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The Changing Face of Prostate Cancer

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A B S T R A C T

Prostate cancer remains the most common noncutaneous human malignancy, and the second most lethal tumor among men. However, the natural history of the disease is often prolonged, and the survival benefits of local therapy for men with low-risk tumors may not be realized for a decade or more, as is increasingly well demonstrated in long-term observational cohorts in both the United States and Europe. A significant proportion of men with prostate cancer may be overdiagnosed, in the sense that diagnosis may not improve their lifespan or quality of life. However, the extent to which overdiagnosis represents a true problem relates to the consistency with which diagnosis leads invariably to active treatment. Prostate cancer is diagnosed at progressively earlier stages and with lower risk features; despite these trends, patients are less likely now than a decade ago to undergo a trial of active surveillance. Rates of brachytherapy and hormonal therapy use, in particular, have risen markedly. Important progress has been made in recent years in prostate cancer risk assessment. These advances, in combination with biomarkers in later stages of development, should be expected in the coming years to yield further improvements in clinicians' ability to diagnose prostate cancer early, and guide appropriately selected patients toward increasingly tailored treatment.

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INTRODUCTION

In 2005, prostate cancer will strike an estimated 232,090 men in the United States, and 30,350 are expected to die as a result of the disease. This incidence is the highest among all noncutaneous malignancies, and the mortality among men is second only to lung cancer.¹ Nonetheless, most men diagnosed die with rather than as a result of prostate cancer, and management strategies must balance the desirability of early curative treatment of localized tumors with what may be a prolonged natural history of many such cancers, and with the potential negative impact of all active treatments on patients' health-related quality of life.² Advances in screening and diagnostic techniques have resulted in detection of prostate cancer at progressively earlier stages and lower levels of prognostic risk; trends in approaches to primary treatment, however, do not necessarily reflect these changes. This review will present contem-

porary data on trends in presentation, natural history, and primary management of prostate cancer, and will consider innovations in approaches to risk assessment that may facilitate improved decision making at the time of diagnosis.

Research in these areas has been facilitated greatly by the advent of two large, nationally based, longitudinal databases that enroll prostate cancer patients regardless of stage at diagnosis or primary treatment modality. The Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) was initiated in 1995. Thirty-one urologic practice sites, primarily community-based, consecutively invite all men with biopsy-proven prostate cancer to join the registry. Clinical data are reported by participating urologists, and patients complete questionnaires addressing treatments and health-related quality of life at regular intervals. Patients in CaPSURE are treated according to their physicians' usual practices.³

The Department of Defense Center for Prostate Disease Research (CPDR) has collected data on men with prostate cancer at Walter Reed Army Medical Center since 1994, and at eight other military sites around the country since 1997. Unlike CaPSURE, the CPDR database is used as a means toward standardizing prostate cancer practice across military sites.⁴ These two databases, each comprising well over 10,000 patients, represent highly useful, complementary sources of data. CPDR is the largest prostate cancer database in the nation, and includes full participation by radiation and medical oncologists. The patients are all military affiliated, but ethnically are relatively diverse. CaPSURE is not a random sample of prostate cancer patients, and includes only patients managed at least in part by urologists. As the only community-based registry of its kind, however, it provides the best available portrayal of “real-world” trends in disease presentation and management.

RISK MIGRATION

Downward stage and risk migration during the era of prostate-specific antigen (PSA) screening is a well-established phenomenon. In CaPSURE, on the basis of the criteria published by D’Amico et al,⁵ the proportion of patients presenting with low-risk disease (ie, PSA ≤ 10 ng/mL, Gleason score below 7 with no pattern 4 or 5 disease on biopsy, and clinical stage T1 or T2a) has increased from 31% of patients in 1989 to 1990 to 47% in 2001 to 2002. Conversely, high-risk diagnoses (PSA > 20 ng/mL, biopsy with Gleason score of 8 to 10, or stage T3 to 4) have decreased from 41% to 15% of patients (Fig 1).⁶

