

Prospective analysis of a radical cystectomy series at a tertiary care center in Sri Lanka – is there room to improve the outcome?

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Abstract

Introduction

Bladder cancer (BC) is a common malignancy and ranks tenth globally. Radical cystectomy remains the gold standard for organ confined muscle invasive bladder cancer (MIBC). It has proven efficacy on local disease control and tumour free survival (TFS). Notwithstanding the improvement of techniques and peri-operative care, this procedure is associated with high peri-operative morbidity. Despite the abundance of descriptive studies on demography there are only a few local studies published on the long-term outcome of surgical treatment. Present analysis of radical cystectomy series with minimum 3-year follow up will fill the gap in literature as first reported long-term study in the local setting

Methodology

Twenty-six consecutive cystectomies performed over two years from April 2016 at a single tertiary center were prospectively analysed for demography peri-operative and long-term outcome. Median follow-up was 43.5 months.

Results

Median age was 60 (range 35-74) years. Ninety-two percent were males. Twenty-two out of 26 (85%) were presented with haematuria. Eighty-one percent (21/26) had urothelial bladder cancer (UBC) out of which, 77% (20/26) were males with a mean age of 59.6 years. Four out of five who had non-urothelial bladder cancer (NUBC) were males.

Forty-two percent (11/26) were smokers and death percentage was markedly high among smokers than non-smokers. No other known risk factors were identified among the rest.

Thirty-eight-point five percent (10/26) were pT3b and pT4a, while 53.8% (14/26) were pT3 or above tumours.

Majority (62%) of complications fell into minor category (Clavien-I/II) with an average blood loss of 850 ml and a transfusion rate of 15% (4/26).

Thirty day and 90 day mortality rates were 3.8% and 7.7% respectively rising to one-year mortality of 23%. Four out of twenty-six cystectomy operations were done for palliation. Three-year overall survival (OS) was 61% [CI 41.5% - 79.7%]. Out of the 12 deaths, 8 (67%) were due to cancer progression while 4 had local recurrences. Among the patients who were cancer free, three-year survival was at 84% [CI 68.1% - 93.7%], while cancer-specific three-year survival rate was at 72% [CI 54.3% - 87.2%]. With majority of survivors, 57% (8/14) were maintained normal renal functions.

Summary

Despite the fact that radical cystectomy which undoubtedly provide significant improvement in cancer free survival in high-risk MIBC, the present study emphasized relatively inferior outcomes in the developing world due to the delayed presentation.

Fifty-three point eight percent (14/26), pT3 or pT4a tumours which is associated with poor cancer specific survival and partly due to the nativity of the caregivers in offering early radical surgery with acceptable complication rates. It was also evident from this study that not only tobacco smoking seems to be the most prevalent risk factor but also associated with significantly poor long term survival

Introduction

Bladder cancer (BC) ranks as the tenth commonest malignancy among all genders and the seventh common cancer in men worldwide [1]. Age standardized global incidence is 9 per 100,000 persons a year for men and 2.2 for women [2]. According to National Cancer Registry in Sri Lanka reported crude incidence rate was 3.7 per 100,000 male population [3]. Prompt radical cystectomy performed as open, laparoscopic or robotic with pelvic node dissection and urinary diversion as a urostomy or neobladder, remains the gold standard for muscle invasive bladder cancer (MIBC) or recurrent high-grade non-invasive disease [4].

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Surgical techniques and peri-operative care of radical cystectomy were improved over the years [5]. Despite its proven efficacy on local disease control and long-term cancer free survival, the procedure is associated with a significant peri-operative morbidity [6]. Considering the risk factors, tobacco in addition to its direct oncogenicity leads to higher morbidity and mortality secondary to respiratory and cardiovascular comorbidities [5].

Due to facts such as advanced local staging at presentation and reluctance of the caregivers in offering timely cystectomy it is apparent that a considerable number of patients in the developing world are offered alternative suboptimal therapies such as chemo-radiation. Despite the abundance of descriptive demographic and pathological studies on bladder cancer, there are hardly any local studies of prospective analysis and the long-term outcome of the surgical treatment [8,9,10,11].

