# PRESENTING PATTERN AND TREATMENT MODALITIES OF PROSTATE CANCER IN NICRH

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**Abstract**

***Objective:*** *The aim was to describe the clinicopathological presentation of prostate cancer and the treatment modality in patients seen in Uro-oncology department of National Institute of Cancer Research & Hospital (NICRH), Bangladesh.*

***Methods:*** *Data were collected prospectively from all patients with diagnosed prostate cancer and managed in Uro-oncology department of NICRH from January 2016 to December 2017. Patient's age, clinical presentation, prostate specific antigen(PSA) level, mode of diagnosis, Gleason sum score, stage of the disease at presentation and modality of treatment were recorded and analyzed.*

***Results:*** *There were 407 cases of histologically proven prostate cancer. Mean patient age was 69 years. About 87% presented as diagnosed prostate cancer. Twenty one(5%) patient presented with features of metastasis with unknown primary , we confirmed after prostate biopsy. About 77% of patients had a serum PSA above 20 ng/ml. Gleason sum score was 8 or more in 46% of patients. Metastases were found at the time of presentation in 85% of patients. Ten (2.5%) patients underwent radical radiotherapy, while two patients had radical prostatectomy. Most (68%) of the 347 patients who required androgen deprivation therapy had surgical orchiectomy.*

***Conclusion:*** *Bangladesh appear to be having a low incidence of prostate cancer, but a larger proportion of advanced and high grade cancers in comparison to the UK and USA. Although genetic differences may exist, a dietary or an environmental factor is more likely to be the cause for these changes. The protective effect of this factor appears to wane as South Asians emigrate and live in UK and USA.*

***Key words:*** *Clinical presentation, Treatment modality, Prostate cancer, South Asia*

*Bangladesh J. Urol. 2018; 21(2): 56-61*

## Introduction

Prostate cancer is the most common noncutaneous cancer detected among American men. More than 200,000 cases are detected annually. Approximately 30,000 men die of the disease annually- more than any other tumor except lung cancer[1]. Despite being a global disease, significant variations in the pattern of incidence and mortality by region and race have been observed. In USA, African American men are at the highest risk of developing prostate cancer experiencing 59% higher incidence rates than whites, with an annual incidence of 178/100,000[2,3]. Among Asian Americans the incidence is 88.3/100,000. It is 49.5/100,000 among South Asians residing in the UK. Although the leading cancer in South Asian men in USA is prostate, the incidence of prostate cancer in native Indians is 9/1,000,000, which is 15 fold less than their counterparts residing in the USA [4]. These variations may be due to genetics, culture, diet, and other environmental factors.

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**Received:** 9 August 2017 **Accepted:** 05 March 2018

According to the cancer registry report maintained by the Department of Cancer Epidemiology, National Cancer Institute of Bangladesh, in 2010 prostate cancer was the ninth commonest cancer among geriatric men in Bangladesh with 120(2.2%) new cases reported [5]. Accurate prostate cancer estimates in less developed countries are often unknown due to incomplete case reporting to tumor registries[6].

Most metastatic prostate cancers can be managed by surgical orchiectomy as the mode of androgen deprivation therapy (ADT) and hence these patients do not seek oncological services and escape being recorded in cancer registries. Stigma related to cancer in South Asian countries make matters worse as patients and their families shun dedicated oncology services. There are no electronic data storage systems in Bangladeshi hospitals for gathering patient data; hence retrospective studies based on cancer registries are bound to be flawed. Therefore, the true incidence of prostate cancer in Bangladesh is probably underestimated. Under these circumstances hospital based prospectively collected data are useful to identify morbidity patterns and complement the information available from cancer registries.

Data related to characteristics and morbidity pattern of Bangladeshi patients with prostate cancer are sparse[5]. Hence, we conducted a prospective hospital based cohort study over a period of 2 years from January, 2016 to December, 2017 among diagnosed patients of prostate cancer in Uro-oncology department of the National Cancer Institute of Bangladesh. The objectives of the study were to describe the clinicopathological characteristics of prostate cancer and the treatment modality in a cohort of native Bangladeshi patients seen in Uro-oncology department of NICRH in Bangladesh.

## Patients & Methods

Data were collected prospectively from all patients with diagnosed prostate cancer and managed in the Uro-oncology department of NICRH over a period of 2 years (January 1, 2016-December31, 2017). Data were recorded in individual files maintained in the Uro-oncology dept. updated as the patient follow up continued in the outpatient clinic. Every patient was given information regarding their disease in order to educate them regarding the importance of regular follow up. All patients with histologically proven carcinoma of prostate were included in the study.