The majority of cases are now detected at clinical stage T1c. Even among low-risk patients, very few patients are diagnosed after transurethral resection of the prostate for benign hyperplasia: The proportions of T1a and T1b tumors have fallen to 1.6% and 0.5%, respectively,⁷ presumably due to both increasing medical management of lower-urinary tract symptoms⁸ and relatively intense

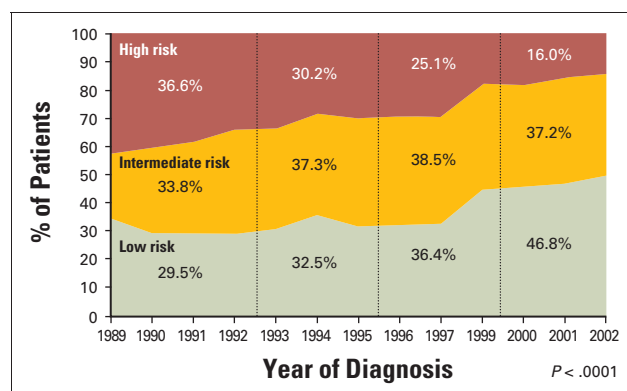


Fig 1. Time trends in patient clinical risk stratification at time of diagnosis risk stratification of Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) patients over time by risk groups as defined by D’Amico et al.⁵ Reprinted with permission from Cooperberg et al.⁶

prostate cancer screening among patients with these symptoms.⁹ These studies focused on patients with localized disease; complementary data from the CPDR registry found downward migration at higher-stage disease as well. The percentage of patients presenting with locally advanced (T3 to 4) disease fell from 19.2% in 1988 to 4.4% in 1998; rates of metastatic disease at diagnosis likewise declined from 14.1% in 1988 to 3.3% in 1998.¹⁰ These trends are likely attributable to both increasing implementation of PSA-based screening protocols and the adoption of extended-template prostate biopsy techniques,^{11,12} both of which facilitate the earlier detection of small tumors.

In the early years of the CaPSURE study, patients were most likely to be classified as high risk because of a high PSA level, whereas more recently high-risk patients were more likely to have a low PSA and a high Gleason score.⁶ Such a combination is consistent with observed improvements in outcomes for men in this group. Gleason scores have been rising during the last decade as a result of changes in pathologic grading practices: In one study, re-analysis of biopsy specimens from 1989 to 1991 led to upgrading in more than one third.¹³ Gleason pattern 1 or 2 disease is essentially a vanishing diagnosis; fewer than 4% of low-risk patients had a biopsy Gleason score lower than 6.⁶ This latter trend is artifactual rather than indicative of changes in cancer biology, again reflecting changes in pathologists’ standards in grading the disease.

NATURAL HISTORY OF PROSTATE CANCER

Recent updates to long-established observational studies have shed important light on the natural progression of prostate cancer and the impact of local therapy on ultimate survival. A Scandinavian observational study of prostate cancer’s natural history, reported by Johansson et al,¹⁴ confirmed that many tumors follow an indolent course for the first 10 to 15 years after diagnosis, but that beyond 15 years the prostate cancer-specific mortality rate triples. In this series, cause-specific survival fell from 79% at 15 years to 54% at 20 years. Twenty-year results were likewise published by Albertsen et al¹⁵ from an observational cohort followed in the Connecticut Tumor Registry. These authors reported that overall prostate cancer mortality was 33 per 1,000 person-years up to 15 years, and 18 per 1,000 person-years after 15 years, a statistically non-significant difference. This study stratified outcomes by Gleason score, finding that mortality rates ranged dramatically, from six per 1,000 person-years for tumors with a Gleason score of 2 to 4, to 121 for tumors with a Gleason score of 8 to 10, with progressive rises in cancer-specific mortality through Gleason scores 5 to 7.

