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European Association of Urology

Letter to the Editor

Re: Annika Herlemann, Janet E. Cowan, Samuel L. Washington 3rd, et al. Long-term Prostate Cancer-specific Mortality After Prostatectomy, Brachytherapy, External Beam Radiation Therapy, Hormonal Therapy, or Monitoring for Localized Prostate Cancer. Eur Urol. In press. https://doi.org/10.1016/j.eururo.2023.09.024

Information obtained from extensive real-world cohorts provides valuable insights for patient management. Although randomized trials contribute robust evidence to the field of medicine, they can be challenging to design, conduct, and complete. While real-world practices can supplement these trials, analyses based on real-world data require caution in interpretation owing to the inherent risk of selection biases [1].

Herlemann et al [2] reported long-term prostate cancer–specific mortality (PCSM) after various treatments for localized prostate cancer (LPC), including radical prostatectomy (RP) and active surveillance/watchful waiting (AS/WW), among others. The study was based on CaPSURE registry data and included 11 864 men across 45 urology practices. The analysis considered both PCSM and all-cause mortality (ACM), with patients stratified into prognostic groups according to their CAPRA score using a validated nomogram. The analysis was controlled for tumor risk factors and age and revealed statistically significant and clinically meaningful differences in ACM and PCSM across primary treatments.

Notably, PCSM was lowest after surgery, while the highest PCSM rates were observed following castration and AS/WW. The study further highlighted minimal differences in outcomes for low-risk disease. The authors conducted a comparative analysis by juxtaposing their findings with those of the ProtecT study [3]. They emphasized that the men recruited in ProtecT had low- or intermediate-risk PC at diagnosis, which posed challenges in assessing mortality criteria, especially for RP, even up to the 15-yr mark. Acknowledging the intricacies of their study, they discussed limitations, noting that patients from practices contributing to the CaPSURE registry do not represent a random sample of the overall PC population in the USA. They candidly identified potential sources of bias, such as confounding by indication and other unmeasurable factors that could influence their results.

A crucial aspect highlighted in their analysis pertains to the inherent limitations linked to real-world practice. The authors underscored that treatments in practical settings are allocated to patients on the basis of a combination of risk stratification, age, and health status.

While the researchers conducted adjustment for survival analysis, it is noteworthy that not all confounding elements, such as comorbidities, were comprehensively addressed. Despite their efforts, the authors acknowledge that the results do not solely reflect the exclusive impact of treatment on outcomes.

Analysis of cause-and-effect relationships using methods such as Pearl's do-calculus can help in elucidating results that reveal causal information in terms of statistical measures. This entails demonstration that a parameter derived from a directed acyclic graph for an intervention aligns with a real-world parameter [4]. If the assumptions hold, non-randomized real-world data can yield estimates for causal variables akin to those from ideal experiments such as randomized trials [5].

While real-world data are valuable sources of information, their interpretation requires caution and specialized tools. Comprehensive registries, for instance, serve as a pertinent foundation for validation of prognostic tools such as risk scores and nomograms. The value of well-conducted randomized clinical trials in providing unbiased high-level evidence remains inescapable.

Conflicts of interest: The authors have nothing to disclose.

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Olivier Cussenot [a,b,*]
Antoine Chambaz [c]
Freddie C. Hamdy [a]

[a] *Nuffield Department of Surgical Sciences, University of Oxford, Oxford, UK*
[b] *Centre for Research on Prostatic Diseases, Paris, France*
[c] *CNRS, MAP5, Université Paris Cité, Paris, France*

*Corresponding author. Centre for Research on Prostatic Diseases, Paris, France.
E-mail address: o.cussenot@cerepp.org (O. Cussenot).

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