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Overview of benign and malignant prostatic disease in Pakistani patients: A clinical and histopathological perspective

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RESEARCH ARTICLE

Overview of Benign and Malignant Prostatic Disease in Pakistani Patients: A Clinical and Histopathological Perspective

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Abstract

Background: To present the overall clinical and histological perspective of benign and malignant prostatic disease as seen in our practice in the Section of Histopathology, Department of Pathology and Microbiology, Aga Khan University Hospital, Karachi, Pakistan. Materials and Methods: All consecutive prostate specimens (transurethral resection or TUR, enucleation, needle biopsies) received between July 1, 2012 and December 31, 2012 were included in the study. Results: Of the total of 785 cases, 621 (79.1%) were TUR specimens, 80 (10.2%) enucleation specimens, and 84 (10.7%) needle biopsies. Some 595 (75.8%) were benign, while 190 (24.2%) were malignant. Mean weight of BPH specimens was 19 grams and 43 grams for TUR and enucleation specimens respectively. Almost 67% of adenocarcinomas were detected on TUR or enucleation specimens. Of the above cases, 41.7% were clinically benign while 58.3% were clinically malignant. The average volume of carcinoma in all cases ranged between 60 to 65%. The average number of cores involved in needle biopsies was 5. In general, higher Gleason scores were seen in TUR/enucleation specimens than in needle biopsies. Overall, in all types of specimens, commonest Gleason score was 7, seen in 74 (38.9%) cases, followed by Gleason score 9 seen in 47 (24.7%) cases. Out of the 63 needle biopsies with carcinoma, radical prostatectomy was performed in 16 cases (25.4%). Conclusions: Benign prostatic hyperplasia (BPH) is extremely common and constitutes the bulk of prostate specimens. TMajority of prostatic carcinomas are still diagnosed on TUR or enucleation specimens. These included both clinically benign and clinically malignant cases. The volume of carcinoma in these specimens was quite high indicating extensive disease. Gleason scores were also generally high compared with scores from needle biopsies. Commonest Gleason score in all type of specimens was 7. Pathologic staging was possible in very few cases since radical prostatectomies are rarely performed.

Keywords: Benign prostatic hyperplasia - prostatic carcinoma - TUR - enucleation - needle biopsy - Pakistan

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Introduction

Pakistan is a large South Asian country with a population of over 180 million. The Section of Histopathology at the Aga Khan University Hospital in Karachi (Pakistan's largest city) is the biggest and premier center for Histopathology in Pakistan. We receive specimens from the entire country through our collection points located throughout Pakistan. We annually report over 50,000 cases of surgical pathology.

We commonly see cases of benign prostatic hyperplasia (BPH) and prostatic adenocarcinoma in our practice, and our studies have shown that prostatic carcinoma is among the commonest malignancies in older males (Zubair et al., 2007a; 2007b). In the West, owing to the availability of other treatment options e.g. pharmacologic for BPH, the frequency of transurethral resection (TUR) or open transvesical prostatectomy (enucleation) specimens has greatly reduced (Epstein and Netto, 2010). However, this is not the case in Pakistan where the treatment of BPH remains overwhelmingly surgical. In fact, TUR and enucleation are performed for diagnostic and therapeutic purposes even in those cases where there is clinical suspicion of carcinoma. These cases include nonpalpable tumors with raised serum prostate specific antigen (PSA) levels (clinical stage T1c), and palpable tumors (clinical stage T2 or T3). Serum PSA testing is becoming more common in Pakistan, and the number of prostatic needle biopsies (and T1c cancers detected on these) is also increasing albeit gradually. However, the majority of prostatic adenocarcinomas in Pakistan are still diagnosed on TUR or open transvesical prostatectomy specimens.

We had earlier published two studies on radical prostatectomy specimens and needle biopsies (Memon et al., 2009; Ahmad et al., 2012) The aim of the current study is to present the overall clinical and histological perspective of benign and malignant prostatic disease as seen in our practice.

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Materials and Methods

All consecutive prostatic specimens (TUR, enucleation and needle biopsies) received in the Section of Histopathology, Department of Pathology and Microbiology, Aga Khan University Hospital, Karachi over a six month period (July 1 to December 31, 2012) were included in the study. Cases of both BPH and adenocarcinoma were included. All specimens were processed and reported according to standard protocols. All relevant data was recorded and analyzed using commercially available SPSS 19.0 software package. Fisher exact and chi square tests were used to calculate p-values for different variables. P-value equal to or less than 0.05 was considered significant.

