Prostate Cancer: An Evolving Paradigm

Jorge R. Caso, M.D., Vladimir Mouraviev, M.D., Ph.D., Matvey Tsivian, M.D.,
Thomas J. Polascik, M.D., FACS, and Judd W. Moul, M.D., FACS

Abstract

Since at least the early 1990s, stage and risk migration have been seen in patients with prostate cancer, likely corresponding to the institution of prostate specific antigen (PSA) screening in health systems. Preoperative risk factors, including PSA level and clinical stage, have decreased significantly. These improved prognostic variables have led to a larger portion of men being stratified with low-risk disease, as per the classification of D'Amico and associates. This, in turn, has corresponded with more favorable postoperative variables, including decreased extraprostatic tumor extension and prolonged biochemical-free recurrence rates. The advent of focal therapy is bolstered by findings of increased unilateral disease with decreased tumor volume. Increasingly, targeted or delayed therapies may be possible within the current era of lower risk disease.

Introduction

WHEREAS THE DECISION to proceed with prostate biopsy once arose from suspicions based on clinical symptoms and the digital rectal examination (DRE), after the development of serum prostate specific antigen (PSA) as a tumor marker in the 1980s, a diagnostic shift became apparent. Less aggressive cancers were presumably detected earlier in their natural history, leading to more favorable results after therapy.

Prostate cancer remains the most common visceral cancer among men in the United States, with an estimated 192,280 new cases in 2009.¹ The high incidence of these tumors and the current trend toward a greater proportion of lower risk disease underscores the threats of overdiagnosis and overtreatment, which has led to the implementation of focal therapies and the establishment of active surveillance protocols.

Clinical Risk Migration in the PSA Era

In 1991, Catalona and colleagues² investigated the application of PSA—which previously had been used as a marker for prostate cancer progression and therapeutic response—as a screening tool for prostate cancer. A cutoff level of 4 ng/mL was established, and men underwent biopsy for PSA elevations if there was a concurrent abnormality on follow-up DRE or transrectal ultrasonography (TRUS) evaluation of the prostate. In their analysis, PSA was estimated to have a higher calculated positive predictive value (40%) and greater overall accuracy (64%) than DRE or TRUS.

On a subsequent study, among a cohort of men followed with PSA values obtained every 6 months, eventually 42% of

the study population with a positive screening (elevated PSA level) was found to have prostate cancer on biopsy. The authors noted a near doubling of the proportion of organ-confined tumors compared with an age-matched group in whom DRE was the primary form of detection.³

After the establishment of prostate cancer screening in the United States with PSA and DRE, the clinical characteristics of the average patient at presentation changed, including a younger age at diagnosis, increased incidence of nonpalpable cancers,^{4–13} and decreased PSA levels.^{5–7, 10–12} This has occurred in concert with a variable effect on biopsy Gleason score.^{6,12} There is an apparent trend toward more moderately differentiated prostate carcinoma, in part because of an evolving interpretation of pathologic review of specimens over the last decade.^{12,14} In one study, when comparing the original Gleason score of 204 radical prostatectomy samples from 1995 to 1997 to a more recent (2008) grade assignment, upgrading occurred in 30.9% of cases and downgrading in 12.3%.¹⁵

Risk stratification using PSA, clinical stage, and Gleason score was suggested by D'Amico and colleagues¹⁶ in 1998. The low-risk group encompasses men with PSA <10 ng/mL, Gleason score less than 7, and clinical stage T_{1c} or T_{2a}. A recent review of 6652 patients who were treated with radical prostatectomy for clinically localized prostate cancer from 1984 to 2005 revealed a mean age at surgery of 58 years with a median preoperative PSA level of 6 ng/mL.⁶ At the time of diagnosis, 61% of patients in the overall cohort presented with T_{1c} tumors and 63% with a Gleason score of 6 or less, resulting in nearly 60% of men being classified as having low-risk disease

after stratification. Focusing on the years from 1998 to 2005, 72.6% of tumors were T_{1c}, and 67.7% of men were classified as low risk.⁶

