental threats (infections, toxins, climate change, air pollution).[5,7] These threats disproportionately affect people in LICs and LMICs.[8]

Undetected and untreated CKD is more likely to progress to kidney failure and cause premature morbidity and mortality. Globally, more people died in 2019 of cardiovascular disease (CVD) attributed to reduced kidney function (1.7 million people) than kidney disease alone (1.4 million).5 CKD is expected to rise to the 5th most common cause of years of life lost by 2040, surpassing type 2 diabetes, Alzheimer's disease and road injuries.[9] The rising mortality of kidney disease is remarkable in contrast to other non-communicable diseases (NCDs) such as CVD, stroke and respiratory disease, which are projected to experience a decline in mortality.[8] Even in early stage CKD, multi-system morbidity decreases quality of life. In particular, mild cognitive impairment is associated with early stage CKD and it is possible that early CKD detection and treatment could slow cognitive decline and reduce the risk of dementia.[10] CKD in children has profound additional effects, threatening growth and cognitive development and with lifelong health and quality of life implications.[11,12] The number of people on kidney failure replacement therapy (KFRT) – dialysis and transplantation - is anticipated to more than double to 5.4 million from 2010 to 2030.[13,14] KFRT, especially haemodialysis, is unavailable or unaffordable to many in LICs and LMICs, contributing to millions of deaths annually. LICs and LMICs comprise 48% of the global population but account for only 7% of the treated kidney failure population.[15]

Who is at risk of kidney disease?

Testing people at high-risk for kidney disease (case-finding) limits potential harms and false-positive test results compared with general population screening that should only be considered in high income countries (HICs). Limiting testing to those at increased risk of CKD would still capture a large proportion of the global population. Moreover, targeted case-finding in patients at high risk of CKD, is not optimally performed even in HICs. About 1 in 3 people worldwide have diabetes and/or hypertension. There is a bidirectional relationship between cardiovascular disease and CKD, with each increasing the risk of the other. The American Heart Association and European Society of Cardiology call for testing those with cardiovascular disease for CKD, as part of routine cardiovascular assessments.[1,16]

Other CKD risk factors include family history of kidney disease (e.g. APOL1-mediated kidney disease common in people of West African ancestry), prior AKI, pregnancy-related kidney disease (e.g. pre-eclampsia), malignancy, autoimmune disorders (systemic lupus erythematosus, vasculitis), individuals born with low birth weight or pre-term, obstructive uropathy, recurrent kidney stones, and congenital anomalies of the kidney and urinary tract (CAKUT), see Figure 1.[3] The

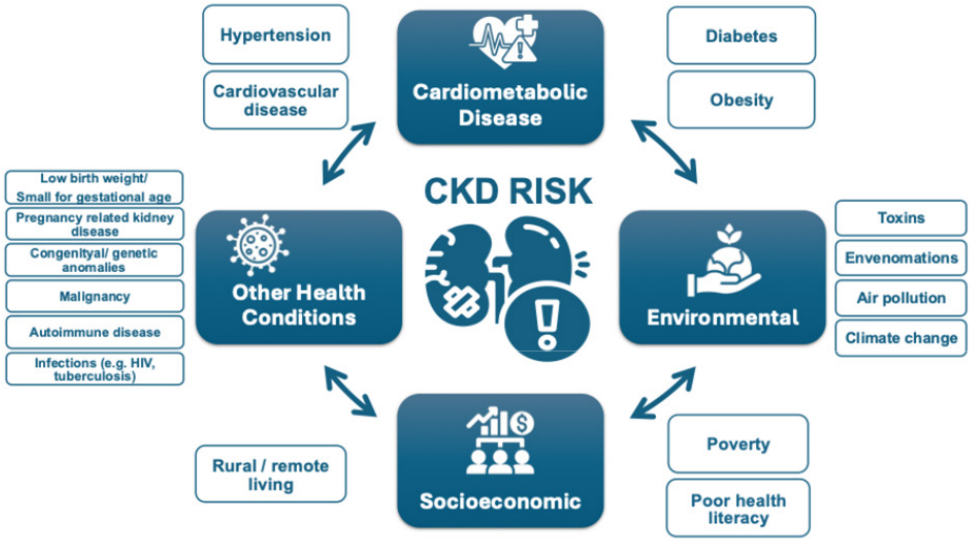

Figure 1. Risk factors for chronic kidney disease

social determinants of health strongly affect CKD risk, both for individuals and at a country level. In LICs and LMICs, heat stress for agricultural workers is thought to cause CKD of unknown etiology, an increasingly recognized major global cause of CKD.[17] In addition, envenomations, environmental toxins, traditional medicines and infections (viral hepatitis B or C, HIV, and parasites) deserve consideration as risk groups, especially in endemic areas.[18,19]

How can we check kidney health?

Conceptually, there are three levels of CKD prevention. Primary prevention reduces the incidence of CKD by treating risk factors; secondary prevention reduces progression and complications in those with detected CKD; and, tertiary prevention improves outcomes in those with kidney failure by improving management, such as improved vaccination or optimal dialysis delivery.[20] Primary and secondary prevention strategies can utilise the 8 golden rules for kidney health promotion; healthy diet, adequate hydration, physical activity, blood pressure monitoring and control, glycaemic monitoring and control, avoidance of nicotine, avoidance of regular use of non-steroidal anti-inflammatory drugs and targeted testing for those with risk factors.[21] Five of these are identical to 'Life's Essential 8' rules for improving and maintaining cardiovascular health which also include healthy weight, adequate sleep and lipid management.[22] Early detection focuses on secondary CKD prevention that involves protecting kidney health and reducing cardiovascular risk.

Are your kidneys okay?

Globally, early detection of CKD is rare, haphazard and even less likely to occur in LICs or LMICs. Currently, only three countries have a national program to actively test for CKD in at-risk populations and a further 17 countries actively test at-risk population during routine health encounters.[23] Even in HICs, albuminuria is not assessed in over half of people with T2DM and/or hypertension.[24-26] Startlingly, in those with documented reduced kidney function, a diagnosis of CKD is often missing. A study in HICs showed absence of CKD diagnosis among 62-96% of the population with laboratory evidence of CKD stage G3.[27]

We recommend that healthcare professionals perform the following tests for all risk groups to assess kidney health, see Figure 2:

a) Blood pressure measurements as hypertension is the most prevalent risk factor for kidney disease worldwide.[3,28,29]

b) Body mass index (BMI) since obesity is epidemiologically associated with CKD risk indirectly through T2DM and hypertension and as an independent risk factor. Visceral adiposity contributes to monocyte microinflammation and cardiometabolic kidney risk.[3,28,29]

c) Testing for diabetes with glycosylated haemoglobin or fasting blood sugar or random glucose is part of kidney health assessment as T2DM is a common risk factor.[3,28,29]

d) Evaluating kidney function by using serum creatinine to estimate GFR (eGFR), is recommended in all settings.[3] GFR should be estimated with a validated, race-free equation appropriate

