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Renal function and metabolic change after, orthotopic bladder substitution in males: A Single-Institution Study.

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ABSTRACT

To evaluate metabolic outcomes, renal function and metabolic change after, radical cystectomy (RC) and orthotopic bladder substitution in single-institution. A retrospective review of bladder cancer (BC) patients, who received radical cystectomy with orthotopic bladder substitution were identified from a medical record. We collected data from the years; 2007 to 2016. We enrolled 26 patients, who received RC, with their creatinine level and electrolyte having been collected as well as their longitudinal change of creatinine and electrolyte were assessed. From these 26 patients, the median age was 62.6 years. Median followup, after radical cystectomy from patients still living at last follow up was; 87.35 weeks. The mean preoperative creatinine level was 1.15 mg/dL, whilst the mean creatinine levels, at 1, 3, 6, 12, 24 months, were; 1.69 mg/dL, 1.64 mg/dL, 1.66 mg/dL, 1.82 mg/dL, 1.97 mg/dL respectively. BC patients, with RC with orthotopic bladder substitution, have the potential of renal deterioration and a lifelong risk of chronic kidney disease (CKD). Regular monitoring of upper urinary tract imaging, and renal function will delay CKD status along with early diagnosis and treatment of modifiable factors.

Keywords: Bladder cancer, radical cystectomy, bladder substitution, renal function, metabolic complication

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INTRODUCTION

Bladder cancer (BC) is the ninth most common cancer worldwide, With more than 330,000 new cases being diagnosed every year, and more than 30,000 people suffering death each year. At present, approximately 30 % of patients already having a muscle invasive disease (Kiss et al., 2016). In Thailand, the prevalence of bladder cancer is; 4.5/100 000 in males and 1.2/100 000 in females. The mortality rate is; 2.2/100 000 in males and 0.6 /100 000 in females(Lojanapiwat, 2015). A radical cystectomy, with lymphadenectomy is the operation of choice for treating muscle invasive bladder cancer(Bianchi et al.,2016; Imbimbo et al.,2015). In general, an ileal conduit, the continent pouch and orthotopic bladder substitution, is the surgical procedure that is usually used following radical cystectomy(Goldberg et al., 2016). Orthotopic bladder substitution offers superior body image and, possibly, improved overall quality of life, having similar oncological outcomes to ileal conduit diversion(Todenhofer et al., 2013; Lantz et al., 2010; Mano et al., 2014). Most large centers, worldwide, are reporting an increasing number of orthotopicbladder substitution diversion compared to the classical technique of ileal conduit (Lee et al., 2014; Ali wt al., 2015). However, orthotopic bladder substitution is associated with significant morbidity, mostly related to infectious complications and renal deterioration(Daneshmand, 2015; Eisenberg et al., 2014; Minervini et al., 2010). Decline in renal function is particularly concerning. The etiology of renal function decreases, after RC is associated with multifactorial factor including age related changes, potential nephrotoxic chemotherapy, postoperative urinary tract obstruction and infectious process (Rouanne et al., 2015). Most seriously, most literature shows an association between severe CKD and mortality (Ahmadi et al., 2013; Antonelli et al., 2016).

In this study we attempt to report renal function and post operative outcome, after perform radical cystectomy with orthotopic bladder substitution in our institution.

PATIENTS AND METHODS

Ethical approval for the study was obtained from the Institutional Review Board of Songklanagarind Hospital. The medical records of all bladder cancer patients, who were treated primarily with radical cystectomy with orthotopic bladder substitution in Songklanagarind Hospital from: January 2008 to May 2016 were reviewed.

From this review, 26 patients were identified, and met all entry criteria. All data were obtained by reviewing; patient histories, imaging studies, operative records as well as discharge summaries. Patients and disease characteristics, including; age, initial presentation, pathologic grade and stage, pre and post operative imaging, pre and post operative serum creatinine, time of follow-up, post operative status and treatment modality upon disease progression were reviewed.

Statistical Analysis

Statistical analysis was carried out using the R software 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria) continuous variables were presented as mean, with standard deviation (SD), or as median and interquartile range (IQR). Categorical variables were presented as count and percentage. Compare serum creatinine at time and preoperative by Fit Generalized Estimating Equations (GEE) with $P<0.05$ being considered to be statistically significant.

