Effect of Treatment Modality on Long Term Renal Functions in Patients With Muscle Invasive Bladder Cancer

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Purpose: To compare of changes in glomerular filtration rate (GFR) in patients who underwent radical cystectomy (RC) and multimodal treatment (MMT).

Materials and Methods: We identified 472 consecutive patients who underwent RC or treated with MMT for muscle invasive bladder cancer (MIBC) at our institution, between January 1995 and December 2010. After excluding the patients who died within 5 years or without 5 years of follow-up, 175 and 59 patients who were treated with RC and MMT, respectively were included to the study. GFR was measured before treatment and every 6 months after treatment till the end of 60th month.

Results: The mean age and mean baseline GFR were 66.5±5.7 years and 85.1±18.2 mL/min/1.73m2, respectively for all patients. We detected statistically significant higher decrease rates for GFRs in MMT group compared to RC group at every follow up period till 42nd month. Renal function decreasing was found to be more prominent during first year of follow-up (79.1 to 65.9 mL/min/1.73m2) in MMT group. However, GFR decreased more regularly in RC group (~4 mL/min/1.73m2 per year). MMT, lower baseline GFR, Diabetes Mellitus, hypertension, and ureteroenteric anastomotic stricture development were associated with low GFR under 60 and 45 mL/min at the end of five years.

Conclusion: Decreased renal function is noted in many MIBC patients after RC or MMT in the long-term follow-up. Renal function deterioration is more prominent within the first year after MMT.

Keywords: bladder cancer; multimodal treatment; radical cystectomy; renal deterioration; urinary diversion

INTRODUCTION

Bladder cancer (BC) is the eleventh most commonly diagnosed cancer in both genders and approximately 25% of BC patients present with muscle invasive disease.[1] Standard treatment of muscle invasive bladder cancer (MIBC) is radical cystectomy (RC) with urinary diversion (UD). Furthermore, bladder preservation with multimodal treatment (MMT) including radiotherapy, chemotherapy and complete transurethral resection of bladder tumor is recommended in unwilling patients or patients who were unfit for RC.

To date, several UD techniques were described by many authors and two mostly used UD types are ileal conduit diversion (ICD) and orthotopic neobladder (ON).[2] The choice of UD type depends on many factors including patient preference, age, tumor stage, presence of urethral recurrence risk, surgeon experience, patient's neurological and psychological disorders.[3] Patient's renal function is also another important parameter for choosing the type of UD. ON is recommended in patients who have less than 1.7 to 2.2 mg/dL of serum creatinine level or greater than 40 mL/min of the glomerular filtration rate (GFR).[4]

Another important issue is renal deterioration after treatment in MIBC patients. Renal deterioration develops in most patients regardless of the treatment modality.4 The risk of renal impairment after treatment depends on many factors including, preoperative patient co morbidities and renal function, age-related renal function loss, stricture of ureteroenteric anastomosis, urinary stone development after RC and nephrotoxic chemotherapeutic drugs used during MMT.[2,5,6]

To the best of our knowledge, there is no publication comparing renal function impairment after RC and MMT for MIBC patients. In this study, we aimed to evaluate the changes in GFR values in bladder cancer patients who had minimal 5 years of follow-up period after RC (with either ICD or ON) and MMT.

MATERIALS AND METHODS

We included 472 consecutive patients who underwent RC or treated with MMT for MIBC at our institution, between January 1995 and December 2010. Patients who died within 5 years (143 patients after RC, 64 after MMT), lost to follow-up (17 patients after RC, 2 patients during MMT), GFR value under 60 ml/min per 1.73 m^2 (12 patients), were excluded. Finally, 175 and 59 patients who were treated with RC or MMT, respectively were included to the study. Data of age, gender, baseline GFR (immediately before treatment), tumor histology, tumor stage, co morbidity history, presence of hydronephrosis (before treatment), carcinoma in situ

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Table 1. Patients' characteristics.