Results

A total of 785 prostate specimens were received during the study period. These included 621 (79.1%) TUR specimens, 80 (10.2%) enucleation specimens, and 84 (10.7%) needle biopsies. Out of 785 cases, 595 (75.8%) were benign, while 190 (24.2%) were malignant (carcinoma). The breakup of all 785 cases is shown in Table 1. BPH was most commonly seen in the seventh decade. The decade wise breakup of BPH is shown in Table 2. Age range of BPH was 41 to 92 years. The weight of BPH specimens treated by TUR ranged from 2 to 72 grams with mean weight of 19 grams. On the other hand, the weight of BPH specimens treated by enucleation ranged from 6 to 150 grams with mean weight of 43 grams.

Out of the 574 cases of BPH detected on TUR or enucleation specimens (Table 1), 28 (4.9%) had serum PSA in the borderline range (4-10) and a suspicion of malignancy was raised by the clinician. The average number of sections submitted in both benign (BPH) and malignant TUR and enucleation specimens was 3 to 4. However, in cases with borderline serum PSA or clinical suspicion of malignancy, the specimens were submitted entirely. Similarly, the 21 cases which turned out to be benign on needle biopsy (Table 1) had serum PSA in the borderline range.

Carcinoma was most commonly seen in the seventh decade. The decade wise breakup of cases of carcinoma is shown in Table 3. Age range for adenocarcinoma was 45 to 86 years. Mean and median age was 56 and 59 years respectively. Overall 130 out of 190 patients (68.4%) were 65 years in age or older. As seen in table 1, 127 (66.8%) out of total 190 cases of adenocarcinoma were detected on TUR and enucleation specimens, 53 (41.7%) were clinically benign (clinical stage T1a or T1b), while 74 (58.3%) were clinically malignant. The breakup is shown in Table 4. Out of 53 cases which were clinically

Table 1. Breakup of Prostate Specimens According to Type of Specimen (n=785)

	Type of Specimen	Total No.	BPH	Carcinoma
1	TUR	621	527 (84.9%)	94 (15.1%)
2	Enucleation	80	47 (58.8%)	33 (41.2%)
3	Needle Biopsy	84	21 (25%)	63 (75%)

Table 2. Decade Wise Breakup of Cases of BPH (n=595)

	Age (years)	Number of cases	Percentage (%)
1	41-50	31	5.20%
2	51-60	140	23.50%
3	61-70	239	40.20%
4	71-80	145	24.40%
5	>80	40	6.70%

Table 3. Decade Wise Breakup of Cases of Carcinoma (n=190)

	Age (years)	Number of cases	Percentage (%)
1	41-50	7	3.70%
2	51-60	38	20.00%
3	61-70	74	38.90%
4	71-80	50	26.30%
5	>80	21	11.10%

Table 4. Breakup of Carcinomas Detected on TUR and Enucleation Specimens According to Clinical Impression (n=127)

	Type of Specimen	Total No.	Clinically Benign	Clinically Malignant
1	TUR	94	31 (33%)	63 (67%)
2	Enucleation	33	22 (66.7%)	11 (33.3%)

Table 5. Breakup of Gleason Score in Our Cases (n=190)

Gleason score	Number of cases	Percentage (%)
4	---	---
5	2	1.00%
6	29	15.30%
7	74	38.90%
8	37	19.50%
9	47	24.70%
10	1	0.50%

Table 6. Breakup of Gleason Score in Carcinoma Detected on TUR and Enucleation Specimens (n=127)

Gleason score	Clinically Benign	Clinically Malignant	Overall
4	---	---	--
5	---	2 (2.7%)	2 (1.6%)
6	11 (20.7%)	4 (5.4%)	15 (11.8%)
7	19 (35.8%)	23 (31.1%)	42 (33.1%)
8	10 (18.9%)	16 (21.6%)	26 (20.5%)
9	12 (22.7%)	29 (39.2%)	41 (32.2%)
10	1 (1.9%)	---	1 (0.8%)

Table 7. Breakup of Gleason Score in Patients 65 Years and Older (n=130)

