TIME TRENDS IN CLINICAL RISK STRATIFICATION FOR PROSTATE CANCER: IMPLICATIONS FOR OUTCOMES (DATA FROM CaPSURE)

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ABSTRACT

Purpose: Many instruments designed to predict prostate cancer risk use a combination of clinical T stage, biopsy Gleason score and serum prostate specific antigen (PSA). We designed a study to characterize time trends in these parameters and their impact on patient risk stratification.

Materials and Methods: Data were abstracted from CaPSURE (Cancer of the Prostate Strategic Urological Research Endeavor), a disease registry of 8,685 men with prostate cancer. The 6,260 men diagnosed since 1989 who had complete clinical information reported were categorized into low, intermediate or high risk groups based on established parameters for T stage, Gleason score and PSA.

Results: Between 1989 to 1990 and 2001 to 2002 the proportion of patients presenting with high, intermediate and low risk disease changed from 40.9%, 28.0% and 31.2% to 14.8%, 37.5% and 47.7%, respectively (p < 0.0001). The incidence of T1 tumors increased from 16.7% to 48.5% and that of T3–4 tumors decreased from 11.8% to 3.5%, respectively (p < 0.0001). The incidence of Gleason 2 to 6 tumors decreased from 77.1% to 66.4%, while that of Gleason 7 tumors increased from 12.9% to 24.8%, respectively (p = 0.0030). PSA levels 10 ng/ml or less increased from 43.6% to 77.7%, respectively, while PSA 10 to 20 and greater than 20 ng/ml decreased accordingly (p < 0.0001). These trends were mirrored in subset analysis of black patients.

Conclusions: A significant downward risk migration has occurred over time. Gleason score is now more likely and PSA less likely than previously to drive risk assignment. This shift is most likely attributable to changes in practice patterns with respect to screening and pathological grading. These changes should be considered when applying nomograms derived from earlier datasets to contemporary cases.

Key Words: prostatic neoplasms, risk factors, prognosis, prostate-specific antigen

In the absence of data from randomized clinical trials establishing definitively the optimal treatment for localized prostate cancer, clinicians must rely on estimates of prognostic derived from clinical variables to guide patients in therapeutic decision making. In recent years increasingly sophisticated nomograms and related instruments have been designed to facilitate and improve these estimates. Virtually all such instruments incorporate the Gleason score of the diagnostic biopsy and serum prostate specific antigen (PSA), and many schemes, particularly earlier ones from the mid 1990s, also consider clinical T stage.1

PSA screening has effected downward biochemical and clinical stage migrations, with the result that a given newly diagnosed prostate cancer is likely to be of lower stage and associated with a lower serum PSA than previously.2–4 On the other hand, recent reports have illustrated a trend during the last decade toward upgrading in terms of Gleason scoring.5 The risk assessment system devised by D’Amico et al assigns patients to low, intermediate or high risk groups based on clinical T stage, serum PSA and Gleason score.6,7 Such a schema has been shown to predict accurately outcomes of management with either surgery or radiation.6,7 Using this system as a model instrument, we characterized trends over time in these 3 variables and in risk stratification as a function of these variables. We then explored the evolution of the relative importance of each variable in determining risk assignment.

MATERIALS AND METHODS

CaPSURE (TAP Pharmaceutical Products, Inc., Lake Forest, Illinois) is a longitudinal, observational database of men with biopsy proven prostate adenocarcinoma recruited from more than 30 academic and community based urology practices across the United States. All patients with prostate cancer are recruited consecutively by participating urologists who report complete clinical data. Data for patients diagnosed before 1995 were initially entered retrospectively, while all data entry has been prospective for those diagnosed during and after 1995. Completeness and accuracy of the data are assured by random sample chart review every 6 months.8

A total of 8,685 patients were enrolled in the CaPSURE database between June 1, 1995, when the database was opened, and July 31, 2002. Of this group 2,387 patients were excluded from study because they had unknown or missing risk parameters of PSA at diagnosis (692, 29% of those excluded), biopsy Gleason score (327, 14%) clinical T stage (358, 15%) or multiple parameters (1010, 42%). The proportion of patients excluded from the study due to missing data did not trend significantly over time. Another 321 patients diag-
nosed before 1989 were also excluded from study, leaving 6,260 patients for analysis.