Those with diagnosed prostate cancer referred from other hospital,those who had clinically suspicious malignant prostate(features of metastasis with unknown primary) with little or no bladder outflow obstruction underwent trans rectal prostate biopsy, those with raised prostate specific antigen (PSA) only or with abnormal digital rectal examination underwent trans rectal core biopsy of prostate were included in this study. Once histologically proven to have prostate cancer, all patients were advised to have an isotope bone scan. If the bone scan was negative for metastases they underwent cross sectional imaging with a computed tomography (CT) scan or a magnetic resonance imaging (MRI)scan of pelvis/prostate to assess the local spread of the disease.

Patients with metastatic disease decided on the mode of hormonal treatment of their choice. Most opted for surgical orchiectomy as the form of ADT due to financial reasons.The luteinizing hormone releasing hormone (LHRH) agonists are not available in the National Health Service of Bangladesh. Those with localized disease were offered surveillance, radical prostatectomy or radical radiotherapy according to the grade of the tumor and patient's wishes. Follow up included 3 monthly PSA levels initially for 1 year and thereafter 6 monthly.

## Results

There were 407 patients with histologically proven prostate carcinoma. Average age at diagnosis was 69 years (range: 48-88 years). Two hundred and seventy-two (67%) patients had a clinically malignant prostate on digital rectal examination. Most patients presented with diagnosed prostate cancer[Table 1]. There was no screening programme for detecting prostate cancer in Bangladesh. Serum PSA was available for 334 patients. More than half (67%) of the patients had a serum PSA more than 50 ng/ml [Table 1]. Histopathology was ascertained byTRUS guided trans rectal core biopsy in 2%, trans rectal digital guided prostate biopsy in 24% and TURP chips in 74%. The vast majority (401/407) were acinar adenocarcinomas. There were six unusual histological types – two ductal carcinomas, two undifferentiated carcinomas, one neuroendocrine tumors and one sarcomatoid. Gleason sum score was availablein all patients [Table 1]. Gleason sum score was 8or more in 46% of the patients.

**Table-I**

*Patient and tumor characteristics*

| Variable | Total (n) | Percentage (%) |
|---|---|---|
| 1. Age | | |
| <50 | 13 | 4% |
| 50-59 | 63 | 16% |
| 60-69 | 175 | 43% |
| ≥ 70 | 156 | 37% |
| Average age (Mean) | | 69 |
| **2**.Clinical presentation (at OPD) | | |
| Diagnosed prostate cancer | 354 | 87% |
| Raised PSA | 18 | 5% |
| Raised PSA with abnormal DRE | 14 | 3% |
| Features of metastases with unknown primary | 21 | 5% |
| **3**.PSA level (ng/ml) at diagnosis | | |
| <10 | 2 | 0.5% |
| 11-20 | 19 | 4.5% |
| 21-50 | 42 | 10% |
| 51-100 | 130 | 32% |
| >100 | 141 | 35% |
| Data not available | 73 | 18% |
| **4**.Mode of diagnosis | | |
| TRUS biopsy | 8 | 2% |
| Transrectal biopsy | 98 | 24% |
| TURP chips | 301 | 74% |
| **5**.Gleason sum score | | |
| ≤6 | 35 | 9% |
| 7 | 181 | 45% |
| ≥8 | 191 | 46% |

*OPD= Out Patient Department, DRE= Digital Rectal Examination, PSA=Prostate specific antigen, TRUS= Transrectal ultrasound, TURP=Transurethral resection of the prostate

Stage of the disease was determined at the end of clinical, biochemical and radiological assessment. Doubtful cases were discussed with the medical oncology and radiation oncology team at tumor board and a decision was arrived at. Accordingly 85% (345/407) had metastatic disease at thetime of presentation. Twenty patients had soft tissue (extra regional lymph nodes 8, liver 6, lungs 5, brain 1) metastases. Ten patients underwent radical radiotherapy while two patients had radical prostatectomy [Table 2]. Four patients decided not to have any intervention. One hundred and ninety-seven patients with metastatic disease and 38 patients with locally advanced disease underwent bilateral orchiectomy. Even among patients who had to have ADT as neoadjuvant therapy before other forms of treatment, most opted for bilateral orchiectomy. One hundred –nine patients decided to buy LHRH agonists as ADT. Hence 68% patients opted to have surgical orchiectomy as the mode of ADT. The main reason for a large majority undergoing surgical orchiectomy was the nonavailability of LHRH agonists in the National Health Service of Bangladesh due to high cost.