Present study analyses twenty-six consecutive cases of newly diagnosed patients with bladder carcinoma who underwent radical cystectomy at a tertiary referral center in Sri Lanka.

Methodology

Twenty-six consecutive patients who underwent cystectomies were included in the study. The procedures were performed over a period of two years from April 2016 to March 2018 at a single unit in the National Hospital of Sri Lanka. Patients' demographic data, clinical presentations, pre-operative staging, pathological staging, peri-operative and follow up details were collected using medical records and telemedicine approach. Informed written consent and ethical committee approval was obtained for compilation and publication of the information. The median follow up period of our study was 43.5 months (36 -61 months). We considered the follow up time duration of 36 months or end point of death in view of calculating overall survival (OS) and the cancer specific survival (CSS) in our study.

Despite current guidelines none of them were offered neo-adjuvant chemotherapy. While one patient received full course of adjuvant chemotherapy, two patients refused post-operative chemo-radiation plans.

Results

In the present cohort the age range was 35 to 74 years with median age of 60 years. Eighty percent of patients were aged above 50 years. Out of a total 26 patients, 92.3% were male with the male to female ratio of 12:1.

Most prevalent symptom was haematuria. Eighty-five percent (22/26) had painless haematuria at initial presentation. Eighteen had visible haematuria, while four had non-visible haematuria. Two out of 26 were presented with lower urinary tract symptoms. Obstructive uropathy and severe backache were other rare presentations, seen among 4% of cases.

The average delay for cystoscopy and diagnostic work up until cystectomy was six weeks in the present study.

Table 1 – Analysis of symptoms at initial presentation

Symptom	Percentage %
Hematuria	84.6
Dysuria	11.5
LUTS	7.7
Metastatic	0
Obstructive Uropathy	3.8

Risk factors

With regard to risk factors, 42% (11/26) were cigarette smokers, one worked in a rubber factory, and another had a large bladder stone. Most prevalent risk factor was cigarette smoking at 42.3%. However, half of the cohort (13/26) had no identifiable risk factors.

Table 2 – Analysis of prevalence of risk factors for bladder cancer.

Risk Factor	Count	Percentage %
Smoking	11	42.3
Industry Hazard	1	3.8
Chronic bladder irritation	1	3.8

As per Table 3 give below, it can be clearly seen that death percentage is markedly high among smokers (73%) than among non-smokers (27%).

Table 3 – Impact of smoking on bladder cancer survivalcancer.

Smoking	Dead		Alive	
	Count	Percentage %	Count	Percentage %
No	4	26.7	11	73.3
Yes	8	72.7	3	27.3

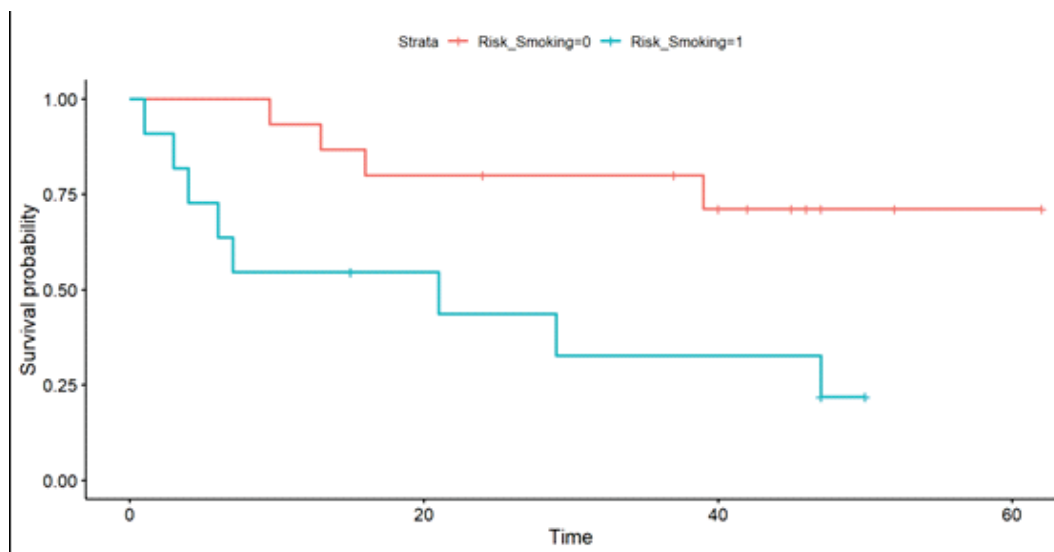


Figure 1 - Comparing Survival rates among smokers and non-smokers.