Characteristic	Total (n=234)	RC group (n=175)	MMT group (n=59)	*p* value
Mean age ± SD	66.5 ± 5.7	65.3 ± 6.2	67.4 ± 4.9	.07[a]
Baseline GFR, Mean ± SD	85.1 ± 18.2	91.8 ± 18.8	79.1 ± 16.3	*.001[b]
Gender				
Male, n (%)	197 (84.2)	132 (73.7)	41(69.4)	.6[c]
Female, n (%)	37(15.8)	43(26.3)	18 (30)	
Histological type				.07[c]
Transitional cell carcinoma, n (%)	210 (89.7)	157 (89.7)	53 (89.8)	
Squamous cell carcinoma, n (%)	13 (5.5)	7 (4)	6 (10.2)	
Transitional cell carcinoma with squamous differentiation, n (%)	6 (2.6)	6 (3.4)	-	
Adenocarcinoma, n (%)	3 (1.3)	3 (1.7)	-	
Other, n (%)	2 (0.9)	2 (1.2)	-	
Comorbidity				
Hypertension, n (%)	88 (37.6)	60 (34.3)	28 (47.5)	.07[c]
Diabetes Mellitus, n (%)	62 (26.5)	40 (22.8)	22 (37.3)	*.03[c]
Hyperlipidemia, n (%)	30 (12.8)	23 (13.1)	7 (11.9)	.8[c]
Preoperative Hydronephrosis, n (%)	47 (20.1)	37 (21.1)	10 (16.9)	.49[c]
Presence of CIS, n (%)	32 (13.7)	20 (11.4)	6 (10.1)	.8[c]

*Statistically significant
Abbreviations: CIS, Carcinoma in Situ; GFR, Glomerular Filtration Rate; MMT, Multimodal treatment; RC, Radical cystectomy
[a] Student *T* test was used for statistical analysis
[b] Mann Whitney test was used for statistical analysis
[c] Chi-square test was used for statistical analysis

(CIS) and postoperative co morbidities (ureteroenteric stricture, pyelonephritis) were recorded. Ethical approval for this retrospective study was obtained from the Institutional Review Board (IRB No: 15.08.2016-246). The study was conducted in compliance with the principles of the Declaration of Helsinki.

Surgical techniques

All procedures were performed by three experienced surgeons (KT, YB, SB). Bricker procedure was performed for ICD. We have isolated 15-20 cm ileal segment about 25-30 cm proximally from ileocecal valve. Both ureters dissected proximally and anastomosed separately in a standard end-to-side technique by two running absorbable 4/0 or 5/0 sutures. Ileal segment anastomosed to the skin in a nipple fashion. In patients who had ON, Studer and Mainz pouch II procedures were performed in 39 and 20 patients, respectively. Selection of diversion type was performed based on patient's age, comorbidity, neurological and psychological impairment, serum creatinine value and patient's preference.

Multimodal treatment: After maximal transurethral resection of bladder tumor, patients received 64-66 Gy (fraction dose, 200 cGy/day) radiation to the pelvis over 4 weeks time with concurrent cisplatin (20 mg/day for 5 days) based chemotherapy during the first and fourth weeks of RT. MMT response was evaluated by computed tomography (CT) scan, cystoscopy, urine cytology and tumor site biopsy. Clinical complete response was defined as no tumor palpable on bimanual examination under anesthesia (BEUA), no tumor visible on cystoscopy, negative tumor site biopsy and negative urine cytology. Patients who had complete response were followed with cystoscopy, tumor site biopsy, BEUA, urine cytology and CT scan.

Follow-up periods and renal function assessment

For BC patients, follow-up period is usually 4 times for the first 2 years, 2 times for the next 3 years and then annually at outpatient clinic. At each visit, we evaluated renal function tests (including serum creatinine, blood urea nitrogen) serum electrolytes, complete blood cell count, urine analysis and urine culture, residual urine volume (in patients with ON), renal ultrasonography and computed tomography of abdomen and chest. GFR was calculated with the Modification of Diet in Renal Disease (MDRD) equation:[7]

GFR (ml/min per 1.73 m^2)= 175x(serum creatinine)-1.154 x(age)-0.203 x(0.742 if female)

We also recorded the patients who had GFR below 60 and 45 ml/min per 1.73 m2 at follow up periods. This study was retrospective and most patients had irregular follow-up visits. Thus, we considered GFR values between 3-9 months after treatment as first GFR measurement (6 months after treatment) and GFR values between 9-15 months as second GFR measurement (12 months after treatment). All subsequent GFR measurements were obtained at every 6 months. GFR change was calculated according to formula= GFRchange (GFRFollow-up time- GFRBaseline)/ GFRBaseline

Pyelonephritis was defined as hospitalization by both a febrile episode and flank pain tenderness with a positive urine culture (>105 colony-forming units) after excluding other indications for fever. Ureteroenteric anastomotic stricture was defined as newly developed hydronephrosis by ultrasonography and/or CT.

Statistical analysis: All statistical analysis was done with SPSS 16.0(IBM Company Chicago, Illinois, USA). Student T test was used for comparison of parametric variables. Mann-Whitney and Chi Square tests were used to compare non-parametric variables. Percentage change of GFRs were compared with Wilcoxon test and Logistic regression analyses were performed to determine predictive factors of GFR decrease. For statistical significance p values of < .05 was accepted.