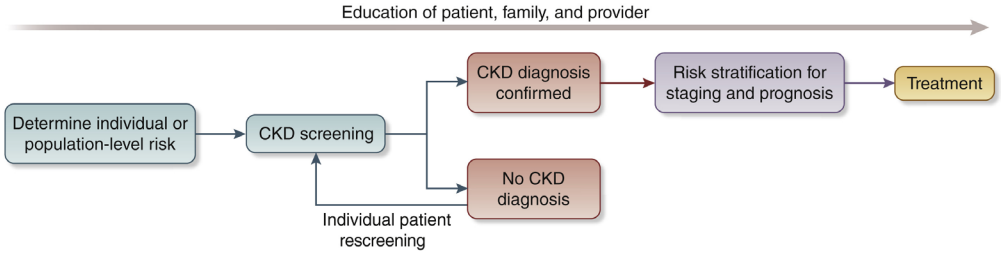

Figure 2. Conceptual framework of a chronic kidney disease testing, risk stratification, and treatment program, see reference.[30]

for the country or region and age group.[3] In general, the eGFR < 60 ml/min/1.73 m^2 is the threshold for CKD in adults and children, although a threshold of < 90 ml/min/1.73 m^2 can be flagged as "low" in children and adolescents over the age of 2 years.[3] A limitation of creatinine-based eGFR is that creatinine is also a marker of nutrition and muscle mass. Therefore, states of malnutrition and frailty overestimate kidney function.[3,30] Thus, eGFR using the combination of serum creatinine and cystatin C is generally more accurate than either biomarker alone in most clinical contexts. However, the feasibility of cystatin C use is mainly limited to HICs because of assay availability and cost relative to creatinine.[3,30,31]

e) Testing for kidney damage (albuminuria). In adults and children, a first morning sample is preferred for assessing albuminuria.[3] In adults, quantitative urinary albumin-creatinine ratio (uACR) is preferred as the most sensitive test.[3] Importantly, urinary albumin is in the process of being standardized analytically, which should ultimately facilitate worldwide uACR standardization.[32] In children, both protein-creatinine ratio (uPCR) and uACR should be tested in order to assess tubular proteinuria.3 Semiquantitative albuminuria testing allows for flexibility for point of care or home-based testing.[33] Semiquantitative or qualitative screening tests should be positive in >85% of individuals with quantitative uACR 30 mg/g or more to be useful.[34] In resource-constrained settings, urine protein dipstick testing may be used with a threshold of +2 proteinuria or greater to reduce false positive results for repeat confirmatory testing.[35]

In specific populations, the following can be considered:

f) Testing for haematuria is notable as the forgotten risk factor in recent clinical practice guidelines. It is particularly important for those at risk for glomerular disease, particularly IgA nephropathy.[36]

g) Baseline imaging in groups with signs or symptoms of structural abnormalities (eg pain and haematuria) to evaluate for kidney masses, cysts, stones, hydronephrosis or urinary retention is important. Antenatal ultrasound can detect hydronephrosis and other CAKUT.

h) With increasing availability of genetic testing, family cascade CKD testing is indicated when there is a known genetic risk of kidney disease.[37]

i) In those who have an occupational risk of developing kidney disease, kidney testing should be offered as part of occupational health programs.

j) Those who donate kidneys should be included in a post-donation surveillance program to assess kidney health over the long-term.[38]

Potential benefits of early detection

Screening for CKD fits with many of the World Health Organisation's Wilson-Jungner principles. Early stage CKD is asymptomatic and effective treatments, including lifestyle modification, interdisciplinary care and pharmacologic interventions are established.[2,3,30,35] WHO essential medicines that improve CKD outcomes should be widely available, including ACE inhibitors, angiotensin receptor blockers, statins and sodium glucose co-transporter-2 inhibitors (SGLT2i).[2,39] SGLT2i alone are estimated to decrease the risk of CKD progression by 37% in people with and without diabetes.[40] For a 50-year old person with albuminuria and non-diabetic CKD, this could extend their future period of healthy kidney function from 9.6 years to 17 years.[41] These essential medicines reduce progression to more advanced CKD stages and limit cardiovascular hospitalization to provide short-term cost-effectiveness, especially for LICs. Where available and affordable the range of new paradigm-shifting medications to slow CKD progression also includes glucagon-like peptide-1

receptor antagonists, non-steroidal mineralocorticoid receptor antagonists, endothelin receptor antagonists and specific disease-modifying drugs (e.g. complement-inhibitors) that herald an exciting new era for nephrology.

Considering the significant healthcare costs associated with CKD, particularly hospitalization and kidney failure, effective preventive measures offer clear economic benefits for both high- and low-income countries. CKD confers enormous costs to the individual, their families, healthcare systems and governments worldwide. In the United States, CKD costs Medicare over US$ 85 billion annually.[13] In many high- and middle-income countries, 2-4% of the health budget is spent on kidney failure care alone. In Europe, healthcare costs associated with CKD are higher than those associated with cancer or diabetes.[42] Reducing the burden of kidney care worldwide will also have profound environmental effects, as it will save water and plastic waste, especially associated with dialysis.[43] On an individual level, CKD costs are frequently catastrophic, particularly in LICs and LMICs, where the individual largely bears the burden of payment. Only 13% of LICs and 19% of LMICs cover the costs of KFRT for adults.[15] CKD causes 188 million people in low and lower-middle-income countries annually to be faced with catastrophic healthcare expenditures.[44]

The most widely cited and studied incremental cost effectiveness ratio (ICER) threshold to assess screening is US$ <50,000 per quality-adjusted life year (QALY).[45] If the prevalence of CKD is high, a population-wide screening strategy should be considered in HIC.[33,46] For example, in the United States, a recent Markov simulation model of population-wide screening for CKD, which included appropriate SGLT2i treatment added to standard of care ACE inhibitors or angiotensin receptor blockers for adults age 35 to 75 years old with albuminuria, concluded that screening to identify CKD would be cost-effective.[46] In addition, an analysis of a home-based general population semiquantitative albuminuria screening in Holland was also found to be cost effective.[33] Case finding to detect CKD in higher risk groups rather than mass or general population screening will reduce costs and other harms whilst increasing the true positive rate of the screening tests.[3,35,45] An alternate ICER threshold proposed by WHO is <1-3 times the ratio of the gross domestic product per capita income per QALY can be used to assess case finding approaches in LIC and LMIC.[45] The recommended tests for detecting kidney disease are low-cost and minimally invasive, facilitating their administration across diverse settings. Basic testing of eGFR and urinary ACR are widely available and using urine dipstick testing where quantitative proteinuria testing is unavailable or unaffordable will drastically reduce testing costs.[31]

If coupled with effective intervention, early identification of people with kidney disease will benefit the individual, the health care system, governments and the economy.[44] Health and quality of life benefits for the individual would lead to improved productivity, especially in the young with more working years ahead, and to developmental/educational improvements in children and young adults. Individuals would face less catastrophic health expenses, governments and healthcare systems will save money not only on CKD care, but also on cardiovascular disease costs, and economies will benefit from more worker participation. This is especially crucial for lower-income countries, where the greatest burden of CKD exists and is cruelly coupled with the lowest ability for governments and individuals to afford kidney care.

