Demographics, pathological characteristics and survival in urothelial bladder cancer in a cohort of Sri Lankan patients

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Abstract

Introduction: Bladder cancer has the 9th highest incidence among Sri Lankan males. This study describes the demographic profiles and survival in bladder cancer patients at two tertiary care centres in Sri Lanka.

Methods: A group of patients with urothelial bladder cancer, presenting for the first time for definitive treatment, were prospectively enrolled from 2013 to 2017.

Results: There were sixty-six patients, with median age of 65 years and male to female ratio of 7:1. Histopathologically pTa 24%, pT1 47% and pT2 29%. Of the pT1 tumours 61% were low grade (LG). The majority (71%) of non-muscle invasive bladder cancer (NMIBC) patients underwent transurethral resection of bladder tumour only.

For the entire cohort the 5-year overall survival was 59% and cancer specific survival (CSS) was 65%. CSS in NMIBC was 75% and 30% in muscle invasive bladder cancer (MIBC). The 5-year female CSS (22%) was significantly lower than in males (71%).

Conclusions: Our cohort has a high male to female ratio. The percentage of MIBC was lower than reported in previous Sri Lankan studies. Of the pT1 tumours there is a higher percentage of pT1 LG patients in comparison to Western reports. There is low utilisation of intravesical mitomycin / bacillus Calmette-Guérin (BCG) in the treatment of NMIBC. The 5-year CSS in the Sri Lankan (lower middle-income economy) cohort lies between the values of high-income economies and upper middle-income economies in Asia. The reasons for poor CSS among Sri Lankan women with bladder cancer needs to be further investigated.

Introduction

Bladder cancer (BC) is the 12th most common cancer worldwide with the 14th highest mortality[1]. It had the 9th highest incidence among Sri Lankan males in 2019 [2]. Over 90% of bladder cancers are urothelial cancers derived from the urothelium. In Western statistics 75-80% [3] of the urothelial cancers are non muscle-invasive bladder cancers (NMIBC) and these patients have a much better prognosis compared to the muscle-invasive bladder cancers (MIBC). This contrasts with the largest cohort of bladder cancer patients from Sri Lanka in 1993-2000 [4] which showed MIBC at presentation in almost 50%. Subsequent studies have shown a lesser percentage, ranging from 23-35%, of MIBC among the urothelial cancers in Sri Lanka [7-10] [5-8].

Worldwide bladder cancer statistics report a 4:1 male to female ratio [9]. The Sri Lankan statistics vary from 3:1 to 9:1[8]. While the incidence of urothelial cancer in women is less compared to men, they seem to fair worse especially in the first 3-4 years following diagnosis [10]. In a Sri Lankan study of 55 women, a disproportionately higher incidence of MIBC (45%) was seen [11].

Statistics indicate a 77% 5 year relative/net survival among all stages of bladder cancer patients in the USA [12] and 53% in UK [13]. There is sparse published survival statistics of bladder cancer patients in Sri Lanka. This study was conducted to describe the demographic profiles and survival in BC patients at two institutions in Sri Lanka.

Methodology

A group of patients with urothelial bladder cancer were prospectively enrolled, by convenient sampling, from

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June 2013 to January 2017. An information leaflet was provided and written informed consent obtained. The inclusion criteria were Sri Lankan males or females ≥18 years; first presentation or intervention for a suspected bladder tumour; a clinical and, imaging and / or endoscopic diagnosis of bladder tumour and ability to provide written informed consent. Patients who had received previous or neoadjuvant treatment for bladder tumour; irradiation of the pelvis for other diseases; and those with non-urothelial bladder carcinomas were excluded from the study. Demographic, histopathological, management and survival data were collected prospectively from June 2013 to November 2020.

Kaplan-Meier survival analysis was used to analyse the cancer specific survival (CSS) and overall survival (OS). Survival rates were compared using Kaplan-Meier estimate curves with log-rank test. Significance was set at a probability value of less than 0.05. Statistical package R was used for the computations. (Version 3.6.0; R Foundation). Ethical approval was obtained from the Ethical Review Committee of the Faculty of Medicine, University of Colombo.

