Original Article:
Variations of Serum PSA Values at Different Time Points of Treatment Based on D’Amico Risk Stratification Groups- An Observational Analysis

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Abstract: Prostate cancer-the most common malignancy-among men worldwide, is among ten leading cancers in Kerala. The changes in serum PSA values at different time points of treatment might be of prognostic importance. The objective of this retrospective study was to stratify patients with prostate cancer according to D’AMICO risk stratification groups and correlate it with pre and post treatment PSA values. PSA, ALP as well as Gleason score noted in initial stage of diagnosis and during follow-up. There is a significant difference between pre and post treatment PSA (p <0.001). PSA values in risk assessment groups based on D’Amico Risk stratification was found significant (p<0.001). The number of patients in high risk category at 3 months follow-up (70%) indicating a slower response to treatment of prostate cancer and maximum in intermediate risk (82.4%) and low risk (64%) category at 12 and 24 months interval indicating a better response to treatment.

Key Words: Prostate Cancer, D’Amico risk stratification, Prostate Specific Antigen, Gleason Score, Alkaline Phosphatase

Introduction: Prostate cancer is primarily a disease of the elderly with more than three quarters of the cases occurring in men above 65 years of age. This disease has become a major health problem globally during the last few decades. Studies have shown that prostate cancer is the second most frequently diagnosed cancer in men worldwide and the fifth most common cancer overall.

Various parameters have been routinely assessing as it relates to prostate cancer treatment. These prostate cancer endpoints are usually clinical (overall survival, disease-free survival, metastasis-free survival), surgical (rates of extra capsular disease, seminal vesicle involvement, positive margins and lymph node positivity) or biochemical (Prostate specific antigen (PSA)). Pre-treatment PSA, clinical T category and biopsy-based Gleason score have been shown to be independently predictive of various combinations of prostate cancer related endpoints in a variety of treatment scenarios in the non-metastatic setting.

Increased levels of PSA prior to treatment have been shown to be associated with increased tumour volume/ stage and Gleason score, the risk of extra capsular/semenal vesicle failure after radical prostatectomy and external-beam radiotherapy. This system divided non-metastatic patients into low-, intermediate-, and high-risk based on initial PSA clinical T stage and biopsy Gleason score. Low-risk prostate cancer defined as T1/T2a, and PSA =10 ng/ml, and Gleason score =6. Intermediate-risk prostate cancer defined as T2b, and/or PSA 10-20 ng/mL and/or Gleason 7 disease. High-risk disease classified as the following high-risk features: T2c, PSA >20 ng/mL or Gleason 8-10 disease. Risk-stratification for prostate cancer, both at the time of diagnosis and at subsequent decision points, is critical to guide appropriate treatment decision-making. The venerable risk classification published by D’Amico et al in 1998, a closely related classifications adopted by the American Urological Association (AUA), the National Comprehensive Cancer Network (NCCN), and the Genitourinary Radiation Oncologists of Canada (GUROC), are no longer sufficient for this task. These classification systems do not distinguish between Gleason 3 + 4 or 4 + 3, outweigh clinical T stage,
and do not account for extent of biopsy involvement, and most importantly do not account for multiple adverse risk parameters. The Prostate Cancer Risk Stratification (ProCaRS) risk groups offer improved granularity within the D’Amico/ NCCN intermediate- and high-risk groups, but still reflect an ad hoc, rather than mathematically derived model, and do not perform well as linear predictors. The utility of integrating novel prognostic factors into an updated risk stratification schema is an area of current debate. The purpose of this work is to find the novel pre-treatment prognostic factors and alternative prostate cancer risk stratification schema to assess the feasibility and need for changes to existing risk stratification systems and its relevance in Indian population.

Materials and Methods
The present study is a prospective observational analysis in patients diagnosed with prostate cancer during the period of January 2008 to may 2018 at Malabar Cancer Center, Kerala, India. Since there were no ethical issues in this study, we could easily cope up with the further formalities. The Institutional Review Board of Malabar Cancer Centre approved this study and data was abstracted from Cancer registry and Medical records division. We consecutively analysed case reports of 201 patients who were diagnosed and treated for Prostate Cancer. All patients underwent a physical examination, digital rectal exam, prostate biopsy and histological findings to determine clinical stage. We restricted the analysis to those patients with complete laboratory data in the medical records. Among the 201 case reports, we analysed the medical records of those patients who underwent chemotherapy and radical prostatectomy as a part of their treatment. Those case reports with laboratory test results of the patients prior to treatment and after treatment were abstracted. It was found that 199 records maintained complete treatment data of the patients with prostate cancer. The following clinical and laboratory parameters were available at the time of diagnosis: MRD No., age, gender, prostate volume, diabetic history, alkaline phosphatise (ALP) levels prior to treatment, treatment protocols opted, pre and post treatment PSA values as well as Gleason score. PSA values of pre-treatment, treatment and post-treatment time points were recorded in a computerized database. Patient files with missing data on PSA values or treatment protocols as well as those undergoing palliative radiotherapy were excluded from this study.

Statistical Analysis
Statistical analysis was done by SPSS software. A non-parametric test called Friedman test was chosen for comparison since the data obtained was asymmetric in nature.