Challenges and solutions for implantation

Structural barriers to widespread identification and treatment of people with CKD include cost, reliability of testing and lack of health information systems to track CKD burden. These are underpinned by a lack of relevant government and healthcare policy, low healthcare professional knowledge and implementation, poor general population perceived kidney disease risk and low patient CKD awareness. Solutions for implementing effective interventions include tying CKD identification to existing screening programs, educating the public and primary care professionals and leveraging non-governmental organization (NGO) joint advocacy programs to focus health policy agendas on kidney disease. Any solutions must balance the potential benefits and harms of screening and case-finding programs. Ethical implications for consideration include the availability of resources (such as health care workers and medicines), the affordability of testing and treatment, false positives or negatives and anxiety for patients and their families.[47]

Screening and case-finding programs require workforce capacity, health information systems, reliable testing equipment and equitable access to medical care, medicines, vaccines and medical technologies. Primary care is at the front lines of the battle to protect kidney health, particularly in low and lower middle-income countries. The tiny nephrology workforce, with a median global prevalence of 11.8 nephrologists per million population and an 80-fold difference between LICs and HICs, is inadequate to detect and manage the vast majority of CKD.[23] As for other chronic diseases, primary care clinicians and other frontline health workers are foundational to early detection of CKD.[48] Testing must be affordable, simple and practical, with point-of-care creatinine testing and urine dipsticks useful in resource-limited settings.[31] Educational efforts directed at primary care clinicians are key to integrating CKD detection into routine care, despite constrained time and resources.[49-51] Automated clinical decision support could leverage electronic health records to identify people with CKD or at high-risk of CKD and recommend appropriate actions to clinicians (Fig. 2).

Currently, few countries have CKD registries, limiting our ability to highlight the disease burden to governments. Knowledge of CKD burden assists in prioritizing kidney health needs, which should then progressively expand to encompass the full spectrum of kidney care.[52] A global survey revealed only a quarter of the countries (41/162) had a nation specific CKD strategy and fewer than a third (48/162) recognized CKD as a public health priority.[23] WHO's recognition of CKD as a major driver of NCD mortality would be impactful in increasing awareness, improving local surveillance and monitoring to implement clinical practice guidelines and improving resource allocation.[2]

Programs for the early detection of CKD will require extensive coordination and engagement of stakeholders, including governments, health systems and insurers. International and national kidney organisations, such as the International Society of Nephrology (ISN), already advocate to the WHO and individual governments for the prioritisation of kidney disease. We must continue this work, collaborating to streamline early detection program planning and implementation. Connection to existing community interventions (e.g. cardiovascular disease prevention) in LMICs and HICs can decrease cost and maximize efficiencies by integrating into existing programs. Such programs will need to be adapted to the local context and can be held in a variety of settings, such as individual healthcare practices, hospitals, as well as regional or national healthcare facilities or as outreaches in rural communities. Depending on local regulations and resources, screening and case-finding can also take place outside of medical settings such as town halls, churches or markets. Volunteers in the community can also assist with community-based screening and case-finding efforts.

In conjunction with reorienting the clinical practice of health care professionals to a greater focus on timely detection of CKD, we must focus on general population perceived risk education and health promotion activities, as well as education programs aimed at patient awareness and empowerment. General population awareness of kidney disease is poor, with 9 out of 10 people with CKD unaware they are affected.[53] Coverage of kidney disease is missing from the mainstream conversation, with an analysis of lay press showing kidney disease was 11-times under-represented in discussed compared to the actual cause of death.[54] A number of national and international organizations have developed public-facing quizzes on risk of kidney disease, supported by a regional study that showed socially vulnerable patients with hypertension do not understand their kidney risks.[21,55-57] Online and direct education for healthcare professionals can improve consumer health literacy. Patient activation, engagement, and shared decision-making are downstream impacts of awareness. Awareness education is nuanced for CKD, including detection and risk stratification to inform and empower rather than frighten regarding the timing and extent of interventions (see Box 1).[4,27,57] Getting the balance right will optimize self-efficacy and patient, family and caregiver engagement.

Conclusion: A Call to Action

We call on all healthcare professionals to check the kidney health of their patients at risk of kidney disease. In tandem, we must work with public health organizations to improve the general population's perceived risk of kidney disease and empower people at risk to seek kidney health

Box 1. Are your kidneys okay? person perspectives on CKD awareness, detection and treatment from the literature, see references.[4,57]

I actually didn't fully understand because nobody had actually given me the full information of what I had in a way that I could kind of go, 'Well this is what I've got [CKD], and this is why I've got it.'
[the clinicians] they can answer those [kidney health] questions, ... but it's all very jargonistic.
I didn't know what it [CKD] meant so I couldn't really share it with other people.
I may not know what my [kidney health] numbers are, but I do know what the tests are, and I do know that I've had them done before.
Well, let me put this way: I'm now well aware now of the significance of the kidneys and about what the issues are here. And I would definitely consider... When I go to the doctor, I would say to him, "Now, listen. You did the blood tests. But how are my kidneys doing? What are the numbers?
I know that they have done urine tests in the past, and I know protein and sugar was in my urine.
I went from never taking a tablet to taking 22 tablets. What going on here? I didn't know what they were. But I just number them and that did help me a lot because I realized what was going on but some of them, every time I went there [to see the doctor], I'd get another tablet. I knew that I had to take it because they knew what they were doing, the doctors that I went to see.
This [CKD] is something new, so immediately I was like, just another thing to be concerned about. But then I felt kind of empowered, and like I really do want to get ahead of this thing. I feel like I do want to have a conversation with my primary care physician.
What I would be mostly interested in is what is happening, why is it happening, and what can I do to slow it [CKD] down?

checks. To ensure this change can be delivered, we must work with healthcare systems, governments and the WHO to prioritize kidney disease and create effective and efficient early detection programs for kidney disease. Only then will the paradigm-shifting benefits of lifestyle change and pharmacologic treatments translate to better kidney and overall health for people all around the world.

Appendix

The World Kidney Day Joint Steering Committee includes Valerie A. Luyckx, Marcello Tonelli, Ifeoma Ulasi, Vivekanand Jha, Marina Wainstein, Siddiq Anwar, Daniel O'Hara, Elliot K. Tannor, Jorge Cerda, Elena Cervantes, and María Carlota González.

Conflict of Interest

All the authors declare no conflict of interest.

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Invited Review Article

Parenchymal volume analysis and functional recovery after partial and radical nephrectomy for renal cell carcinoma

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Abstract

Renal cell carcinoma (RCC) accounts for 2-3% of adult malignancies and has the highest mortality among genitourinary cancers. With the increasing use of cross-sectional imaging, RCC is now frequently diagnosed incidentally and at earlier stages, and partial nephrectomy (PN) has become the standard treatment for small renal masses. In appropriately selected patients, PN can significantly reduce the risk of chronic kidney disease (CKD), CKD-related mortality, and cardiovascular events. In cases where PN is high-risk or not feasible, radical nephrectomy (RN) remains a valid alternative, particularly when the new baseline glomerular filtration rate (NBGFR) is anticipated to be greater than 45 ml/min/1.73 m^2.

Functional recovery after surgery depends on multiple factors. Among these, parenchymal volume loss has been identified as the primary determinant, accounting for 70–80% of the decline in function associated with PN. Ischemia, particularly warm ischemia exceeding 30 minutes, can also contribute to renal impairment albeit to a lesser extent. Cold ischemia has a comparatively minor effect and is generally protective. Vascularized parenchymal loss results from both tumor resection and devascularization during reconstruction, with the latter playing the predominant role. Preserving well-perfused renal parenchyma is thus crucial for optimal recovery.

To analyze functional recovery after PN, accurate estimates of split renal function (SRF) are required to evaluate outcomes specific to the kidney exposed to ischemia. Our recent studies have used parenchymal volume analysis (PVA) rather than nuclear renal scans to estimate SRF, and this has allowed us to provide a more discerning analysis. PVA presumes that the amount of parenchyma on each side is proportionate to its function and this approach has proven to be more accurate than nuclear renal scans

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for estimating SRF. PVA also provides more accurate and objective measurements of the percent of parenchymal volume preserved (PPVP). Finally, PVA only requires availability of preoperative and postoperative imaging studies for analysis, allowing more robust cohorts of patients to be studied.