Patients were stratified into low, intermediate and high risk groups. Low risk patients had PSA 10 ng/ml or less, biopsy Gleason score 6 or less, and clinical stage (1997 TNM system) T1 or T2a. Intermediate risk patients had PSA 10.01 to 20 ng/ml, Gleason score 7 or clinical stage T2b. High risk patients had PSA greater than 20 ng/ml, Gleason score 8 or greater, or clinical stage T3 or T4. These are the criteria described by D’Amico et al, with the exception that the original classification was based on the 1992 TNM staging system and defined T2a as low, T2b as intermediate and T2c as high risk. These risk strata predict approximately 85%, 50% and 33% of 5-year biochemical recurrence-free survival, respectively. Data were analyzed by year of diagnosis. Of note, CaPSURE underwent a structural transition in 1998, and while the data before and after that time are fully comparable, overall accrual in that year was only 50 patients, and therefore data for 1998 and 1999 were combined when plotting individual years.

We first studied movements in the distribution of patients across the 3 risk strata. We then analyzed trends in clinical T staging, Gleason grading and serum PSA for the whole database and for the intermediate and high risk subsets. We also performed a subset analysis for the black patients in the dataset (615, 9.3%). Statistical significance of temporal trends was assessed using the Mantel-Haenszel chi-square test for trend, and all analyses were performed using SAS software, version 8.2 (The SAS Institute, Cary, North Carolina).

RESULTS

Overall trends in the distribution of patients among the low, intermediate and high risk groups are presented in figure 1. The proportion of patients presenting with high risk disease declined by nearly two-thirds during the study period, from 40.9% in 1989 to 1990 to 14.8% in 2001 to 2002. Much of the corresponding increase has been in the low risk group, which has grown by half from 31.2% to 47.7% of patients during the same period. The intermediate risk group also increased from 28.0% to 37.5% of patients.

Figure 2, A demonstrates that clinically organ confined tumors (stage T1–2) represent the overwhelming majority ofrogen confined cancers, having increased from 88.2% in the first 2 years to 96.5% in the last 2 years of the study. The largest shift has been a dramatic increase in the relative incidence of T1 tumors, particularly in the last 5 years (only 16.7% of cases in 1989 to 1990 and 48.5% in 2001 to 2002). Declines in locally advanced and T2a tumors appear to account for most of this shift, as the proportion of T2b tumors decreased only slightly, from 24.2% in 1989 to 1990 to 20.1% in 2001 to 2002.

The incidence of Gleason scores 6 or less has decreased from 77.1% to 66.4% of the dataset (fig. 2, B). However, within this group, the proportion of Gleason 5–6 tumors has increased from 44.1% to 64.8%, while Gleason 2–4 tumors have decreased from 33.3% to 1.6%. The incidence of Gleason 7 disease has nearly doubled from 12.9% to 24.8%, and the incidence of Gleason 8–10 tumors has varied between 7.2% and 13.8% with no significant trend in either direction. PSA levels greater than 20 ng/ml decreased from 32.8% in 1989 to 1990 to 7.2% in 2001 to 2002 (fig. 2, C). PSA 10 to 20 ng/ml also decreased, from 23.7% to 15.1%, while PSA 10 ng/ml or less increased from 43.6% to 77.7% between the 2 time periods. This increase in low PSA tumors occurred exclusively in the PSA 4 to 10 ng/ml range (29.0% to 64.3%). The proportion of tumors with PSA less than 4 ng/ml varied from 8.4% to 20.3% but did not trend consistently. Of note 9.7% of and 3.3% of intermediate and high risk tumors, respectively, were diagnosed in the context of PSA less than 4 ng/ml.

There were no significant trends in distributions of T stages among high risk patients (fig 3, A) or high risk patients. Gleason scores increased significantly in both groups (fig. 3, B and E) with Gleason 2 to 6 diagnoses decreasing from 75.0% in 1989 to 1990 to 43.9% in 2001 to 2002 among intermediate risk patients and from 61.8% to 15.1% among high risk patients. PSA levels decreased accordingly with levels 10 ng/ml or less increasing from 30.8% to 66.0% and from 9.2% to 35.1% for intermediate and high risk patients, respectively (fig. 3, C and E). The numbers of intermediate and high risk patients with multiple adverse risk factors did not vary significantly within each risk group during the study period.

Results of the subset analysis for black patients are presented in the table. Black patients had consistently higher T stage, Gleason score, PSA and overall risk category in each time period. Time trends among these patients exactly mirrored those of the overall dataset, with the exception that the upward migration of Gleason scores did not reach statistical significance in this group.

