Competing Risks for Patients With Localized Prostate Cancer

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In health care, as in the rest of life, decisions have consequences. A chosen treatment for prostate cancer can yield benefits, but it can also cause harm. In localized prostate cancer, as in most diseases, baseline characteristics influence the natural history of the disease and thus a treatment’s potential for benefit. The most relevant estimates for an individual come from studies involving patients who are similar to the individual selecting treatment.

The recently updated guideline from the American Urological Association lists the following primary treatments for localized prostate cancer: watchful waiting, active surveillance, interstitial brachytherapy, external beam radiotherapy, radical prostatectomy, primary hormonal therapy, and others (e.g., cryotherapy) (1). To choose from this menu, patients must first weigh their individualized risk of death from prostate cancer in the absence of treatment and then each treatment’s likely effect on that risk, along with associated specific types and risks of complications. These guidelines caution patients that there are important limitations to the available studies because follow-up is often insufficient for most treatment options, researchers use inconsistent definitions for the most commonly reported complications, and authors often fail to adequately detail baseline patient characteristics. Finally, because most evidence is derived from case series and small randomized trials that frequently pool data from patients with various levels of disease burden, the evidence base is subject to selection and other biases.

Selecting a primary therapy is not the only choice facing patients with localized prostate cancer. Some patients are offered androgen deprivation therapy (ADT) after prostatectomy or radiation therapy (adjuvant ADT) that can continue for years. Others are offered several months of ADT (neoadjuvant ADT) before definitive primary therapy. Many trials on adjuvant or neoadjuvant ADT for localized or locally advanced prostate cancer fail to report the key outcome of interest, and most do not report outcomes stratified by risk groups. Some reviews address side effects of ADT (2,3) but focus primarily on morbidity and quality of life. A recently published Cochrane systematic review (4) reported estimates for outcomes of treatment efficacy by primary therapy (prostatectomy or radiation therapy) and by type of hormonal deprivation (adjuvant or neoadjuvant). ADT use for patients with localized prostate cancer has increased substantially over time (5), and recent evidence suggests that ADT may be associated with increased risk for diabetes and cardiovascular disease (6). In this issue of the Journal, Tsai et al. (7) use registry data from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database to evaluate effects of ADT on risk for cardiovascular death.

Tsai et al. (7) analyzed results for 3262 prostatectomy patients (of whom 266 also received ADT) and for 1630 patients treated with external beam radiotherapy, brachytherapy, or cryotherapy (of whom 749 also received ADT). They used competing risk methods to analyze time to cardiovascular death and to account for competing risks of death (prostate cancer and other noncardiovascular deaths) by informative censoring (8). They also used competing risk regression analysis to control for age and risk factors for cardiovascular disease and to test whether use of ADT was statistically significantly associated with a shorter time to cardiovascular death. Tsai et al. (7) report that ADT statistically significantly shortens time to cardiovascular death and increases its cumulative incidence at 5 years among prostatectomy patients, regardless of age. They also noted a greater incidence of cardiovascular death among patients 65 years and older who were treated with ADT and managed with external beam radiotherapy, brachytherapy, or cryotherapy, but the difference from those not given ADT did not reach statistical significance.

How should readers interpret and act on these results from a retrospective series susceptible to selection bias? Can we conclude that ADT increases risk of cardiovascular death? Data in table 1 of the study by Tsai et al. (7) indicate that men given ADT in both the prostatectomy and nonprostatectomy groups were more likely to have higher tumor burdens (higher prostate-specific antigen levels, larger tumors, and higher Gleason scores). They may also have differed from those not given ADT in ways not captured by CaPSURE’S data elements. Regression analysis and competing risk methods adjust for known risk factors but cannot adjust for unknown or unmeasured factors in nonrandomized groups. In Tsai et al. (7), tables 3 and 4 show that only a minority of the deaths from risks other than cardiovascular causes were deaths from prostate cancer (e.g., for the 114 deaths in the prostatectomy group, 61 were from cardiovascular causes, 16 from prostate cancer, and 37 from unreported causes). Risk factors contributing to the noncardiovascular, non–prostate cancer deaths could not be controlled for in the competing risk regression analysis.

Because conclusive evidence is not available from randomized studies, should patients and clinicians ignore the possibility that ADT may increase the risk of cardiovascular death when evaluating the advisability of adding adjuvant or neoadjuvant ADT to primary therapy for localized disease? Dismissing this hypothesis seems imprudent. The authors’ recommendation that patients considering adding ADT should undergo careful cardiovascular evaluation makes sense.
Do these results suggest that ADT increases risk of cardiovascular death only among men given prostatectomy but not among men managed with other primary therapies? This possibility seems less likely. A pooled analysis of three trials that randomly assigned patients to radiation therapy, either with or without short-course ADT, showed statistically significantly shorter times to fatal myocardial infarction among men aged 65 years or older treated with ADT and radiation therapy than among those treated only with radiation therapy (9). As Tsai et al. (7) point out, the CaPSURE sample treated with prostatectomy was nearly twice as large as the sample treated with other primary therapies, which may have limited the statistical power to detect a statistically significant effect of ADT in the nonprostatectomy group. Finally, it seems unlikely that the metabolic impact of ADT (6) occurs only or even more frequently in patients managed with prostatectomy.

Ideally, the hypothesis that ADT increases risk of cardiovascular death should be studied in groups given the same primary therapy and randomly assigned to ADT or to placebo, in separate studies for adjuvant and neoadjuvant ADT. These studies would help elucidate whether the duration of ADT influences its effect on risk of cardiovascular death and would stratify patients to take baseline cardiovascular risk into account. Researchers need to address whether cardiovascular death continues to increase with longer follow-up than a median of 4 years, particularly in patients aged 40–59 years whose cardiovascular risks increase as they age. Researchers must also ask whether ADT increases the risk of death from causes unrelated to either prostate cancer or cardiovascular events. The article by Tsai et al. (7) has raised an interesting hypothesis, but patients and clinicians need better risk estimates for cardiovascular death associated with ADT use that are based on randomized trials rather than retrospective analysis.

References