

RESEARCH COMMUNICATION

Staging of Prostatic Adenocarcinoma with Radical Prostatectomy Specimens in Pakistan

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Abstract

Objectives: Data for pathological staging of radical prostatectomy specimens reported in the Section of Histopathology of a large tertiary care hospital in Pakistan were compared with sextant biopsy findings to determine whether clinically localized disease is actually localized pathologically. **Design:** A study was conducted of radical prostatectomy specimens reported in the Section of Histopathology from Jan 2001 to July 2008, with cases staged according to the pathologic TNM staging system. Other variables such as amount of tumor in prostatectomy specimens and lobes affected were also determined. **Results:** Out of 65 cases, 83.3% were clinical stage T1c. 29.2% were pT3a, 24.6% were pT3b and 3.1% were pT4. Therefore, in the majority of cases, disease was not localized to the prostate and perineural invasion was seen in all. Comparison with biopsy results showed Gleason's grade to be altered in 20% cases. **Conclusions:** The large majority of prostatic carcinomas in Pakistan are advanced cancers with pathologic stage more advanced than evident on clinical staging. On average, tumors involved 35-40% of the prostate with a particular preponderance in posterior lobes.

Key Words: Prostate cancer - radical prostatectomy - pathological staging

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Introduction

Although prostate carcinoma is extremely common in Pakistan, diagnostic and therapeutic modalities are limited. People with symptoms of enlarged prostate undergo transurethral resection, which is used as a diagnostic as well as therapeutic modality. Transurethral ultrasound and determination of serum PSA levels are performed in only a small percentage of cases. Sextant core biopsies are fewer still. If cancer is discovered on TUR (as happens very frequently in our setting), patients are given radio- or chemotherapy without any further surgery or attempt at staging. So a large majority of patients are managed and treated suboptimally. This is extremely unfortunate for a heavily populated country with a population of 170 million. Radical prostatectomy is offered to patients who are considered candidates for curative treatment (Cheng et al., 1999), but it is a new procedure in Pakistan and is performed at very few institutions as there are hardly any surgeons in the country who can perform this procedure. However, it has been performed regularly in our institution for the last few years. Here, early detection, by means of serum PSA levels and sextant biopsies have led to an increasing number of patients diagnosed with clinically localized carcinoma. The major aim of this study is to present background pathological data.

In the Section of Histopathology at our institution which is a major tertiary care center affiliated with a prestigious medical college of the country, radical prostatectomy specimens are comprehensively evaluated. Staging pelvic lymphadenectomy with frozen sections is performed prior to every radical prostatectomy. Positive nodes are generally indicative of disseminated carcinoma and thus in most settings the prostatectomy procedure is abandoned once node metastases are detected (Garrett et al., 2003)

The Gleason histological grade is a powerful prognostic indicator in prostate cancer and has widely been used for the characterizing tumor properties (Tomioka et al., 2006). It is based on the degree of architectural differentiation and tumor heterogeneity is accounted for by assigning a primary grade for the dominant pattern and a secondary grade for the next most common pattern (Cam et al., 2002). The Gleason score is advantageous as it takes remarkable morphological heterogeneity into account, but the lack of tumor representation on biopsies becomes problematic during grading (Ooi and Samali, 2007). The Gleason score also correlates strongly with tumor stage and prognosis and plays an important role in determining treatment (Fukagai et al., 2001). Several studies have shown that the extent of agreement between the Gleason scores of needle biopsies and of prostatectomy specimens varies widely.

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(Fukagai et al., 2001; Cam et al., 2002; Ooi and Samali, 2007) These discrepancies may be attributable to sampling errors and problems of pathological interpretation. Prostate cancer concordance rates can be improved by increasing the number of biopsy samples (Ooi and Samali, 2007).

Clinical staging is very important to determine treatment and stage T1c (non-palpable) and T2 (palpable) adenocarcinomas detected by needle biopsy are treated by radical prostatectomy (James and Montie, 1995). Stage T1a tumors in older patients are not treated further, however younger patients need follow up by monitoring serum PSA levels (Carter et al., 1990).

The present study aimed to assess pathological staging with radical prostatectomy specimens for the first time in Pakistan. A particular focus was on whether Gleason's grade on radical prostatectomy specimens correlates with Gleason's grade on sextant biopsies. In addition, the average tumor volume and distribution in the different regions of the prostate were assessed.

Materials and Methods

All 65 radical prostatectomy cases reported in the Section of Histopathology from Jan 2001 to July 2008. were included. Exclusion criteria were transurethral resection (TUR) and transabdominal suprapubic specimens. The sextant biopsies and radical prostatectomy specimens were processed according to published protocols (Hall et al., 1992) and the entire prostates with seminal vesicles were serially sectioned at 2 to 3 mm intervals. Division was into quadrants i.e. the right anterolateral and right posterolateral, and left anterolateral and left posterolateral quadrants. The reporting was done according to the recommendations of the College of American Pathologists (CAP) (Compton, 2003).