Gleason Score	Number of cases	Percentage (%)
6	20	15.40%
7	49	37.70%
8	22	16.90%
9	38	29.20%
10	1	0.80%

Table 8. Breakup of Gleason Score 7 (n=74)

Types of specimens	3+4	4+3	Total	%
Needle Biopsy	21	11	32	43.20%
Clinically benign TUR/enucleation	12	7	19	25.70%
Clinically malignant TUR/enucleation	9	14	23	31.10%

benign, 2 (3.8%) were clinical stage T1a, while 51 (96.2%) were clinical stage T1b. Out of the 74 cases which were clinically malignant, 10 (13.5%) were T1c, while 64 (86.5%) were T2 or T3.

The average volume of carcinoma in clinically benign TUR/enucleation specimens was 60%, while average volume of carcinoma in clinically malignant TUR/enucleation specimens was 65%. Of the 63 needle biopsies with carcinoma, 53 (84.1%) were sextant and 10 (15.9%) were octant. The average volume of carcinoma in needle biopsies was 60% and the average number of cores involved was 5.

The breakup of Gleason score in all 190 cases is shown in Table 5. The breakup of Gleason score in clinically benign and clinically malignant TUR/ enucleation specimens is given in Table 6. As shown in Table 6, Gleason score was 8 or above in 43% of clinically benign and 61% of clinically malignant TUR/enucleation specimens. The p-value was significant (0.013). In needle biopsies, Gleason score was 6 in 14 cases (22.2%), 7 in 32 cases (50.8%), 8 in 11 cases (17.5%) and 9 in 6 cases (9.5%). Out of the 63 needle biopsies with carcinomas, radical prostatectomy was performed in 16 cases (25.4%).

As mentioned above, 130 (68.4%) of patients with carcinoma were 65 years or older. The average volume of carcinoma in specimens from these patients was 63%. The breakup of Gleason score in these 130 patients is shown in Table 7. Out of 190 patients, 60 (31.6%) were under 65 years of age. The average volume of carcinoma in these patients was 57%. In these 60 patients, Gleason score was 6 in 7 cases (11.7%), 7 in 20 cases (33.3%), 8 in 13 cases (21.7%), 9 in 18 cases (30%) and 10 in 2 cases (3.3%). So Gleason score was 7 and above in almost 85% patients who were 65 years or older and in over 88% patients under 65 years of age. The difference was not statistically significant (p-value 0.578).

A total of 74 cases of carcinoma out of 190 had Gleason score 7. Of these, 42 had Gleason grade 3+4=7, and 32 had Gleason grade 4+3=7. The breakup is shown in Table 8. So, Gleason score 7 was overall the commonest score in our series followed by Gleason score 9.

As shown in Table 6 and in our results above, almost 86% of all TUR/enucleation specimens showed a Gleason score 7 or above, while almost 73% of needle biopsies had a Gleason score 6 or 7. The difference was statistically significant (p-value: 0.000).

Discussion

Benign prostatic hyperplasia is extremely common and constitutes the bulk of prostatic specimens. As seen in our results, most cases of BPH are treated by TUR rather than suprapubic prostatectomy, although studies have shown that chances of a patient undergoing another surgery for BPH is much higher after TUR than suprapubic prostatectomy (Roos et al., 1989). The mean weight of BPH specimens in our series was 19 grams for TUR and 43 grams for enucleation specimens. According to literature, the average weight of BPH specimens obtained by TUR and enucleation is around 33 (±16) and 100 grams respectively (Rosai, 2011).

Clinical staging of prostatic adenocarcinoma is based on the TNM system (Epstein et al., 2007).

Clinical stage T1a and T1b carcinomas are tumors that are not suspected clinically and are discovered in TUR or enucleation specimens removed for BPH. T1a is carcinoma involving less than 5% of the specimen, while T1b is carcinoma involving more than 5% of the specimen (Epstein and Netto, 2010). Clinical stage T1a carcinomas may only be monitored with serum PSA levels, however sometimes radical prostatectomy is performed (Larsen et al., 1991). T1b carcinomas are usually treated by radical prostatectomy or radiotherapy (Christensen et al., 1990). Clinical stage T1c carcinomas are non-palpable tumors which are diagnosed by needle biopsy in patients with raised serum PSA levels. T1c carcinomas are usually treated by radical prostatectomy. Clinical stage T2 carcinomas are palpable tumors which are still confined to the prostate. T2 carcinomas are also usually treated by radical prostatectomy. Clinical stage T3 carcinomas are tumors which have extended beyond the prostate and are usually treated by radiotherapy (Epstein and Netto, 2010).

