Prostate Cancer and the Evolving Role of Biomarkers in Screening and Diagnosis

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KEYWORDS

• Prostate • Cancer • Biomarkers • Screening • PSA

KEY POINTS

- Prostate-specific antigen (PSA) testing has contributed to a decline in prostate cancer–specific mortality observed over the last 30 years.
- PSA lacks specificity and leads to overdiagnosis and overtreatment when used indiscriminately.
- Harms from screening can be reduced by advocating active surveillance for low-risk cancers.
- There are several serologic and pathologic biomarkers with higher specificity than PSA that can limit unnecessary biopsies and inform treatment decisions.

INTRODUCTION

Prostate cancer will account for ~26,000 deaths in the United States in 2017.[1] The current, age-adjusted mortality of 19 per 100,000 men is a 50% improvement compared with the early 1990s.[2] Modifications in screening, diagnosis, and management have dramatically impacted incident rates and survival. Recent efforts have focused on limiting the diagnosis and treatment of indolent disease, while treating those with more aggressive features within a window of curative potential. Consequently, several biomarkers have been developed to more selectively identify men likely to benefit from timely diagnosis and effective treatment. The authors review the evolution of prostate cancer risk assessment in the United States with an emphasis on biomarkers.

BACKGROUND

Autopsy studies have identified prostate cancer in ~5% of specimens from men younger than 30 to ~60% from those aged greater than 79 years.[3] Pathologic examination after biopsy or surgery identifies patterns used to grade disease. Gleason score is based on the 2 most prevalent of these patterns and often informs prognosis more than tumor stage.[4] Gleason 6 (3 + 3) represents the most indolent pattern, whereas Gleason 10 (5 + 5) represents the most aggressive. In 2014, grade groups 1 to 5 were established to simplify pathologic interpretation for patients and physicians and have been validated to predict risk of recurrence (**Table 1**).[5,6]

The natural history of prostate cancer varies widely by stage and grade.[7] Men with metastatic disease have a median survival of 30 months. In contrast, men with low-grade organ-confined

Disclosures: None (J.F. Rodriguez). S.E. Eggener has served as a research investigator and speaker for MDx Health and OPKO health.
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Radiol Clin N Am 56 (2018) 187–196
https://doi.org/10.1016/j.rcl.2017.10.002

Table 1
Gleason grade groupings and risk of biochemical recurrence following radical prostatectomy

Grade Group	Gleason Score	Hazard Ratio for Recurrence
1	≤6	(Reference)
2	3 + 4	1.9
3	4 + 3	5.1
4	8	8.0
5	9–10	11.7

Data from Epstein JI, Zelefsky MJ, Sjoberg DD, et al. A contemporary prostate cancer grading system: a validated alternative to the Gleason score. Eur Urol 2016;69(3):428–35.

disease can often live decades without any treatment. Popiolek and colleagues[8] closely followed a population-based cohort of 223 Swedish men diagnosed with localized disease for 30 years until 99% had died. There was no screening, and these men were untreated except with hormonal therapy if they developed symptomatic local progression or metastases. All patients with poorly differentiated tumors died within 10 years of cancer or other causes, but 64% of men never required hormonal therapy. Although overall survival declined steadily over the observation period, cancer-specific mortality increased rapidly from 15 to 20 years after diagnosis, illustrating the oft-prolonged natural history expected from low-grade, localized disease.

PROSTATE CANCER IN THE "PRE–PROSTATE-SPECIFIC ANTIGEN ERA"

Through the 1980s, prostate cancer diagnosis was often not made until a patient was symptomatic from advanced disease, and 5-year relative survival was 70%.[2] For nonmetastatic disease, up to 50% of men did not undergo any primary treatment.[9] Prostatectomy was associated with 3% mortality, high rates of total incontinence, and universal impotence.[10] The introduction of serum prostate-specific antigen (PSA) in the latter part of the decade spurred a dramatic shift.[11]

The addition of PSA to the digital rectal examination (DRE) significantly improved the sensitivity of screening, and as early as 1992, organizations recommended PSA testing for men over the age of 50.[12–14] Urologists began adopting surgical techniques pioneered by Patrick Walsh to decrease the morbidity of radical prostatectomy, including the use of nerve sparing for potency preservation.[15,16] With an increasing pool of patients diagnosed with localized disease and an improved surgical treatment option, rates of radical prostatectomy increased by a factor of 6.[17]

The latter half of the 1990s showed declining rates of prostate cancer mortality and advanced disease, but there was a disproportionately larger increase in cancer incidence and use of radical treatment.[18] Refinements to therapy, such as minimally invasive approaches to surgery and less toxic radiation delivery methods, decreased morbidity, but treatments were still associated with a risk of incontinence, erectile dysfunction, cystitis, proctitis, and urethral strictures.

In the "PSA era," many questioned whether benefits of screening outweighed the harms of overtreatment.[19,20] Two prospective randomized trials were therefore conducted to answer this question: the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial in the United States (PLCO) and the European Randomized Study of Screening for Prostate Cancer (ERSPC) in multiple European countries.

PROSTATE-SPECIFIC ANTIGEN SCREENING TRIALS

In the PLCO trial, more than 75,000 men aged 55 to 74 years were randomly assigned to annual screening with PSA and DRE or usual care.[21] Men with suspicious DRE or PSA greater than 4 ng/mL were advised to undergo diagnostic evaluation. In 2009, the first results were reported after a median follow-up of 11.5 years. Through year 10 of the study, there were 92 prostate cancer deaths in the screening arm and 82 in the control arm (rate ratio 1.11; 95% confidence interval [CI], 0.83–1.50) with no apparent benefit to screening.

In the ERSPC trial, greater than 160,000 men aged 55 to 69 years were randomized to PSA screening (typically every 2–4 years) or usual care.[22] Most centers involved used PSA greater than 3.0 ng/mL as a cutoff to recommend diagnostic evaluation, although there was some variation between sites. With a median follow-up of 9 years, there was a 20% decreased mortality in the screened group (95% CI 0.65–0.98; adjusted $P = .04$). Given low prostate cancer–specific mortalities overall, this translated into the requirement of 1410 men screened and 48 men diagnosed to prevent 1 death from prostate cancer. An updated report in 2014 with 13 years median follow-up suggests a number needed to screen of 781 and a number needed to diagnose of 27 to prevent one death from prostate cancer.[23]

The contradictory results of PLCO and ERSPC can be explained by high rates of PSA testing in the United States around the study period contaminating the control arm. Contamination in PLCO