This article reviews and summarizes the modern perspectives regarding the preoperative, intraoperative, and postoperative factors influencing renal functional recovery after renal cancer surgery, aiming to guide surgical planning and improve patient outcomes.

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Introduction

Historically, most patients with renal cell carcinoma (RCC) presented with large, palpable renal masses, abdominal pain, and gross hematuria. However, with the widespread use of advanced imaging, more than 50.0% of renal tumors are now detected incidentally, often at a smaller size than seen in previous decades.[1]

As a result, partial nephrectomy (PN) has become the standard of care for most patients with RCC. PN improves functional outcomes, and in appropriately selected patients the associated morbidity remains low, with an overall complication rate of approximately 3.0-5.0%.[2,3] In cases where PN is not feasible or high risk, radical nephrectomy (RN) remains a viable treatment option. Prior studies have shown that patients who maintain a NBGFR >45 ml/min/1.73m² following RN have strong overall survival comparable to patients without CKD after surgery.[2,4,5] Therefore, RN may be considered in patients with high tumor complexity or aggressive tumor biology, provided the postoperative NBGFR exceeds this threshold.

Given the kidney's highly vascular nature, vascular occlusion is often required during PN to ensure a bloodless surgical field and facilitate tumor resection. However, this introduces ischemia, which may adversely affect postoperative renal function. Previous studies, particularly one titled "Every minute counts" suggested that ischemia was rather important, reporting that each additional minute of warm ischemia time associated with a 5.0% increased risk of acute kidney injury (AKI) and a 6.0% increased risk of stage 4 CKD.[6]

However, this data was misleading, because the analysis did not include parenchymal volume loss. When parenchymal volume loss was incorporated into the analysis, it proved to be the most significant determinant of functional recovery following PN, with ischemia playing a less critical role. Ischemia was essentially found to be a confounder.[7,8]

Further studies using more advanced methodologies and robust study populations have recently shown that warm ischemia actually can deleteriously impact functional recovery after PN to a modest degree, while hypothermia is protective. To drill down on the outcomes in the kidney exposed to ischemia, accurate estimates of split renal function (SRF) are required. Since 2022 we have used parenchymal volume analysis (PVA) rather than nuclear renal scans to estimate SRF and this has revolutionized the field. PVA has facilitated a more robust and intensive analysis of the impact of ischemia and other secondary factors on functional recovery after PN.[9-12]

While it has been interesting to learn more about such secondary factors, these studies have also confirmed that PPVP during PN is of paramount importance. PPVP is the king, and ischemia and other secondary factors are the jesters. Achieving a bloodless surgical field introduces ischemia, but more importantly it facilitates maximal preservation of functioning renal tissue and thus optimizes functional outcomes.[13]

Interestingly, analysis of long-term follow-up after PN demonstrates that the functional trajectory of the kidney exposed to ischemia, after initial recovery, is comparable to that of the contralateral kidney. Both kidneys exhibit similar rates of age-related decline, even though the ipsilateral kidney has been exposed to ischemia.[14,15]

The objective of this article is to comprehensively review the factors influencing renal functional recovery following PN, in contrast to RN, based on current literature and evidence (KEY POINTS).

KEY POINTS

- Software based parenchymal volume analysis (PVA) has revolutionized the analysis of functional outcomes after renal cancer surgery. PVA allows more patients to be analyzed and provides more accurate estimates of split renal function and percent parenchymal volume preserved.
- Preserving parenchymal volume is the most important factor in determining functional recovery after PN. Loss of parenchymal volume accounts for approximately 70–80% of the decline in function associated with the procedure.
- Ischemia can also contribute to the decline of function following PN as a secondary factor, but this typically is only seen with prolonged warm ischemia (> 30 minutes).
- Limiting warm ischemia time to less than 30 minutes and using cold ischemia are associated with negligible functional decline related to ischemia.
- Zero ischemia PN can provide a benefit for functional recovery; however, the difference is marginal and may be associated with an increased risk of perioperative complications.
- The reconstructive phase of PN is the most critical in terms of parenchymal volume preservation and functional recovery.
- For tumors with increased oncologic risk or for those with increased tumor complexity, radical nephrectomy may be a reasonable consideration, particularly if the NBGFR is anticipated to be >45 ml/min/1.73 m^2.
- NBGFR after radical nephrectomy can be estimated as: 1.25 × (Preoperative GFR_{Global}) × (Split Renal $Function_{Contralateral}$).

Prediction of New Baseline GFR after Radical Nephrectomy (RN)

According to current consensus, the new baseline GFR (NBGFR) measured 1-12 months after PN or RN serves as a reliable indicator of functional recovery.[7,8] Using GFR values measured earlier than this may lead to inaccurate assessments, because some patients may develop AKI following PN, requiring time for the nephrons to recover. After RN, the contralateral kidney will undergo renal functional compensation and typically requires several weeks to establish its NBGFR. GFR values beyond 12 months may reflect the impact of other medical comorbidities and the aging process and are not preferred for analysis of recovery from surgery. Between 1-12 months postoperatively, the GFR tends to remain stable and is defined as the NBGFR.[7,8,16]

For patients undergoing RN, a predictive formula for estimating NBGFR has been established as follows:

NBGFR after RN = 1.25 × (Preoperative GFR_{Global}) × (Split Renal $Function_{Contralateral}$)

This SRF-based formula has outperformed all other algorithms for predicting NBGFR after RN. The coefficient 1.25 represents the average amount of renal functional compensation observed in adults after loss of a kidney.[17,18]

The SRF used in this formula has traditionally been derived from nuclear renal scans but recent studies have demonstrated that PVA is more accurate for this purpose (Fig. 1). Such measurements are now facilitated by readily accessible software platforms capable of producing precise estimates of both tumor and parenchymal volumes. The incorporation of direct measurements of vascularized parenchymal volume represents a significant advance in predicting postoperative renal function, enabling more individualized surgical planning and improved prediction of functional outcomes.

Predicting New Baseline GFR after Partial Nephrectomy (PN)

For patients who undergo PN, the preferred formula for predicting NBGFR is even more simple:[12]

NBGFR = 0.9 × (Preoperative Global GFR)

This formula has proven to be equivalent to or superior to all other algorithms that have been published, most of which are rather complex. The average PN is associated with only a minimal loss of parenchyma, and thus function, so the NBGFR is strongly anchored by the preoperative global GFR. While this estimate tends to be very accurate, it can be influenced by the complexity of the surgery. In cases involving high tumor complexity, one can assume that approximately 80.0-85.0% of renal function may be preserved, whereas in cases of low to intermediate tumor complexity, 95.0% of renal function may be retained.[19,20]