Results

Study group characteristics

Sixty-six patients, with median (interquartile range (IQR)) age of 65 (IQR: 57.8-69.3) years and males 88% (58) and females 12% (8) were included. The male to female ratio was 7.3:1. Pathological assessment showed 71% (47/66) to be NMIBC and 29% (19/66) MIBC (Table 1).

Table 1. Histological staging and grading of study sample

Stage	*Number (%)*
pTa	24%(16)
pT1	47%(31)
• Low grade	61%(19)
• High grade	39%(12)
pT2	29%(19)

Treatment

The majority 27/38 (71%) of NMIBC patients underwent transurethral resection of bladder tumour (TURBT) only. Only 5 patients (13%) had mitomycin or Bacillus Calmette-Guérin (BCG) intravesical therapy following surgery. Of the MIBC patients, one had undergone radical cystectomy following neo-adjuvant chemotherapy while (7/13) had TURBT followed by chemo-irradiation. The rest (5/13) had undergone only TURBT (Supplementary data 1).

Survival analysis of the entire cohort

Follow-up was available in 74% (n=49) with a median follow up time of 38 (IQR: 17 - 64) months. The 5-year OS for the entire cohort was 58.9% (95%CI: 46.0%-75.3%). The 5-year CSS for the entire cohort was 64.9 (51.7%-81.5%), which was 75.1% (61.4%-91.9%) in NMIBC and 29.7% (95%CI: 10.0-88.0%) in MIBC (Table 2 and Figure 1 and 2).

Survival analysis of pT1 patients

The pT1 LG showed better OS and CSS over HG (P=0.003 and P=0.01 respectively). The overall pT1 progression-free survival (PFS) was 60.9% (43.9% - 84.5%). The PFS in pT1 LG was higher than pT1 HG (P value < 0.001) where the 5-year PFS for pT1 LG was 85.7% (69.2% - 100.0%) and for pT1 HG 22.2% (6.5% -75.4%) (Supplementary data 2).

Table 2. Five-year survival in urothelial cancer

	Total	*Deaths by 2020*	*Lost to follow up by 2020*	*Total alive at 2020*	*Overall survival - 5 year*	*Cancer specific survival - 5 year*
pTa LG	16	4	3	9	75.2% (54.8%-100%)	82.1% (62.1%-100%)
pT1 LG	19	2	5	12	92.9% (80.3%-100%)	100% (100%-100%)
pT1 HG	12	6	3	3	29.6% (10.0%-87.5%)	29.6% (10.0%-87.5%)
pTa + pT1 (NMIBC)	47	11	11	25	70.4% (56.4%-87.8%)	75.1% (61.4%-91.9%)
pT2 HG (MIBC)	19	10	6	3	19.2% (5.8%-63.7%)	29.7% (10.0%-88.0%)

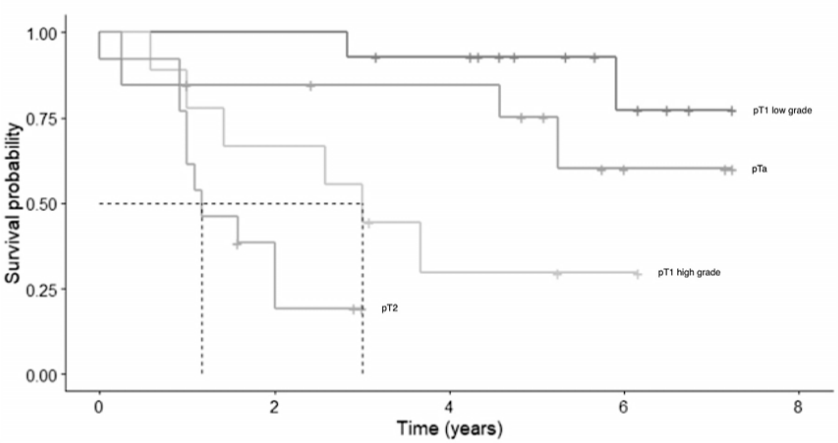


Figure 1. **Overall survival among bladder cancer patients with respect to the pathological stages.**

