Handbook of Prostate Cancer and Other Genitourinary Malignancies

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To our patients, who have taught us so much; and to our trainees, who have worked so hard to ensure that our patients get the best care possible.
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Preface

Genitourinary malignancies represent a wide spectrum of risk and prognosis. The last decade or more has brought an extraordinary evolution in outcomes for patients with these diseases at advanced stages, mainly through development and adoption of new systemic therapies. In addition, greater attention is being paid to comprehensive assessment of the patient before, during, and after treatment. More systematic measurement of influential medical and psychosocial factors has allowed for better treatment selection and symptom management.

This handbook aims to provide a broad overview and current summary of the state of assessment, diagnosis, and treatment of these malignancies. It will be useful for clinicians at multiple stages in medical and surgical specialties: in training, early in a career, and looking for updated information. With the ability to reference quickly for a specific question, or review a larger section all at once, the reader can customize the depth with which he or she uses the handbook.

This remains an exciting time for those dealing with many of these malignancies, with advances and innovations continuing in both the medical and surgical arenas. The dissemination of these developments and collaboration among specialists will continue to bring improved outcomes to our patients living with or surviving these diseases. We are grateful to the patients and providers who work together in clinical trials, which are the foundation of the progress and drive the evolution of the field forward.

We welcome your feedback and suggestions as you use this handbook in practice.

Jennifer Marie Taylor, MD, MPH
Acknowledgments

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Handbook of Prostate Cancer and Other Genitourinary Malignancies
INTRODUCTION

Prostate cancer is the most common visceral cancer in the United States and the second leading cause of cancer death after lung cancer. In the United States, approximately one in seven men will be diagnosed with prostate cancer. One in 39 prostate cancer patients will die from the disease. Survival of prostate cancer is related to many factors, including age and stage at diagnosis (1). Although the 5-year survival rate for early localized prostate cancer is 100%, survival is only 29.3% for distant metastatic disease.

With the goal of reducing cancer-related morbidity and mortality by early detection, screening strategies are employed in common and lethal cancers such as prostate cancer. Prostate-specific antigen (PSA) was initially developed as a tumor marker to assess the extent of disease and detect treatment response. Despite a lack of efficacy data from randomized controlled trials (RCTs), PSA was incorporated into prostate cancer screening in the early 1990s, which subsequently lead to a peak increase in the detected incidence of prostate cancer. Most of the cancers detected were early stage disease, which otherwise would have not been discovered and may not have been clinically relevant. However, early detection often led to aggressive treatment. Since then, the benefits of PSA screening have been questioned and have been a major topic of debate among clinicians and guideline organizations.
VARIATIONS OF PSA LEVEL

PSA is a glycoprotein expressed in both normal and neoplastic prostatic epithelial tissue. The PSA level reflects the amount of prostate glandular epithelium in normal healthy men. Prostate size increases with age and in turn increases the PSA level. The PSA increases by 3.2% (0.04 ng/mL) per year for a 60-year old, and reference ranges for different age groups have been proposed.

In addition, multiple factors may influence the PSA level in healthy individuals. African American men have higher PSA levels when compared to White men. Prostatitis, perineal trauma, benign prostatic hypertrophy, prostate biopsy, and ejaculation can elevate the PSA level. Medications such as 5-alpha reductase inhibitors can reduce the PSA level by up to 50%. Nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, statins, and thiazide diuretics can lower the PSA level to varying degrees. Despite these variations, a traditional cutoff of 4 ng/mL or more has been considered abnormal by most clinicians.

PSA TESTING IN MALIGNANCY

PSA levels are raised in malignancy, not only due to increased production by malignant epithelial cells but also due to disruption of vasculature and release of PSA into the bloodstream. Multiple studies have shown that a rise in PSA precedes the development of prostate cancer by 5 to 10 years. Different cancers have varying levels of PSA elevation, and poorly differentiated cancer can have a large tumor burden with minimally elevated PSA.

Using a cutoff value of 4 ng/mL, the estimated sensitivity is 21% for detecting any prostate cancer and 51% for high-grade cancer in pooled analyses. Specificity is estimated to be 91%. Positive predictive value (PPV) is 30%, which means that one in three men with PSA more than 4 ng/mL has prostate cancer. Negative predictive value (NPV) is 85% for a PSA level lower than 4 ng/mL (2). Different strategies have been tested to improve the performance of PSA testing in prostate cancer. Lowering the cutoff level increases the sensitivity level but in turn reduces specificity. Various tests such as PSA velocity, PSA
density, the ratio of free to total PSA, 4 Kallikrein tests (4Ktest), and [-2] ProPSA have been explored, and none of the tests have shown improvement in clinical outcomes.