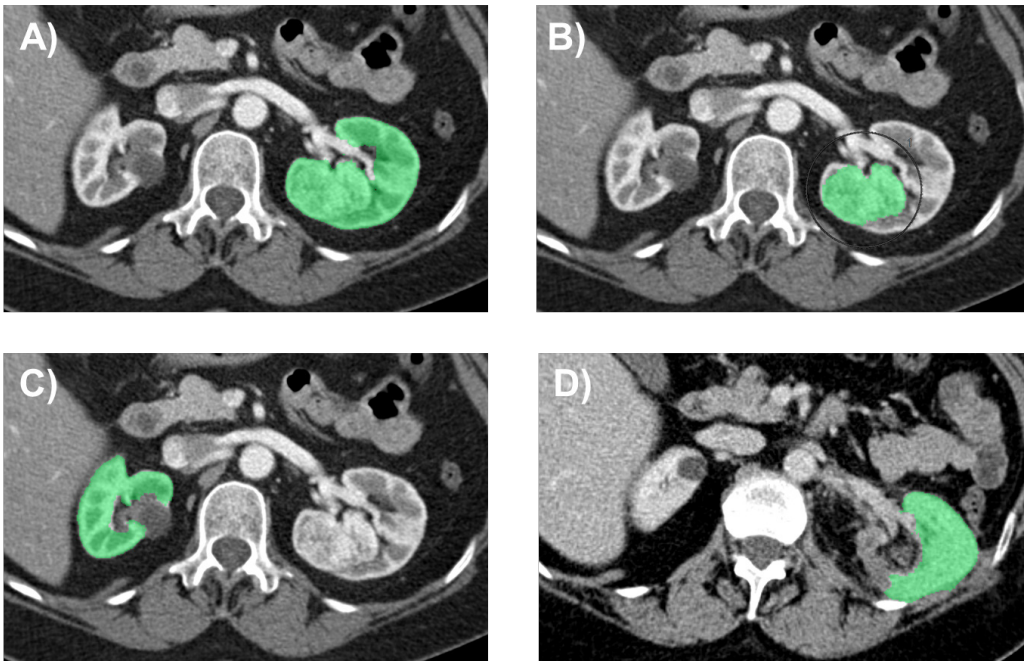

Figure 1. Parenchymal volume analysis (PVA) using three-dimensional volumetric software. Methodology for PVA using three-dimensional volume-calculating software (Fujifilm Medical Systems Inc., Tokyo, Japan). A) Measurement of the left (ipsilateral) kidney and tumor combined, with a total volume of 260 ml. B) Measurement of the tumor alone, calculated at 30 ml, resulting in an ipsilateral parenchymal volume of 230 ml (260 ml – 30 ml). C) Measurement of the right (contralateral) kidney, excluding a renal cyst, with a volume of 140 mL, consistent with a modest degree of atrophy. D) Measurement of the ipsilateral kidney following PN, excluding devascularized/atrophic parenchyma identified by reduced contrast enhancement, which was 180 ml. Using these measurements, the preoperative ipsilateral SRF could be calculated as the ipsilateral parenchymal volume normalized by the total parenchymal volume, which in this case was (230 ml ÷ (230 ml + 140 ml)) x 100% = 62%. This confirms that the ipsilateral kidney was the predominant functioning kidney despite the presence of the tumor. The ipsilateral percent parenchymal volume preserved (PPVP) could also be calculated as follows, PPVP = postoperative ipsilateral parenchymal volume normalized by preoperative parenchymal volume. In this case the PPVP was (180 ml ÷ 230 ml) x 100% = 78%.

Short- and Long-term Effects of Renal Parenchymal Reduction on Renal Function

Following RN, a decline in renal function typically occurs in the short term. However, compensatory mechanisms in the contralateral kidney are initiated to offset the loss.[21,22] Despite the reduction in nephron complement, the intake of nutrients, salts, and fluids remains constant. Therefore, the remaining nephrons must increase their workload to maintain fluid and electrolyte homeostasis. While this adaptive mechanism is beneficial, over time, chronic hyperfiltration may develop, primarily due to elevated glomerular pressure, potentially leading to progressive renal damage or contributing to further functional decline.[23] However, this is only seen when the NBGFR falls below critical levels, such as <30 ml/min/1.73m^2 [24,25]

Studies have shown that in patients with a healthy contralateral kidney managed with PN, renal function tends to remain stable for several years, with only modest age-related changes. However, in elderly patients or those with risk factors such as smoking, hypertension, and diabetes, postoperative decline in renal function may exceed the rate of decline expected from the normal aging process.[8,13,25-27]

Preoperative Factors Affecting Functional Recovery after PN

Recent studies suggest that nonmodifiable preoperative factors can influence functional recovery after PN, including patient age and significant renal comorbidities, such as:[8,14,27]

- Hypertension (HTN) that requires more than three medications for control,
- Insulin-dependent diabetes mellitus (DM) or diabetes with end-organ damage, and
- Preexisting chronic kidney disease (CKD) stage 4-5.

Recent reports suggest that patients with CKD stage 4 and an GFR of less than 25-30 ml/

min/1.73m² may be a special consideration. Tumors in this population are often less aggressive, and these patients are generally not very healthy. As such, they can experience increased morbidity and unfavorable perioperative outcomes following PN. Therefore, in this high-risk population, PN should be approached with caution.[28,29] In selected cases, alternative strategies such as active surveillance with delayed RN may be more appropriate, depending on the patient's overall condition and oncologic risk. With this, RN is delayed until the patient has developed end stage renal failure.

Age-related decline in renal function is well documented. In the general population, GFR declines by approximately 0.8 mL/min/1.73m² per year (0.4 ml/min/1.73m² per kidney per year) after age 40.[30,31] Patients with medical comorbidities may experience a more rapid decline of 1.6–2.0 mL/min/1.73m² annually.[15,32] Similarly, individuals with hypertension tend to show faster deterioration compared to healthy peers. For patients with and without pre-existing CKD, the annual decline differs significantly—about 0.7% in non-CKD patients versus 4.7% in patients with preexisting CKD.[33]

Another important factor affecting PN outcomes is surgical experience. High-volume centers (performing more than 42 PN cases/year) show better oncologic and functional outcomes and fewer complications than low-volume centers.[34]

Intraoperative Factors Affecting Functional Recovery after PN

Among intraoperative variables, parenchymal volume preservation is the most critical determinant of functional recovery. During PN, meticulous surgical technique is essential. While the primary goal remains oncological efficacy, maximizing preservation of vascularized parenchymal volume is crucial for functional outcomes.[2,8,19]

Vascularized parenchymal volume loss occurs in two ways: 1) excised parenchymal volume—parenchyma removed along with the tumor to ensure negative margins; and 2) devascularized parenchymal volume—preserved tissue that becomes non-functional due to loss of blood supply during reconstruction.[35,36]

On average, about 20.0% of the vascularized parenchyma volume in the ipsilateral kidney is lost with PN, with about one-third due to excision and two-thirds due to devascularization. Hence, precision in renal reconstruction is crucial to optimizing functional outcomes.[8,37,38]

Intraoperative mannitol administration during PN was thought to help preserve renal function; however, more recent studies have shown that intraoperative mannitol administration in patients with normal preoperative renal function does not improve functional outcomes at 6 months postoperatively.[39-41]

In terms of ischemia type, patients undergoing zero ischemia PN have the potential for optimal functional outcomes, followed by cold and then warm ischemia. However, zero ischemia cases have typically been less complex (e.g., lower RENAL scores, smaller tumor size) so direct comparisons are difficult to support.[8,42] Two randomized trials showed no functional advantage of zero ischemia PN over clamped PN, although the patients enrolled in these studies mostly had low complexity tumors, so the comparison was zero versus limited warm ischemia.[43-45] With prolonged warm ischemia, particularly beyond 30 minutes, functional outcomes worsen—ipsilateral recovery from ischemia decreases by approximately 9.0% for every 10 minutes beyond the 30-minute mark. In contrast, cold ischemia serves as a protective factor (Fig. 2).[46]