Table 4 - Kaplan-Meier estimates with respect to smoking status.

Smoking	Time in Months	Survival Probability	95.0% CI	
			Lower	Upper
No	9.5	0.933	0.807	1.000
	13	0.867	0.695	1.000
	16	0.800	0.598	1.000
	39	0.711	0.467	0.955
Yes	1	0.909	0.739	1.000
	3	0.818	0.590	1.000
	4	0.727	0.464	0.990
	6	0.636	0.352	0.921
	7	0.545	0.251	0.840
	21	0.436	0.133	0.740
	29	0.327	0.034	0.621
	47	0.218	0.000	0.480

As displayed in figure 1 and Table 4, a clear distinction of the survival rates can be seen with respect to the smoking status. One- year survival rate is at 87% for non-smokers whereas it is 54.5% for smokers. Two-year survival is at 71% for non-smokers whereas it drops down to 43.6% for smokers. Further, a log-rank test, which performs a hypothesis test to check whether survival rates are significantly different between two groups, was done and results were as follows. .

Table 5 - Log-Rank test for Smoking status

Method	Chi-Square	DF	P-Value
Log-Rank	5.99577	1	0.014
Wilcoxon	6.22486	1	0.013

The p-values of the test is less than 0.05 indicates that there is a significant difference among the survival rates of smokers and non-smokers at 5% level of significance.

Histology types and grading

Twenty-one individuals (80.7%) had urothelial bladder cancer. Twenty of them were males. The mean age of males with urothelial bladder cancer (UBC) and non-urothelial bladder cancer (NUBC) was 59.6 and 59.4 years respectively. Histological types are depicted in table 6.

Table 6 - Prevalence of bladder cancer histology types

Type of cancer	n	Percentage
UBC	25	96.2
Secondary bladder cancer	1	3.8
NUBC	5	19.2
Low Grade UBC	4	15.4
High Grade UBC	17	65.4

A hypothesis test for comparison of survival rates with respect to type of bladder cancer was done since counts of patients are not comparable across the two types (25 patients had Primary Urothelial Bladder Cancer (UBC) and only one patient had secondary Bladder Cancer. With respect to Cancer (CA), the majority (65%) had high grade UBC.

Results of the log-rank test for testing for a significant difference in the survival rates with respect to the type of urothelial cancer are given in the table 7 below.

Table 7 - Log-Rank test for type of urothelial cancer

Method	Chi-Square	DF	P-Value
Log-Rank	1.06606	2	0.587
Wilcoxon	0.96962	2	0.616

Since p-value is above 0.05, it can be concluded that there is no significant difference in the survival rates among three groups of non-UBC low/intermediate grade UBC and High grade UBC at 5% level of significance.

Only one had high-grade pT1, while all others had high-risk carcinoma invading bladder muscle pT2 or above. This male patient with pT1 underwent laparoscopic assisted right nephroureterectomy in addition to radical cystoprostatectomy.

Pathological staging revealed 38.5% (10/26) was pT3b or pT4a, and another 15.4% (4/26) were pT3a indicating the delayed presentations for cystectomy among a significant proportion. Less than half of the cohort, 12 patients presented as pT2 and pT1 disease that were 42.3% (11 /26) and 3.8% (1/26) respectively. Nodal stage of majority 69.2% (18/26) was N0. Only 7.7% (2/26) were in N1 stage. Twenty-three percent (6/26) had reached N2 stage, which would have contributed to the overall poor outcome.