RESULTS

We evaluated data of 234 patients (130 and 45 of them underwent RC with ICD, and ON, respectively and 59 of them were treated with MMT) retrospectively. The mean age, mean baseline GFR and mean follow-up were 66.5 ± 5.7 years, 85.1 ± 18.2 mL/min and 71 ± 8

Table 2. Mean glomerular filtration rates and comparison of percentage change from baseline between two groups.

GFR rates (mL/min/1.73 m^2)	Total (n=234)	RC group (n=175)	MMT group (n=59) from baseline in RC group	Percentage change from baseline in MMT group	Percentage change	*P* value
Baseline, Mean ± SD	85.1 ± 18.2	91.8 ± 18.8	79.1±16.3	-	-	-[a]
6 months after, Mean ± SD	84.8 ± 19	88.7 ± 17.9	73.2 ± 17.8	3.4%	7.5%	*.001[a]
12 months after, Means ± SD	81.4 ± 20.6	87.1 ± 17.7	65.9 ± 20.1	5.1%	16.7%	*<.001[a]
18 months after, Means ± SD	79 ± 20.8	82.6 ± 18	65.1 ± 24.9	10.1%	17.7%	*.001[a]
24 months after, Means ± SD	78.2 ± 20.9	82.1 ± 17.8	65 ± 25	10.6%	17.8%	*.001[a]
30 months after, Means ± SD	77.5 ± 20.7	81.1 ± 18.3	64.8 ± 23.8	11.7%	18.1%	*.001[a]
36 months after, Means ± SD	75 ± 20.9	78.3 ± 19.1	64.4 ± 23	14.7%	18.6%	*.004[a]
42 months after, Means ± SD	73.4 ± 21	76.6 ± 19.8	63.7 ± 21.8	16.6%	19.5%	*.01[a]
48 months after, Means ± SD	70.9 ± 21.6	74 ± 21	62 ± 21	19.4%	21.7%	.08[a]
54 months after, Means ± SD	68.7 ± 21.9	71.7 ± 59.6	59.6 ± 19.4	21.9%	24.7%	.24[a]
60 months after, Means ± SD	64.9 ± 21.8	67.5 ± 22.3	57.2 ± 18.3	26.5%	27.7%	.4[a]

*Statistically significant
Abbreviations: GFR, Glomerular Filtration Rate; MMT, Multimodal treatment; RC, Radical cystectomy.
aWilcoxon test was used for statistical analysis

months, respectively for all patients. Patient characteristics were given in **Table 1**. Pathological stage T0, Ta-1, T2 and T3+4 disease were detected in 13 (5.6 %), 24 (10.3 %), 137 (58.5 %) and 60 (25.6 %) RC patients, respectively. In MMT group, clinical stage T2 and T3+4 diseases were detected in 35 (59.3 %) and 24 (40.7 %) patients. In RC group, 30 (17.1 %) patients received platinum based chemotherapy during the perioperative period. After surgery, we detected ureteroenteric stricture in 9.1% (16 patients) of RC patients with ICD and 6.7% (2 patients with Studer, 2 patients with Mainz-II procedure) of RC patients with ON. Pyelonephritis occurred in 6.2% (11 patients) and 3.3% (2 patients in Studer procedure) of patients with ICD and ON, respectively. In MMT group, unilateral ureteral stricture and bladder contracture developed in 4 (6.6%) and 5 (8.4%) patients, respectively. Two patients underwent salvage cystectomy for severe bladder contracture.
The mean baseline GFRs were 91.8 and 79.1 in RC and MMT groups, respectively. The mean GFR was statistically significant lower in MMT group compared to RC group at baseline($P < 0.001$). Therefore, we compared two groups based on percentage change from baseline at follow up periods. We detected statistically significant higher decrease rates for GFRs in MMT group compared to RC group at every follow up period till 42nd months. Decrease rates of GFRs similar between two groups after 42nd months. For two groups, mean GFRs and percentage change of GFRs from baseline were detailed in **Table 2** and **Figure 1**.
During follow-up, we detected GFR below 60 mL/min/1.73 m2 in 52 (40%), 23 (51%) and 28 (47.5%) patients in subgroup 1, 2 and 3, and GFR below 45 mL/min/1.73 m2 in 17 (13%), 8 (17.8%) and 14 (23.7%) patients in subgroup 1, 2 and 3, respectively.
Logistic regression analyzes including age, baseline GFR, gender, comorbidity status, treatment method (MMT or RC), presence of CIS, presence of preoperative hydronephrosis, ureteroenteric anastomotic stricture development and pyelonephritis development variables were performed to determine factors associated with GFR under 60 and 45 mL/min/1.73 m^2 at the end of five years. Advanced age, lower baseline GFR, treatment with MMT, ureteroenteric anastomotic stricture development, presence of diabetes mellitus or hypertension history were found to be associated with with GFR under 60 and 45 mL/min/1.73 m^2 at the end of five years in univariate analysis. On multivariate logistic analysis; lower baseline GFR, treatment with MMT, ureteroenteric anastomotic stricture development, diabetes mellitus and hypertension were associated with GFR under 60 and 45 mL/min/1.73 m^2 at the end of five years (**Table 3**).

