

Prostate Cancer Pathologic Parameters and Clinical Outcome : Results from the Cooperative Prostate Cancer Tissue Resource

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ABSTRACT

Background: The NCI-funded Cooperative Prostate Cancer Tissue Resource (<http://www.prostate-tissues.org>) contains over 3318 prostate cancer cases, including 2895 prostatectomy specimens from 12 hospitals representing four separate academic institutions. In each case the pathologic specimens were reviewed by academic pathologists using defined criteria as established by the AFIP Prostate Fascicle (Third Series) and the Gleason grading web site at Johns Hopkins University (<http://162.129.103.34/prostate/>).

Design: The average duration of follow-up including prospectively collected frozen tissue cases is 4.4 years (range 0 to 13 years). The mean patient age is 62.7 years (range 35 to 85 years). Pathologic review identified the following number of cases with specific Gleason scores; 1 Gleason 2, 10 Gleason 4, 120 Gleason 5, 1089 Gleason 6, 1362 Gleason 7, 181 Gleason 8, 117 Gleason 9, and 4 Gleason 10. Pathologic staging included 386 pT2a, 1545 pT2b, 553 pT3a, 241 pT3b, 12 pT4 cases. PSA recurrence data was calculated on 1276 patients with a mean follow-up period of 40 months. Of these patients, 125 (9.8%) had post-prostatectomy residual tumor. Of the 1151 patients who underwent PSA nadir, 325 (25.5%) have undergone a PSA recurrence, with the average time to recurrence of 17.5 months, and 826 (64.7%) are without evidence of recurrence with a mean follow-up period of 32.6 months. In addition, 42 have clinical evidence of recurrence, and 252 (8.7%) have died.

Results: Significant associations were noted between post-prostatectomy residual tumor and Gleason Score, seminal vesicle invasion, and higher pathologic stage (pT2 vs. pT3). In addition, significant associations were noted between PSA recurrence and Gleason score, percent gland involved, margin positivity, seminal vesicle invasion, and African-American ethnicity. When Gleason Score 6 or 7 tumors were compared, a significant difference was seen for PSA recurrence, but not for post-prostatectomy residual tumor. Within Gleason score 7 tumors, pattern 4+3 tumors were not more likely than 3+4 tumors to have either PSA recurrence or post-prostatectomy tumor. In addition, a trend was seen between higher percentages of Gleason pattern 4 or 5 tumor and PSA recurrence. No significant association was identified between PSA recurrence or post-prostatectomy elevated PSA and initial PSA value, size of the largest tumor nodule, perineural invasion, family history of prostate cancer, or smoking history.

Conclusion: The results of this study, the largest multiple institution study of its kind, represent the level of pathologic evaluation obtained in current academic institutions, and can serve as a general guide for expected clinical outcomes based on current pathologic standards. In addition, as a component of an NCI-funded Cooperative Prostate Cancer Tissue Resource, the described findings represent an available patient dataset that may be used for tissue based prostate cancer studies through such technologies such as tissue microarrays.

INTRODUCTION

Prostate cancer is the most common tumor in American men, and comprises approximately 220,900 new cancer diagnoses and 28,900 cancer related deaths each year. The majority of men treated in the United States undergo radical prostatectomy for treatment of the disease. For prostate confined disease it is estimated that the potential for cure ranges between 80 and 96%. Evidence of prostatic adenocarcinoma is associated with elevated levels of prostate specific antigen (PSA) which used to lead to diagnostic biopsies for evidence of tumor. PSA levels decrease to undetectable levels in patients when entire prostate gland and tumor have been removed. This PSA nadir can be subsequently followed and evidence of rising PSA values (PSA recurrence) occurs in approximately 15-19% of patients and relates to recurrent prostate cancer. The relative rates of increase of the PSA values has been associated with either local tumor recurrence, or growth of metastatic disease. The presence of PSA recurrence often leads to the use of secondary treatment modalities including radiation, hormonal and chemotherapy. While of some benefit, the presence of disseminated disease reflects a poor prognosis, and currently there is no effective treatment for hormone refractory disease. The ability to predict what patients will undergo PSA recurrence would allow for the identification and focused examination and treatment of these high risk patients. Towards this end The Co-Operative Prostate Cancer Tissue Resource (CPCTR) has been established to develop a repository of prostate tissues with detailed annotated clinical, demographic and outcomes data for use in the examination potential biomarkers for prostate cancer diagnosis and treatment. Here we present the current status of the CPCTR database, including an analysis of the retrospective prostate specimens currently banked by the CPCTR and their associated clinical data.