Results
Prostate volume
An enlarged prostate gland was observed in 85% (n=164) of the total cases. About 8% (n=16) had mildly enlarged prostate gland and the rest of the patients had normal volume (Table 1).

| Table 1: Percentage of prostate volume in patients diagnosed with prostate cancer |
|-------------------------------------------------|---|---|
| Prostate Size | No. of Patients | Percentage |
| Enlarged | 164 | 85% |
| Mild Enlarged | 16 | 8% |
| Normal | 13 | 7% |

Alkaline phosphatase levels
The ALP levels were analysed to rule out cases with bone metastasis. About 64% (n=60) cases had ALP levels within the normal ranges. However, 36% (n=34) cases had raised ALP levels which were an indicator of bone metastasis. (Table 2)

Table 2: Percentage of normal and abnormal level of ALP at the time of treatment in patients diagnosed with prostate cancer

<table>
<thead>
<tr>
<th>ALP levels (IU/L)</th>
<th>Number of patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal range</td>
<td>60</td>
<td>64%</td>
</tr>
<tr>
<td>Abnormal range</td>
<td>34</td>
<td>36%</td>
</tr>
</tbody>
</table>

Diabetic history
All the cases were evaluated for diabetic history. About 54 cases were found diabetic however, 145 were non-diabetic patients. No significant correlation was observed between diabetic history and serum PSA levels.

Risk stratification based on pre-treatment PSA values
Considering pre-treatment PSA values alone, the patients were stratified as high risk, low risk and intermediate risk. About 70% (n=130) of patients were categorized under high-risk group. Patients with intermediate risk were observed for 6% (n=12) and 24% (n=45) of patients were included in the low risk category. (Table 3)

| Table 3: Percentage of patients in different risk groups of risk stratification based on pre treatment PSA level |
|-------------------------------------------------|---|---|
| Risk groups | Number of patients | Percentage |
| High risk | 130 | 70% |
| Low risk | 45 | 24% |
| Intermediate risk | 12 | 6% |

Risk stratification observed at 3 months post treatment
Among 199 patients, 187 had a follow up with PSA values of 3 months after the onset of treatment. About 70% (n=130) of patients were categorized under high-risk group. About 6% (n=12) patients were belonged to the intermediate risk and 24% (n=45) patients in the low risk category. These findings are indicated that there is no significant reduction in PSA values obtained after 3 months of treatment compared to the baseline values.

Risk stratification observed at 6 months post treatment
All the patients had a follow up with PSA values of 6 months after the onset of treatment. About 18% of patients were categorized under high-risk group. Among this 5% belonged to the intermediate risk and 76% of patients were included in the low risk group. Majority (76%) of the patients had shifted to the low risk group 6 months after the onset of treatment. (Table 4)

| Table 4: Comparison of PSA values obtained during different time points |
|-------------------------------------------------|---|---|
| Time points | PSA levels (ng/ml) | p value |
| Pre-treatment | 205.53+616.04*** | <0.001 |
| 6 months | 131.11+721.23*** | <0.001 |
| 12 months | 119.57+490.07*** | <0.001 |

Risk stratification 12 months post treatment
Among 199 patients, 197 had a follow-up with PSA values of 12 months after the onset of treatment. About 14.21% of patients were categorized under high-risk group, 82.7% belonged to the intermediate risk, and 3.04% of patients were included in the low risk category. Majority (82.7%) of the patients had shifted to the intermediate risk group 12 months after the onset of treatment. (Table 4)

Risk stratification 24 months after treatment
Among 199 patients, 197 had a follow-up with PSA values 12 months after the onset of treatment. About 28.8% of patients were categorized under high-risk group. It was observed that 8.08% of patients were belonged to the intermediate risk and 64.4% of patients were included in the low risk category. Majority (64%) of the patients had shifted to the low risk group 24 months after the onset of treatment. (Table 4)
Comparison of PSA values obtained during different time points of treatment

Base line PSA values along with PSA values obtained during different time points were compared by using SPSS software. The sample size was 81 and since the data had a non-uniform distribution, non-parametric Friedman test was chosen. Since we got p <0.001 there is a significant difference between pre and post treatment PSA values taken during different time points after the onset of treatment. (Table 4)

Discussion and Conclusion

The usefulness of PSA testing has been shown for early diagnosis, assessing the response of treatment, and determining tumour progression. (6) In a report using the PSA level to identify non–organ-confined disease, the percentage of tumours with extra prostatic extension increased when patients had a high PSA level. The incidence of extra prostatic extension was 50% and 80% at a PSA level of 4 to 10 ng/mL and >20 ng/mL, respectively. (7) In 1998, D’Amico et al. suggested a model stratifying patients with prostate cancer into those with low, intermediate, or high-risk of biochemical recurrence after surgery according to the clinical TNM stage, biopsy Gleason score, and preoperative prostate-specific antigen level etc. (8). We aimed to study the relevance of this classification system in Indian population who are undergoing prostate cancer treatment.

From the results obtained, great variations can be seen in PSA values and risk assessment groups based on D’Amico Risk stratification (p<0.001). The number of patients being maximum in high risk category at 3 months’ follow-up (70%) indicating a slower response to treatment of prostate cancer and being maximum in intermediate risk (82.4%) and low risk (64%) category at 12 months and 24 months’ interval respectively. All the results were giving better information regarding the response to the treatment. Both clinical and pathologic factors play a role in determining a patient’s likelihood of having an undetectable serum PSA level at 10 to 15 years following surgery. The most predictive of these factors include pre-treatment PSA level, pathologic stage, and Gleason score; however, other microscopic features and biomarkers have also been suggested to identify patients at risk for failure following surgery. Between 27% and 53% of men, undergoing radical prostatectomy will have a detectable serum PSA elevation within 10 years following surgery. PSA closely calibrates with PSA and hence it considered as a sensitive marker for early detection of prostate cancer and a surrogate for recurrence and prognosis after radical treatment procedures. (9) Until now, there have been no reliable data concerning the timing and natural history of disease progression for men with an isolated PSA level elevation after radical prostatectomy (10-12). These findings should allow physicians and patients to make educated decisions about the progression of disease and need for treatment and to facilitate the design of clinical trials.

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References