RESULTS

Patient characteristics and tumor profile

A total of 26 patients were treated with RC coupled with orthotopic bladder from; June 2007 to June 2016. (The characteristics of the patients are shown in Table 1.) All patients were male in gender, with the mean age being; 62.6 ($\pm$11) years when patients received RC. Twenty-two patients (84.6%) had gross hematuria as initial presentation, while 2 patients (7.7%) had presentation without hematuria. The most common pathologic result was; transitional cell carcinoma high grade (TCC HG), occurring in 21 patients (80.8%), with transitional cell carcinoma low grade (TCC LG), occurring in 4 patients (15.4%), and Adenocarcinoma, in 1 patient (3.8%). Mean operation time as well as operative blood loss were; 378mins and

1940mL, respectively. The waiting time was 10.8 weeks. Pre-operative imaging with computer tomography (CT) showed no hydronephrosis (HN) in 21 cases.

Renal function and metabolic profile

Mean pre-operative creatinine was 1.15mg/dL, after performing surgery renal function with a trend to decline. (show as figure 1) The mean creatinine (Cr) level at 1, 3, 6, 12, 24 months were; 1.69 mg/dL, 1.64 mg/dL, 1.66 mg/dL, 1.82 mg/dL, 1.97 mg/dL, respectively.

Most patients had an increase of their creatinine levels < 20% (58%,42%, 50%,42%,37%, at 1, 3 ,6 ,12 ,24 months, respectively). Five patients had increased serum Cr of more than; 100% from base line, at 1 month after surgery, which was persistent after 24 months of follow up time. (show as table 2)

A postoperative serum sodium (Na) decline from pre-operative level. At 1 month after surgery, serum Na was; 136.8 (±4.1) mmol/L, and increased slightly to; 138.2 (±4.2) mmol/L, after a follow up of 24 months.(shown as figure 2) This was the same approach of Serum chloride (Cl), as it decreased slightly from pre-operative. One month after follow up it showed as; 104.88 (±6.12) mmol/L, and then change to; 104.28 (±5.26) mmol/L, at 24 months.(shown as figure 3) Instead of serum potassium (K) having an increased level up to 4.18 (±0.64) mmol/L, after a follow up of 1 month. (shown as figure 4). All serum chemistry profiles are shown in table 3

Table 1: Demographic and clinical characteristics

	Overall
Mean age (yr)	62.6
BMI	23.1
Presentation Gross hematuria Microhematuria No hematuria	22 (84.6) 2 (7.7) 2 (7.7)

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Hydronephrosis No Mild Moderate Severe	21 (81) 3 (11) 1 (4) 1 (4)
Follow-up (weeks)	87.35
Pathologic TCC HG TCC LG Adenocarcinoma	21 (80.8) 4 (15.4) 1 (3.8)
Waiting time (weeks)	10.8
Pathologic staging Tis T1 T2 T3 T4a Lymph node status N0 N1	 3 10 7 5 1 23 3
Mean operative time (mins)	378.65
mean Blood loss (mL) (max, min)	1940 (800,6500)

Table 2: Percent change of serum creatinine from baseline

Post operative (month) % change	1 month	3 months	6 months	12 months*	24 months**
<20	15 (58%)	11 (42%)	13 (50%)	10 (42%)	7 (37%)
21-40	0	8 (31%)	3 (11%)	5 (21%)	3 (16%)
41-60	2 (8%)	0	3 (11%)	1 (4%)	4 (21%)
61-80	1 (4%)	1 (4%)	0	1 (4%)	0
81-100	3 (11%)	1 (4%)	0	0	0
> 100	5 (19%)	5 (19%)	7 (28%)	7 (29%)	5 (26%)

*Loss Follow 2 cases; ** Loss Follow up 7 cases

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Table 3: Serum chemical profile, after surgery

	Pre operative	Post operative				
		1 month	3 months	6 months	12 months	24 months
Cr	1.15 (±0.67)	1.7 (±1.5)	1.64 (±1.04)	1.67 (±0.96)	1.83 (±1.26)	1.97 (±1.64)
Na	141.23 (±2.93)	136.8 (±4.1)	138.0 (±4.18)	138.4 (±2.77)	138.1 (±3.38)	138.2 (±4.2)
K	3.89 (±0.36)	4.18 (±0.64)	3.87 (±0.66)	4.05 (±0.46)	4.01 (±0.36)	4.19 (±0.45)
Cl	105.54 (±5.43)	104.88 (±6.12)	105.04 (±5.99)	105.76 (±6.06)	104.83 (±3.94)	104.28 (±5.26)
HCO_3^-	21.69 (±4.39)	19.31 (±3.54)	20.38 (±4.7)	19.88 (±5.34)	20.83 (±3.65)	20.44 (±4.78)