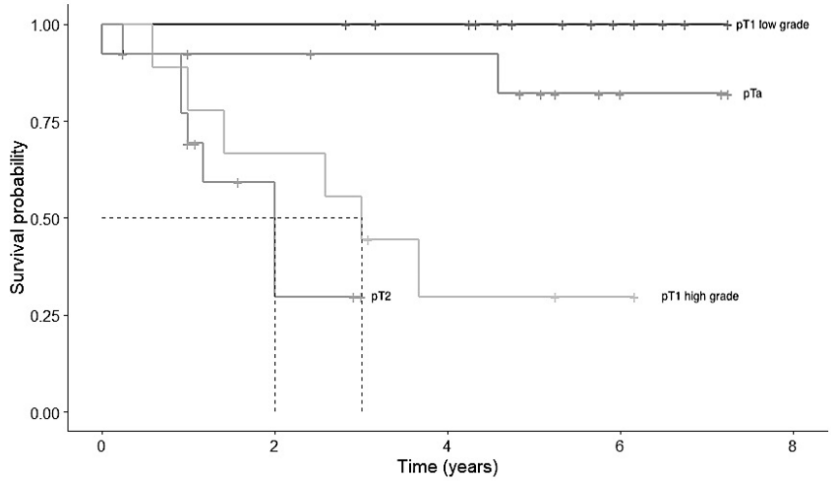


Figure 2. **Cancer specific survival among bladder cancer patients with respect to the pathological stages.**

Survival analysis in females versus males

The 5-year OS in females was lower 22.2% (4.1% - 100%) than in males 61.2% (47.9% - 78.4%), however, this was not statistically significant (P=0.2). The 5-year female CSS was significantly lower than in males 22.2% (4.1% - 100%) versus 71.0% (57.6% - 87.5%) respectively, P = 0.03 (Figure 4).

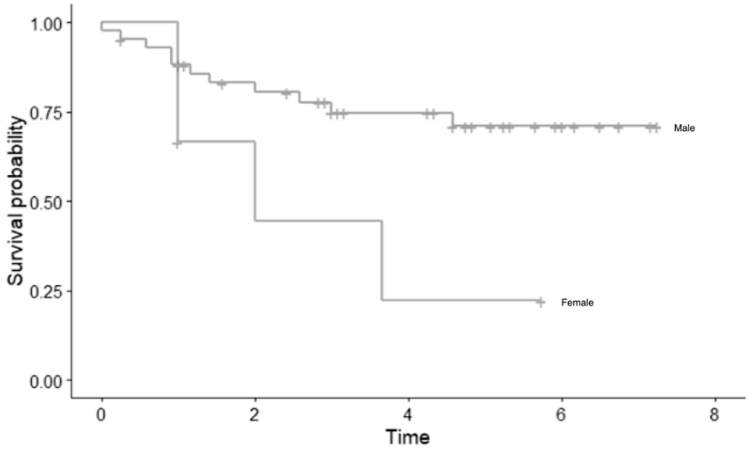


Figure 3. **Five-year CSS in males versus females.**

Supplementary files for *CMJ* article

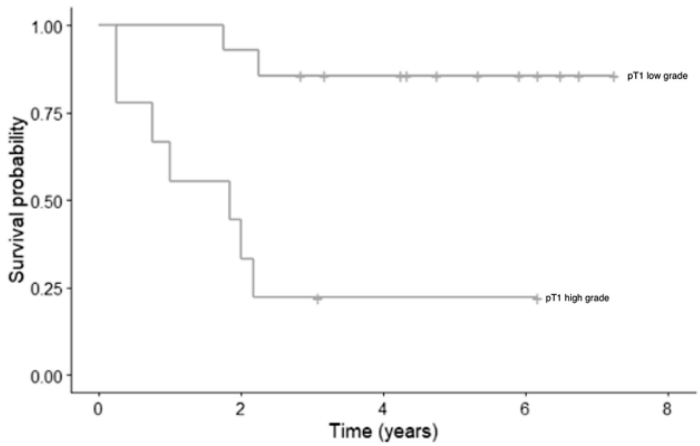
Supplementary data 1: Table summarises the treatments undergone following transurethral resection of bladder tumour (TURBT) by the cohort of patients.