Table 8 - Clinico-pathological characteristics

Characteristics		Urothelial CA n = 21	Non-Urothelial CA n = 5
Median age	Male	59.6	59.4
	Female	60	45
Sex	Male	20	4 (3 Adeno CA + 1 Squamous CC)
	Female	1(Sarcomatoid CA)	1(Adeno CA)
Smoking	Smokers	7	3 (AdenoCA)
	Never smoke	14	1(Squamous CA)
			1
T-Stage	pT1	1	-
	pT2	11	-
	pT3	2	2
	pT4	7	3
N-Stage	N0	17	2
	N1	1	1
	N2	4	2
CSM		5	3

CA: carcinoma CSM: Cancer specific mortality

Surgical Management and complications

Open Radical cystectomy was followed by a standard pelvic lymphadenectomy in all cases (n=26) and the urinary diversion method was ileal conduit urostomy (n=24) and bowel neobladder (n=2). The majority (18/26) were initially managed in the ICU or and HDU. Median ICU-stay was 18 hours. Though, ERAS (Enhanced Recovery After Surgery) protocol was not strictly implemented, optimization of pre-operative comorbidities and nutritional status, early post-operative feeding, and mobilization had been routinely carried out in all patients.

Average blood loss during surgery was 850 ml and 15.4% (4/26) needed peri-operative blood transfusions. Common peri-operative complications included surgical site infections (6/26) and paralytic ileus (5/26). One female patient had post-operative myocardial infarction.

Only one patient had a massive blood transfusion as a consequence of iliac artery invasion, which needed additional vascular grafting. This also accounted for the single death that occurred within 30 days due to iliac artery mycotic aneurysm.

Overall surgical complications emerged in 61.5% of cases according to Clavien-Dindo classification majority being minor (Clavien I/II). The average ICU stays of Clavien IV was 84 hours. [7]. (Table 9)

Table 9 - Post-operative complications following radical cystectomy and urinary diversion

Clavien-Dindo Complication Grade	Number (percentage) N=26
None	10(38.46%)
I	4(5.38 %)
II	6(23%)
IIIa	2(7.69%)
IIIb	1(3.85%)
IVa	2(7.69%)
IVb	0
V	1(3.85%)

Thirty and. 90-day mortality rates were 3.8% and 7.7% respectively rising to one-year mortality of 23%. Four out of twenty-six cystectomy operations were done for palliation. Three-year overall survival (OS) was 61% [CI 41.5% – 79.7%]. Out of the 12 deaths occurred, 67% (8/12) were due to cancer progression while 4 had local recurrences. Among the patients who were cancer free, three-year survival was at 84% [CI 68.1% - 93.7%], while cancer-specific three-year survival rate was at 72%[CI 54.3% - 87.2%].

One out of 26 died due to mycotic aneurysm indicating 30-day mortality of 3.8%. Another patient died post operatively after 30th day due to terminal disease leaving 90-day mortality of 7.6% (2/26).

Infections and venous thrombosis were noted as complications within initial post operative 90 days. One patient got deep vein thrombosis of unilateral femoral and popliteal veins. Eight patients out of 26 were re-admitted with urinary tract infections or pyelonephritis within first 90 days. Three patients developed acute kidney injury (AKIN stage 2) as immediate post- operative complication that did not require long-term renal replacement therapy.

Fifty-three point eight percent (14/26) were pT3 and pT4a, extending into peri vesical tissue, adjacent organ or beyond respectively.

Post cystectomy median ICU-stay was 18 hours. Overall surgical complications emerged as 61.5% (16/26) with majority 10/16 (62%) falling into minor category (Clavien-I/II). Average blood loss was 850 ml with a transfusion rate of 15% (4/26). Other complications within 90 days included urinary infections (8/26), surgical site infections (6/26), paralytic ileus (5/26), acute kidney injury (3/26), myocardial infarction (1/26) and venous thrombosis (1/26).

The overall survival and death rates are given in Table 10 below along with 95% confidence intervals.

As given below, one-month survival rate was 96%, while one-year survival rate further dropped up to 76%. The median survival time was approximately 44 months.