Cr= Creatinine, Na=Sodium, K=potassium, Cl= chloride, HCO_3^-= bicarbonate

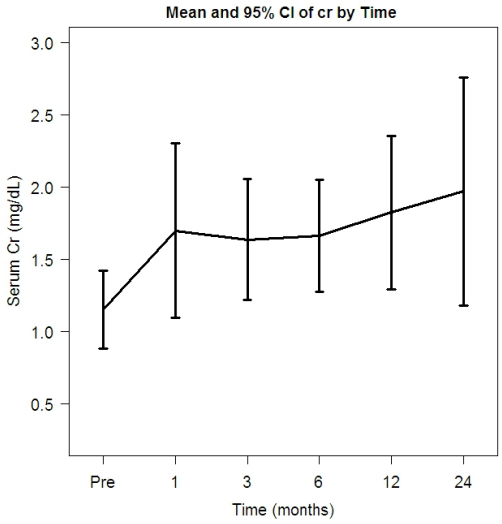

Figure 1: Mean creatinine, after radical cystectomy with orthotopic bladder substitution

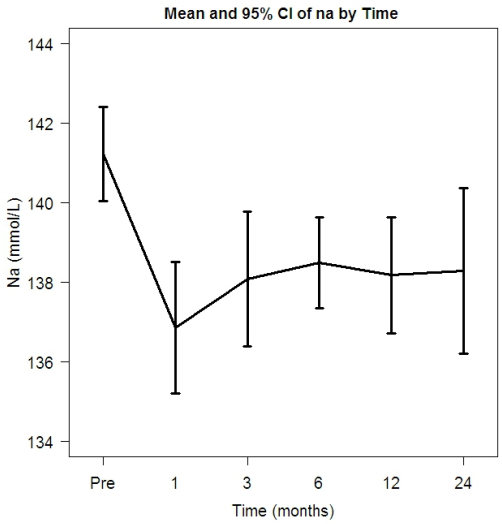

Figure 2: Mean sodium, after radical cystectomy with orthotopic bladder substitution

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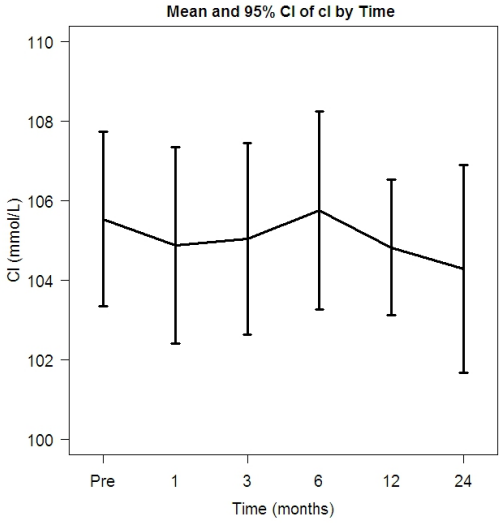

Figure 3: Mean chloride, after radical cystectomy with orthotopic bladder substitution

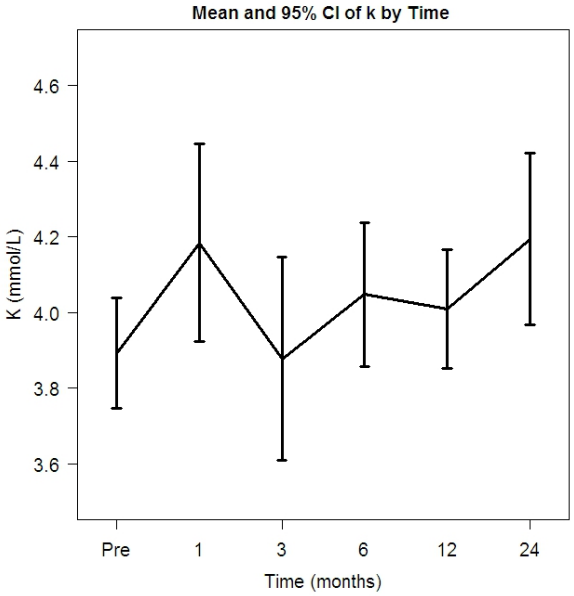

Figure 4: Mean potassium, after radical cystectomy with orthotopic bladder substitution