Treatment modality	**pTa LG** [16]	**pT1 LG** [19]	**pT1 HG** [12]	**pT2 HG** [19]
Only TURBT	13	9	5	5
Mitomycin C (MMC) x 6 doses	1	4		
Bacillus Calmette-Guérin (BCG) x 12 doses		1		
Chemotherapy (CTX) only				1
CTX and DxRT (radiotherapy)			3[#]	4
CTX and DxRT stopped halfway due to side effects				1
Recommended CTX and DxRT – refused or not fit			1[†]	1
Radical cystectomy				1[¥]
Developed recurrence – refused further treatment		1		
Lost for follow up	2	4	3	6

Notes for the table:
(3 patients)
1. Progressed to MIBC. Died at 7 months after TURBT with brain metastasis
2. Progressed to MIBC and received CTX and DxRT. Developed recurrence and awaiting patient decision regarding radical surgery.
3. Progressed to MIBC and received CTX and DxRT. Developed metastases and died

† Progressed to MIBC - refused further treatment.
¥ Received neo-adjuvant CTX

Supplementary data 2: Progression free survival in pT1



	Total	*Deaths by 2020*	*Lost to follow up by 2020*	*Total alive at 2020*	*Overall survival - 5 year*	*Cancer specific survival - 5 year*
pTa LG	16	4	3	9	75.2% (54.8%-100%)	82.1% (62.1%-100%)
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pT2 HG (MIBC)	19	10	6	3	19.2% (5.8%-63.7%)	29.7% (10.0%-88.0%)

Discussion

The median age of our cohort at diagnosis was 64.5 years. It is 73 years in the USA[12] and 60 years in India[14]. Only 8% of our cohort were over 80 years at the time of diagnosis while in the UK it was 34% in 2012 [15]. The higher proportion of cancer patients in older ages in the UK data has been attributed in part to the effects of an ageing population. Another factor which may have contributed to a higher incidence of bladder cancer in older patients is the lower levels of industrial exposure and smoking prevalence in the recent past compared to the post world war II period [15]. In keeping with the reduced exposure to potential carcinogenic agents, the European age standardised bladder cancer incidence rates have been falling in the UK by 42% between 1993-1995 and 2015-2017 [13]. The effects of industrial safety measures and antismoking campaigns, or the lack of it, on bladder cancer incidence in Sri Lanka needs to be monitored by future studies.

This cohort showed a high male preponderance where male to female ratio was 7.3 to 1 as previously shown in SL, where it ranged from 3:1 to 9:1 [8]. However, worldwide statistics for bladder cancer report a 4 to 1 male to female ratio [9]. The lower female prevalence may be due to the low prevalence of daily tobacco smoking, the strongest identified risk factor for bladder cancer, among Sri Lankan women (0.1%) compared to men (19.9%) [16]. The male to female ratios are also skewed in Indian studies that show the ratios to be 8.6:1 and 8.9:1. In the US the prevalence of current cigarette smoking has reduced from 42% in 1965 to 14% in 2018 [17]. In SL the adult current smokers were 18.3% in 2005-2006 while in 2019 total current smokers were 15% [18] showing marginal improvements in the risk behaviour situation in Sri Lanka.

The percentage of MIBC was 29% in our study which supports a falling prevalence of MIBC amongst Sri Lankans, where this was 48% during 1993-2000 period, and it is approximately 23-35% in the recent times [5-8]. However, our percentages are high compared to Europe where it is 20-25% [19]. The muscle invasive tumours, when compared with non muscle invasive tumours, have a much graver prognosis with approximately 55% mortality at 5 years [20, 21].

Asian countries such as Japan [22], China [23] and India [14] have reported MIBC proportions of 20-25% similar to western statistics. However, studies in Indonesia [24, 25] and Malaysia [26] show a higher preponderance of MIBC, similar to the early statistics in Sri Lanka. In the Indonesian studies (1995-2005 and 2008-2012) the ratio of NMIBC to MIBC was 27.1-37.4% to 62.6-72.9%, while in Malaysia (2005-2009) the ratio was 58.6% to 41.4%. Egypt also demonstrates a high rate of muscle invasive disease, with 57-59% of urothelial cancers and 87% of squamous cancers presenting with invasive disease [27].