DISCUSSION

Recent data indicate that of the 220,900 new prostate cancer cases expected in 2003, as many as 85% will be diagnosed at local or regional stages. Of these nearly 188,000 cases a recent analysis suggested that 15% of white patients and 37% of black men patients may be over-diagnosed by PSA screening. This significant fraction of patients may be diagnosed with a cancer that would not substantially shorten their lives if left untreated. Furthermore, in an additional subset of patients clinically localized disease eventually progresses to lethal metastatic disease despite optimal local therapy. The goal of risk assessment in prostate cancer, then, is to identity those patients with low risk disease who can be safely observed, those who will likely benefit from standard local therapy and those who should be treated presumptively for advanced disease.

A recent study revealed that nomograms were comparable to expert opinions in predicting organ confined disease at surgery, and performed better in predicting 5-year recurrence-free survival in a clinical practice setting. A concomitant review of the performance of nomograms for other disease prognoses revealed that nomograms outperformed expert predictions in 13 of 22 (59%) studies. Nomograms are intended to predict a given clinical outcome but they must necessarily be developed via retrospective analysis of data from patients whose outcome is known. Their relevance to clinical practice is predicated on the assumption that the risk characteristics of the patients whose clinical data were used to build and validate the nomogram have a
distribution comparable to those of the patients for whom the nomogram is intended to be used.

We found significant trends during the last decade in the principal determinants of prostate cancer risk and distribution of patients among risk groups. At the dawn of the PSA era, a plurality of patients presented with tumors with high risk features and even into the mid 1990s patients were distributed almost equally across the 3 risk groups. However, in the first years of the new decade, nearly half of patients presented with low risk tumors. This risk migration is apparently continuing, as even from 2000 to 2002 the proportion of patients with high risk tumors decreased from 17.8% to 14.0%, while that of patients with low risk tumors increased from 45.5% to 49.5%.

T1 tumors represent a growing fraction of prostate cancers, increasing steadily through the early 1990s and then more sharply during the last 5 years to greater than 50% of cases for the first time in 2002. It is interesting that while the rates of high risk, locally advanced tumors (T3 or T4) and unilateral organ confined (low risk) tumors (T2a) have decreased steadily, the relative incidence of intermediate risk bilateral disease (T2b) has decreased only slightly. In addition to PSA screening, an additional factor contributing to the detection of progressively lower stage disease may be the increased use of extended pattern biopsy schemes, which have been shown to be more sensitive than standard sextant templates, possibly allowing them to detect disease earlier. PSA levels at diagnosis have likewise decreased dramatically in the era of PSA screening. These stage and PSA trends are largely consistent with those reported previously. The relatively consistent proportion of cases diagnosed with PSA less than 4 ng/ml, including many that have intermediate or high risk features based on Gleason score and/or T stage, underscores the continued importance of digital rectal examination in detecting cases that are false-negative by PSA screening alone.

Overall, we found a trend toward higher Gleason scoring with time. Gleason 2 to 6 tumors decreased from nearly 80% to two-thirds of diagnoses, and they are now almost exclusively Gleason 5 to 6 cancers. The diagnosis of Gleason score 2 to 4 disease, which once accounted for a third of all tumors,
has all but vanished. Most of the increase in grade is to Gleason 7 tumors whose incidence has roughly doubled. There were no consistent trends in the diagnosis of Gleason 8 to 10 tumors. Unlike the downward trends in clinical stage and PSA, the change in Gleason grading patterns appears to be attributable to changes in interpretation of histological slides. Smith et al systematically reevaluated 2 series of prostate cancer specimens from 1989 to 1991 and 1998 to 2000, upgrading and downgrading 35% and 9%, respectively, of the earlier series and 9% and 22%, respectively, of the contemporary specimens.5

One of the most important findings of this study is the change with time in the determinants of intermediate and high risk disease. In the early years of the analysis patients were likely to be assigned to intermediate risk based on PSA 10 to 20 ng/ml or to high risk based on PSA greater than 20 ng/ml. More contemporary patients, on the other hand, are more likely to have PSA levels in the low risk range and to be considered to have intermediate or high risk disease based on Gleason score 7 or 8 to 10, respectively. Because the increase in Gleason scores may be in part artificial, as noted previously, it is possible that contemporary intermediate and high risk patients actually have somewhat better biological risk than previous patients in the same risk groups. The distribution of T stages, meanwhile, did not vary significantly within the intermediate or high risk groups.

Fig. 3. Time trends in risk characteristics among intermediate and high risk patients. A and D, clinical T stage. B and E, Gleason score. C and F, serum PSA levels.