DISCUSSION

Muscle invasive bladder cancer (MIBC) is usually characterized by aggressive pathologic features, and the Treatment of choice requires aggressive management to achieve favorable oncologic outcomes. Therefore radical cystectomy, with urinary diversion, is the standard treatment for these patients (Stamatakis et al., 2012). Based on the results of prospective randomized trials, most guidelines recommend; cisplatin- based neoadjuvant combination chemotherapy (NAC) for patients with MIBC in stage T2-4acN0M0 before, undergoing RC.NAC improves overall survival by; 5% to 8%, after 5 years (Martini et al., 2017). Renal impairment is one common issue to significantly increase the risk of post operative mortality (Bianchi et al., 2016; Ahmadi et al., 2013; Antonelli et al., 2016). Maintenance of renal function, or slow process development to CKD status is an important issue for patients after surgery. In our hospital, we routinely use the serum creatinine levels as parameters in the evaluation of renal function.

In our study, Cr were increased from; 1.15 mg/dL to 1.97 mg/dL within 24 months. Cr were increasing approximately 95%. Nishikawa et al. reported a decline in renal function to be approximately 19.68%, and was

found in only 39% of patients (Nishikawa et al., 2014). Jin (2012) also reported 21% of bladder substitution patients had a decrease in renal function, approximately 2.9%. This was a markedly big difference between previous studies, and our study, in which renal deterioration looks more severe, hence, the potential risk factors have to be more defined in the future.

Makino (2017) described risk factors, with associated renal function deterioration, as being divided into two groups; early and late period. In the early period (within the first year) ureteroenteric anastomosis was associated with renal deterioration, while in the late period; diabetic and pyelonephritis were associated with a decrease in renal function. In our study we found only 2 patients had ureteroenteric anastomosis stricture, and this finding cannot be explained by the rising of Cr in our study.

The reabsorption of Cr and BUN from ileal segment is a speculation, but currently there is no consensus. Contact time and surface area are larger in ileal bladder substitution than ileal conduit, as well as the reabsorption of creatinine may be more pronounced in patients with ileal neobladder (Rinnab et al.,2005). In our study, Cr trended to be rising after ileal bladder substitution, which may have been caused by reabsorption from ileal mucosa. Further Investigation and systematic review may further support this theory.

Electrolyte imbalance may result from the reabsorption of excreted metabolites from bowel mucosa. The semipermeable property and metabolically active nature, when it contacts with urine metabolic change, may occur due to a difference electrolyte transport. The incidence of electrolyte disorder was; 21%-48%, in difference series reports (Megias and Delgado, 2015). The most common electrolyte change in ileal bladder substitution were; hyperchloremic metabolic acidosis with hypokalemia, however metabolic complications are almost, always subclinical (Douglas et al., 2012; Cho et al., 2017).[24,25] A surprising finding was detected in our study, in that we found hypochloremia and hyperkalemia, after perform bladder substitution, and no patient had clinical problems from metabolic complications.

Complications from bowel resection are very few due to use of short of bowel segment. Malabsorption mostly occurs if the resected ileal segment is more than 60 cm (Mill and Studeret, 1999). Vitamin B12 deficiency occurred in long term follow up, and will happen in up to 21% of patients (Rosenbaum et al., 2008). Thus, we should concern ourselves in megaloblastic anemia within patient bladder substitution groups.

There were several limitations in our study. First, it is a retrospective design and dependent on data that may have effected the accuracy of the results. Second, there was no standard follow-up, or imaging protocol. Third, the population in this study was too small. We believe these data could be useful to decide on the best treatment strategy and guide for creating follow up programs.

CONCLUSION

Substitution has a decline in renal function along with a lifelong risk of chronic kidney disease (CKD). Regular monitoring of the upper urinary tract imaging, and renal function will delay CKD status as well as the early diagnosis and treatment of modifiable factors.

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CONFLICT OF INTEREST: All authors declare that that they have no competing interests.

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