Table 3. Multivariate analysis according to decrease in Glomerular filtration rates under 60 and 45 mL/min/1.73 m^2 at the end of five years

Variables	GFR under 60 mL/min/1.73 m^2 OR	95% CI	*p* value	GFR under 45 mL/min/1.73 m^2 OR	95% CI	*p* value
Age (older)	1.1	0.952-1.458	.9	1.2	1.131-3.941	.6
Sex(Female)	0.9	0.530-1.882	.86	1.3	1.202-1.536	.5
Lower baseline GFR	2.6	1.462- 5.639	*.001	2.2	1.088-4.414	*.04
Treatment with MMT	3.2	1.248-5.481	*< .001	2.8	1.106-4.982	*.02
Presence of CIS	1.3	0.526-3.289	.6	1.1	0.224-4.816	.9
Presence of preoperative HN	1.1	0.824-2.268	.8	1.9	0.674-5.474	.2
Diabetes Mellitus history(+)	4.9	2.575- 9.706	*< .001	4.7	1.380-8.143	*< .001
Hypertension history(+)	3.6	2.019-6.552	*< .001	4.2	1.562-7.898	*< .001
Hyperlipidemia history(+)	1.6	0.512-4.166	.2	1.1	0.538-16.192	.7
Ureteroenteric anastomotic stricture development	3	1.46-6.074	*.001	3.2	1.264-5.872	*< .001
Pyelonephritis development	1.2	0.52-1.241	.7	1	0.434-2.162	.8

*Statistically significant
Abbreviations: CI, Confidence interval; CIS, Carcinoma in situ; HN, Hydronephrosis; MMT, Multimodal treatment; OR, Odds ratio

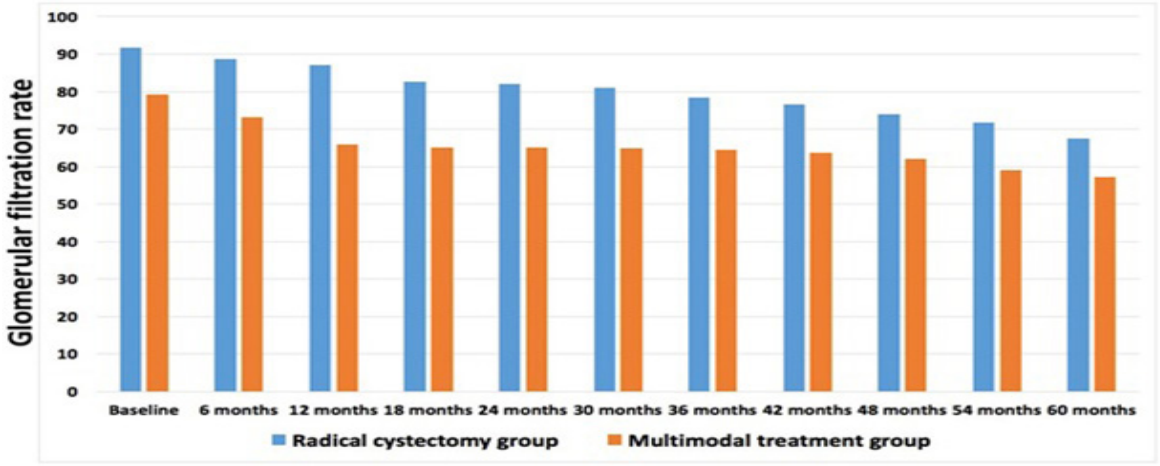

Figure 1. Mean glomerular filtration rates of Radical cystectomy and multimodal treatment groups

DISCUSSION

Many studies regarding renal function deterioration after RC have been published; however data regarding the effect of MMT on renal function is scarce.[8-10] The most common blamed factors of renal function deterioration after RC are patient comorbidities such hypertension or diabetes mellitus, lower baseline renal function, history of cisplatin-based chemotherapy in perioperative period, stricture of ureteroenteric anastomosis, pyelonephritis and development of urinary stones.2,5,6 Primary aim of this study was to compare of renal functions of MIBC patients who had RC and MMT.