Table 10 - Kaplan-Meier Estimates for overall survival and death rates

Time in Months	Survival Probability	95.0% CI		Death Probability	95.0% CI	
		Lower	Upper		Lower	Upper
1	0.962	0.888	1.000	0.038	0.000	0.112
3	0.923	0.821	1.000	0.077	0.000	0.179
4	0.885	0.762	1.000	0.115	0.000	0.238
6	0.846	0.707	0.985	0.154	0.015	0.293
7	0.808	0.656	0.959	0.192	0.041	0.344
9.5	0.769	0.607	0.931	0.231	0.069	0.393
13	0.731	0.560	0.901	0.269	0.099	0.440
16	0.690	0.512	0.869	0.310	0.131	0.488
21	0.650	0.465	0.835	0.350	0.165	0.535
29	0.606	0.415	0.797	0.394	0.203	0.585
39	0.556	0.357	0.755	0.444	0.245	0.643
47	0.463	0.229	0.698	0.537	0.302	0.771

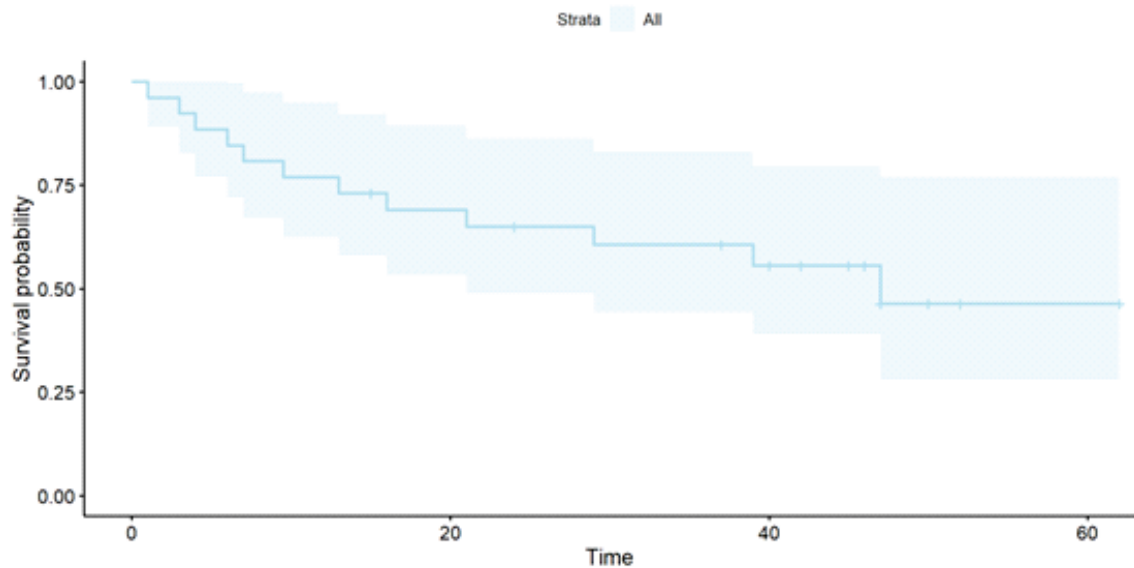


Figure 2 – Kaplan Meier plots showing overall survival following radical cystectomy for high-risk bladder cancer.

Despite post-operative adjuvant therapy, disease progression led to death in five cases, keeping in mind that 4/5 of them was turned in to palliative cystectomies after reviewing the post-operative histology. One patient who had an urachal adenocarcinoma pT3 developed peritoneal and liver metastasis followed by a fatal intestinal obstruction within a year.

Out of 14 survivors at 3 years, 4 (16.67%) developed disease progression and recurrence. Two of them had pelvic lymph node recurrence. One had distal liver metastasis and para-aortic lymph nodes involvement, while another had urethral recurrence.

At the end of three years, eight patients died due to the malignancy, while two died from unrelated causes, indicating cancer specific mortality (CSM) of 33% [CI 14.7% - 49.8%] at 3 years and other cause mortality of 8.3% at 3 years.

Out of 14 survivors, 57% (8/14) had normal renal functions. Twenty-one-point four percent reached stage I/II chronic kidney disease (CKD). Another 21.4% reached stage III CKD at 3 years. There were none beyond stage IV CKD.

Statistical software 'R-version 4.2.1' was used for performing advanced statistical analysis.