The slides were evaluated using Hematoxylin and eosin (H&E) stains. Immunohistochemical stains were performed (PSA, cytokeratin 5/6, 34 beta E12) when required. Staging pelvic lymphadenectomy was performed prior to radical prostatectomy.

All biopsies and radical prostatectomy specimens were graded according to the Gleason grading system, which included the Gleason major and Gleason minor score, and the combined score. Prostatic adenocarcinoma shows remarkable histologic heterogeneity and usually exhibits a dominant and a less dominant histologic pattern. The Gleason score is calculated by adding the grades. The lowest major or minor grade is 1, while the highest major or minor grade is 5. The Gleason score therefore varies anywhere between 1+1=2 (the lowest) to 5+5=10 (the highest). If only one histologic pattern is present, score is still assigned, for example 3+3=6. All cases were assigned Gleason major and minor grades based on the dominant and the less dominant pattern. Pathologic staging was performed strictly according to the TNM staging system.

The correlation between the Gleason grading on sextant biopsies and in the radical prostatectomy specimens was looked at. The cases were staged as T3a only if the tumor reached the inked margins. So called 'capsular penetration' was disregarded. Other variables such as amount (percentage) of tumor in radical

Table 1. Pathologic Staging of Tumors with Radical Prostatectomy Specimens

Stage	Number	Percentage
pT2a	2	3.1%
pT2b	16	24.6%
pT2c	10	15.4%
pT3a	19*	29.2%
pT3b	16**	24.6%
pT4	2*	3.1%

*all with positive inked margins; **13 with positive inked margins

Table 2. Differences in Gleason Grade between Sextant Biopsies and Radical Prostatectomy Specimens

S #	Sextant biopsies	Radical prostatectomy
1	3+3=6	3+4=7
2	3+3=6	3+4=7
3	2+3=5	3+3=6
4	3+3=6	3+5=8
5	3+3=6	4+3=7
6	3+3=6	3+4=7
7	3+3=6	3+4=7
8	3+4=7	3+5=8
9	3+4=7	3+5=8
10	3+3=6	3+4=7
11	3+3=6	3+4=7
12	2+3=5	3+3=6
13	3+3=6	3+4=7

prostatectomy specimens, presence (or not) of perineurial invasion and the lymph node status etc were also determined.

Results

A total of sixty five cases were included in the study. Clinical stage before radical prostatectomy procedure was T1c in 50 cases (83.3%), T1a in 2 (3.3%), T1b in 4 (6.6%), T2 in 3 (5.0%), T3 in 1 (1.6%) and not known in 5. Pathologic stages from radical prostatectomy specimens are shown in Table 1. The majority of cases (35/65) were T3. Of the 16 cases which were pT3b, 13(81.2%) also showed evidence of pT3a (extra prostatic extension shown by positive inked margin). Both pT4 cases showed evidence of pT3a, while one of them also showed evidence of seminal vesicle invasion i.e. pT3b.

Lymph nodes were not sent in three cases. Of the sixty two cases in which staging pelvic lymphadenectomy was performed, 55(88.7%) were negative for metastatic disease; while in 7 cases (11.3%) lymph nodes were positive for metastatic tumor. Among these 7 cases, 5 cases were pT3b, while 2 were pT3a.

In five out of sixty five cases, Gleason grade on sextant biopsies was not known. Of the remaining sixty cases, the Gleason grade was the same on sextant biopsies and radical prostatectomy specimens in 47 cases (78.3%); and it was altered on radical prostatectomy specimens in 13 cases (21.6%) (Table 2). Overall, in this study, 53 cases (81.5%) had a Gleason score of 5 to 7; 11 (16.9%) had a score of 8 to 10; while 1 (1.5%) case had a score of 4.

Perineurial invasion was seen to a variable extent in multiple sections. High grade prostatic intraepithelial neoplasia (PIN) was reported in 3 cases (4.6%).

Volume of tumor in the radical prostatectomy specimen varied from < 5% to > 90% with an average volume of 35–40%. There was roughly even distribution of the tumor in all four lobes of the gland.

In this study, both distal and proximal margins were positive in 6 cases (9.2%), distal margin (apex) alone in 10 cases (15.4%), and proximal margin alone in 1 case (1.5%). However, in all these 16 cases, in which these margins were positive, inked surgical margins in lobes of the prostate were also positive.

Discussion

Radical prostatectomy is performed for clinical stage T1b, T1c and T2 prostatic carcinoma. However, for a cancer which is so common in Pakistan, this surgical procedure is hardly performed in any center in the country except at Aga Khan University resulting in suboptimal treatment of patients with prostate cancer. This is the first study on radical prostatectomy specimens in Pakistani patients. All the cases were staged according to strict TNM guidelines. This study demonstrates that like all malignant tumors in Pakistan, the majority of prostatic adenocarcinomas were also advanced cancers, with extra prostatic extension and seminal vesicle involvement (see results). However, a study published in USA showed that at 10 years post operatively, radical prostatectomy was effective for cancer confined to the prostate (92.2% progression – free probability) and also not confined (52.8%), including 71.4% progression – free probability for patients with only extra capsular extension and 37.4% with seminal vesicle invasion without lymph node metastasis (Hull et al., 2002).

