The Quest for an Evidence-Based Approach to Intermediate-Risk Prostate Cancer

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By Theodore R. Saitz, MD [3] and Jen-Jane Liu, MD [4]

We must now come to a uniform consensus regarding the descriptions of these risk groups in order to truly determine which treatments have the best oncologic efficacy, while minimizing overtreatment and optimizing patients’ quality of life.

The goal of risk classification in prostate cancer should be to accurately characterize the likelihood of disease recurrence and the potential for prostate cancer–related death. Based on an individual patient’s risk, physicians can present him with appropriate treatment options to maximize survival and quality of life, in the context of his particular comorbid conditions and life expectancy. Accurate risk stratification is crucial, whether it is used to avoid overtreatment of very-low-risk or low-risk prostate cancer, or to identify subgroups of intermediate-risk patients who may benefit from more aggressive, and in some cases, multimodal therapy. The challenge in basing treatment on risk stratification is not at the far ends of the spectrum (very-low-risk or very-high-risk disease), where treatment paradigms are established, but rather in the middle, where intermediate-risk disease exhibits a broad range of behavior. The oncologic behavior of tumors in the intermediate-risk category is highly variable, demonstrating a wide range of prostate cancer–specific mortality, prostate-specific antigen (PSA) progression, and clinical disease recurrence across different treatment modalities.[1]

This review by Serrano and Anscher focuses on the substantial group of patients who fall into the intermediate-risk prostate cancer category as defined by the National Comprehensive Cancer Network; the authors advocate further subclassification of this group into favorable intermediate-risk (FIR) and unfavorable intermediate-risk (UIR) prostate cancer.[2] Studies from both surgical[3] and radiation[4,5] series have shown that men with UIR disease had inferior outcomes compared with men with FIR disease with regard to biochemical recurrence–free survival, distant metastasis, and cancer-specific survival. These varying outcomes suggest that FIR and UIR prostate cancer have different oncologic potentials and should be managed differently. The authors also point out that FIR prostate cancer behaves in a more indolent fashion than UIR disease and may not always warrant treatment. A recent update by Klotz et al on a large active surveillance (AS) cohort included a substantial percentage of patients (21%) with intermediate-risk prostate cancer (Gleason score 3+4 only).[6] After 15 years of follow-up, 85% of the initial 993 patients were still alive, and only 15 deaths (1.5%) were attributed to prostate cancer, even though 21% of the patients included were diagnosed with intermediate-risk prostate cancer.[6] Others have also suggested that there is a divide within intermediate-risk prostate cancer (Gleason score = 7), with the oncologic behavior of primary Gleason pattern 3 prostate cancer mimicking that of low-risk disease, and with primary Gleason pattern 4 prostate cancer mirroring high-risk disease.[7-9]

Risk stratification is further confounded by a heavy reliance on Gleason scoring from prostate biopsy specimens. Recent revisions to the Gleason scoring system have resulted in improved outcomes in both low-risk (Gleason score 6) and intermediate-risk (Gleason score 7) prostate cancer, as patients who were once considered low-risk have been reclassified into the intermediate-risk category. This phenomenon is known as the Will Rogers effect. The 2005 (and now 2014) International Society of Urological Pathology revision of Gleason scoring[10,11] may hamper efforts to study long-term outcomes of intermediate-risk prostate cancer patients, given that extended follow-up is required to recognize oncologic outcomes in prostate cancer on account of its slow growth pattern. Gleason scoring is also prone to interobserver variability by pathologists.[12] Finally, there are frequent discrepancies between prostate needle biopsy and radical prostatectomy Gleason scoring.[13] Most recently, Epstein et al have proposed and validated a new risk classification system that would replace the Gleason scoring system and take into account the distinction of FIR and UIR, as supported here by Serrano and Anscher.[11] In this new grading system, patients with Gleason 3+4=7 prostate cancer would be considered risk group 2, and those with Gleason 4+3=7 would be
considered risk group 3. Of course, the adoption of an entirely new grading system, even if it is more accurate in terms of oncologic potential, will undoubtedly pose challenges for the study of intermediate-risk prostate cancer outcomes over time.

Evidence clearly suggests that UIR prostate cancer behaves similarly to high-risk prostate cancer.[14,15] The outcomes for radiation therapy are summarized nicely in this review; however, we believe that surgery should remain a fundamental management option for clinically localized UIR and high-risk prostate cancer. Recent studies suggest that surgery may lead to improved survival compared with radiotherapy in patients with intermediate- or high-risk localized prostate cancer.[16] Additionally, improvement in cancer-specific survival has been noted in high-risk patients undergoing surgery compared with those treated with external beam radiation therapy.[17] The results of the ProtecT trial (ClinicalTrials.gov identifier: NCT02044172) will provide additional insight into the role of surgical management in intermediate-risk prostate cancer.[18]

Conversely, with an armamentarium of treatment options available, it is also necessary to consider which patients truly do require treatment and which are suitable for AS. Intermediate-risk prostate cancer patients with favorable features (eg, low-volume Gleason 3+4=7 disease, PSA level < 10 ng/mL) may be more appropriately grouped with their low-risk counterparts in terms of treatment. Some large AS cohorts have included significant numbers of these intermediate-risk patients, and have demonstrated satisfactory outcomes, particularly in older patients,[6] suggesting that AS may be expanded to include carefully selected intermediate-risk prostate cancer patients with favorable features.

We have made great progress in stratifying the large and heterogeneous group of prostate cancer patients based on the oncologic potential of their cancers. However, we must now come to a uniform consensus regarding the descriptions of these risk groups in order to truly determine which treatments have the best oncologic efficacy, while minimizing overtreatment and optimizing patients’ quality of life.

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