

Bladder cancer in women: a Sri Lankan study

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Abstract

Introduction Bladder cancer (BC) is the ninth commonest cancer globally, and ranks 19th among women. The literature on BC in women is sparse, and the knowledge on the variations of tumour characteristics in South Asian female BC is limited. The objective of this study was to describe the clinicopathological characteristics of BC in women and compare them with male BC.

Methods A retrospective analysis of all female patients with histopathologically proven newly diagnosed primary BC from January 2007 to January 2017 was done at the Urology Unit, National Hospital of Sri Lanka, and the findings were compared with men with BC during the same period.

Results There were 314 patients with primary BC, of which 55 (17.5%) were women, with a male:female ratio of 4.7:1. Only 70.9% of women had haematuria at presentation. Forty-four women (80%) had urothelial bladder cancers (UBC). The mean age of women with UBC was 67±SD13.2 years, and for non-urothelial bladder cancers (NUBC) was 62.5±SD 12.7 years. NUBC in women accounted for a disproportionately higher percentage in comparison to men (20% vs.5.4%, p<0.001). Of the UBCs, muscle invasive BC accounted for 45.5% (20/44) in women as opposed to 33.5% (82/245) in men. Women had a significantly higher proportion of solid tumours (40%vs.22.8%, p=0.008) compared to men.

Conclusion Primary BC in women has a significantly higher proportion of NUBC and muscle invasive UBC, which are more aggressive cancers, compared to men. Furthermore, the lack of haematuria in >25%, and higher incidental diagnosis, with inherently thinner bladder wall, makes primary BC in women more likely to present late, in a more advanced state.

Introduction

Bladder cancer is one of the most common malignancies worldwide [1]. It is the ninth most common cause of cancer for both sexes combined. Bladder cancer is relatively more common in more developed regions, where around 60% of all incident cases occur [1]. Urothelial bladder cancer (UBC) accounts for >90% of primary BC in Sri Lanka with a male preponderance (male:female ratio of 6:1) [2]. While men are at a higher risk than women for developing UBC, women present with more advanced disease [3, 4].

Gender specific variations in the incidence, diagnosis and survival have been reported in several malignancies, such as lung, colorectal and head and neck cancer. These variations were found to be significant and thus have resulted in implementation of gender-specific recommendations in clinical oncology [5]. Similarly, gender specific variations were also described in bladder cancer. Compared with women, men are at a 3.5-fold higher risk of developing bladder cancer. In Sri Lanka, it is reported to be much higher, with a male to female ratio of 5.6 : 1 [1, 2]. Furthermore, a 25% faster increase in incidence was noted in men compared to women during the past decade [6]. Despite the commoner occurrence and increasing incidence in men, there is increasing evidence to suggest that women present with more aggressive cancers and advanced disease stages, and thus experience worse outcomes [7]. In most cancers of the head and neck, oesophagus, stomach, liver and pancreas, the risk of death for women is significantly lower. For bladder cancer, the risk of death is significantly greater for women [8].

Although it is well established that men are more greatly affected by bladder cancer, there is limited data in

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terms of other biological tumour differences in women including grade, stage, location, and recurrence compared with men, particularly in the South Asian region. This retrospective analysis was aimed at describing the biological tumour characteristics in females while eliciting the differences compared with male bladder cancers

Methods

This is a retrospective analysis. All patients with newly diagnosed bladder cancer with histological confirmation at one of two Urology Units of National Hospital of Sri Lanka, Colombo, between January 2007 and January 2017 (over 10 year period) were analysed.

All patients underwent transurethral resection of the bladder tumour (TURBT) which is the standard procedure in the initial diagnosis and treatment of bladder cancer. In cases of papillary tumours and superficial solid tumours, every attempt was taken to perform a complete resection of the tumour during the first surgery. In cases of invasive solid tumours, the treatment was generous debulking of the exophytic component followed by radical therapy which includes chemoradiation or cystectomy. Data were collected at the time of hospital discharge/clinic visit on a separate file for each patient, rendering accurate documentation and easy retrieval of details. The clinical, cystoscopy and histopathological findings, such as tumour type, staging, grading and location were entered into the database. Tumours other than primary bladder cancers were excluded after initial evaluation. Pathological grading was assessed according to the World Health Organisation (WHO) and International Society of Urological Pathology (ISUP) classification 2004 [9]. Tumours were staged according to TNM classification: pTa = non-invasive papillary carcinomas, pT1 = tumours

that invade sub-epithelial connective tissues and pT2 = muscle-invasive tumours [10].

Data were analysed using SPSS® software version 17 and were expressed in terms of frequency and percentages. The mean with standard deviation (SD) was calculated for continuous variables, whereas frequencies and percentages were used for discrete data. Comparisons between groups were conducted by using the t-test or chi-square test as appropriate. A $p < 0.05$ was considered statistically significant. Approval for the study was obtained from the Ethics Committee of National Hospital of Sri Lanka.