METHODS

Data collection sites

Cooperative Cancer Tissue Resource was established by the National Cancer Institute as a source for prostate cancer tissues for biomarker validation studies. This resource consists of four academic institutions (George Washington University Medical Center, Washington, DC, Medical College of Wisconsin, Milwaukee, WI, New York University, New York, NY, and the University of Pittsburgh, PA) and their associated hospitals (Howard University Medical Center, Fairfax INOVA Hospital, Fairfax, VA, Milwaukee VAMC, Community Memorial Hospital, Monomonee Falls, WI, Tisch Hospital, New York, NY, Bellevue Hospital, New York, NY, NYC VAMC, and the Pittsburgh VAMC). Thus this resource represents a broad range of American males undergoing prostate cancer surgery.

Pathologic evaluation

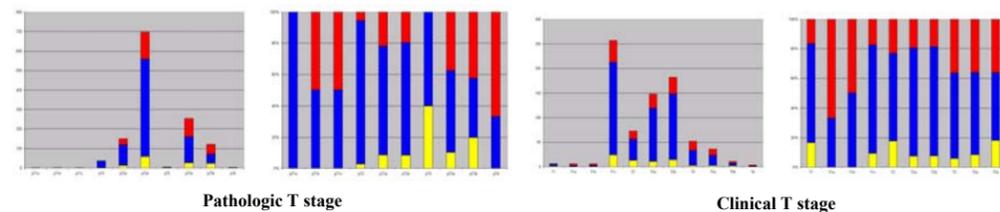
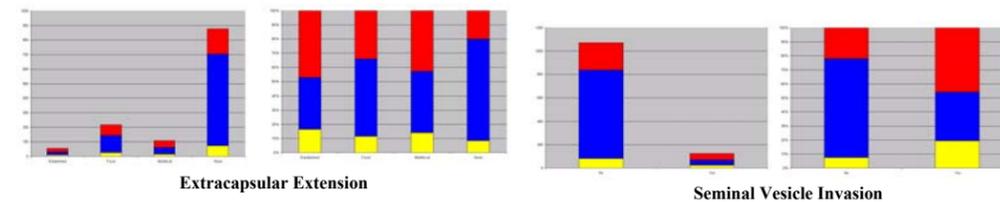
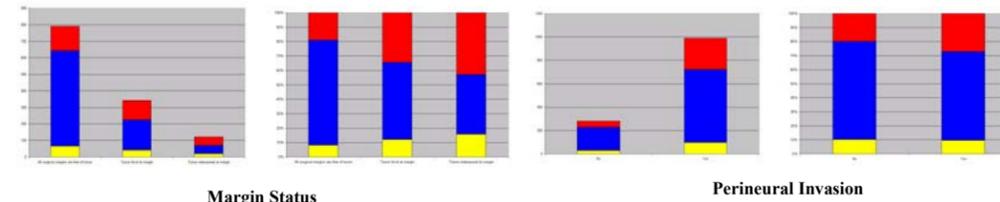
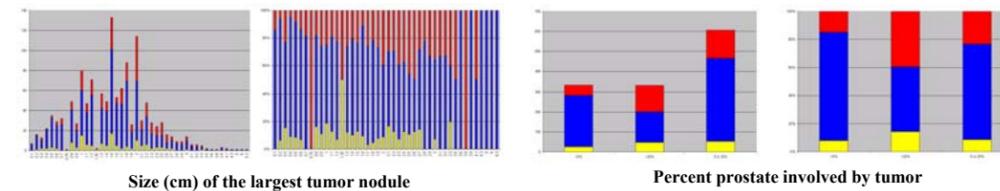
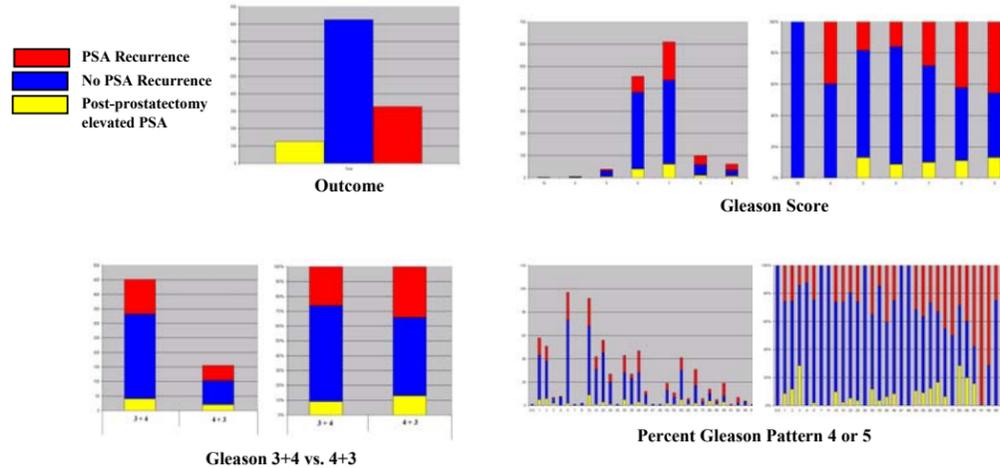
At each institution all the radical prostatectomy specimens from 1990 to 1995 were identified, and all pathologic material reviewed under standardized criteria using the Armed Forces Institute of Pathology Fascicle, Third Series, and the Johns Hopkins grading website (<http://162.129.103.34/prostate/>). In each of these cases review was done by academic pathologists including urologic pathology sub specialists. From these cases the associated archived paraffin embedded tissues were obtained for the CPCTR repository. In addition, prospective prostatectomy cases have been accrued over the last 2-5 years at the participating institutions.