Risk distribution and clinical characteristics of black patients

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<tbody>
<tr>
<td>No. pts</td>
<td>48</td>
<td>186</td>
<td>215</td>
<td>166</td>
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<tr>
<td>% Risk group (p &lt; 0.0001):</td>
<td></td>
<td></td>
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<tr>
<td>Low</td>
<td>26.8</td>
<td>21.0</td>
<td>30.2</td>
<td>36.8</td>
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<tr>
<td>Intermediate</td>
<td>22.9</td>
<td>32.8</td>
<td>35.8</td>
<td>39.2</td>
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<tr>
<td>High</td>
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<td>46.2</td>
<td>34.0</td>
<td>24.1</td>
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<tr>
<td>% Clinical T stage (p = 0.0006):</td>
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<tr>
<td>T1–2a</td>
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<td>61.4</td>
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<tr>
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<td>30.7</td>
<td>27.4</td>
<td>23.5</td>
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<tr>
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<td>59.1</td>
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<td>18.3</td>
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<td>% PSA (ng/ml) (p &lt; 0.0001):</td>
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<tr>
<td>10 or Less</td>
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<td>36.0</td>
<td>51.6</td>
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<tr>
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<td>Greater than 20</td>
<td>41.7</td>
<td>38.2</td>
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the clinical data used to build the instruments continue to represent contemporary prostate cancer cases seen in clinical practice. For example, Partin et al recently published revisions to their widely used nomogram based on a contemporary cohort of patients with more favorable clinical characteristics than their original patient set.14 Also, if the reporting of comparative outcomes for radical prostatectomy or other treatment modalities is to become a reality,17 such reporting must include risk adjustment based on contemporary risk distributions to avoid case-selection bias.

Our study does have limitations. We selected a risk classification system based on clinical T stage, Gleason score and PSA because these 3 variables are nearly universally measured in practice and because they form the basis for some of the most widely cited nomograms.18, 19 However, recent reports, including an updated nomogram by D’Amico et al, have demonstrated the importance of the percent of positive biopsies in predicting treatment outcomes.20, 21 CaPSURE has only collected these data consistently relatively recently, preventing the longitudinal analysis of this variable. We have begun to analyze biopsy data in risk algorithms among the patients for whom they are available22 and expect that they may eventually supplant clinical T stage in our risk stratification model. Clinical T stage may become even less useful in the future, as T1c tumors account for an increasing proportion of new diagnoses. Since the CaPSURE practice sites have not been chosen at random, they may not constitute a statistically valid sample of the United States patient population. However, the practice sites do represent a broad range of geographic locales and a mix of academic and community sites, which we believe to be the best available sample for the analysis of temporal trends.

CONCLUSIONS

We have demonstrated an ongoing downward risk migration among patients with prostate cancer during the last decade. Moreover, we found a significant shift in the determinants of prostate cancer risk stratification, with Gleason score now more likely and serum PSA less likely to drive risk assignment. These shifts are unlikely to be attributable to changes in tumor biology, but rather to changes in practice patterns with respect to Gleason grading, prevalence of PSA screening and staging. These changes support the movement in the literature away from the use of T stage in modern nomograms, and should underscore the importance of periodic revalidation of all nomograms and other risk algorithms using contemporary patient data.

REFERENCES


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DISCUSSION

Dr. Philip W. Kantoff. What was the end point in this particular study?

Dr. Peter R. Carroll. We wanted to test the hypothesis that intervention changes the prostate microenvironment, and so we were not looking at a clinical end point. The end point would be a change in our expression arrays. We conducted an earlier trial using intensive dietary therapy in which we had no idea what the lowering of PSA values was doing to the prostate microenvironment. PSA varies quite a bit and is not a great end point in low risk patients. So in this study we are testing the hypothesis that intervention changes the prostate microenvironment using gene expression arrays.

Doctor Kantoff. To my knowledge CaPSURE represents the only population based look at surveillance. One of the challenging things that we confront in following patients on surveillance is fluctuation of PSA with time. We think, but we have not proved, that PSA is an important parameter to watch in these patients, and that patients will be driven by PSA before treatment. Can you comment on PSA fluctuations in your dataset? Of your 2 groups the one in which the PSA went from 11 to 19 received treatment, and the patients who did not receive treatment remained stable. Is there inter-PSA variability within a patient and what does that look like?