**DIGITAL RECTAL EXAMINATION**

Digital rectal examination (DRE) is one of the oldest methods used to diagnose prostate cancer. DRE can detect tumors in the posterior and lateral aspects of the prostate gland. Because only 85% of prostate cancer is peripherally located, some cancers may be missed by DRE. A meta-analysis shows the positive predictive value of DRE is 28% with sensitivity 59% and specificity 95% (3). However, DRE is not recommended as a stand-alone method for screening of prostate cancer, since it is operator dependent and studies have shown no improvement in outcome with DRE screening alone. When combined with PSA testing, DRE can increase the rate of detection of prostate cancer by 1%, but combined PSA and DRE has not shown a benefit in reducing cancer morbidity and mortality.

**IMPACT OF PROSTATE CANCER SCREENING**

The efficacy of PSA screening has been investigated in multiple observational studies and RCTs. Two large RCTs, the European Randomized Study of Screening for Prostate Cancer (ERSPC) and the Prostate, Lung, Colorectal, and Ovarian (PLCO) screening trial performed in the United States, produced different outcomes and increased the controversy about prostate cancer screening.

The ERSPC trial, which spanned across seven centers in Europe, enrolled 182,160 men between the ages of 50 and 74 who were randomly assigned to PSA screening (an average of once every 4 years) or a control group without screening. With a follow-up of 13 years, prostate cancer mortality was reported to be 21% lower in the screening group than in the control group. The absolute risk reduction was 0.11 per 1,000 patient years between the two groups (4).

In the PLCO screening trial, 76,693 men between the ages of 55 and 74 were randomly assigned to annual screening with PSA and DRE or to usual care. In contrast to the ERSPC, there
was no reduction in the primary outcome of prostate cancer mortality after 7 years of follow-up, and the 13-year update similarly showed no difference in mortality between the screening and control groups (5).

There were differences in the design of the two trials. The ERSPC trial was a combination of results from multiple centers across Europe. Different centers used DRE and transrectal ultrasonography and employed varying PSA cutoffs between 2.5 and 4 ng/mL. The majority of the centers used 3 ng/mL. In the PLCO trial, PSA was combined with DRE and the cutoff was set at 4 ng/mL. The overall rate of contamination PSA screening in the control group is not reported in the ERSPC trial. Up to 24% of patients with prostate cancer in the control arm did not undergo aggressive treatment with surgery or radiation in the ERSPC trial. The difference in treatment in both arms may explain the positive outcome in reducing cancer-related mortality. In the PLCO trial, the control group had a high contamination rate, with up to 80% of subjects receiving PSA screening, which might contribute to the null result.

**RISKS ASSOCIATED WITH PROSTATE CANCER SCREENING**

In both the ERSPC and PLCO trials, the incidence of cancer was higher in the screening group than in the control group. In the ERSPC trial, 24% of all cancers diagnosed were stage T1c, that is, clinically unapparent tumor detected by needle biopsy due to elevated PSA level. This highlights the possible overdiagnosis resulting from screening methods. Studies have shown that screening with PSA can lead to an overdiagnosis rate of up to 50%.

Many patients with early prostate cancer do not develop symptoms for many years. Some cancers are indolent, and many may not ever need treatment. However, diagnostic intervention and treatment-related complications are immediate, can be morbid, and can lead to both physical and psychological harm. An elevated PSA often leads to prostate biopsy, which can lead to complications such as infection and bleeding requiring hospitalization. Radical prostatectomy can cause urinary incontinence, sexual problems, and bowel dysfunction, and has
an operative mortality from 0.1% to 1%. Radiation therapy can also cause erectile dysfunction up to 45%, urinary incontinence up to 16%, and bowel problems up to 25%.

**PROSTATE CANCER SCREENING: DO OR DO NOT?**

Currently, the United States Preventive Services Task Force (USPSTF) recommends against screening for prostate cancer. Given the contrasting reports and limitations of both ERSPC and PLCO trials, the benefit of prostate cancer screening is uncertain. Though cancer screening may benefit some patients by early detection and treatment, the number needed to treat is very high (781 in the ERSPC trial) to save one patient from prostate cancer–related death. Since the hazards of diagnostic tests and treatment potentially outweigh the benefits, it is very important to inform patients, and the decision to screen should not be taken lightly. The American Cancer Society (ACS) and American Urological Association (AUA) have both emphasized informed decision making and recommend against screening in patients with life expectancy less than 10 years (6).

In patients who have decided to get screened, ACS recommends screening with PSA and/or DRE beginning at the age of 50 and screening discussions at age 40 to 45 for high-risk patients such as African American men and men with a family history of a first degree relative with prostate cancer diagnosed earlier than age 65 (6). Referral for biopsy is indicated at a level above 4 ng/mL, although many experts suggest repeating levels several weeks later if the PSA is below 7 ng/mL.

Further studies are needed to develop new screening methods and identify potential groups of patients who would potentially benefit from screening with minimal risk.

**KEY POINTS**

- Prostate cancer screening is highly controversial.
- Screening should be individualized based on patient interest and degree of risk for developing prostate cancer.
- Screening is not recommended for men with life expectancy less than 10 years.
REFERENCES


INTRODUCTION

In this chapter, we go into more detail’s about the following controversies in management of metastatic prostate cancer:

• Timing of initiation of systemic therapy for patients with elevated prostate-specific antigen (PSA) as only evidence of disease when local therapies are no longer available.