Clinical Data Collection

IRB approval was obtained for all data and specimen collection. Clinical data was abstracted from the medical records, clinic patient charts, and cancer registries, and included demographic, clinical staging, and PSA recurrence data. Quality assurance testing is performed on 10% of the entire database on an annualized basis through random review of patient data and re-review of the pathologic specimens. Additional quality assurance includes multi-site review of cases from each contributing site.

Data used for analysis and statistical evaluation

Through June 2002 the CPCTR has collected identified 3318 prostate cancer cases, including 2895 prostatectomies. There are 939 cases with both the prostatectomy specimen and an associated diagnostic biopsies prior to surgery. PSA nadir values were calculated based on residual elevated PSA values and took into account the serum PSA half-life. For PSA nadir the PSA values needed to drop below 0.4 ng/dl at a timepoint greater than 59 days (if the initial PSA was less than 50 ng/dl – 2406 cases) or a timepoint greater than 89 days (if the initial PSA was greater than 50 ng/dl – 61 cases). For PSA recurrence serum PSA values needed to increase above 0.6 ng/dl (single value) or have a value between 0.4 – 0.6 ng/dl and demonstrate a continued rise in the subsequent PSA values. In the latter situation the PSA recurrence data was calculated based on the initial elevated PSA value above 0.4 ng/dl. 1766 cases had associated PSA follow-up data status post prostatectomy. PSA outcomes were evaluated on all cases with follow-up PSA values and 1276 demonstrated interpretable outcomes. Loss of cases included no post-surgical PSA values (1653 cases) or no initial PSA values (851 cases). Statistical analysis was performed using Chi-squared probability analysis and corrected for multiple tests using the Bonferroni method.



PSA Recurrence (red)
No PSA Recurrence (blue)
Post-prostatectomy elevated PSA (yellow)

FIGURES

Graphs represent the analyzed data in the Co-Operative Prostate Cancer Tissue Resource. Paired graphs demonstrate the data as either the total count of samples in the evaluated subgroup, or as the percent of the evaluated subgroup. The bar code is presented as Post-prostatectomy elevated PSA (yellow), PSA nadir without recurrence (blue) or PSA nadir with PSA recurrence (red). Significant studies are shown in table 1.