The median follow up was 12 months (range: 3-27 months).We follow mostly 3 monthly PSA levels initially for 1 year and thereafter 6 monthly. Most of our patient could not attend OPD for follow-up regularly. Eight(2%) patients died during the study period.

**Table-II**

*Different forms of treatment given according to the stage of the disease*

| Stage of disease | | Total (*n*) | *Percentage* (%) |
|---|---|---|---|
| 1. | Localized | (*n*=16 | 4%) |
| | Radical prostatectomy | 2 | 0.5% |
| | Radical radiotherapy | 10 | 2.5% |
| | Surveillance | 4 | 1% |
| 2. | Locally advanced | (*n*= 46 | 11%) |
| | ADT* (surgical) followed by radiotherapy | 23 | 5.3% |
| | ADT* (medical) followed by radiotherapy | 8 | 2% |
| | ADT* only (all surgical) | 12 | 3% |
| | ADT*(surgical) and TURP | 3 | 0.7% |
| 3. | Metastatic disease | (*n*=301 | 74%) |
| | Bilateral orchiectomy as ADT | 185 | 45.3% |
| | LHRH agonists as ADT | 101 | 25% |
| | LHRH antagonist as ADT | 3 | 0.7% |
| | Bilateral orchiectomy and TURP | | 12 3% |
| 4. | Metastatic CRPC | (n=44 | 11% ) |
| | Abiraterone | 3 | 0.7% |
| | Referred to medical oncology | 41 | 10.3% |

(For systemic chemotherapy)

*ADT=Androgen deprivation therapy, LHRH= Luteinizing hormone releasing
Hormone, CRPC= Castrate Resistant Prostate Cancer

## Discussion

Average age (69 years) at diagnosis of prostate carcinoma among men in Bangladesh is higher than that in the developed world where the median age is approximately 67 years [7]. Incidence of familial cancer was 2% in our patient cohort. Worldwide it is 9%.[8,9] Bangladesh's neighboring country, India has a familial cancer rate of 3% which is closer to the rate of Bangladesh.[10] It has been shown that introduction of PSA testing does not appear to alter the familial risk of prostate cancer significantly[11]. Therefore genetic differences between prostate carcinoma in South Asians and the developed world is a possibility which needs further evaluation.

At present, data collection is done through patient registries maintained at Oncology Departments of the NICRH. According to the latest cancer registry data, the total number of prostate cancer in 2010 was 120. According to our study, in our Uro-oncology department there have been 200 cases of prostate cancer a year on average. Patients with prostate cancer are managed by all two hundred- fifty urological surgeons working in Bangladesh and by the general surgeons too, especially the patients with metastatic disease. Therefore, cancer registry data in relation to prostate cancer appears to be underestimated, and the urological community in Bangladesh and the health planners should formulate a better strategy to compile a proper database of prostate cancer in order to collect robust data which can be used for more meaningful planning and resource allocation to control and treat the disease.

National Institute of Cancer Research and Hospital is the only cancer centre in government sector in Bangladesh. All doctors community particularly from district general hospital and medical college hospital from all corner of Bangladesh refer prostate cancer patients to this centre, with partially treated or without any diagnosis and treatment. So there is large number of prostate cancer patients in this institute.For this reason we found mostly diagnosed prostate cancer here.

Ninety-six percent of the patients in our study had locally advanced (11%) or metastatic disease (85%) at the time of presentation to us. According to a study done in India from 2003 to 2005, 71.1% had metastases at the time of diagnosis[10]. In the west before the advent of serum PSA, two thirds of patients had locally extensive or metastatic disease at the time of diagnosis[12]. These figures remain same for nonscreened groups in the Europe even now[13]. In countries with widespread testing of PSA, only 12-16% will present with locally advanced (T3 or T4) and metastatic disease now[7,14].

