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Thwarting High-risk Prostate Cancer: The Right Treatments for the Right Patients

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Age-adjusted prostate cancer mortality rates have fallen roughly 40% in the United States since the advent of prostate-specific antigen (PSA)-based screening two decades ago [1]. Notwithstanding widely acknowledged problems with overtreatment of low-risk disease and controversies surrounding optimal screening strategies, the preponderance of evidence suggests that this favorable trend in mortality rates can be attributed in large part to some combination of earlier detection and better management of high-risk prostate cancer. In fact, many of the challenges going forward in prostate cancer research and clinical care might be summarized in the quandary of how to continue driving mortality rates downward while minimizing both overtreatment and the collateral impacts of treatments when they are required. Greater acceptance of active surveillance and ongoing technical refinements will continue to support the latter half of this equation; the former will depend on better management—identification and treatment—of high-risk disease.

The timely and comprehensive review by Bastian et al. [2] covers many important issues within the broad topic of high-risk prostate cancer, the majority of which boil down to two critical questions: How should high-risk prostate cancer be defined? And by what approach should it best be managed initially?

The review impartially summarizes many of the commonly cited definitions of *high risk* but does not comment as to which may be more or less suitable [2]. Various definitions will vary in terms of precision, discrimination, calibration, and ease of calculation. The venerable D'Amico classification and its variants are easy to determine with a glance at a medical record but yield highly heterogeneous groups [3]: By this definition, a man with a low-volume, Gleason 8, PSA 4

tumor may be placed in the same group as a man with a PSA 32, Gleason 9 tumor in multiple cores.

A specific drawback of this definition is the inclusion of cT2c as a determinant of high risk. In one analysis of the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) registry, 24% of men in contemporary practice were classified as high risk, but >40% of these were in the high-risk group only because of stage cT2c; in fact, these patients had lower recurrence rates after surgery than those classified as *intermediate risk* [4]. As pointed out in the review [2], variations of the D'Amico classification are endorsed by guidelines on both sides of the Atlantic; however, definitions based on a multivariable analysis of pretreatment risk factors, such as the Cancer of the Prostate Risk Assessment (CAPRA) score or various published nomograms, are preferable for predicting tumors with uniformly aggressive biology. One drawback to nomograms in this setting is the lack of consistent score thresholds accepted to define high risk [5].

A stricter definition of high risk will naturally identify a smaller proportion of all diagnosed men, but given the relative numbers of men diagnosed with versus dying of prostate cancer in screened populations, it is appropriate to focus the most intense therapeutic efforts on a relatively small proportion of men. A point worth emphasizing is that in screened populations, men with high-risk disease tend to be older and frequently are not offered potentially curative local therapy (see [6]). However, older men with high-grade disease, even those diagnosed in their 80s, face a substantial risk of cancer-specific mortality in the absence of local therapy [7]. Treatment decisions should reflect tumor risk characteristics and patient comorbidity rather than age per se.

Assuming men with high-risk, localized disease can be identified reliably, whether with current clinical parameters alone or together with emerging biomarkers or imaging tests, the critical question becomes how best to treat them. Bastian et al. [2] summarize a number of important recent themes from within-modality outcomes research. A few points are relatively uncontroversial but bear brief emphasis. First, in the contemporary era, surgery can be performed safely and effectively for men with high-risk disease, via either an open or a minimally invasive approach, in high-volume centers of excellence. Second, if surgery is elected for high-risk disease, a lymph node dissection should be performed, perhaps using an extended template, for more accurate staging and for potential cure of micrometastatic disease in a few cases. Third, radiation for high-risk disease must include androgen-deprivation therapy (ADT), with duration of treatment associated directly with severity of disease risk. Fourth, combination radiation including brachytherapy may offer better cancer control than external-beam radiation alone.

The review [2] also discusses proton-beam therapy. Although there are theoretical reasons in radiation physics to believe this approach may be better than traditional photon-based therapy, no study has ever demonstrated improved oncologic cure or improved quality-of-life outcomes with proton-beam treatment. Given the extraordinarily high costs associated with this treatment, it seems difficult to endorse from a cost-effectiveness standpoint [8]. Clearly, proton-beam therapy should not be reimbursed at such high multiples relative to brachytherapy and other treatment options until there is evidence of its superiority.

In their review, Bastian et al. [2] spend relatively little time on the crucial question of comparative effectiveness across modalities. Randomized trials have not been completed comparing surgery and radiation, and even when the only ongoing trial (Prostate Testing for Cancer and Treatment [ProtecT]) is completed, it is not clear how many high-risk patients will be included in the final trial cohort. However, with prolonged follow-up of very well-described, prospectively accrued observational cohorts, important insights may be gained from appropriately risk-adjusted analyses. A key general principle for such comparisons—and a major reason they have been rare until recently—is that only metastasis and mortality end points are meaningful in comparing surgery and radiation. Because of differences in the way biochemical recurrence is determined between these modalities [9], comparisons based on such definitions (see, eg, [10]) ultimately are not informative.

The Memorial Sloan-Kettering Cancer Center [11] and the CaPSURE [12] analyses discussed in the review [2] both found consistently lower rates of metastasis and mortality for men treated initially with prostatectomy compared to those treated with external-beam radiation. In both analyses, absolute differences in outcomes were small for men with low-risk disease but became highly clinically meaningful for those with high-risk disease. Both analyses were notable for rigorous risk adjustment using multiple different multivariable risk-stratification tools. The two studies are also complementary in that one used high-volume, academic

center data whereas the other used primarily community-based data, and there was variation between the two in terms of ADT use and radiation dosing. Clearly, despite careful risk adjustment, unmeasured confounding may persist that could explain these findings; however, a sensitivity analysis in the CaPSURE study demonstrated that such confounding would have to be very large and extremely pervasive to explain away the findings.

Bastian et al. [2] suggest that with longer-duration ADT and use of brachytherapy boosts, the radiation outcomes likely would have been equivalent to the surgical outcomes. This may or may not be true; longer-term ADT improves cancer-specific survival but to a relatively modest degree and does not necessarily improve all-cause survival [13]. Few prospective studies with adequate follow-up have compared brachytherapy directly with other modalities. A recent paper, published since the review article was finalized, reported risk-adjusted mortality outcomes from Washington University and the Cleveland Clinic. Once again, men treated with external-beam radiation had higher mortality rates than those treated primarily with surgery. In this study, those treated with brachytherapy had intermediate outcomes between surgery and external-beam radiation [14].

Better randomized trials focusing on outcomes across modalities for men with high-risk disease are essential; however, none is ongoing. In the meantime, with recurring back-and-forth debates between proponents of surgery and radiation therapy, prostate cancer may be lagging behind other areas in oncology, such as breast cancer and rectal cancer, in which the standard clinical paradigm has recognized for years that aggressive cancer requires equally aggressive, multimodal treatment, usually including surgery, radiation, and systemic therapy. The relative rarity of this combination for high-risk prostate cancer reflects, to an extent, the high prevalence of lower-risk disease, which by its pervasiveness drives a high proportion of clinical research.

There is also no question, however, that practice patterns have been driven by health care systems that offer wildly variable incentives for different treatments, that consistently fail to reward interdisciplinary cooperation, and that reimburse based on high-throughput treatment rather than high-quality outcomes. Continued progress in reducing prostate cancer mortality rates will require redoubled efforts—in research, in clinical care, and in health system reforms—to identify men with high-risk disease early and to offer appropriately intensive treatment that is both effective and cost-effective.

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