Approach to the Patient with High-Risk Prostate Cancer

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KEYWORDS

• Prostate cancer • High risk • Management

KEY POINTS

- There are multiple definitions of high risk prostate cancer and each definition is associated with a different prognosis.
- Men classified as having high-risk disease warrant treatment because durable outcomes can be achieved.
- Radical prostatectomy, radiation therapy, and androgen deprivation therapy play pivotal roles in the management of men with high-risk disease, and potentially in men with metastatic disease.
- The optimal combinations of therapeutic regimens are an evolving area of study and future work looking into therapies for men with high-risk disease will remain critical.

INTRODUCTION

Prostate cancer (PC) is the second most common cancer in men, accounting for 1 in 5 new cancer diagnoses in the United States.[1] In 2016, more than 180,000 new cases were diagnosed and more than 26,000 men died of disease.[1] Although the majority of men are diagnosed with low- or intermediate-risk disease, upwards of 15% of men are diagnosed with high-risk disease.[2–4] Importantly, the incidence of high-risk and metastatic PC seems to be increasing.[5] Although this has been attributed in part to the 2012 recommendation by the US Preventive Services Task Force against screening for PC, the true long-term impact of these recommendations on advanced disease and mortality remains to be determined.[6]

In the face of these changes in disease presentation, the management of high-risk disease is evolving. Recent examinations in patterns of care suggest continued undertreatment of high-risk disease and overtreatment of low-risk disease.[7] Men with high-risk disease have a higher relative risk of PC-specific mortality than men with intermediate-risk disease.[8] Moreover, because they represent a substantial proportion of PC patients at legitimate risk of metastatic disease and death, our treatment must evolve to improve cure rates in this population.[9] In this review, we discuss the approach to management of men with high-risk PC, including diagnosis and treatment strategies.

DEFINITION OF HIGH-RISK DISEASE

Multiple schemas exist to define high-risk PC. However, there is a lack of consensus on which is the optimal definition. The 3 components that comprise

Disclosure Statement: No disclosures.

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Urol Clin N Am 44 (2017) 635–645

http://dx.doi.org/10.1016/j.ucl.2017.07.009

the definition of PC typically include Gleason grade, prostate-specific antigen (PSA), and rectal examination findings.[10] **Table 1** provides commonly used definitions incorporating these parameters. Other definitions use additional readily available clinical data to provide a more precise risk of failure. For example, the Cancer of the Prostate Risk Assessment (CAPRA) score uses age, PSA, clinical stage, Gleason score, and positive biopsy cores to predict risk of recurrence for localized disease.[11] The Kattan nomograms do not categorize patients into risk groups, but instead give a probability of 5-year treatment failure after radical prostatectomy or radiation by using multiple clinical variables including PSA, Gleason score, and clinical stage.[12]

A clear benefit to standard risk stratification is clear communication with the patients as to their disease state. However, the risk of recurrence varies greatly depending on the definition used for the same patient. An evaluation of 4708 patients treated with radical prostatectomy at Memorial Sloan-Kettering Cancer Center examined 8 different definitions of high-risk disease and found that, depending on the definition used, the proportion of patients defined as high risk ranged from 3% to 38% and 5-year relapse-free probability varied between 49% and 80%.[13] Revision of risk stratifications has been an active area of research and will likely continue to evolve in the future.[14] Consistent schemas are critical because, with standard definitions, providers may better determine ideal treatment strategies for patients, compare outcomes across clinical studies, and share expectations for clinical outcomes with patients.[15]

SCREENING

The impact of US Preventive Services Task Force recommendations on primary care and urologist practice patterns differs and optimal PSA screening strategy is in evolution, but does not clearly apply to men at high risk for PC, particularly aggressive disease.[21] Screening of men at risk for aggressive disease should consider additional factors. A family history of high-grade, high stage, or lethal PC is particularly important because cancer-specific survival in parents predicts survival from PC in their children.[22] The survival of a son correlates linearly with the survival of his father.[23] In addition, ethnic background is important because African American men may have up to a 60% higher risk of developing PC than Caucasians and have a worse prognosis[24] with an approximately 2-fold increased risk of diagnosis and death owing to PC.[25] Unfortunately, the rates of PSA screening are lower in African Americans when compared with non-Hispanic whites throughout multiple geographic regions in the United States.[26] As a result of the increased risk of death owing to PC in African American men, more frequent PSA testing and aggressive treatment may be appropriate for these men.[27] More recent data across all ethnic groups shows PSA levels in midlife correlate future lethal PC suggesting that risk stratified screening may be valuable in men aged 45 to 59 years.[28] Considering these aspects of a patient's history are important when evaluating men for screening, diagnosis, and treatment.

ROLE OF IMAGING IN IDENTIFYING HIGH-RISK PATIENTS

The role of MRI in the diagnosis and management of localized PC is expanding rapidly,[29] because MRI can accurate identify men with potentially aggressive disease.[29,30] The use of ultrasound fusion biopsy, which uses MRI to identify regions

Table 1
Definitions of high-risk prostate cancer

Professional Organization	Definition(s)	Notes
American Urologic Association[16,17]	PSA ≥20 ng/mL or GS ≥8 or c ≥ T2c	Guidelines are based on the D'Amico Criteria.[14]
European Association of Urology[18]	PSA ≥20 ng/mL or GS ≥8 or c ≥ T3a	
National Comprehensive Cancer Network[19]	PSA >20 ng/mL or GS ≥8 or c ≥ T3a	Multiple adverse factors can be categorized in the next level. Very high risk includes: T3b-T4, primary GS = 5, or >4 cores with GS 8–10.
Radiation Therapy Oncology Group[20]	GS = 7 with cT3 or N1 GS ≥8 and cT1-2	Very high risk includes: T3b-T4.

Abbreviations: c, clinical stage; GS, Gleason score; PSA, prostate-specific antigen.