• Timing of initiation of therapy for patients with asymptomatic low-volume metastases.

• The role of first-generation antiandrogens in castration-sensitive disease.

TIMING OF INITIATION OF THERAPY FOR PATIENTS WITH ELEVATED PSA AS ONLY EVIDENCE OF DISEASE

Case 1: A 74-year-old male was found to have Gleason’s 10 prostate cancer after evaluation for elevated PSA detected in screening. He underwent prostatectomy with evidence of extraprostatic extension and negative margins. He underwent adjuvant radiation and proceeded with surveillance. PSA went from less than 0.06 ng/mL to 5.1 ng/mL. Should you recommend androgen ablation therapy?

Patients with prostate cancer who have persistently elevated PSA despite surgical treatment or radiation are considered to have persistent disease. If salvage therapy is not an option, the next question is whether the patient should receive systemic therapy with androgen deprivation therapy (ADT).
While earlier initiation might prevent prostate cancer-related morbidity and improve survival, in some cases disease can be very indolent and ADT has potential adverse effects as well. Unfortunately, there are no randomized trials concluded that have addressed this question. In a natural history study of 201 patients on ADT with PSA progression and no radiographic evidence of metastases, median bone-metastasis-free survival was 30 months. Thirty-three percent of patients developed bone metastases at 2 years. Predictors of shorter time to bone metastasis and overall survival (OS) were baseline PSA greater than 10 ng/mL and PSA doubling time of 10 months (1). If clinical trial is not an option, these factors may be useful in making the decision about starting ADT in patients with PSA-only relapse even in the ADT-naive setting. The Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database in 2012 described a series of 2,022 patients with PSA only relapse who had not been treated with ADT. 34.8% of patients had a Gleason score ≥7. After adjusting for poor prognostic factors (Gleason score, PSA velocity), there was no significant difference in OS or prostate cancer specific mortality between patients who started within 3 months of diagnosis or patients who started 2 or more years later or when they presented with metastasis, symptoms, or short PSA doubling time (defined as 6 months or less for PSA <10 ng/mL) (2). Mean time to progression was 35.8 months.

If ADT is started for these patients, there is also the consideration about whether to administer it continuously or intermittently, which is addressed further in the “Intermittent Androgen Ablation in Metastatic Prostate Cancer” subchapter.

### TIMING OF INITIATION OF THERAPY FOR PATIENTS WITH ASYMPTOMATIC LOW-VOLUME METASTASES AND USE OF FIRST-GENERATION ANTIANDROGENS IN CASTRATION SENSITIVE METASTATIC PROSTATE CANCER

**Case 2:** A 63-year-old male was found to have a PSA of 48 ng/mL after screening evaluation. A CT scan showed evidence of right pelvic bone metastasis, with uptake on a
nuclear bone scan. Biopsy of a bone lesion was consistent with prostate cancer. The patient is otherwise asymptomatic.

**Question 1: Should you recommend ADT?**

The study of this issue has been limited by heterogeneity in the populations included in clinical trials, different triggers on initiation of ADT, and the fact that some patients do not defer therapy as originally planned (3). Also, many of the trials did not take into account prognostic factors (Gleason score, PSA response, PSA doubling time, life expectancy) into the decision-making progress. Also, while survival is a desired outcome, other factors like disease morbidity have not been consistently examined. With these limitations known, a meta-analysis looking at this question has concluded that early ADT was associated with a decrease in prostate cancer-related death, without a benefit in OS. More clinical trials are needed to answer this question; however, the information suggests that initiation of therapy should be individualized for each patient.

**Question 2: Would you recommend a first-generation antiandrogen monotherapy or combined androgen blockade to this patient?**

First-generation antiandrogens (e.g., bicalutamide, flutamide, nilutamide) are competitive inhibitors of androgens. They are typically recommended as initial bridging with a gonadotropin releasing hormone (GnRH) agonist and/or after disease progression to medical or surgical castration (castration-resistant disease) (3). A meta-analysis looking at the question of using castration or antiandrogen therapy alone as initial therapy for castration-sensitive prostate cancer found a trend toward shorter OS with antiandrogen monotherapy, although it was not statistically significant (hazard ratio [HR] 1.22, 95% confidence interval [CI] 0.99–1.40) (4). Although some studies have shown a progression free survival benefit of castration combined with antiandrogens as initial therapy (combined androgen blockade), it risks higher toxicity, and the benefit has not been consistently reproduced in clinical trials. Because of this, combined androgen blockade is not widely used (5).
KEY POINTS

- For patients with PSA-only disease who are not candidates for salvage therapy, deferred ADT seems to be a reasonable option, particularly for patients with low baseline PSA (<10 ng/mL) and low doubling time (<10 months).
- For patients with asymptomatic metastatic prostate cancer with low-volume disease, there is some suggestion of prostate-cancer-related mortality benefit of early ADT.
- First-generation antiandrogen monotherapy or combined androgen blockade should not be routinely used for patients with castration-sensitive prostate cancer.

REFERENCES