Furthermore, recent studies have reported that patients undergoing off-clamp PN may have a higher rate of conversion to RN and a greater incidence of perioperative blood transfusion. In the authors' opinion, the subgroup of patients most likely to benefit from off-clamp PN are those with severe CKD bordering on end stage renal failure for whom prolonged ischemia is anticipated, as this approach may help avoid dialysis both short and long term. Nonetheless, the precise indications for zero ischemia PN remain poorly defined, and further investigation is warranted to clarify its clinical utility.[47-49]

Pneumoperitoneum during laparoscopic or robotic PN may influence postoperative renal functional outcomes due to its impact on renal perfusion. The elevation of intra-abdominal pressure to levels typically ranging from 12 to 15 mmHg can reduce renal blood flow by compressing renal vasculature and increasing renal vascular resistance.[50] Prolonged duration of pneumoperitoneum and higher insufflation pressures have been associated with worsened

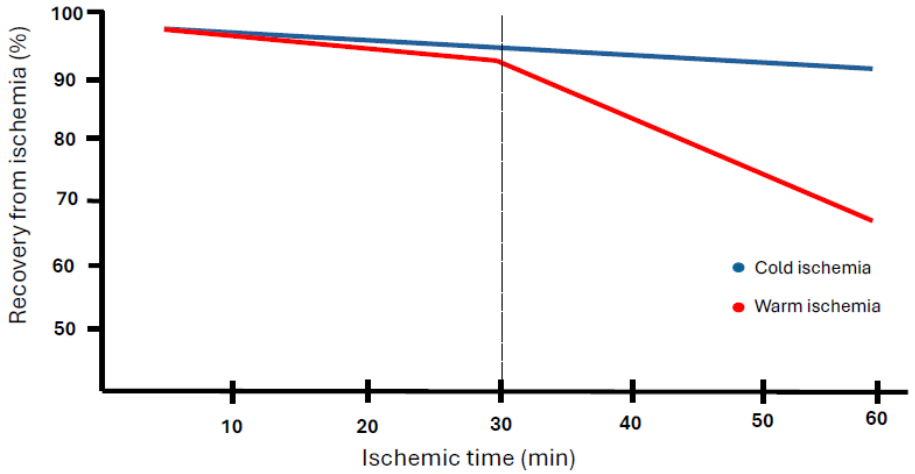

Figure 2. Functional recovery following clamped partial nephrectomy related to type and duration of ischemia. Recovery from ischemia is defined as percent GFR saved normalized by parenchymal volume saved, all specific to the operated kidney, and would be 100% if all of the preserved nephrons recovered completely from exposure to ischemia. Patients undergoing PN with limited warm ischemia (<30 minutes) or any duration of cold ischemia tend to experience minimal impact on postoperative functional recovery (recovery from ischemia ≈94.0%). In contrast, prolonged warm ischemia (>30 minutes) is associated with a significant decline in functional recovery. Recent studies have shown that recovery from ischemia in the ipsilateral kidney decreases by approximately 9% for every additional 10 minutes of warm ischemia beyond 30 minutes. Therefore, if the patient undergoes warm ischemia for 60 minutes, recovery from ischemia in the ipsilateral kidney will be approximately 68.0%. This is in addition to the baseline 20% loss of function in the ipsilateral kidney that typically occurs with PN related to parenchymal volume loss. In the final analysis then, the loss of function in the ipsilateral kidney associated with PN with 60 minutes of warm ischemia will be approximately 50.0%.

postoperative renal function.[51] However, these effects are generally transient, and the incidence of clinically significant AKI related solely to pneumoperitoneum is low. Overall, long-term renal functional outcomes appear to be primarily determined by the amount of preserved renal parenchymal volume rather than the effects of intraoperative pneumoperitoneum.[50]

Postoperative Factors Affecting Functional Recovery

AKI is a common short-term complication after PN, particularly in patients with a solitary kidney, where the incidence approaches 50.0%.[19,52] Causes include ischemia and parenchymal volume loss. The severity of AKI correlates with reduced functional recovery and is closely associated with ischemia duration, and can be seen with both cold and warm ischemia.[19,53] Overall, however, AKI is a minor contributor to reduced NBGFR after PN. Most kidneys recover well from AKI and parenchymal volume loss remains much more important, accounting for the lion's share (70.0-80.0%) of the loss of renal function after PN.[8,19,54]

Furthermore, AKI has minimal effect on long-term functional decline. Once NBGFR is reached, GFR gradually declines as the years go by, and atrophy generally follows the natural aging process (~1.0% per year).[14,30,31] Previous exposure to ischemia does not leave the kidney vulnerable to long-term atrophy or functional loss. In a subset of patients, however, GFR deterioration exceeds aging norms, particularly in those with significant renal comorbidities (severe HTN, insulin DM)—affecting both kidneys, not just the one previously exposed to ischemia.[14,15] Consultation and long-term follow-up by nephrology can help to maintain optimal renal function for such patients.[2]

Optimal postoperative renal perfusion and functional recovery are closely associated with appropriate fluid management and stable hemodynamic parameters, particularly blood pressure. Inadequate intravascular volume or hypotension may impair renal perfusion and exacerbate ischemic injury, especially in the context of a solitary kidney or reduced nephron volume following PN.[50]

Several studies have suggested that perioperative hypotension is a significant predictor of AKI and long-term renal dysfunction. De Backer et al. found that intraoperative episodes of mean arterial pressure below 55 mmHg for prolonged periods were independently associated with

increased risk of postoperative AKI.[55,56] Furthermore, sustained postoperative hypovolemia or excessive diuresis may compound ischemic insults and delay functional recovery.[57]

Accordingly, perioperative protocols emphasizing euvolemia, the avoidance of nephrotoxic agents, and careful hemodynamic monitoring have been proposed to support renal recovery after nephron-sparing surgery.[58]

Conclusions

Renal functional recovery following PN and RN is a multifactorial process influenced by preoperative, intraoperative, and postoperative factors. The use of PVA has greatly improved our analysis of functional outcomes after PN, allowing us to more accurately determine the impact of ischemia during PN. Parenchymal volume preservation has emerged as the most critical determinant of long-term renal function after PN, whereas ischemia plays a secondary role unless warm ischemia time is prolonged. While zero ischemia techniques may offer theoretical benefits, current evidence suggests that their advantages over conventional approaches are marginal and can be offset by increased perioperative risks.

Preoperative risk stratification, including assessment of baseline renal function, comorbid conditions, and tumor complexity, is essential for selecting the most appropriate surgical strategy. Intraoperatively, techniques aimed at minimizing both excised and devascularized parenchymal volume are paramount. Though intraoperative mannitol use remains common practice, studies do not support its benefit in patients with normal preoperative renal function.

Postoperatively, maintaining adequate hydration and hemodynamic stability is crucial for supporting renal perfusion and minimizing ischemic injury. AKI remains a significant concern in the immediate postoperative period, especially in patients with solitary kidneys or compromised renal reserve. However, long-term functional decline typically follows the natural aging trajectory, unless compounded by underlying comorbidities that specifically affect the kidneys.

Taken together, a patient-centered approach that incorporates individualized surgical planning, careful intraoperative management, and vigilant postoperative care remains the cornerstone of optimizing functional recovery following nephron-sparing and radical renal surgery.