The majority of prostatic carcinomas in our practice are still diagnosed on TUR or enucleation specimens. Owing to the availability of non-surgical treatment options, the number of TUR and enucleation specimens has declined in the west (Epstin and Netto, 2010). However, this is not the case in our country, and TUR and enucleation specimens remain the most common prostatic specimens received in the surgical pathology laboratory. As shown in the results, the overwhelming majority of clinically unsuspected carcinomas which were discovered in TUR or enucleation specimens performed for BPH (i.e. clinical stage T1a or T1b) were T1b (more than 5% of the specimen involved by the tumor). The presence of carcinoma in a TUR specimen may signify extensive spread from the periphery of the gland. The probability of detecting carcinoma in TUR specimens is directly related to the amount of sampling (Newman et al., 1982). If five to eight blocks are submitted, all clinical stage T1b carcinomas are detected, and if eight to ten blocks are submitted, more than 90% stage T1a carcinomas are detected (Murphy et al., 1986; Vollmer 1986; Eble and Epstein, 1990). Remaining tissue should be submitted if cancer is stage T1a, but not if cancer is stage T1b (McDowell et al., 1994). The average volume of carcinoma in our clinical stage T1 cases was 60%. The fact that an average of three to four blocks was originally submitted in these cases indicates the presence of extensive and widespread cancer. One plausible reason why we see so much carcinoma in ostensibly benign cases is that no investigations e.g. serum PSA, transrectal ultrasound (TRUS) were carried out in many of these cases. It must be noted that carcinoma can diffusely infiltrate the gland without causing a palpable nodule. At other times, the carcinoma may be well defined and peripherally located but may remain unpalpable for reasons that are still not clear (Epstein and Netto, 2010). However, the main reason in our scenario probably is the failure to carry out any investigations due to lack of availability of these tests, patient non-affordability etc.

Our results show that the majority (58.3%) of carcinomas detected on TUR or enucleation specimens

were clinically malignant (clinical stage T2 or T3). However, even in such cases, TUR or enucleation rather than radical prostatectomy was performed, simply because the latter option is not available anywhere in Pakistan except at our center in Karachi. This is the situation in a country with a population of 180 million people. As shown in table 4, as many as 67% of carcinomas detected on TUR and over 33% detected on enucleation specimens were clinically malignant. Following TUR or enucleation, these patients then underwent radiotherapy. As shown in the results, TUR or enucleation was also performed in 10 cases which were stage T1c.

The average volume of carcinoma in clinically malignant TUR or enucleation specimens was 65% which was not significantly higher than the average volume of 60% seen in clinically benign T1 specimens. Only 33% of carcinomas in our series were detected on needle biopsies. Our practice does not demonstrate the trend of most cases being diagnosed on needle biopsies which is evident even in some Asian countries (Kuo et al., 2012). The average overall volume in our needle biopsies was 60%. It may be mentioned here that those TUR and enucleation specimens which were clinically suspicious for carcinoma but in which no carcinoma or only limited carcinoma (involving less than 5% of the submitted tissue) was found, were then submitted entirely. The algothims for additional sampling of TUR specimens were followed (McDowell et al., 1994). Studies have shown that patients in whom carcinoma is discovered in clinically benign TUR specimens have higher rates of tumor dissemination than those diagnosed by needle biopsy because tumors diagnosed incidentally in TUR specimens are usually more advanced (Forman et al., 1986).

The average volume of carcinoma in patients 65 years or older was 63%, while in those under 65 years of age, it was 57%.

It is important to note at this point that tumor volume whether on needle biopsies or TUR is an important prognostic marker that correlates well with Gleason score, extraprostatic tumor extension, seminal vesicle invasion, positive surgical margins and lymph node metastases on radical prostatectomy specimens (Schmid and McNeal, 1992). In fact, one study has shown that a simple visual estimate (eyeballing) of tumor volume is more closely associated with survival than serum PSA level and microscopic Gleason score (Vollmer, 2009). A recent study which looked at the current trends in visually estimated tumor volume found a rising incidence of very low volume (0-1%) tumors in radical prostatectomy specimens (Green et al., 2012). In needle biopsies, the number of positive cores and percentage of tumor in each core are very strong predictors of adverse prognostic features in radical prostatectomy specimens (Sebo et al., 2000; Freedland et al., 2002; 2003).