Eisenberg et al. reported renal function outcomes of 1631 RC (76% underwent incontinent diversion and 24% underwent continent diversion) patients who were alive at least 10 years after RC.8 They defined renal deterioration as a decrease in GFR >10 mL/min/1.73 m^2 before and after RC. Median GFRs were 62, 55 and 51 mL/min/1.73 m^2 at baseline, 5 and 10 years of follow-up, respectively. Similar to Eisenberg's study, in another study, renal deterioration was defined as a decrease in GFR >10 mL/min/1.73m^2.[9] They reported that 36% of RC patients with ICD and 21% of RC patients with ON had renal function deterioration at 10 years of follow-up. In Nishikawa et al's study the mean GFR (169 patients) declined from 69.6 to 55.9 mL/min/1.73 m2 during follow-up (median 106 months) and renal deterioration was observed in 46.2 % of patients.[10] More recently, Makino et al. reported their renal function outcomes after RC with UD.[11] They emphasized that rapid decline of GFR observed in the first year after RC (65.1 to 58.9 mL/min/1.73 m^2) followed by a continuous decline of ~1.0 mL/ min/1.73 m^2 per year thereafter. In our study, patients were treated with MMT or RC either with ICD or ON and mean GFR in the whole group declined from 85.1 to 64.9 mL/min/1.73 m^2 at the end of five years. The rate of mean GFR decrease in our study is consistent with those reported in previous studies.8-11 To the best of our knowledge, in our study, for the first-time comparison of renal function impairment after RC and MMT is performed. We observed higher decrease rate of GFR values in MMT group. In this group, renal function deterioration was found to be more prominent during the first year of follow-up (79.1 to 65.9 mL/min/1.73 m^2). On the other hand, GFR decreased more regularly in RC group (~4 mL/ min/1.73 m2 per year).

Studies focusing on long-term renal function deterioration after MMT are scarce. Renal function deterioration due to radiation seems to be related to bladder contracture and ureteral stricture. In a retrospective review of long-term survivors in patients who underwent trimodal therapy, Zietman et al. reported 21% of bladder hypersensitivity, involuntary detrusor contractions and incontinence.[12] Rödel et al. demonstrated 3% of bladder contracture and 2% of salvage cystectomy due to bladder contracture.[13] Our study exhibited significantly higher decline in renal function in the MMT group compared to RC group. This can be related to several factors. In our study, 4 patients (6.6%) developed unilateral ureteral stricture and 5 (8.4%) developed bladder contracture due to radiation. Two patients underwent salvage cystectomy for bladder contracture. All these complications occurred in the first year of treatment, which may explain the sharp decrease in mean GFR in the MMT group. On the other hand, higher rates of diabetes mellitus in MMT group at the beginning of treatment may play a role for this finding.

According to previous studies, several factors have been identified to be associated with the decline in renal function after RC such as older age, patients' co morbidities, pre-op GFR, post-op hydronephrosis or anastomotic strictures.9,11 Makino et al. evaluated renal function deterioration in the early and late postoperative period.11 Ureteroenteric anastomotic stricture was identified as a sole significant predictive factor of early postoperative (one year after RC) renal function deterioration, whereas diabetes mellitus and pyelonephritis episodes were identified as factors resulting late renal function decline. Perioperative chemotherapy and hypertension were not associated with the risk of renal function decline. Differently from Makino's study, Jin et al. identified chronic hypertension (P = 0.001, HR 1.2) as independent predictive factor for renal deterioration.9 In our study, ureteroenteric anastomotic stricture occurred in 20 patients who underwent RC and this parameter was found to be a significant factor for renal function deterioration on multivariate analysis.

The present study is limited by its retrospective nature. There was heterogeneity between groups. As known,

other significant important factor on renal deterioration after RC is reflux development. We could not obtain documentation related to refluxing after RC. The time frame of the study was large and several developments took place for both treatment modalities. We were unable to obtain 10 year of renal function outcomes due to inadequate follow-up, which may demonstrate the long-term renal function better. Finally, 19 patients (17 patients after RC, 2 patients during MMT) lost to follow-up. This situation has reduced the number of our patients

CONCLUSIONS

Decreased renal function is noted in many MIBC patients after RC or MMT in the long term follow-up. Renal function deterioration is more prominent within the first year after MMT. In the long term, MMT, development of ureteroenteric anastomotic stricture, diabetes mellitus and hypertension were found to be significant factors associated with lower GFR levels.

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