A second Scandinavian study,¹⁶ the only randomized trial reported to date of initial surveillance versus radical prostatectomy (or any active treatment, for that matter), found that after 5 years of follow-up, overall survival

diverged between the two treatment arms. At a median of 8 years of follow-up, the relative risks in the surgery arm were 0.74 (95% CI, 0.56 to 0.99) for all-cause mortality, 0.56 (95% CI, 0.36 to 0.88) for cause-specific mortality, and 0.60 (95% CI, 0.42 to 0.86) for distant metastases. Although on balance these articles support a role for early prostate cancer treatment, they strongly reinforce the importance of patient selection for aggressive therapy: Patients with low-risk tumors and/or without extended life expectancy may well not benefit from treatment.

Both Scandinavian studies enrolled patients with relatively high stage disease: The patients in the observational study were diagnosed before the advent of widespread PSA screening.¹⁴ In the randomized trial, although accrual continued until 1999, only 5% of prostate cancers were screen detected; more than three quarters were palpable, stage T2 tumors; and about half were diagnosed with a PSA level > 10 ng/mL. Furthermore, patients diagnosed younger than 65 years had a 19% risk of cause-specific mortality on observation, a rate cut nearly in half by surgery, but among those older than 65 years, there was no statistically significant difference in mortality outcomes.¹⁶

These data highlight concerns regarding the prevalence of overdiagnosis of prostate cancer, concerns that are all the more salient given well-supported arguments that prostate biopsy among men with PSA levels as low as 2.6 ng/mL will frequently detect clinically significant tumors, with Gleason scores ≥ 7 in 50%.¹⁷ Estimates of rates of overdiagnosis vary tremendously—from 15 to 84% in recent studies¹⁸⁻²⁰—depending on the definition of overdiagnosis used, as well as such factors as the pattern and method of screening, the average lead time between detection and expected clinical presentation, and secular trends in cancer incidence. Regardless of the specific number, it is certainly true that a significant fraction of men assigned the diagnosis of prostate cancer would not suffer any adverse impact to their quantity or quality of life were the cancer never detected. An argument can certainly be made, however, that overdiagnosis is a problem only to the extent that diagnosis is followed inevitably by invasive treatment, whether surgical, radiation based, or hormonal.

TRENDS IN PRIMARY MANAGEMENT OF PROSTATE CANCER

Given downward risk migration of newly diagnosed prostate cancer, high-quality data on the natural history of low-risk disease, and increasing awareness of the health-related quality-of-life (HRQOL) implications of both local and systemic prostate cancer treatments, increasing attention is being paid to the alternative of active surveillance for carefully selected patients with favorable risk characteristics. Active surveillance might be distinguished from watchful waiting on the basis of the intensity of monitoring and the expectation of delayed but successful definitive

treatment for those patients showing signs of disease progression. This strategy has been piloted successfully in large academic series using protocols involving variations of PSA, transrectal ultrasound, and/or repeat biopsy monitoring.²¹⁻²³ Despite the promise that surveillance holds for HRQOL preservation and potential treatment avoidance, its use has actually declined precipitously in recent years.

Data from the Prostate Cancer Outcomes Study (PCOS) collected from 1994 to 1995 found that 47% of patients underwent prostatectomy, 23% received radiotherapy, 11% underwent primary androgen-deprivation monotherapy, and 19% chose observation.²⁴ During the 1990s overall, 8.2% and 13.8% of patients in CaPSURE²⁵ and CPDR,²⁶ respectively, were observed initially. In both registries, older patients and those with favorable risk characteristics were more likely to elect observation. Forty-four percent and 39%, respectively, of the observed CaPSURE²⁵ and CPDR²⁶ patients progressed to active treatment, with age and PSA at diagnosis driving treatment in both studies; in both cohorts, androgen deprivation was the most common secondary treatment among those progressing. A more recent analysis has found that the use of initial observation has in fact fallen in CaPSURE from 9.5% in 1992 to 1994 to 5.5% in 1998 to 2000, with the sharpest declines among low-risk patients.²⁷