Discussion

Bladder cancer is one of the common urological malignancies occurring worldwide, in less than 1 year of diagnosis, 63% of these patients with MIBC who have not been offered curative treatment would die of the disease. The median overall survival reported is 8 -13 months with a cancer specific survival of 11 months (12 months for men; 9 months for women) in published data. On multivariable analysis, tumour stage at diagnosis, older age, increased comorbidity, delayed diagnosis, and female gender increased the risk of death.

Bladder cancer treatment outcomes in Sri Lanka are sparse. This is the first outcome analysis of patients undergoing radical cystectomy in Sri Lanka up to date.

Median age of our cohort who underwent cystectomy for primary bladder cancers is 60 years. As per previous studies the average age at diagnosis of bladder cancer in Sri Lanka is 65 years [8]. In the present series the youngest was 35 years without identifiable risk factors who required a radical cystoprostatectomy and orthotopic neo-bladder formation (STUDER's neo-bladder) for muscle invasive urothelial bladder cancer.

In the present study male to female ratio was 12:1 compared to the ratio of 3:1 quoted worldwide [4, 9]. Previous studies published in Sri Lanka demonstrated a diversity of male female ratio ranging from 9:1 [10], 4.1: 1 [8] and 5.7:1 [9] at different centers. In India male to female ratio is 8.6: 1 [9]. However, all the studies agreed upon the male preponderance, which is similar to other South Asian countries. The low female preponderance compared to western countries might be explained by the lower prevalence of smoking among women in South Asian countries.

Painless visible haematuria was the commonest presentation (18/26) in this cohort similar to many other studies [12]. In 7-year study on bladder cancer in Pakistan and Multan showed 88% of female cases (total 44 cases, median age 55 years) presented with haematuria [12].

Another study on bladder cancer in Sri Lanka showed painless visible haematuria encountered in 148 (52%) of cases, while 110 (39%) of patients had haematuria associated with pain. Only 8% of cases (22 patients) denied haematuria [13].

Bladder cancers have been associated with well-known risk factors such as tobacco smoking, occupational exposure to chemicals such as aromatic amines, dyes, paints, and chemicals used in rubber and textiles. Further, schistosomiasis and radiotherapy are important risk factors. In the present cohort, we could not identify any known risk factor among half of cases. Tobacco smoking is the single most significant cause for bladder cancer accounting for 25% - 65% of all cases [13]. Smokers have two-to- four-fold risk of developing bladder cancer when compared to the general population [14].

In the present group 42% were cigarette smokers. The World Health Organization data reveals, Sri Lankan adult daily smoking prevalence of 10% in 2019 [15]. All smokers were male in our cohort, which depicts the typical behaviour pattern seen in South Asian region. It was reiterated the fact that patients with high-risk bladder cancers who did not smoke had better survival rates in present study.

Historically, the rubber industry was considered to increase the risk of bladder cancers due to exposure to a contaminant beta naphthyl-amine. However, more recent studies since 1982 do not show an increased risk. Present cohort had a single rubber factory worker who had Sarcomatoid variant of urothelial cancer, while another diagnosed with squamous cell type bladder cancer, the risk factor was a large bladder calculus in the bladder [14].

Authors offered cystectomy primarily for patients with muscle invasive BC, of which twenty-one individuals (80%) had primary urothelial bladder cancer (UBC). Twenty out of 21 who had primary urological cancers were male which is similar to the published data, which showed higher male preponderance. Mean age of male patients with primary bladder cancers were 59.6 years in our cohort.

Literature revealed a higher proportion of female bladder cancers as more non-urothelial bladder cancer (NUBC), incidentally found, solid and muscle invasive compared to males. Further, NUBC in women constituted 20% whereas in men it represented only 5.5% of patients [12]. In contrast to these findings, four out of five individuals who had NUBC were males in our study with a median age of 59.4 years. However, NUBC is considered a more aggressive form of BC compared with the more common UBC [12]. Histological types of NUBC that we experienced were adenocarcinoma, squamous and squamous papillary.

Pathological staging revealed 38.5% (10/26) were pT4, extending beyond serosa of the bladder, which indicate the delayed presentations for cystectomy among significant proportion.