These findings are consistent with other US studies that document an evolution into an increasing proportion of low-risk disease at the time of diagnosis,^{5,10} with a consequently marked decrease in the high-risk group and less apparent changes in the intermediate group.^{5,6} In addition, they have been confirmed in large pooled patient cohorts.^{9,12,13,17} In the Department of Defense Center for Prostate Disease Research (CPDR) database, 2042 patients were identified over the years 1988 to 1998. The number of men who presented with metastatic disease decreased significantly from 14.1% and 19.8% during the first 2 years of study to only 3.3% in the final year. In addition, clinically staged T₄, T₃, T₂, T_{1a}, and T_{1b} tumors all decreased significantly over the 11-year span, with a correspondingly significant increase in T_{1c} tumors from 0 to 47.8%.¹³

A total of 5343 patients in the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database were evaluated from 1989 to 2001.⁹ Overall, 37.5% of patients were low risk during the years of study, the proportion increasing from 29.8% in 1989 to 1992 to 45.3% in 1999 to 2001.⁹ In a separate analysis that encompassed the years 1995 to 2007, 42% of patients presented with low-risk features. Socio-demographic factors that were associated with a more favorable classification on multivariate analyses were age younger than 60, education beyond high school, and income greater than \$50,000, while nonwhite race was associated with high-risk disease.¹⁸

The Shared Equal Access Regional Cancer Hospital (SEARCH) database was reviewed from 1988 to 2002 and identified 1684 patients undergoing radical prostatectomy. More favorable PSA levels and clinical stage trends were noted in the most recent era.¹²

Outside of the United States, the use of PSA values for routine screening is limited. In Canada, recommendations vary among different health organizations,¹⁹ and the Canadian Urological Association is in the process of publishing PSA screening guidelines.²⁰ Almost half the men over the age of 50, however, have been screened at some point in their lifetimes, the majority of these within the previous year.²¹ An ongoing trial in the United Kingdom, where there is negligible opportunistic PSA testing, enrolled 94,427 men between the ages of 50 and 69 who were screened with a single PSA reading. Nine percent of the screened men had a PSA value greater than the cutoff of 3 ng/mL, and almost a quarter of these were later found to have cancer on biopsy. Compared with newly diagnosed cancers in the national registry, which was used as a control, the screened cancers were of lower biopsy Gleason grade, lower PSA level, and lower clinical stage. The authors concluded that the rate of cancer detection would be greatly increased if PSA testing were instituted, but with an attendant risk of overtreating low-risk disease.²²

In Tyrol, Austria, one of nine federal states in the country, men between the ages of 45 and 75 or those younger with a positive family history were offered free screening by age-specific PSA testing and percent-free PSA. Approximately one third of eligible men participated in this program; during the study period, the incidence of organ-confined disease increased while the incidence of metastatic disease declined.²³ In the rest of Europe, the exact rate of PSA screening is un-

known, although a rate of 10% to 20% of the general population has been assumed.²⁴

Pathologic, Biochemical, and Cancer-Survival Correlation with Low-Risk Disease

These more favorable clinical parameters have pathologic correlation with a noted decline in the rate of extraprostatic tumor extension (EPE) on review of radical prostatectomy specimens,^{4-7,10-12} dropping from 81% to 36% over a decade in one review⁴ and 79% to 25% over nearly two decades in another.¹⁰ The authors in this latter study evaluated the percent change in nonorgan-confined disease as calculated over three periods: 1987 to 1992, 1992 to 1995, and 1995 to 2005. The trend was -2.9%, -16.9%, and -4.2%, respectively, indicating that stage migration accelerated during the middle period and has continued changing more recently at a slower rate.¹⁰ This decrease in EPE appears to have occurred independent of prognostic indicators, such as clinical stage, preoperative PSA score, and biopsy Gleason grade.⁴

Overall rates of PSA recurrence have also decreased significantly,^{5-7,11} with one group noting their 10-year biochemical progression-free rates after radical prostatectomy in the PSA era increased from 59% to 75%.⁷ Significant differences over a 10-year span were noted both for patients with and without organ-confined disease.⁷ On univariate analysis, men who were identified in the SEARCH database actually had a higher rate of PSA recurrence if they were treated during the most recent era. This was present despite lower rates of EPE and a greater number of organ-confined tumors; lead time bias from more sensitive PSA testing and an increase in nerve-sparing procedures were suspected to be factors.¹² The recurrence rate was also not significant after controlling for PSA, Gleason score, and clinical stage.¹²