Conflict of Interest

The authors declare no conflict of interest.

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Case Report

A large urinary bladder sarcoma treated with transurethral resection: a case report

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Keywords:
Urinary bladder sarcoma, urinary bladder tumor, undifferentiated sarcoma, transurethral resection

Abstract

The objective of this study is to report a case of a large urinary bladder sarcoma treated with transurethral resection and to evaluate the feasibility and efficacy of endoscopic surgery for urinary bladder sarcoma. We present a case report of a 64-year-old woman who underwent transurethral resection of a large urinary bladder sarcoma. Pathologic findings and immunohistochemistry were used to confirm the diagnosis of undifferentiated sarcoma. The patient was followed up for 48 months for local recurrence and distant metastasis. Nearly complete transurethral resection was performed, yielding 500 g of tissue. The patient underwent repeated transurethral resection because she declined radical surgery. The patient has survived for 48 months without local recurrence or metastasis. Transurethral resection could be an alternative option for urinary bladder sarcoma, particularly in cases where radical resection may not be feasible or desired by the patient. Careful selection of appropriate patients and long-term follow-up are crucial. Further studies are needed to evaluate the efficacy and safety of endoscopic surgery for urinary bladder sarcoma.

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Introduction

Urinary bladder sarcoma is a rare malignant tumor that arises from the mesenchymal tissue of the urinary bladder and represents 0.4% of all histological subtypes of primary invasive urinary bladder tumors.[1] Leiomyosarcoma and rhabdomyosarcoma are the two most prevalent subtypes, accounting for 50.0% and 20.0% of urinary bladder sarcoma, respectively. Additional subtypes include osteogenic sarcoma, angiosarcoma, myxoid liposarcoma, malignant fibrous histiocytoma, and carcinosarcoma.[2]

The standard treatment for urinary bladder sarcoma has not been established due to its rarity and the lack of randomized controlled trials. However, radical resection with negative margins is the cornerstone of treatment due to the aggressive nature of the disease.[3,4] There have, however, been no reports of endoscopic surgery as the only treatment for a large tumor. We thus present the case of a large undifferentiated urinary bladder sarcoma treated with transurethral resection, including the disease-free survival outcome.

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Case Report

A 64-year-old woman presented with painless gross hematuria and had experienced frequent urination for four months. She also felt a lump in her lower abdomen. Ultrasound from the referral hospital revealed a large pelvic mass in the differential diagnosis of an ovarian tumor. The gynecologist performed an exploratory laparotomy; however, no gynecological abnormalities were found intraoperatively except for a substantial anterior pelvic mass. The patient was, therefore, referred to our center for further evaluation.

Upon physical examination, a previous Pfannenstiel incision was observed, and a large firm pelvic mass was palpated two-thirds of the distance between the umbilicus and the pubic symphysis. Ultrasound revealed a 10-cm homogeneous hypoechoic mass in the pelvic cavity. Subsequent magnetic resonance imaging demonstrated a heterogeneous, hypo-intensity, intravesical mass measuring 9.4 x 8.9 x 7.7 cm on T1- and T2-weighted images, without definitive evidence of invasion into the perivesical tissue, although invasion into the detrusor muscle cannot be excluded. Hydronephrosis was not observed (Fig. 1). Based on these findings, the tumor was suggested to be at clinical stage T2, with no regional lymph node involvement or distant metastasis (N0M0). The cystoscopic findings showed a large pedunculated intravesical mass with a stalk located at the posterior wall of the urinary bladder and smooth overlying mucosa (Fig. 2). Both ureteral orifices were seen. The differential diagnoses from the cystoscopic findings included urothelial carcinoma or non-urothelial tumor (i.e., urinary bladder sarcoma).

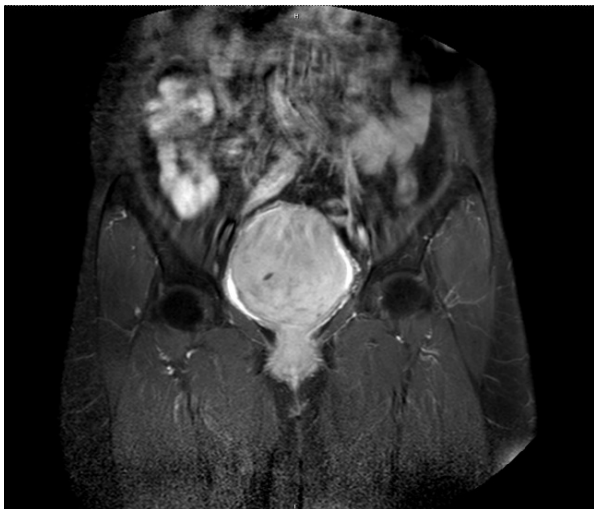

Figure 1. Coronal T2-weighted magnetic resonance imaging demonstrated a heterogeneous hypo-intensity intravesical mass, size 9.4x8.9x7.7 cm.

A nearly complete monopolar transurethral resection (TUR) was performed, yielding a tumor weight of 500 g. The tumor's base measured approximately 2 cm in diameter (Fig. 3). We used 79 l of sterile water for irrigation during the 5-h operation. The hospital course was uneventful, and the patient was discharged on the third postoperative day.

The histopathological findings revealed high-grade tumor cells arranged in sheets demonstrating infiltrative patterns and comprising elongated nuclei, hyperchromatic nuclei, moderate pleomorphism, and a lack of mitotic figures. The tumor invaded the detrusor muscle. Immunohistochemistry revealed GATA3 +, Vimentin +, AE1/AE3 -, Desmin -, SMA -, S100 -, EMA -, CK7 -,

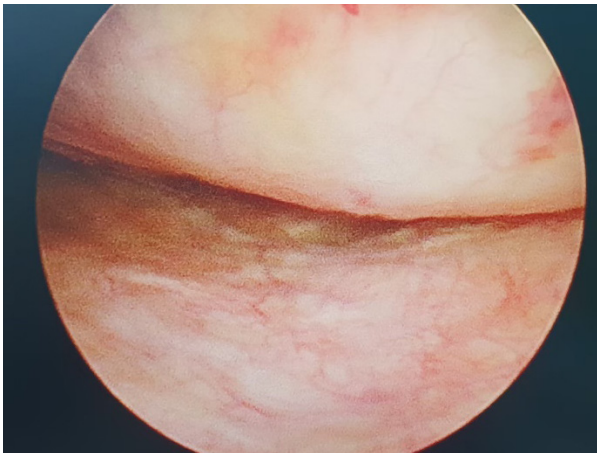

Figure 2. Cystoscopy showed the bladder tumor with normal overlying urothelium.

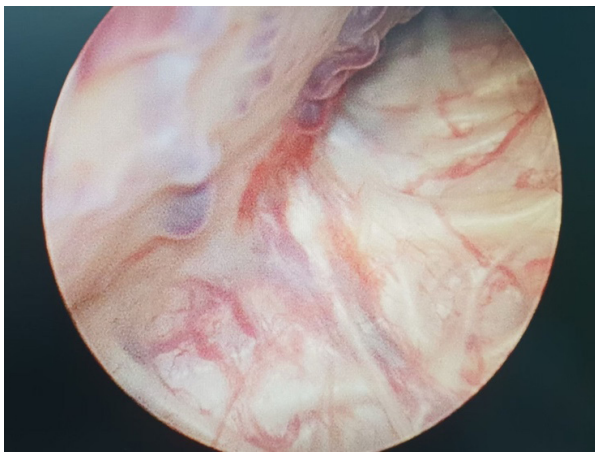

Figure 3. Cystoscopy showed the stalk of tumor.