The gold standard curative option, radical cystectomy is considered as a surgery with high morbidity and mortality [16]. Excluding high volume specialized centers the mortality and morbidity rates are comparable in many parts of the world. Complications related to radical cystectomy are often used as surrogates to indicate surgical competency and quality of care.

According to Clavien-Dindo classification to report surgical complications, 61% of cases had some form of complication. However, out of these two thirds were categorized as Clavien-Dindo grades II or I.

Early complications of radical cystectomy and urinary diversion in the present cohort composed of wound infections (23%), gastro-intestinal (19%), renal (12%) and cardiac (4%). A similar study has reported 29% gastro-intestinal, 25% infections and 15% wound related complications as early post radical cystectomy complications [6]. Infections were most encountered complication among this cohort. Surgical site infections occurred in 23% during the early post-operative period. All were associated with open radical surgery and none of the laparoscopic wounds were infected.

Similar studies support that wound related complications is more common in open cystectomy where a limited laparotomy wound can also become infected. Other less

frequently observed wound complications including dehiscence or incisional hernia were not encountered in the present study [18].

Paralytic ileus was the only complication that we encountered as gastro-intestinal complication. Intestinal anastomotic leak has been rarely reported in similar studies [19].

When it came to the two methods of uretero-ileal anastomosis (Wallace and Bricker) authors preference was for Wallace's technique and without experiencing any long-term urinary leakage although it is often described as a complication. Present series followed the widespread practice of anastomotic stenting, which safeguards the anastomosis and lower the rate of urinary leakage (18). Post-operative infections were noted as late complications within 90 days in which 8/26 had clinically symptomatic urinary tract infections needing re-admission and intra-venous antibiotics. Half of them full filled the AKIN criteria of mild to moderate acute kidney injury. All received specialist nephrology care and recovered without need of renal replacement therapy.

Deep vein thrombosis has been recognized as a serious post-operative complication following radical cystectomy affecting up to 4.7% in literature [20]. Despite preventive measures for peri-operative venous thromboembolism such as TED stockings, prophylactic low molecular weight heparin, one patient was diagnosed with thrombosis of unilateral femoral and popliteal veins indicating a rate of 3.8%.

A significant number (43%) developed mild to moderate chronic kidney disease at 3 year follow up. Pyelonephritis, obstructive uropathy and episodes of acute kidney injury are well known to cause negative impact on renal reservoir. Our analysis was not extended to describe the aetiology of chronic kidney disease in the cohort. Renal insufficiency among survivors is a significant challenge in case of long-term dialysis dependence state, in a resource poor setting like ours where maintenance of dialysis is not entirely a free health facility due to unmet needs of chronic kidney disease burden.

In the current series the 90-day mortality rate was 7.6%. According to published data, SEER database reported 90-day mortality as high as 10.75% among 7076 patients [21]. In-hospital mortality rate of 0.54% was reported in a large volume academic referral center in the USA after 6728 cystectomies [18]. In our series, inward mortality was 3.8% (1/26) which is probably attributed to the small sample size.

Present study observed 33% cancer specific 3-year mortality among our cohort. These figures compare well with other

larger studies, which reveal 5-year progression-free survival rate of 51% and an overall survival rate of 50% [22]. Studies have also shown that 3-year survival figures have 80% correlation and predictive value with 5- year survival [23]. Furthermore, a study from the Netherlands has shown that cancer specific survival in 3 years was 67%, which was more closure to our cohort as well [24].

Conclusion

In the present study, pathological staging of pT3b and pT4 in 38.5% indicates delayed presentation for cystectomy among a significant proportion of patients in a developing country. Delay in cystectomy conferred an increased risk of cancer specific mortality among high-risk BC.

Study also emphasises higher vigilance on investigation of haematuria and availability of expertise for radical surgery and routine use of neoadjuvant chemotherapy, which could have improved the overall outcome.

Most importantly the present study has demonstrated a significant difference among the survival rates of smokers and non-smokers. And the fact that a majority of complications falls into minor or intermediate category which should not discourage the surgeon or the patient from going through the radical cystectomy which improves cancer free survival in high risk MIBC even in resource poor setting in the developing world.

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