Results

There were 314 patients with primary BC of which 55 (17.5%) were women with a male:female ratio of 4.7:1. Forty-four women (80%) had urothelial bladder cancers (UBC). Non-urothelial bladder cancers (NUBC) in women accounted for a disproportionately higher percentage in comparison to men (20% vs. 5.4%, $p < 0.001$). The mean age of women with UBC was $67 \pm \text{SD } 13.2$ years and for NUBC was $62.5 \pm \text{SD } 12.7$ years. Overall, female patients were diagnosed at a mean age of $65.2 \pm \text{SD } 12.6$ years which was comparable with males ($65.2 \pm \text{SD } 11.1$ years).

Considerable differences in the clinical presentation between genders were noted. Visible haematuria was the commonest presentation seen in females (70.9%, $n=39$). However, the proportion of females who presented with haematuria were significantly lower compared with males (70.9% vs. 89.6%, $p < 0.001$). The mean duration of haematuria was 3.6 months which was greater than that of males. However, the difference was not statistically significant. The proportion of females with incidental finding of bladder cancer was significantly higher compared with males (20% vs. 8.9%, $p=0.016$) Table 1.

Table 1. Comparison of clinical parameters between the two sexes

	Male		Female		Odds ratio (95% CI)	p value
	N/ Mean	%/ SD	N/ Mean	%/ SD		
Age	65.21 \pm SD 11.12	65.20 \pm SD 12.59	-	-		1.00
Haematuria	232	89.6	39	70.9	3.5 (1.7-7.1)	<0.001
Duration of haematuria	2.35 \pm SD 4.04	3.63 \pm SD 6.53	-	-		0.10
Supra pubic pain	22	8.5	5	9.1	0.9 (0.3-2.6)	0.886
Loin pain	14	5.4	2	3.6	1.5 (0.3-6.9)	0.588
Incidental	23	8.9	11	20.0	0.4 (0.2-0.85)	0.016

CI: Confidence interval

Around 58% of females had tumours >3cm in diameter. Around 82% ($n=45$) of tumours in females were solitary tumours whereas in males, 67.2% were solitary tumours ($p=0.032$). In females, the majority were papillary tumours (47.3%), followed by solid tumours (40%) and papillary with solid components (12.7%). Compared with males, females had a significantly higher proportion of solid tumours (males vs. females: 22.8% vs. 40%, $p=0.008$) (Table 2).

Table 2. Comparison of cystoscopy findings in the two sexes

		Male		Female		Odds ratio (95% CI)	p value
		N	%	N	%		
Size	<3cm	93	35.9	23	41.8	0.8 (0.4-1.4)	0.409
	>3cm	166	64.1	32	58.2		
Multiplicity	1	174	67.2	45	81.8	-	0.197
	2	40	15.4	5	9.1		
	3	21	8.1	2	3.6		
	>3	24	9.3	3	5.5		
Focality	Solitary	174	67.2	45	81.8	0.5(0.2-0.9)	0.032
	Multiple	85	32.8	10	18.2		
Tumour morphology	Papillary	139	53.7	26	47.3	-	0.018
	Solid	59	22.8	22	40.0		
	Papillary with solid components	61	23.6	7	12.7		
Solid vs. Papillary	Solid	59	22.8	22	40.0	0.4 (0.2-0.8)	0.008
	Papillary	200	77.2	33	60.0		

CI: Confidence interval

Females had significantly higher muscle-invasive tumors (n=29, 52.7%) compared with males (n=88, 34.0%) (p=0.009). This was also the case in the UBC subgroup where females had higher proportion of muscle invasive tumours (n=20, 45.5%) compared with males (n=82, 33.5%), however it was not statistically significant (p=0.13). The proportion of lymphovascular invasion and pT1 high grade tumours were comparable in both sexes (Table 3).

Table 3. Comparison of histopathological features between the two sexes

		Male		Female		Odds ratio (95% CI)	p value
		N	%	N	%		
Tumour type	UBC	245	94.6	44	80.0	4.4 (1.9-10.3)	<0.001
	NUBC	14	5.4	11	20.0		
Tumour stage (All tumours)	pTa	77	29.7	11	20.0	-	0.032
	pT1	94	36.3	15	27.3		
	pT2	88	34.0	29	52.7		
Muscle invasiveness (All tumours)	MIBC	88	34.0	29	52.7	0.5 (0.3-0.8)	0.009
	NMIBC	171	66.0	26	47.3		
Presence of LVI (All tumours)	17	6.6	3	5.5	1.2 (0.3-4.3)	0.76	
Tumour Stage (UBC)	pTa	77	31.4	10	22.7	-	0.276
	pT1	86	35.1	14	31.8		
	pT2	83	33.5	20	45.5		
Muscle invasiveness (UBC)	MIBC	82	33.5	20	45.5	0.6 (0.3-1.2)	0.13
	NMIBC	163	66.5	24	54.5		
Tumour Grade (UBC)	High Grade	131	53.5	25	56.8	0.9 (0.5-1.7)	0.68
	Low Grade	114	46.5	19	43.2		
pT1HG (Urothelial NMIBC)		48	29.4	7	29.2	1.0 (0.4-2.6)	0.977
Presence of LVI (UBC)		17	6.9	2	4.5	1.6 (0.4-7.0)	0.555

