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European Association of Urology

Letter to the Editor

Re: Sebastian Berg, Alexander P. Cole, Marieke J. Krimphove, et al. Comparative Effectiveness of Radical Prostatectomy Versus External Beam Radiation Therapy Plus Brachytherapy in Patients with High-risk Localized Prostate Cancer. Eur Urol 2019;75:552–5

Comparing Apples to Oranges: A Self-fulfilling Prophecy?

We read with interest the National Cancer Data Base (NCDB) study by Berg et al. [1] comparing overall survival (OS) between men aged ≤65 yr with high-risk prostate cancer (PC) receiving radical prostatectomy (RP) and those receiving external beam radiotherapy with a brachytherapy boost (EBRT + BT). The authors conclude that EBRT + BT was associated with significantly worse OS, with a hazard ratio of 1.22 for all-cause mortality. When considering the validity of this conclusion, three salient points must be considered.

First, cancer registries inherently cannot capture the selection bias that affects treatment allocation to RP or EBRT + BT, even among "healthy" patients. For example, several different registry studies have shown implausible OS differences among patients with low- and intermediate-risk disease, with divergence of survival curves for RP and EBRT—favoring RP—within 3 yr post-treatment, in stark contrast to the level 1 evidence provided by the ProtecT trial, which found no differences in all-cause mortality at median follow-up of 10 yr [2,3].

Second, the dominant cause of death even in high-risk PC is other-cause mortality [4]. The NCDB provides no information on tumor control specifically, and one cannot correct for unmeasured confounding variables that would favor improved other-cause mortality in RP patients. Therefore, any difference identified in OS is most likely attributed simply to differences in other-cause mortality.

Third, the authors state that they did not account for the use of androgen deprivation therapy (ADT) in the treatment groups. Both the European Association of Urology/European Society for Radiotherapy and Oncology/International Society of Geriatric Oncology and National Comprehensive Cancer Network guidelines recommend long-term ADT with EBRT + BT, reflecting the multiple randomized trials that have demonstrated a robust OS benefit for use of long-term ADT with EBRT. No high-level evidence exists to suggests that ADT can be foregone with EBRT + BT, and hence all professional societies consider it to be the standard of care to use ADT of sufficient duration with EBRT + BT. Thus, the inclusion of patients not receiving ADT (31% of EBRT + BT patients) and the inability to account for ADT duration in this analysis are troubling. This is evident if the results are contextualized with two other studies with biopsy Gleason score 9–10 disease. The first found a PC-specific mortality benefit for EBRT + BT (with median ADT duration of 12 mo) over RP [5]. The second found an OS benefit for EBRT + BT (with median ADT duration of 6 mo) over RP without postoperative therapy, and equivalent OS between EBRT + BT and RP with adjuvant EBRT [6]. Given the inherent differences between patients who receive RP and those who receive EBRT + BT, we acknowledge that all retrospective analyses are intrinsically an "apples to oranges" comparison. However, in any such comparison, it is even more imperative to enrich for explicitly codified standard-of-care treatments.

Ultimately, the superiority or noninferiority of RP versus EBRT + BT needs to be determined in a prospective, randomized fashion. We would be highly supportive of a clinical trial to help answer this question for the thousands of patients diagnosed with high-risk disease annually.

Conflicts of interest: Amar U. Kishan has received honoraria from Varian Medical Systems and ViewRay and has served on an advisory board for Janssen. William A. Hall has received institutional research support from Elekta and grant funding from the American Cancer Society. Daniel E. Spratt has served on an advisory board for Janssen.

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