Other recent papers from CaPSURE have yielded further insights into changes in treatment patterns during the last decade. One such study focused on treatment of patients classified as low-risk according to the D'Amico criteria described in the preceding paragraphs. Among these low-risk patients, rates of observation have fallen by more than half, from 20% of patients in 1993 to 1995 to 8% in 1999 to 2001. Over the same period, use of external beam radiotherapy fell from 13% to 7% while that of RP fell slightly, from 55 to 52%. In contrast, use of androgen deprivation monotherapy and brachytherapy increased significantly, from 7% to 12% and 4% to 22%, respectively. Even among patients 75 years of age or older, initial observation fell from 52% to 24%, while androgen-deprivation monotherapy increased from 23% to 30%, and brachytherapy from 3% to 31% of patients. Overall, roughly half of all patients older than 75 years received either primary or neoadjuvant androgen deprivation. There was no significant influence of ethnicity on treatment patterns in CaPSURE.⁷

The finding of highly prevalent use of androgen deprivation echoed an earlier cross-sectional observation reported from PCOS²⁸ suggesting higher-than-expected use of primary androgen-deprivation monotherapy among localized prostate cancer patients. Another study focused on patterns of androgen-deprivation utilization, finding that the use of androgen deprivation as monotherapy has risen dramatically across all patients during the last decade, from 5% to 14%, 9% to 20%, and 33% to 48% among low, intermediate, and high-risk patients, respectively, from 1989 to 1990 to 2000-2001. Neoadjuvant

androgen deprivation use, likewise, rose from 3% to 8% of patients undergoing prostatectomy, from 10% to 75% of those receiving external beam radiotherapy, and 7% to 25% of those receiving brachytherapy (Fig 2).²⁹

These data suggest that a significant number of patients, particularly older patients with low-risk disease, may be overtreated. On the other hand, patients with high-risk prostate cancer face a high rate of biochemical recurrence after either prostatectomy³⁰ or radiation³¹ monotherapy. Androgen deprivation is now well established to improve outcomes among men with high-risk tumors in association with radiotherapy,³²⁻³⁴ as does adjuvant radiation for selected patients after prostatectomy, though the efficacy of this latter combination remains somewhat controversial.³⁵⁻³⁷ Only 8% of high-risk patients in CaPSURE managed primarily with radical prostatectomy received adjuvant radiation therapy. Fifty-two percent of high-risk patients managed primarily with radiation therapy received neoadjuvant or adjuvant androgen deprivation³⁸; this proportion has been rising in recent years.²⁹

FUTURE DIRECTIONS

Multiple ongoing, parallel lines of research promise to improve the current standard of care in terms of screening efforts, diagnosis, risk stratification, and primary manage-

ment. Attempts to identify men at high risk for prostate cancer who would benefit from earlier and more aggressive screening have focused principally on family history and African American ethnicity. Given the well-recognized epidemic of obesity in the United States,³⁹ obesity has been explored as a potential risk factor for prostate cancer. Some recent studies have suggested that prostate cancer is more likely to present with high-risk features in the setting of obesity, but others have not confirmed this finding.^{40,41} Obesity has likewise been related to increased risk of recurrence after surgery in multivariate analysis,^{42,43} but this again is not a consistent finding.⁴⁴ Obesity is the result of a complex set of genetic, metabolic, dietary, environmental, and sociodemographic determinants. Identification of the specific factors associated with obesity that predict both incidence and high-risk presentation of prostate cancer will certainly remain an important and fruitful line of future research.

Obvious deficiencies in the accuracy of PSA as a screening test for clinically significant prostate cancer continue to drive efforts to develop better tests. Although fractionated PSA assays such as free and complexed PSA have been shown to improve specificity when calculated as ratios to the total PSA, neither has been able to improve sufficiently on total PSA as an initial screening test.^{45,46} ProPSA, a transcriptional splice variant of PSA with a truncated leader sequence, shows significant potential for improved performance as a screening tool,⁴⁷ but is not yet widely available. Serum assays based on simultaneous assessment of multiple proteins hold great promise,⁴⁸ but remain at early stages of development.

