RE: Mortality After Radical Prostatectomy or External Beam Radiotherapy for Localized Prostate Cancer

We read with interest the report from Hoffman et al. (1) and its accompanying editorial (2) comparing mortality in men treated in the mid-1990s with radical prostatectomy or external beam radiotherapy (RT) for prostate cancer. This study highlights the difficulty of comparing mortality among treatments in prostate cancer using observational studies.

As the authors discuss, RT evolved substantially since 1994, with more than 15 randomized trials performed, the most of any treatment modality in localized prostate cancer. The two most notable findings were the addition of androgen deprivation therapy (ADT) to RT and dose escalation. Randomized trials including more than 6000 patients demonstrated an overall mortality reduction when ADT is added to RT for patients with intermediate- and high-risk prostate cancer, with a relative reduction of approximately 50% (3). This alone would make up the mortality difference between RT and prostatectomy the authors observed. Additional trials also demonstrated that long-term ADT further reduces mortality compared with short-term ADT (4,5). Unfortunately, in the mid-1990s, ADT use with RT was uncommon and long-term ADT was rare; this study included only 56 patients who received ADT, with unclear timing and duration. Although subgroup analysis was performed, the results are unreliable because of the small sample size and unknown treatment details. Further, five additional randomized trials published after 2000 consistently demonstrated a 15% to 20% reduction in prostate cancer recurrence with dose escalation (6).

Together, these trials demonstrated that modern RT, compared with that used in this study, reduces prostate cancer recurrence and overall mortality, which must be a central consideration when interpreting the authors’ results. Although radical prostatectomy has also evolved, evidence clearly supporting improved survival with modern prostatectomy compared with older techniques is lacking.

Another notable challenge is the ability of sophisticated analytic methods to fully control for confounding among patients who received radical prostatectomy vs RT—an especially relevant concern when mortality is the outcome of interest. The authors should be applauded for applying several propensity score methods to analyze the data; however, as they admit, residual confounding is likely. It would have been helpful to provide the adjusted overall mortality and cancer-specific mortality plots, which would enable examination of the absolute magnitudes of difference among patient groups and to assess how well the adjustment worked to balance confounders. If indeed the patient characteristics are well balanced and if the mortality difference is solely attributable to the differences in treatment (prostatectomy more effective than RT), then the absolute overall mortality difference between the two groups should be no greater than the cancer-specific mortality difference.

Therefore, we disagree with the potential conclusion that the findings of this study represent a true survival advantage of radical prostatectomy vs RT. As noted (2), a number of other retrospective or population-based studies have reached similar conclusions, but all also ignored the changes in RT over the last 20 years. Unfortunately, these studies, although well designed, do not provide information about the relative efficacy of contemporary RT vs prostatectomy to help patients today make treatment decisions; therein lies the difficulty of assessing mortality as an endpoint for observational comparative effectiveness research in localized prostate cancer.

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