	Post-prostatectomy Elevated PSA	PSA recurrence
Race (African American)	N.S.	< 0.000005
Gleason Score	0.0000001	0.000005
Gleason score 6 vs. 7	N.S.	0.000001
Gleason pattern 3+4 vs. 4+3	N.S.	N.S.
Percent of Gland involved by tumor		
Extraprostatic extension		
cutoff 5%	N.S.	< 0.000005
cutoff 25%	N.S.	< 0.0000001
Extraprostatic extension		
none vs focal	N.S.	0.0000175
focal vs. established	N.S.	N.S.
focal vs multifocal or established	N.S.	N.S.
Margins		
Positive vs. negative	N.S.	< 0.0000001
focal vs. established	N.S.	N.S.
negative vs. focal	N.S.	< 0.0000001
Perineural invasion	N.S.	N.S.
Seminal Vesicle Invasion	0.000011	< 0.0000001
Pathologic Stage		
pT2a vs. pT2b	N.S.	N.S.
pT3a vs. pT3b	N.S.	N.S.
pT2 vs pT3	< 0.00000001	N.S.
Clinical Stage		
cT2a vs. cT2b	N.S.	N.S.
cT3a vs. cT3b	N.S.	N.S.
cT2 vs cT3	N.S.	N.S.

Extraprostatic extension definitions:
Focal = 1 site less than 0.8 mm.
Established = at least one site greater than 0.8 mm.
Multifocal = more than one site involved.

Margin positivity definitions:
Focal = 1 site less than 2 mm.
Established = multiple sites or at least one site greater than 2 mm.

RESULTS

Of the 1276 cases that could be evaluated, 125 (9.8%) demonstrated residual elevated PSA status post prostatectomy, and 1151 (90.2%) cases underwent PSA nadir. Of these 1151 that underwent PSA nadir, 325 (28.2% of nadir, 25.5% of total) cases underwent PSA recurrence. Overall average PSA follow-up time is 40.0 months (standard deviation 34.7 months), for PSA nadir patients the average is 41.0 months, (standard deviation 34.2 months). Average time to recurrence is 17.5 months, and the average recurrence free duration is 32.6 months. Results are summarized in Table 1 and figures 1-12. Features significantly associated with elevated post prostatectomy PSA value included higher Gleason score, seminal vesicle invasion, and increased pathologic stage (PT3 vs. PT2). Features associated with PSA recurrence include African American race, Gleason score, Gleason score 6 vs 7, percent of gland involved by tumor, xtraprostatic extension, margin positivity, and seminal vesicle invasion.

DISCUSSION

Multiple large data sets have been described in evaluating outcome status post radical prostatectomy. These have included the Johns Hopkins, Mayo, UCLA data sets. In each of these data sets the focus has been on the PSA recurrence rate status-post radical prostatectomy and PSA nadir. Only limited evaluation is described regarding the incidence of post-surgical elevated PSA as the assumption has been that these rates are low (less than 0.5%). These single site studies are often conducted by a single urologist and pathologist, and using a selected patient population. In contrast this data set represents a large, multi-institutional evaluation of patients undergoing radical prostatectomies and includes over fourteen urologists. For these reasons this data represents a cross section of results being obtained in medical centers across the United States. Of note the high incidence of post prostatectomy elevated PSA values (9.8%) has been suggested in previous results (Schaefer, U., Anticancer Research, 2000) where rates as high as 20% were described. This higher incidence of post prostatectomy elevated PSAs may reflect a more heterogeneous population of patients undergoing radical prostatectomy surgery across the country. The ability to identify these patients could make them eligible for alternative treatment modalities including radiation therapy, hormonal or cryotherapy. Other pathologic findings described in this dataset are similar in nature to those already published in smaller series, and validate these previous studies. In particular, the lack of significance for perineural invasion, of Gleason pattern 3+4 vs 4+3 tumors, suggests that while these findings may be important in individual cases, in a large patient population, these findings may not assist in patient treatment. While the current data is limited to the median follow-up of 40 months, ongoing additional clinical and PSA data accrual will only improve the quality of this data set. The associated tissues on which this data set is constructed are also being made available for tissue microarray studies (<http://www.prostatetissues.org>).