The majority 27/38 (71%) of NMIBC patients underwent transurethral resection of bladder tumour only. The standard guidelines recommend intravesical mitomycin and / or BCG as follow up management to prevent recurrences and progression especially in pT1 HG patients [19] The poor availability of BCG treatment within the government sector hospitals has been also highlighted in a previous study by Goonewardena et al [28].

In the MIBC group in our cohort, 7/13 (54%) underwent definitive treatment following TURBT, with one patient undergoing radical cystectomy, which could have potentially biased the survival results. While radical cystectomy remains the "gold standard" for fit enough and consenting patients, chemo-irradiation is a strong contender and evidence indicates that similar survival outcomes could be obtained in the appropriately selected patient [21]. The reasons why radical cystectomy is less utilised in the management of bladder cancer could be cultural in nature due to disruption of body image; inadequate theatre time and overloading of urology units with patient burden, and other reasons which need to be evaluated by further studies. A study from neighbouring India (Mumbai) showed that in a cohort of 150 patients, 67 (44.66%) underwent a definitive treatment, of which 86.5% of the patients underwent radical cystectomy with pelvic lymph node dissection [29]. In the US in a study of 3262 patients from the SEER database, 21% of patients underwent radical cystectomy, 28% had chemotherapy and/or radiation and 51% had surveillance [30].

We managed to record follow-up data in 74% of patients. Previous studies have also shown a high loss to follow up proportion in urological cancer patients e.g. 21.7% after the initial TURBT on T1 HG patients [28].

Comparing survival statistics can be difficult due to the variations in tumour stage reporting in bladder cancer. Management decisions are more linked to the TNM staging with pTa vs pT1 vs ≥ pT2 being the defining broad categories; non muscle invasive versus muscle invasive is a defining division in prognosis and survival. Also several survival rates are used in analysing survival compounding these difficulties. These are e.g. overall survival, net survival rates or relative survival or cause-specific survival/disease-specific survival, median survival, five-year survival, disease free survival, recurrence free survival, metastasis free survival etc.

The 5-year relative survival (measure of cancer survival in the absence of other causes of death) during the period 1990 and 2001 for urinary bladder cancer in registries in Mumbai and in Chennai was 42% (Mumbai) and 32.3% (Chennai) respectively [31]. In Hong Kong, Singapore, South Korea and urban mainland China (high-income economies) the 5-year relative survival for bladder cancer ranges from 71-78%. In Thailand (upper middle-income economy) it ranges from 46-60% and in India (lower middle-income economy) from 10-48%. The comparable CSS in the Sri Lankan (lower middle-income economy) cohort lies at 65%, and lies between the values of high-

income economies and upper middle-income economies. However it must be noted that relative survival is under reported in population databases [32].

An Indonesian (upper middle-income economy) study from a national tertiary referral hospital in 2010 reported on 105 patients (out of 254; FU available in 41.4%). The 5-year OS for all bladder urothelial cancers was 27.6% [24]. The comparable SL OS was 58.9% in our cohort.

The 5-year relative survival for urinary bladder cancer in the USA as per the American Cancer Society SEER databases between 2009 and 2015 for all stages is 77% [12]. In the UK the age standardised 5 year net survival at 5 years is 52% during 2013-2017 [13]. In Europe the age standardised 5 year relative survival was 68% (95%CI: 68-69) for the period 1997-2007. However the registration of non-invasive (Ta/Tis) bladder cancer is limited and therefore the actual survival for all stages of bladder cancer are probably higher [33].

