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Prostate Cancer: Quo Vadis?

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Several lines of clinical and experimental observation point to a critical inflexion point in prostate cancer research. Progress in the treatment of advanced treatment-refractory disease is reflected in the approval of life-prolonging agents and the integration of these agents in earlier disease states to greater effect [1,2]. These advances have been complemented by the development of informative preclinical model systems and promising therapy targets involved in DNA damage repair, stromal-epithelial interactions in bone, and intracrine and paracrine androgen receptor signaling [3,4]. Similar clarity is emerging for the treatment of localized prostate cancers. It is now widely accepted that prostate-specific antigen (PSA)-based screening exposes men to excess intervention. Patients with low-risk prostate cancer can be spared therapy, while some with more advanced cancers, including those with detectable metastases, will benefit from local control [5]. As a result of these developments, further progress in localized and advanced prostate cancer is expected.

The development of increasingly sensitive diagnostic tests will improve prediction and prognostication, but enthusiastic acceptance of technological advances without critical utility assessment creates new challenges. These advances may expose patients to the risk of technology used for its own sake, without a corresponding clinical benefit. In this perspective, we highlight the need for utility measures to assure beneficial application of potentially transformative technologies at this critical moment of convergent clinical and experimental insights and parallel diagnostics.

The clinical application of novel technologies has led to awareness and acceptance of new categories of patients. For example, new clinical entities such as magnetic resonance imaging "screen-detected" early prostate cancer and marker-only (M0) "oligometastatic" disease have emerged from the application of more discriminating imaging modalities. Men with low-risk cancers like these are at greatest risk of excess treatment, whereas patients with more advanced cancer are at risk of delayed therapy (Fig. 1). The challenge is to estimate those risks.

Most readily accept that a better understanding of individual patients' cancers will be helpful. However, the utility of more precise characterization of primary tumors or more detailed screening of metastases to improve outcomes has not been tested. These assumptions need to be tested with disease state–specific utility measures before novel technologies are considered for clinical application.

The benefits of more precise technologies are evident in efforts to individualize therapy in patients with advanced prostate cancers. The evolving biologic classification of advanced prostate cancer has made the prospect of a marker-informed therapy feasible [6,7]. The link to complex transcriptional, genetic, germline, and metabolomic alterations has been tabulated in available databases to further refine the biologic classification. A primary goal of new technologies is to anticipate progression, predict responsiveness, and monitor the efficacy of specific therapies by linking biologic drivers to individual patient treatment recommendations.

Therapeutically relevant heterogeneity over time ("temporal heterogeneity") in the clinical course of prostate cancer may be greater than that in other cancer types. In bladder, breast, and colon cancers, chemotherapy effective in the metastatic setting has greater impact in the adjuvant or neoadjuvant setting. By contrast, while taxanes are effective in metastatic hormone-naïve and castrate-resistant prostate cancers, studies to date suggest much less efficacy in localized disease [8]. In addition, carboplatin-based therapies are more effective in advanced and aggressive forms of prostate cancer than in earlier disease

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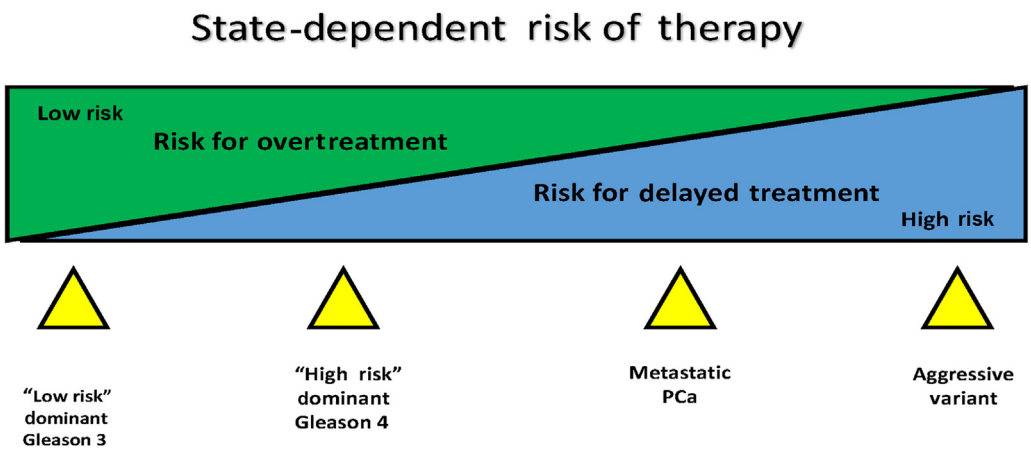

Fig. 1 – Disease state–dependent relative risk of excess treatment (green) or delayed treatment (blue). PCa = prostate cancer.

states. These observations suggest that there is a progression-dependent therapeutic vulnerability and that "earlier may not always be better."