Racial differences in recurrence rates are also present.^{9,11} In one study, 2026 men were evaluated after being followed for a minimum of 1 year after prostatectomy.¹¹ Five-year biochemical progression-free rates in the early PSA era (1987-1997) were 78% in white men and 67% in black men, improving during the late PSA era (1998-2004) to 83% and 71%, respectively. These differences were significant within each racial group; unfortunately, the gap persisted between racial groups despite similar improvements in preoperative and postoperative risk factors.¹¹

The CPDR database revealed an increased 5-year prostate cancer-specific survival rate from 86.9% for patients who received a diagnosis during the years 1988 to 1991 to 93.7% during the years 1992 to 1994. Overall survival also increased from 72.0% to 80.3% during those spans.¹³ In a different study, 15-year prostate cancer-specific mortality in the PSA era (1987-2005) after radical prostatectomy was found to vary from 2% to 19%, depending on risk stratification. Interestingly, for patients in the most recent era (treated after 1998), only 4% had a predicted 15-year prostate cancer-specific mortality greater than 5%.²⁵

There has been recent controversy, however, with the use of PSA as a screening tool when noting its effect on prostate cancer-specific death. In March of 2009, two articles—one from the US-based Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, the other from European Randomised Study of Screening for Prostate Cancer (ERSPC)—were released with differing conclusions.^{26,27} In the US trial, no dif-

ference in prostate cancer-related deaths was noted,²⁶ whereas in the European trial, there was an estimated 20% relative reduction in deaths—albeit with the possibility of overdiagnosis.²⁷ The ESRPC group estimated that approximately 20% of their study population would be “contaminated,” ie, have received PSA testing outside of the protocol.^{24,27} In the US trial, however, there was significant crossover contamination of PSA screened patients in the control arm (reaching 52% in the sixth year); in addition, it is possible the patients were not followed long enough for there to be differences in mortality.^{28,29} Also, it should be noted that there were differences in study design, patient recruitment and patient evaluation between the studies; for example, a PSA cutoff of 4 ng/mL was used in the US trial, whereas in Europe, PSA cutoff levels varied by country, with most using a value of 3 ng/mL.^{26,27}

In an attempt to minimize the effects of contamination, the treatment arm of the Rotterdam section of the ESRPC was compared with a population in Northern Ireland who were known to have very little PSA screening. There was an observed prostate cancer metastases relative risk reduction of 53% and a relative risk reduction in prostate cancer mortality of 37% after a median follow-up of 8.5 years.³⁰

In the earlier study from Tyrol, Austria—unrelated to the ESRPC—prostate cancer deaths in that state (where unlike the rest of the country, PSA testing had been made widely available) were compared to the rest of Austria. All Tyrolean men who received a subsequent diagnosis of prostate cancer on biopsy underwent radical surgery or radiation for clinically localized disease, or were placed on hormonal therapy for positive nodes or metastases. No patient was treated primarily with surveillance. Compared with the rest of the country, a significant difference between the number of expected and observed prostate cancer deaths was observed.²³

There may also be differences between US patients and European patients at the time of surgery, despite being within the “PSA era.” An evaluation was made of 5739 European men and 5611 men from the United States who had undergone radical prostatectomy between 1998 and 2005. Given the caveat that criteria for surgery are likely different among surgeons regionally and continentally, leading to heterogeneity within groups, it was found that patients from the United States were younger, had a higher rate of biopsy Gleason score 7 or greater, and surprisingly had a higher rate of palpable cancer than their European counterparts, notwithstanding the aforementioned favorable US trends.³¹

Focal Therapy

The improved biologic behavior of these tumors has paved the path to more selective therapies. Sartor and coworkers³² defined focal prostate cancer as being less than T_{2b}, with no Gleason pattern 4 or 5, detected by systematic biopsies (with 10 transperineal cores preferred), and with no more than two positive adjacent sectors in a patient with low PSA density of <0.15 ng/mL/g.

