Response

The entrenched belief that prostate-specific antigen (PSA) screening saves sufficient lives to offset the extensively documented harms that follow from surgical and other interventions relies entirely on the European Randomized Study of Screening for Prostate Cancer (ERSPC) and GOTEBO RG trials (1,2). Despite evidence of serious flaws (3) and alternate interpretations of these data (4,5), this hypothesis is defended at all costs, now by Carlsson, Roobol, Schroder, Hugoson, and Auvinen (6) and earlier by Walsh (7). This belief persists, despite publication of the 80000 patient Finnish component of ERSPC (8), which revealed no statistically significant benefit from PSA-screening (hazard ratio = 0.85; 95% confidence interval = 0.69 to 1.05; \( P = .10 \)). Furthermore, Schroder and colleagues made two fatal errors in ERSPC—cutting and pasting 60% of the GOTEBO RG data into ERSPC and pooling heterogeneous data from seven European countries, five of which showed no life-saving benefits. The credibility of the PSA-screening-saves-lives hypothesis now rests entirely on the small 20000-patient GOTEBO RG trial from a single city.

Our evaluation of the GOTEBO RG data (4) highlighted a threefold increase in the usage of primary androgen deprivation therapy (ADT) in the control arm, whereas radiotherapy, radical prostatectomy, and surveillance were largely equivalent between arms (Figure 1). We sought an explanation for this large imbalance.

Because ADT monotherapy is not US Food and Drug Administration approved, we reasoned that initial ADT monotherapy might increase prostate cancer (PCa) deaths. We examined PCa-specific mortality on a country-by-country basis in ERSPC and GOTEBO RG and found a correlation between differential ADT usage and PCa deaths (5). We noted the extraordinary disparity in treatment of similar-risk patients between arms, such that in organ-confined disease, 5% of screened patients received ADT vs 13% of control subjects (9). If this treatment approach in organ-confined disease is not supported by any treatment guidelines, as emphasized by Carlsson et al. (6), then why was it used in so many patients and in such an unbalanced way? In the locally advanced but nonmetastatic group, 18% of screened patients received initial ADT monotherapy vs 53% of control subjects. Furthermore, two large randomized trials revealed that ADT treatment was markedly inferior to radiotherapy plus ADT (10,11), of which the latter is misquoted by Carlsson et al. Despite their claims, this large inconsistency in treatment of similar-risk patients is not at all justifiable because of “increased risk of death.” Differential effects of ADT monotherapy in the screening and control arms could have severely distorted the interpretation of GOTEBO RG (4,5).

Carlsson et al.’s examples distract attention from and studiously avoid the three key issues of differential ADT usage, stage migration, and PCa deaths. First, these authors point out that we did not consider the Scandinavian SPCG-4 trial, which demonstrated a survival advantage for radical prostatectomy over watchful waiting. This was because SPCG-4 was not based on PSA screening but predominantly on a select subset of men who presented with symptomatic PCa and moderately to well-differentiated T1 to T2 carcinomas. Second, instead of engaging in detailed re-evaluation of their own data from ERSPC and GOTEBO RG, they cite an unhelpful meta-analysis of 11 trials, none of which randomly assigned patients to ADT monotherapy as initial treatment. Third, their criticisms about our false assumptions and misunderstandings of correlations are unfounded. We are quite aware that correlation does not equate to causation and that absence of effect does not equal proof of no effect, and we are fully cognizant of current guidelines that only recommend ADT usage for metastatic disease. Their most egregious omission, however, is their failure to cite the high-profile Brawley editorial that appeared in the same issue of the Journal as our commentary (12). It provided a balanced perspective on PSA screening, the benefits of ADT when used appropriately, and the potential harms from inappropriate usage. Brawley’s independent evaluation impinges directly on many of the issues raised by Carlsson et al.

Finally, the relative contributions of initial hormonal monotherapy and stage migration to PCa-specific mortality already exist in the unpublished ERSPC and GOTEBO RG data. Their release would help to clarify the issues raised by Carlsson and the assertion by Walsh (without any quantitative evidence) that stage migration alone completely accounts for differential PCa mortality. If the ADT contribution is small, our hypothesis fails. Alternately, if the impact of ADT monotherapy is sufficiently large, then urologists will need to seriously reconsider the efficacy of PSA screening and the use of ADT monotherapy.

Figure 1. Ratios of treatments for patients in the control arm (black) to the same treatment for patients in the screening arm (shaded) in the GOTEBO RG trial. ADT = primary endocrine treatment; PROST = primary radical prostatectomy; RAD = primary radiation; SURV = surveillance at last follow-up. Data from Table 3 of Hugosson et al. (2).
in the nonmandated condition of localized tumors.

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References

Notes
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