Unlike in lung, colon, and uterine/cervix cancers, the substantial efforts to screen for prostate cancer in the USA and Europe have not demonstrated a clear and unequivocal benefit. This raises the critical question of why the results in prostate cancer differ from those in other common adult solid tumors for which the unequivocal merits of screening have been established [9]. The extensive efforts already expended for PSA-based screening strongly suggest that refinement of this approach will, at best, only result in modest gain. Although speculative, possibilities to consider that could account for this include the fact that (1) PSA does not reflect the form of prostate cancer that requires or benefits from early detection and (2) interaction between age-related comorbidities and prostate cancer may limit the benefits of intervention. The latter concern is reflected in studies that show no clear advantage for prostatectomy when compared to observations in favorable prostate cancers [10,11]. Thus, confusion remains in men at risk for cancer or who have localized cancer with limited lethal potential. Given the absence of therapy benefit, hopes that better characterization of the prostate in this subset will lead to an increase in survival are unfounded. However, advanced imaging may be applied toward the objective testing of focal ablative strategies.

Although it remains clear that alternative concept(s) must be considered, daunting methodologic challenges also need to be understood. The determinants of survival in men with localized prostate cancer are "multidimensional." Mortality and morbidity may be attributed to the host, the cancer, or the interaction between the two. In addition, markers must predict outcomes in the "remote future," which can extend beyond 15 years. To make progress we must acknowledge that the risk of overtreatment is magnified in the prostate cancer population with "low-penetrance cancers" and age-related comorbidities. Focusing our interest on the patient, as opposed to the cancer, may lead to a new definition for early prostate cancer as a component of age-related vulnerabilities. To ensure that promising technologies improve patient care, utility must be demonstrated before application.

The clarity created by the reclassification of prostate cancer based on biology, germline alterations, and improvement in prognostication is converging with the introduction of powerful diagnostics. The development of utility measures is urgently needed to harness potential synergies to the benefit of patients.

Conflicts of interest: The authors have nothing to disclose.

References

[1] Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med 2015;373:737–46.
[2] James ND, de Bono JS, Spears MR, et al. Abiraterone for prostate cancer not previously treated with hormone therapy. N Engl J Med 2017;377:338–51.
[3] de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011;364:1995–2005.
[4] Efstathiou E, Titus M, Wen S, et al. Molecular characterization of enzalutamide-treated bone metastatic castration-resistant prostate cancer. Eur Urol 2015;67:53–60.
[5] Parker CC, James ND, Brawley CD, et al. Radiotherapy to the primary tumor for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomized controlled phase 3 trial. Lancet 2018;392:2353–66.
[6] Logothetis CJ, Gallick GE, Maity SN, et al. Molecular classification of prostate cancer progression: foundation for marker-driven treatment of prostate cancer. Cancer Discov 2013;3:849–61.
[7] Aparicio AM, Shen L, Tapia EL, et al. Combined tumor suppressor defects characterize clinically defined aggressive variant prostate cancers. Clin Cancer Res 2016;22:1520–30.
[8] Fizazi K, Faivre L, Lesaunier F, et al. Androgen deprivation therapy plus docetaxel and estramustine versus androgen deprivation therapy alone for high-risk localised prostate cancer (GETUG 12):

a phase 3 randomized controlled trial. Lancet Oncol 2015;16:787–94.
[9] Schroder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med 2009;360:1320–8.
[10] Wilt TJ, Jones KM, Barry MJ, et al. Follow-up of prostatectomy versus observation for early prostate cancer. N Engl J Med 2017;377:132–42.
[11] Bill-Axelson A, Holmbert L, Garmo H, et al. Radical prostatectomy or watchful waiting in prostate cancer—29-year follow-up. N Engl J Med 2018;379:2319–29.