In the meantime, additional research with large databases of prostate cancer patients has yielded refinements in the use of information available under current clinical practice. The percentage of biopsy cores positive has been shown to contribute significant prognostic information among patients otherwise stratified to both higher^{49,50} or lower⁵¹ risk groups, after both surgery and radiation therapy. The University of California San Francisco Cancer of the Prostate Risk Assessment (CAPRA; San Francisco, CA) is a novel index that integrates the percentage of cores positive with clinical T stage, PSA at diagnosis, Gleason score, and age to predict risk of recurrence after prostatectomy. The CAPRA score is as accurate as the best available multivariate models, yet the 0-to-10 score is notably easier to calculate than existing nomograms.⁵² Finally, PSA kinetics are receiving renewed attention for prognostic ability both before and after treatment. A PSA velocity of 2.0 ng/mL per year or more before prostatectomy has been shown to predict not only biochemical recurrence, but also cancer-specific and overall mortality.⁵³ A PSA doubling time less than 3 months likewise has been shown to predict cancer-specific mortality among patients failing by biochemical criteria after either surgery or radiation.⁵⁴

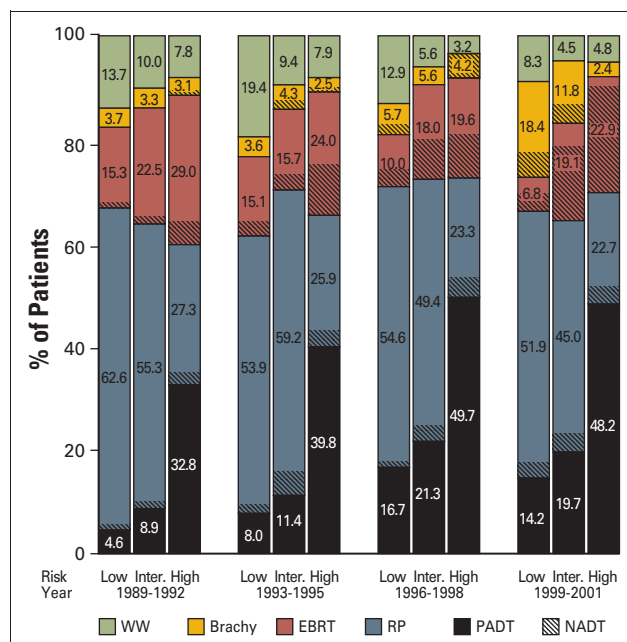


Fig 2. Overall trends in primary treatments for prostate cancer primary treatment selection by patients in Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE), grouped by time period and risk group as defined by D'Amico et al.⁵ For patients electing surgery or any form of radiation therapy, cross-hatched areas of each bar represent the proportion receiving prior neoadjuvant androgen deprivation. Reprinted with permission from Cooperberg et al.²⁹ WW, watchful waiting; Brachy, brachytherapy; EBRT, external beam radiotherapy; RP, radical prostatectomy; PADT, primary androgen-deprivation therapy; NADT, neoadjuvant androgen-deprivation therapy.

CONCLUSION

The management of localized prostate cancer is in rapid evolution. More than ever, treatment decisions must consider patients' life expectancy, baseline quality of life, and treatment preferences as well as their disease characteristics. Critiques that PSA screening efforts lead to overdiagnosis of potentially indolent prostate tumors are relevant primarily to the extent that diagnosis leads invariably to treatment. PSA screening and extended-pattern biopsies have effected a downward risk migration, such that many patients diagnosed today are excellent candidates for either a trial of active surveillance or immediate local monotherapy. Risk of recurrence and progression can now be estimated easily and with increasing accuracy. On the one hand, clinicians must be cautious in the treatment

of those patients with low risk prostate tumors, especially those of advanced age or in poor general health; on the other, younger patients with higher-risk, clinically significant cancer should be offered aggressive, often multimodal, therapy to maximize their odds of long-term disease control and survival. Translational and clinical research on prostate cancer is ever advancing, and it is likely that in the near future novel strategies will become available for both prostate cancer risk assessment and targeted management.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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