Editorial

Tackling Overtreatment of Prostate Cancer

The Role of Comorbidity

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The management of localized prostate cancer continues to be an area of tremendous controversy. In 1 of the only clinical trials supporting an aggressive approach, an overall survival benefit for radical prostatectomy versus watchful waiting was limited to men aged <65 years at diagnosis and could be demonstrated only after 10 years of follow-up.[1,2] In addition, a small minority of the men were diagnosed by prostate-specific antigen (PSA) screening, making generalizability of those results to contemporary prostate cancer cohorts questionable. Moreover, older men or men with low-risk tumors are unlikely to die from their prostate cancer even without any aggressive intervention, such as radical prostatectomy or radiation therapy.[3] Therefore, although a wide variety of treatment options exists, the main challenge has been, and continues to be, how to identify the men for whom it would be more appropriate to adopt a conservative approach.

In this issue of *Cancer*, Daskivich et al add to the literature in this area.[4] By using data from a cohort of nearly 1500 men with prostate cancer from 2 Veterans Affairs (VA) Medical Centers in California, they examined the impact of comorbidity on nonprostate cancer mortality with a competing risks analysis in groups stratified according to the tumor risk criteria described by D'Amico et al.[5] Daskivich et al reasoned that the outcome of nonprostate cancer mortality was of particular interest, because it would help discern which men would be unlikely to benefit from aggressive treatment. In a model adjusted for age, race, D'Amico et al tumor risk, and treatment received, an increasing score on the Charlson comorbidity index predicted higher nonprostate cancer mortality. Men who had a Charlson score $\geq$3, for whom the nonprostate cancer mortality rate was 74% at 10 years, had a greater than 8-fold increase in the hazard of death from causes other than prostate cancer compared with men who had a Charlson score of 0. In general, those men with higher Charlson scores and/or low-risk to intermediate-risk tumors were far more likely to die from causes other than their prostate cancer.

The concept that comorbidity should be incorporated into decision-making about treatment for prostate cancer is not new, with some prior reports dating back more than a decade.[6] The advantages of this study over others include the use of competing risk analyses to account for both nonprostate and cancer-specific mortality in estimating the hazard of death associated with each, coupled with the heterogeneous mix of patients with respect to tumor characteristics and treatment received. In addition, comorbidity was assessed through review of medical records, which may be more accurate than the assessments in many previous studies based on administrative claims data.[7] However, generalizability is likely to be limited given the relatively small sample of patients, the fact that the cohorts were derived from only 2 centers, and the nature of the veteran population, with its particular socioeconomic and comorbidity issues. Previous studies have attempted to derive nomograms to predict 10-year life expectancy and have presented information on predictive accuracy, neither of which were done in this study.[8,9] Thus, the practical utility of the study findings are limited to the generality that men with high degrees of comorbidity and low-risk to intermediate-risk tumors probably should receive conservative management. Ultimately, we believe that the primary value of this particular investigation is that it continues the dialogue about how best to identify the subset of patients who are unlikely to benefit from definitive treatment.

The sobering reality is that, despite calls for more conservative management of localized prostate cancer in both the published literature and in practice guidelines, overtreatment remains rampant.[10,11] An earlier publication by the same

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investigative group reported that 54% of low-risk patients in this population with Charlson scores ≥ 3 were treated aggressively (radical prostatectomy, radiation therapy, or brachytherapy).[12] Similar results were reported from studies that used very large, national samples of men.[13,14] There also is a growing body of evidence to suggest that treatment itself can increase noncancer mortality among patients with pre-existing comorbid conditions. For example, androgen-deprivation therapy has been associated with cardiovascular disease mortality among men with prevalent cardiovascular disease.[15]

Which factors might account for the failure to consider life expectancy in decisions about treatment for localized prostate cancer? There may be concerns about the ability to accurately assess life expectancy. In a Canadian survey study, 191 urologists and radiation oncologists were asked to estimate the life expectancy of patients in clinical scenarios with various patient ages and comorbidities.[16] Life-expectancy estimates were within 3 years of the true value (based on Markov model projections) in only 67% of responses. In another Canadian study, Walz et al reported only "moderate ability" on the part of 19 clinicians and staff to predict 10-year life expectancy in 50 patients with localized prostate cancer when provided with age, a modified Charlson score, and specific comorbidities, with a mean overall predictive accuracy based on an area under the receiver-operating curve of 0.68 (in which 0.5 represented prediction no better than chance, and 1.0 represented perfection).[17] Clearly, any prediction tools developed should at least improve accuracy beyond that based on estimates made by clinicians. However, several published nomograms based on age and comorbidities have not fared substantially better, with predictive accuracies in the range from 0.69 to 0.73.[6,9,18] Even the nomogram by Walz et al, 1 of the most accurate available, which has a predictive accuracy of 0.84, still is far from ideal.[8] Issues relating to the assessment of comorbidity in many of these studies may limit the accuracy of prediction tools. Comorbidity index scores, such as the Charlson, provide a tool to assist clinical researchers with adjustment for the impact of comorbidity on outcomes. However, the Charlson index is limited, in that disease severity for comorbid conditions either is not incorporated or is only crudely incorporated (eg, diabetes with or without end-organ damage). Beyond issues of the accuracy of prediction tools is their ease of use. Some published nomograms probably are too complex for use in clinical practice. Even the Charlson index, although it is implemented readily in clinical research, may be difficult to assess in patients within a busy practice setting. Another issue that may be particularly challenging to overcome is statistical illiteracy, which is exceedingly common in patients.[19] Patients have difficulty dealing with uncertainty and grasping the concept of probabilities. Thus, especially when facing a cancer diagnosis, patients may be unwilling to accept *any* chance of dying from their cancer, even if the actual probability of doing so is very small. The troubling implication is that, unless prediction tools are virtually perfect in their ability to discern which men will or will not die from their prostate cancer, patients may continue to choose aggressive interventions. Ongoing research into how to improve patient decisions in prostate cancer, therefore, certainly is welcomed.[20]

A final point is that many of the treatment dilemmas in localized prostate cancer have their origins in inappropriate use of PSA screening. The vast majority of prostate cancer diagnoses in the current era occur after PSA screening, and the majority of those diagnoses are low-risk to intermediate-risk tumors. Yet large numbers of elderly men with comorbidities undergo PSA screening.[21] If a patient is unlikely to benefit from treatment because of age and/or comorbidity, then they should not be screened in the first place. Efforts directed at ensuring appropriate use of PSA screening should help make treatment decisions for prostate cancer easier. Although there are significant challenges, at the very least, discussions with patients about the risks and benefits of PSA screening in the context of their age and comorbidities would occur in the absence of the tremendous emotion attached to an actual cancer diagnosis.

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