Nearly half (46%) of our patients had a high grade malignancy (Gleason sum score of 8 or more). In the UK and mainland Europe, it is about 16-20%[13,15,16]. Two studies involving a total of 47 patients had shown that most (66%) prostate cancers in Sri Lanka are high grade tumors with a Gleason score of 8 or more[4]. Among native Indians, 72.1% had a Gleason score of 7 or more at the time of diagnosis[10]. However, South Asian i migrants in UK and USA have a much lower incidence of high grade tumors[17]. According to the PROCESS study done in late 1990s only 5% of South Asians with prostate cancer had a Gleason score of 8 ormore[18]. During this time serum PSA was not widely used in the UK for early detection of prostate cancer and only about 10% of patients had screening detected cancers. Hence differences cannot be due to widespread PSA usage. Among Asians living in USA prostate cancer with Gleason score of 8 or more is 18% in a study done from 2004 to 2006[4]. Another study showed that the proportion of poorly differentiated prostate cancer among south Asians was similar to those of whites in USA[17]. The PROCESS study further shows that incidence of prostate cancer among South Asians residing in UK was 6-7 times higher than their native counterparts living in India[18]. These findings suggest that incidence of prostate cancer is lower in South Asia, but the proportion of high grade cancers is more. With the migration of South Asians to UK and USA, these differences tend to reverse leading to a much higher overall incidence with a reduction in high grade cancers.

Although some of these differences could be due to poor access to health care services in South Asian countries, the possibility of dietary or an environmental factor that reduces the overall incidence of prostate cancer in South Asia while increasing the number of high grade tumors is a real possibility.Five alpha reductase inhibitors, finasteride and dutasteride, are known to reduce the number of prostate cancers[19]. At the same time, men taking these drugs are diagnosed to have more higher Gleason score tumors[19]. Therefore, a similar substance in the South Asian diet rich in spices or an effect via exposure to sunlight are potential explanations, which need further study[9]. Furthermore even in unscreened European

populations, the proportion of high grade tumors remains much lower than in South Asians living in their native countries[13]. Similarly, only a small number of patients in the PROCESS study had PSA detected cancers, hence widespread use of PSA is unlikely to be the reason for the differences.

In European countries only about 20% of patients who need ADT opt for bilateral orchiectomy[20]. In our series, 68% (275/407) of them underwent surgical orchiectomy as the mode of ADT. Though the reasons for this were mainly availability and financial, it has been shown that rates of myocardial infarction and cerebrovascular accidents are more after medical forms of ADT (both LHRH agonists and anti androgens), while no such increased association is seen after surgical orchiectomy[20]. Even psychological morbidity appears to be minimal after surgical orchiectomy[4]. Furthermore, the size of the testes become significantly smaller even after medical means of orchiectomy making long term cosmetic differences negligible[21]. Elimination of compliance issues and low cost are more relevant to a country like Bangladesh where resources are scarce and the rural population is large. Additional benefits of surgical castration include certainty in achieving castrate levels of testosterone so that subsequent monitoring of serum testosterone becomes unnecessary[22]. Therefore surgical orchiectomy can be recommended as a cost saving, yet a scientifically acceptable option of ADT in resource poor settings like Bangladesh.

Most urological surgeons in Bangladesh perform TURP as a means of obtaining tissue for diagnosis as well as to relieve significant bladder outflow obstruction in patients already suspected of having prostate cancer by digital rectal examination and elevated serum PSA. This has been our practice too and nearly two third of our patients had the histological diagnosis by TURP chips. This is the more plausible reason for a higher incidence of prostate cancer in prostatic chips after TURP rather than to a change in the incidence or biological behavior of prostate cancer in Bangladeshi patients. Our explanation is further supported by the results of two studies done in Sri Lanka where the incidence of incidental prostate cancer among TURP done for clinically benign disease was around 10% which is the world average[23,24].

Although single center series are naturally prone to selection bias, in the absence of a robust electronic data collecting system and the cancer registry being incomplete and latein publishing its data, our study provides the best possible collection of data under the circumstances. The ideal investigation protocol could not be performed in all patients in our study cohort due to difficulty in access to CT / MRI scanner in our institute. Another limitation was that the histological grade was based on needle biopsy specimen and was not reviewed by a central pathologic committee.

The biggest strengths in our study were its prospective nature and the relatively large number of the sample. This minimized the bias attributed to retrospective studies based on poorly maintained patient records in developing countries as well as deficiencies of secondary analysis of data obtained from incomplete cancer registries.

## Conclusions

Bangladesh like other South Asians appear to be having a low incidence of prostate cancer, but a larger proportion of high grade cancers in comparison to the UK and USA. Although genetic differences may exist, a dietary or an environmental factor is more likely to be the cause for these changes. The protective effect of this factor appears to wane as South Asian emigrants and live in UK and USA. This observational study data should be reviewed as preliminary and hypothesis generating.

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