In all cases included in this study, staging pelvic lymphadenectomy with frozen section was performed prior to every radical prostatectomy procedure. The presence of microscopic metastases in lymph nodes indicates a lack of curability. In the West, radical prostatectomy is often not performed in the presence of microscopically positive lymph nodes on frozen section. However, some surgeons still perform the procedure if the patient has a longer life expectancy. It has been shown that the overall 5 and 10 year survival rates for patients undergoing radical prostatectomy in spite of positive nodes are 97 and 62% (Epstein, 2001). Also studies have been shown that if the preoperative biopsy Gleason Score is less than 8, there is usually a long time interval before distant metastases occur and in such cases, radical prostatectomy is often performed (Sgrignoli et al., 2004). In our institution, recommendation of experts like Epstein is followed to routinely submit all of the tissue removed during lymphadenectomy (including surrounding adipose tissue), because in 5% of cases with positive nodes, metastases were detected only in very small nodes which are not identifiable grossly (7). It must be mentioned that the incidence of pelvic lymph node metastases in prostatic carcinoma patients has declined as more tumors are now detected earlier by better screening techniques (Partin et al., 1997). In this study, lymph nodes were positive in 7 cases (results). However, the surgeon performed radical prostatectomy in these seven cases as well.

The likelihood of adverse findings in the prostatectomy specimen and treatment failure following prostatectomy, is greater with a Gleason Score of 6 or more (Partin et al., 1997; D'Amico et al., 2000). There is also good correlation between the Gleason grade given on a radical prostatectomy specimen and that given earlier on biopsy material especially for Gleason score of 5 to 7 (Steinberg et al., 1997). In our study, there was a change in Gleason score on radical prostatectomy in 20% cases (Table 2). Studies have shown that in the large majority of radical prostatectomy specimens (80%), Gleason scores of 5 to 7 are seen, since Gleason score 2 to 4 tumors are usually small, in the transition zone and not detected on needle biopsy; while Gleason score 8 or 9 tumors are clinically advanced and not amenable to surgery (Epstein, 2004).

Seminal vesicle invasion is a much worse prognostic factor in a radical prostatectomy specimen than extra prostatic extension (Epstein, 2001). Seminal vesicle invasion is diagnosed only when the muscle wall of the seminal vesicle is invaded by the tumor (20). In this study, seminal vesicle invasion was seen in 24.6% cases, indicating a worse prognosis. The apex (distal margin) and the bladder neck (proximal margin) should be examined. The apex is one of the most frequent sites of a positive margin in a radical prostatectomy specimen; however the significance of a positive margin only at the apex is not entirely clear with conflicting reports (Epstein et al., 1993). On the other hand, positive proximal margins usually correlate with extensive tumor. In the current study, both distal and proximal margins were positive in 6 cases (9.2%), distal margin (apex) alone in 10 cases (15.4%), and proximal margin alone in 1 case (1.5%). However, in all these 16 cases in which these margins were positive, inked surgical margins in lobes of the prostate were also positive.

Positive surgical margins (extra prostatic extension) greatly increase the risk of progression of the tumor (Kausik et al., 2002). However, some authorities believe that positive margins do not always translate into residual tumor left within the patient locally and such tumors may remain occult for many years due to their indolent growth. Epstein (1991) believes that the edge of the prostate acts as a fairly effective barrier to the extension of carcinoma into the adjacent soft tissue and emphasizes that the best way to assess the presence of extra prostatic extension is to look at the adjacent edge of the prostate on scanning magnification where there is no carcinoma and to follow the edge of the prostate to the suspicious area. If in this area, the edge is irregular, only then can the margins be considered positive if the tumor reaches the ink.

Epstein (2004) does not recognize capsular invasion as such arguing that the prostatic capsule is not well defined histopathologically, with only a fibrous band at the edge of the gland and in some areas even this may be deficient and normal prostatic glands may be seen to extend to the edge of the prostate (Ayala et al., 1989). In this study, Epstein's recommendations for extra prostatic extension were followed and the margins were considered positive only if the tumor reached the inked margin and the surface of the prostate was irregular.

In conclusion, the present study was to present the first ever pathological data of radical prostatectomy specimens from Pakistan. It demonstrated that radical prostatectomy is indeed the most accurate indicator of tumor extent and prognosis and preoperative staging is generally underestimated compared with pathological staging done on radical prostatectomy specimens. The pathologic staging was more advanced than clinical stage in the majority of patients. Gleason's grade on radical prostatectomy specimens correlated with the Gleason's grade on sextant biopsies in the majority of cases. On average, tumor involved 35-40% of prostate gland and tumor was more common in posterior lobes of the glands. This study demonstrates that like all malignant tumors in Pakistan, the large majority of prostate cancers are advanced cancers, with extraprostatic extension and seminal vesicle involvement.

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