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Re: European Study of Prostate Cancer Screening — 23-Year Follow-up

Roobol MJ, de Vos II, Månsson M, et al.

N Engl J Med 2025;393:1669–80

Experts' summary:

The European Randomized Study of Screening for Prostate Cancer (ERSPC) enrolled >160 000 men aged 55–69 yr across eight countries to evaluate an invitation to repeat prostate-specific antigen testing versus no invitation. At 23 yr, the cumulative prostate cancer mortality rate was 1.4% in the screening group and 1.6% in the control group, which yields a risk ratio of 0.87 and an absolute reduction of 0.22% [1]. Screening prevented one prostate cancer death for every 456 men invited. Crucially, other-cause mortality was identical between the groups (49%; risk ratio 1.00), which indicates that the difference in prostate cancer mortality observed is not attributable to competing risks or baseline health differences. These extended results strengthen confidence in a true screening effect on prostate cancer–specific mortality while supporting ongoing efforts to refine approaches that reduce overdiagnosis.

Experts' comments:

With other-cause mortality similar between the arms and a modest absolute reduction in prostate cancer mortality in favor of prostate-specific antigen screening, any difference in overall mortality in the ERSPC will remain statistically undetectable [1,2]. This finding is often misinterpreted as evidence against screening, which is a misleading criticism.

Barring an increase in deaths from other causes due to screening—a highly improbable scenario—a genuine reduction in prostate cancer mortality conceptually establishes an overall mortality benefit. As prostate cancer represents a small proportion of total mortality, detection of a difference in all-cause mortality would require unfeasibly large trials [3]. Therefore, the common notion that "prostate cancer screening failed to save lives" is misguided. This limitation is not unique to prostate cancer: other screening interventions, including mammography and lung computed tomography, have inevitably failed to demonstrate an all-cause mortality benefit [4].

Trial endpoints must be interpreted within their epidemiologic and clinical context—namely, what they can and cannot demonstrate. Treating the absence of an all-cause mortality reduction as evidence against screening obscures a balanced view of the evidence-based benefits and harms of organized prostate cancer screening revealed by the ERSPC trial [5,6].

Conflicts of interest: The authors have nothing to disclose.

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Re: Tumor Transcriptome-wide Expression Classifiers Predict Treatment Sensitivity in Advanced Prostate Cancers

Grist E, Dutey-Magni P, Parry MA, et al.

Cell 2025;188:5717–34.e10

Expert's summary:

Grist and colleagues [1] address biomarkers to predict the benefit of docetaxel chemotherapy in metastatic hormone-sensitive prostate cancer (mHSPC). The authors analyzed a subset of 1523 men enrolled in the STAMPEDE phase 3 trial who received androgen deprivation therapy (ADT) ± docetaxel or abiraterone, and identified two key transcriptomic signatures using the Decipher RNA platform that were both prognostic for and predicted better survival with docetaxel. While the authors found that all patients benefited from abiraterone irrespective of various signatures, docetaxel was selectively beneficial only in men with high Decipher risk (hazard ratio [HR] 0.64, 95% confidence interval [CI] 0.48–0.86), and not in men with lower Decipher risk (HR 0.96, 95% CI 0.71–1.30; interaction *p* value 0.039). Findings were similar in both high-volume and low-volume disease according to the CHAARTED criteria. Markers of proliferation (cell cycle score, Ki-67) or luminal/basal phenotypes were prognostic but not predictive of docetaxel benefit [2]. Finally, PTEN loss was associated with poor survival in the abiraterone arm, but not in the docetaxel arm; the investigators found that men with mHSPC and tumors with transcriptionally inactive PTEN, but not those with PTEN loss on immunohistochemistry, experienced a survival benefit from docetaxel (HR 0.57, 95% CI 0.42–0.76) in comparison to those with PTEN-intact tumors (HR 1.05, 95% CI 0.77–1.43).

Expert's comments:

This study retrospectively identified two biomarkers predictive of a survival benefit from docetaxel in men with mHSPC. Currently, doublet therapy with ADT and an androgen pathway receptor inhibitor (ARPI) is the clear standard of care for most men. Docetaxel triplet therapy may potentially further prolong life for men with synchronous high-volume disease, such as those with liver or high-volume bone metastases. However, ADT + ARPI doublet therapy is beneficial in some high-volume cases [3], while some men with low-volume disease experience rapid progression despite doublet therapy.

This large analysis of STAMPEDE validated the role of PTEN loss and Decipher high-risk signatures. The presence of both PTEN loss and a high-risk Decipher signature identified a subgroup of patients (28%) who benefited the most from docetaxel (HR 0.55, 95% CI 0.34–0.89). A major limitation of the study is that only 823 of the 3909 STAMPEDE patients had evaluable data in the metastatic setting, and no patients received triplet therapy.

The present biomarkers are not prospectively validated in the context of decision-making between doublet and triplet therapy. This strategy is now warranted; for example, the National Cancer Institute–funded TRIPLE SWITCH trial (NCT06592924) is evaluating the value of docetaxel in patients with a suboptimal prostate-specific antigen response to ADT + ARPI, and is analyzing these and other biomarkers for prediction of a personalized, risk-adapted docetaxel benefit.

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