The Gleason microscopic grade of carcinoma is an important prognostic marker (Zincke et al., 1994). There is convincing evidence that microscopic Gleason score is superior to other variables as an independent prognostic marker (Lilleby et al., 2001). Various studies have shown good correlation between Gleason score and various important pathological features seen in radical prostatectomy specimens, and with outcome following radical prostatectomy and radiotherapy (Epstein et al., 1996; Green et al., 1998; Rubin et al., 2004; Kryvenko et al., 2012). The International Society of Urological Pathology Consensus Conference modified the Gleason grading in 2005 (Shah et al., 2009) according to which Gleason grades were updated according to new criteria. Several studies have validated the prognostic value of these modifications (Billis et al., 2008; Dong et al., 2012). As shown in Table (5), Gleason score 7 was the commonest score in our series, followed by Gleason score 9. As shown in Table 6, higher Gleason scores (8 or 9) were more frequent in clinically malignant than in clinically benign carcinomas detected on TUR or enucleation specimens. On the other hand, Gleason score 6 was much more common in carcinomas which were clinically benign. As shown in table 6, about 43% of clinically benign cases and over 61% of clinically malignant cases had Gleason score 8 and above. The p-value was significant (0.013). Overall, in carcinomas detected on TUR or enucleation specimens, majority of patients had Gleason scores 7, 8 or 9, and Gleason score 9 was, in fact, the most common score. On needle biopsies (see results), Gleason score 7 was the most common (50.8%), followed by scores 6 (22.2%) and 8 (17.5%). In needle biopsies with different cores showing different grades, we report the grades of each core separately as per recommendations. The highest tumor grade is selected as the grade of the entire case to determine treatment, regardless of the percent involvement (Epstein et al., 2010). As shown in table 6, about 86% patients with carcinoma detected on TUR or enucleation specimens had Gleason score 7, 8, 9 or 10, while 73% patients with carcinoma detected on needle biopsies had Gleason score 6 or 7 (see results). The p-value was significant (0.000). As shown in table 7, over 84% patients with carcinoma who were 65 years or older had Gleason score 7 to 10. Similarly, as shown in results, over 88% patients who were under 65 years of age had Gleason scores 7 to 10. The p-value was not significant (0.578%). In our study, therefore, there was no significant correlation of age with adverse prognosis. However, a recent study from China (Wang et al., 2012) reported that prostatic cancer patients under 59 years of age had more aggressive disease. However, another recent study did not find any statistically correlation between Gleason score and age of the patients (Sapira and Obiorah, 2012).

Although clinical stage T1c carcinomas are usually treated by radical prostatectomy (Epstein et al., 2010), this is not the case in our country due to reasons already discussed above. Radical prostatectomy was performed in only 16 out of 63 cases (25.4%). This is only slightly better than what we found in an earlier study (Memon et al., 2009). The number of radical prostatectomies over the years has increased but very slowly. Currently, the total number performed per year is around thirty.

However, our findings on radical prostatectomy specimens in the present study as well as previous studies (Memon et al., 2009; Ahmad and Arshad, 2012) mostly show advanced pathologic stage with majority of cases showing extraprostatic extension, seminal vesicle invasion and positive surgical margins. Because so few radical

prostatectomies are performed, pathologic staging of prostatic carcinoma in our setting is only possible in a very limited number of cases.

Recently, studies have shown the effectiveness and safety of brachytherapy and combined vascular endothelial growth factor receptor/platelet derived growth factor receptor (VEGFR/PDGFR) inhibitor. Therapy in the treatment of localized but high risk prostate cancer (Corn et al., 2013).

The diagnosis and treatment of prostatic adenocarcinoma is in the majority of cases suboptimal at best. Most patients are managed with some form of surgery (TUR or suprapubic prostatectomy) plus radiotherapy and/or antiandrogen therapy. As prostatic carcinoma in general is fortunately a relatively less aggressive type of cancer, many patients respond to some extent to the above mentioned forms of treatment and since the disease affects mainly the elderly, may infact ultimately die from some other cause.

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