The survival of MIBC patients is known to be far worse in comparison to NMIBCs. In 2010 Indonesia's national tertiary referral hospital reported that in a cohort of 105 patients (out of 254; FU available in 41.4%) the 5-year OS for NMIBC was 53.8% and MIBC was 19% [24]. In our cohort the 5 year OS for NMIBC was 70.4% and MIBC it was 19.2%. A study of 150 MIBC patients (Stage II and III) from Indonesia, showed an actuarial 5-year overall survival ranging from 8.3% to 50%, (radical cystectomy, 50%; radiotherapy, 22.7%; and TURBT only, 8.3%) [34] In the UK (2013-2017) the 5 year age adjusted net survival for stage I disease is 75.9% (CI 74.3-77.4) and ranges from 10.7-45.7% for Stage II-IV (MIBC) patients [35].

The overall and cancer specific survival was better in the pT1 LG compared to the pT1 HG group in our study. Similarly the progression free survival (PFS) was also significantly better in the pT1 LG patients when compared with HG patients (85.7% versus 22.2%). This low PFS in HG patients was also identified in a previous study in SL by Goonewardena et al at 18.5% [28]. This compares poorly with other international studies which document a higher PFS rate in pT1 HG patients. In a study looking at 78 patients with pT1 HG from a single institute in Israel treated with intravesical BCG the 5 year progression-free survival rate was 82% [36]. None of the pT1 HG patients in the SL studies had undergone BCG therapy. This highlights the importance of further increasing BCG treatment availability within our government hospital sector to improve the survival in our patients.

In most countries bladder cancer survival is worse in women, which is against the general trend in cancer statistics [15]. In large studies the relative survival for men compared to women was 68% (95%CI: 68-69) versus 66% (95%CI: 66-67) in Europe [33] and 58% compared to 47% in the UK [15]. While the incidence of urothelial cancer in women is less compared to men, they seem to fair worse with less favourable histopathologies, and risks of death especially in the first 3-4 years following diagnosis [10]. In a Sri Lankan study of 55 women a disproportionately higher incidence of muscle invasiveness (45%) was seen [11] which infers a worse prognosis for those individuals. The overall survival difference in men versus women in our cohort was not statistically significant, however the CSS showed a statistically worse outcome in women. This needs further investigation.

There are several limitations in this study. This study included only 66 patients resulting in low power to evaluate statistical significance, and wider 95% CIs. Patient recruitment was non-consecutive due to logistical difficulties. However, our cohort did not reveal major differences in demographic or histopathological details in comparison with other Sri Lankan studies. The 5-year follow up was available in 74% of patients which is again comparable to other cancer outcome studies in Sri Lanka, a challenge to be overcome in future studies.

Conclusions

Our cohort of urothelial bladder cancers has a high male to female ratio in comparison to Western reports. This is similar to regional Asian data. The median age at presentation is lower in comparison to Western reports. Percentage of MIBC remains high compared to western statistics, but the percentage is decreasing when compared with previous Sri Lankan studies. The cohort showed a low utilisation of intravesical MMC/BCG in the treatment of NMIBC in comparison to western literature, despite evidence based advantages. The low OS, CSS and PFS for pT1 HG highlights the importance of further increasing BCG treatment availability. The 5-year CSS in the Sri Lankan (lower middle-income economy) cohort lies between the values of high-income economies and upper middle-income economies in Asia. The reasons for poor CSS among Sri Lankan women with bladder cancer needs to be further investigated.

Declaration

Ethics approval and consent to participate

Ethical approval was obtained from the Ethical Review Committee of the Faculty of Medicine, University of Colombo. (EC-12-088 / 19th October, 2012).

The study was conducted in accordance with the ethical standards of the relevant institutional ethics committee and the Helsinki Declaration of 1975, as revised in 2000.

All study participants have granted their consent as per the institutional review protocols.

The submission has not been previously published, nor is it before another journal for consideration

Consent for publication

The manuscript does not contain data from any individual person.

All authors have granted consent for publication of the final paper

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to the information being private and confidential, but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that there is no conflict of interest regarding the publication of this article.

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Authors' contributions

Conception or design of the work was done by APM, RWJ, VHWD. Data collection was carried out by APM, SASG, NDP, AA and data analysis and interpretation by APM, DE, MDSL. Initial drafting of the article was by APM and DE. Critical revision and final approval of the version to be published was by all authors.

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