CI: Confidence interval; UBC: Urothelial bladder cancer; NUBC: Non-urothelial bladder cancer; LVI: Lymphovascular invasion; MIBC: Muscle invasive bladder cancer; NMIBC: Non muscle invasive bladder cancer

Discussion

Bladder cancer is the ninth commonest malignancy worldwide and BC ranks nineteenth in the female [11]. In a previous study, UBC accounted for 93.4% of primary BC in Sri Lanka [2]. In our cohort of patients with primary BC there was a male preponderance (male: female ratio of 4.7:1) similar to those in the West. There were differences in the clinical and histopathological characteristics of bladder cancer between the genders, where a higher proportion of female bladder cancers were NUBC, incidentally detected, solid and muscle invasive compared with males. NUBC in women constituted nearly 20% whereas in men it represented only 5.5% of patients. NUBC is considered a more aggressive form of BC compared with the more common UBC [12].

In our study, the mean age of women with UBC and NUBC were 67 and 62.5 years respectively. In a 7-year study of BC from Multan, Pakistan, there were 44 women of 204 patients with a median age of 55 years with the majority (88%) presenting with haematuria. All women had UBC with 33 of 44 (75%) having MIBC (T2-T4 disease). Furthermore, all women were non-smokers [13].

Visible haematuria was the commonest initial presentation encountered in 71% of women in the present study. Women are more likely to be diagnosed with urinary tract infection and receive 3 or more courses of antibiotics with longer delays between presentation with haematuria and diagnosis of BC than men [14]. Smoking was known to account for 50% and 31% of BCs in men and women respectively [15]. In a previous study from our urology unit, all women were never smokers [2].

The increase in incidence of bladder cancer in males could be explained by the differences in the exposure to risk factors. Cigarette smoking is the most important risk factor for bladder cancer [16, 17]. Secondly, occupational exposure in several industries including aromatic amines, cable, rubber and dyes are also important risk factors [18, 19]. The higher exposure of these risks factors in males could explain the increased incidence, however this does not explain the reason for the aggressive tumours that occur in female. Furthermore, some authors believe that the observed increase in incidence in males cannot be completely explained by the higher exposure to risk factors in males compared with females [20]. This is because the increased male preponderance remained similar, although the smoking habits and job exposure became quite similar among both sexes over time in industrialised countries [21]. Other factors such as anatomic or hormonal differences, and delay in presentation and diagnoses, may also affect the incidence and clinical behaviour between the gender [22, 23]. Thus further prospective studies are needed to study these variations in detail.

Studies have shown that a significantly greater proportion of women are diagnosed at an advanced stage

compared with men [24, 25]. A large population based study of 5259 patients showed that women were more likely to have muscle-invasive disease at the time of cystectomy [26]. Analysis of all primary UBC patients reported to Swedish National Registry from 1997 to 2011 (30,310 patients) showed a greater proportion of women than men had muscle-invasive disease (stage T2-T4) at presentation (28.6% vs 24.9%, $p < 0.001$) [27]. In the present study, although the age at presentation was similar for both sexes, a significantly higher proportion of bladder cancers were muscle invasive in females compared with males (53% vs. 34%, $p = 0.009$). Analysis of UBC subset also revealed a higher proportion of muscle invasive disease in females however it was not statistically significant (46% vs. 34%, $p = 0.14$). Furthermore in a review paper, females were found to have more advanced tumors at the time of diagnosis [28]. Importantly in our study, a significantly higher proportion of females were incidentally diagnosed while evaluating for a non-related symptom (20% vs. 9%, $p = 0.016$). This may account for the delayed presentation or advanced disease at diagnosis.

There are several limitations in this study. We described the descriptive data for treated patients retrospectively and thus we could not perform further evaluation of the causes and risk factors of bladder cancer. A considerably high proportion were lost to follow up and thus, meaningful analysis related to outcome and survival between the two genders was not possible.

Conclusions

Primary BC in Sri Lankan women is unique. They have a significantly higher proportion of patients with NUBC and muscle invasive UBC-biologically more aggressive states, compared to men. Many factors may be responsible for these gender differences, including exogenous such as exposure to chemical carcinogens and smoking and endogenous such as hormonal factors. Thus, further prospective studies are needed to study this in detail.

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None.

Data availability

All data generated and analyzed in this publication are from our database on bladder cancer prospectively maintained since the year 2002 electronically.

Conflict of interests

The authors declare that they have no competing interests.

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