A higher proportion of men are presenting with pathologic T_{2a} or T_{2b} tumors, which is to say, unilateral disease. This trend was noted in Polascik and colleagues⁸ review of 3676 men who were undergoing radical prostatectomy at the Duke Prostate Center from 1998 to 2006. The patients were classified and divided based on date of surgery as within the early PSA

FIG. 1. Stage migration over time. Duke Prostate Cancer Center data for radical prostatectomy specimens during early PSA era (1988–1995), transitional PSA era (1996–2000), and contemporary PSA era (2001–2006). PSA = prostate specific antigen.

era (1988–1995), transitional PSA era (1996–2000), or contemporary PSA era (2001–2006). Pathologic T_{2a} or T_{2b} disease was found in 14.3% of the overall cohort. This represented an increase from 8% in the early PSA era to 17% in the transitional and contemporary eras. Within the latter two groups, however, the proportion of pT_{2a} tumors increased from 4% to 13%, signifying an overall trend toward a smaller volume of disease (Fig. 1)⁸. When this was correlated by measuring the percent of tumor involvement (PTI), analysis demonstrated a shift to less involvement over time. The number of prostates with PTI ≤ 5% significantly increased from 10% during 1988 to 1995 up to 37% in 2001 to 2006, with a subsequent decline in larger volume (PTI > 15) disease (Fig. 2).

To identify prognostic indicators for unilaterality, Mouraviev and associates³³ studied 1184 men who had undergone radical prostatectomy between 2002 and 2006 and had clinically localized cancer (T_{1c} or T₂) and PSA < 10 ng/mL. Patients who exhibited adverse pathologic prognostic factors, such as seminal vesicle invasion and lymph node involvement, were excluded from analysis, as were those who had previous transurethral surgery or neoadjuvant therapy of any kind. Completely unilateral cancers were found in 19.2% of patients. Multivariate analysis was performed to determine which factors independently predicted this result: Non-African-American race, pathologic Gleason score < 7, negative margins, and < 10% tumor involvement all demonstrated a significant correlation.

At present, prostate cancer is most often managed with radical, whole-gland therapy. This is performed either surgically (radical prostatectomy), with an ablative technique (high-intensity focused ultrasound, cryosurgery), or with radiation (brachytherapy, external beam). Figures from the CaPSURE database estimated that in the years 1999 to 2001, only 8% of men were “treated” with watchful waiting (there was no separate category for active surveillance).^{9,17} A review of the Surveillance, Epidemiology, and End Results registries taken from 2000 to 2002 identified 24,405 men with low-risk disease. Of these, 55% received curative therapy (either from surgery or radiation).³⁴ Certainly, at least a subset of these patients may be overtreated with a subsequent decline in quality of life without improved survival from their therapy.

It is also clear, however, that after long-term (10 year+) follow-up, there are advantages in terms of metastases-free

FIG. 2. Decreased percent tumor involvement over time. Duke Prostate Cancer Center data for radical prostatectomy specimens during early PSA era (1988–1995), transitional PSA era (1996–2000), and contemporary PSA era (2001–2006).

disease and cancer-specific mortality in patients who were treated with radical surgery *vs* those who have opted for watchful waiting.^{35–39} A middle-ground approach in which the most aggressive tumor is ablated while a substantial portion of the gland is spared offers promise for oncologic control with maximal preservation of function in properly selected patients.⁴⁰

Conclusions

Within the PSA era, a well-documented shift to lower risk disease has been present since at least the early 1990s. As the long-term outcomes from these tumors are reported, therapies that reduce morbidity while maintaining oncologic efficacy are becoming increasingly possible. Further research in the tumor biology of early stage prostate cancer is needed to better delineate patients who can be monitored without active treatment or safely treated with focal targeted ablation. Prospective clinical trials addressing those options will aid in determining which patients are the best candidates.

Disclosure Statement

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Address correspondence to:
 Judd W. Moul, M.D., FACS
 Division of Urologic Surgery
 Duke University Medical Center
 Box 3707, Room 1573
 Duke South-White Zone
 Durham, NC 27710

E-mail: judd.moul@duke.edu

Abbreviations Used

CaPSURE = Cancer of the Prostate Strategic Urologic Research Endeavor
 CPDR = Center for Prostate Disease Research
 DRE = digital rectal examination
 EPE = extraprostatic tumor extension
 ERSPC = European Randomised Study of Screening for Prostate Cancer
 PSA = prostate-specific antigen
 PTI = percent of tumor involvement
 SEARCH = Shared Equal Access Regional Cancer Hospital
 TRUS = transrectal ultrasonography