CK20 -, CD117 -, and CD138 -, suggesting an undifferentiated sarcoma.

We discussed the curative treatment options, including partial cystectomy and anterior pelvic exenteration. After understanding the potential risks and benefits, the patient expressed a desire to preserve her bladder and maintain her quality of life, and she elected to undergo repeated TUR as an alternative management strategy, which aimed to remove as many tumors as possible. After resecting all gross disease, the pathological investigation indicated that the residual tumor had persisted. After discussing adjuvant treatment approaches, the patient declined chemo- and/or radiation therapy. We did, however, schedule her for surveillance cystoscopy every three months, which showed scar formation with negative biopsies (Fig. 4). The annual whole-abdomen computed tomography did not detect any abnormalities. Up to the end of our study, she was alive and had survived for 48 months with no evidence of a local recurrence or metastasis.

The Human Research Ethics Committee of Khon Kaen University reviewed and approved the study per the Helsinki Declaration and the Good Clinical Practice Guidelines (HE631371). Furthermore, the eligible patient signed informed consent before enrollment.

Discussion

We presented the case of urinary bladder sarcoma with a large pelvic mass and hematuria, which had been initially misdiagnosed as an ovarian tumor. Most urinary bladder sarcoma patients generally present with painless gross hematuria, followed by lower urinary symptoms.[3-5] However, these patients sometimes present a large mass at the time of diagnosis. According to a systematic review of 210 cases of urinary bladder leiomyosarcoma, the mean tumor size is 6 cm (range, 0.5-16).[5] Our case report highlights the importance of thorough medical history taking, physical examination, and appropriate investigations when diagnosing a patient with a pelvic mass. In particular, patients with a history of gross hematuria must undergo cystoscopy and cross-sectional imaging to initially rule out urinary tract cancer.

Urinary bladder sarcoma has various histopathological features, making a definitive diagnosis difficult; however, immunohistochemistry can help differentiate these subtypes of non-epithelial tumors.[4,6] In our patient, the positive result for the mesenchymal origin marker Vimentin and the negative results for epithelial markers [viz., pan-cytokeratin (AE1/AE3), CK7, CK20, and EMA] gave rise to the differential diagnosis of some type of sarcoma; however, the negative results for myogenic differentiation markers (Desmin and SMA) decreased the likelihood of its being leiomyosarcoma or rhabdomyosarcoma. Thus, the final pathological diagnosis suggested an undifferentiated sarcoma.

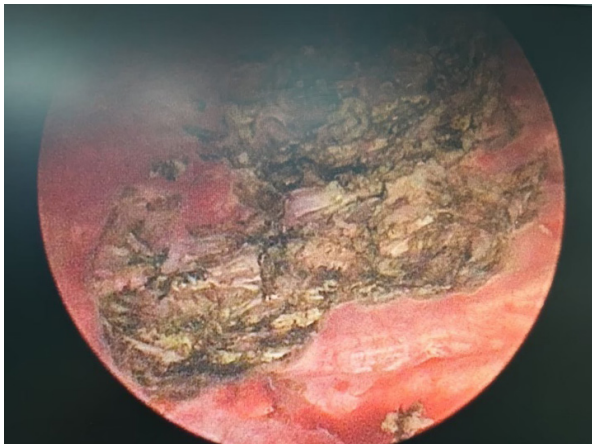

Figure 4. Cystoscopy showed the tumor's base located in the posterior wall of the urinary bladder after transurethral resection.

The Memorial Sloan Kettering Cancer Center (MSKCC) sarcoma staging system has been used to determine the prognosis of urinary bladder sarcoma in a small series. The prognostic factors include grade (low versus high), size of the tumor (≤ 5 cm versus > 5 cm), depth of invasion (superficial versus deep), and the presence of metastasis.[3] Russo et al reported that the 3-year relapse-free survival rate for stage 3 or 4 was only 26.0%. In contrast, Spiess et al reported a series of 19 patients with urinary bladder sarcoma and found that the 5-year disease-specific survival rate was 59.0%, with a median survival rate of 6 years, and the essential factor for recurrence-free survival was surgical margins status, not the stage of disease.[4] Thus, they concluded that complete surgical resection (radical or partial cystectomy) with negative resection margins offers the best treatment outcomes.[3,4]

Only a few studies have reported on the treatment outcomes of transurethral surgery. Russo et al reported that two patients with small leiomyosarcoma (2 cm) underwent complete TUR with

no evidence of local recurrence after seven years of follow-up.3 Rodriguez et al reported 183 cases of leiomyosarcoma of the urinary bladder; those patients who underwent cystectomy appeared to have a higher median disease-specific survival than those undergoing TUR only, albeit the difference was not statistically significant (48 and 24 months, respectively, p = 0.260). However, Rodriguez et al did not mention the size of the tumor.[7] Furthermore, chemotherapy and radiotherapy were proposed as multimodal treatments for local recurrence or distant metastasis, providing a wide range of therapeutic effects.[3-5,8]

We are the first to demonstrate a case of an extremely large urinary bladder sarcoma treated with TUR alone. Although the space for endoscopic resection is quite difficult, it had a narrow base (2 cm in diameter) and was located away from the ureteral orifices. Notwithstanding, we needed to discuss the chances of recurrence and/or metastasis with the patient. In addition, we needed to provide information about the risk of complications (i.e., urinary bladder perforation or TUR syndrome) that can occur due to the prolonged operative time needed for resection of a high-volume tumor.[9] The tumor was completely resectable using TUR without any complications. The patient survived for 48 months after TUR without any recurrence or metastasis; despite having been diagnosed as MSKCC stage 3 (a high-grade tumor > 5 cm). Further research is recommended to understand the nature of tissue invasion in a pedunculated urinary bladder sarcoma, whether it is related to the tumor's size or base diameter.

Conclusion

Urinary bladder sarcoma is a rare tumor, but it should be considered in the differential diagnosis of pelvic mass and hematuria. Although complete surgical resection provides the best curative treatment, TUR could be an alternative option worth considering in terms of its minimal invasiveness and urinary bladder preservation. We suggest that this approach be reserved for narrow-based, pedunculated tumors that can be completely resected, do not involve the ureteral orifice, and where imaging shows no evidence of perivesical invasion. Long-term follow-up should be required to monitor disease progression.

Acknowledgments

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Conflicts of Interest

The authors declare no conflicts of interest.

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- Results
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- Acknowledgement (optional)
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1.3 Table (s) and legend (s)

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3. Case report

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3.2 Not previously published

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Requirements:

4.1 Questions, discussions, and opinions to published articles

4.2 Creative and beneficial to all readers

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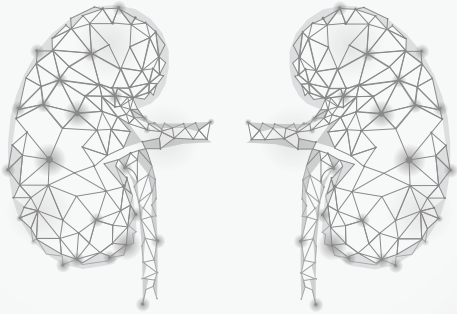

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