Doctor Carroll. I did not look at the individual data points for CaPSURE patients but the PSA variability is considerable. The problem is that PSA is the biggest driver of treatment, and so we are currently struggling in our clinical trials about how to calculate PSA velocity. It is difficult to know at what PSA doubling time do we need to tell the patient that he should be treated. If the PSA is doubling at 3 to 6-month intervals, for example, I would recommend treatment.

Dr. Matthew R. Smith. The surveillance regimen requires an intense regimen of biopsies at baseline, 3 months and then annually. Have you done any modeling to look at what the probability of defined progression is in patients who are otherwise stable, meaning the variation that you would expect just from re-biopsying the patient on 2 different days?

Doctor Carroll. That variability has decreased substantially with extended pattern biopsy schemes. The variability in grading has been reduced from 25% to a much lower number with the extended pattern biopsy. There is no question that you under grade the tumor and under assess its volume with the sextant scheme. The best evidence suggests that this is much less likely with the extended pattern biopsy.

Dr. Mack Roach, III. Some data suggest that the correlation coefficient between tumor volume and PSA is poor when the PSA is less than about 9. You can have a patient who has an aggressive tumor that is making little PSA and a lot of PSA is being made by benign tissue. If you put him on an intensive dietary therapy, as you did in an earlier study, the intervention could lower the PSA due to benign tissue and meanwhile the cancer could be growing.

Doctor Carroll. That is why we want to look at the direct prostate microenvironment and get away from the PSA end point.

Dr. Anthony V. D'Amico. If you take a person who has some finite PSA when they enter a study and the PSA doubles, the baseline value has to double also. This biases doubling times for people who start at a PSA of 7 versus 4. A more correct way of doing this would be to subtract the baseline value from every value, that is start at time zero, and get true doubling times based on a threshold. This would correct for the benign substructure, at least at time zero, by negating the baseline level. The doubling times would fall from 10 or 15-year levels to doubling times that are more within the same group because now you are doubling starting from zero. This might help to make the doubling time a little more relevant.

Doctor Smith. Your point is absolutely correct if you measure the time to PSA doubling. The calculated PSA doubling time is based on a slope and so the baseline PSA value should not affect the determination.

Doctor D'Amico. That isn't quite true because it is an intercept as well as a slope. Take a simple example. If you start out with a PSA of 4 and you go up a point every 6 months, it will take 6 months times 4, or 2 years, to double the PSA. However, if you start at zero and go up a point in 6 months and another point in 6 months, the doubling time is 6 months.

Doctor Roach. The length of time between the data points is an equally critical issue. Some earlier studies looking at PSA slopes suggested that the optimal interval between 2 values to calculate a slope is about 18 months. For example, you draw the PSA today and it is 0.5, and you draw it tomorrow and it is 0.6. If you extrapolated the slope based on these values, you would assume that the patient would be dead in a few years. However, if you separated those readings by 6 months and got the same values (0.5 and 0.6) the slope would be quite different. Most of these studies had a followup of only 2 years, which does not provide a lot of opportunity to have calculated accurate slopes.

Dr. Peter Iversen. You dealt with the problem of whether patients originally assigned to the low risk group would, if treated with watchful waiting, move into moderate or high risk groups. You said that, according to your experience most patients maintained their risk assessment group. There were about 400 patients, of whom 40% later changed to active therapy, and the biggest predictor for that was PSA.
**Doctor Carroll.** The PSA change tended to be within the same risk group. Remember that those were the median levels for the entire cohort of patients who were treated. When you actually look at the individual patients, they tended to change PSA within their risk groups. For example, they might have gone from a PSA of 5 to 8 or from 11 to 16. Another point is that these patients might have gotten treatment for other reasons, such as just getting tired of surveillance.

**Doctor Iversen.** You said that we are going from a period in which we have had significant over diagnosis and overtreatment to a period when we will probably still see over diagnosis but less overtreatment. Isn’t it a paradox that we still want to maintain this aggressive approach, which you see as over diagnosis, while at the same time talking about not intervening in the natural history of early disease? How is that going to be accepted by our patient population?

**Doctor Carroll.** I think that patients need to be reeducated. When a man gets the initial diagnosis, all he hears is cancer. He does not differentiate prostate cancer from pancreatic or lung cancer. We have looked at how they view these cancers. There is no question that if you mention the word cancer to a man, he thinks he is going to die, and if he gets treatment, he will live. We need to educate our patients that prostate cancer is a disease process different than pancreatic or lung cancer. I am a believer in early detection efforts but I think a lot of the controversy will fall by the wayside if we stop equating early detection with treatment for all patients.