

Treating Older Men With Prostate Cancer Survival (or Selection) of the Fittest?

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RECENT DECLINES IN CAUSE-SPECIFIC MORTALITY RATES among men with prostate cancer suggest that early diagnosis and treatment for localized tumors may improve survival.^{1,2} In particular, in a randomized controlled trial from Scandinavia, Bill-Axelsson et al³ demonstrated that patients with clinically detected, early stage prostate cancers who were assigned to radical prostatectomy had better survival than those assigned to watchful waiting.³ An important caveat is that the survival benefits of prostatectomy were concentrated among men younger than 65 years.³ Given that the frequently indolent nature of prostate cancer in older men,^{4,5} this finding begets clinical uncertainty regarding the role of initial local therapy in this population.

In this issue of *JAMA*, Wong and colleagues⁶ address this important gap in current knowledge with data from a well-designed and well-executed observational study. Specifically, the authors used population-based, linked data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program and Medicare to estimate the association between initial treatment (with radical prostatectomy or radiation therapy vs initial observation) and both cause-specific and overall survival among a large sample of men between the ages of 65 and 80 years with low- or intermediate-risk prostate cancer. Their captivating finding is that treated men had longer 5- and 10-year disease-specific and overall survival than did those managed expectantly. The consequent inference is that initial local therapy for low- and intermediate-risk prostate cancer is associated with a decreased risk of death among elderly Medicare beneficiaries.

Duly recognizing the potential for selection bias and confounding, the authors diligently used established econometric techniques^{7,8} to balance the distribution of demographic and clinical variables (eg, age, tumor grade, comorbidity) in an effort to coax a randomized trial out of an observational cohort. Using this rigorous approach, they observed a 30% lower mortality risk for treated patients. Furthermore, they reported remarkably similar results in multiple, clinically relevant subgroups, including men between the ages of 75 and 80 years (27% mortality risk reduction), black men (35% re-

duction), men diagnosed in the era of prostate-specific antigen (PSA) screening (38% reduction), men with no comorbidities (29% reduction), and men with tumors of the lowest stage and grade (21% reduction). These composite data provide arresting evidence that initial local therapy is associated with a survival advantage among older men with lower-risk prostate cancer. Clinicians will be heartened by this valuable addition to the prostate cancer evidence base.

Nevertheless, reasoned interpretation of this study also requires consideration of absolute survival outcomes. That is, during the 12-year follow-up period, Wong and colleagues⁶ identified 926 prostate cancer-attributable deaths, only 2.1% of the sample of 44 630 patients. Likewise, prostate cancer was responsible for fewer than 10% of deaths in both the observation (314 of 4643 deaths, or 6.8%) and treatment (612 of 7639 deaths, or 8.0%) cohorts. Many more men die with prostate cancer than of it.⁴

Furthermore, as with any observational study, the potential for residual bias and confounding remains. In particular, despite the authors' earnest attempts to balance the cohorts, unmeasured differences may persist. For instance, even with established methods for comorbidity adjustment,⁹ claims-based analyses fully characterize neither the nature and severity of concurrent medical conditions nor the general impression of life expectancy that is typically cultivated by clinicians at the time of treatment choice.¹⁰ Most urologists and radiation oncologists will attest that older men who receive active treatment are inherently different from those managed expectantly. A patient who is judged likely to live for more than 10 years is offered aggressive treatment, whereas a man expected to die of other causes in fewer than 10 years is counseled that his best option is watchful waiting.^{11,12} Therefore, despite the authors' methodological rigor, it is difficult in a nonrandomized, claims-based analysis to account fully for this implicit clinical assessment.

Also, selection bias is not likely to be mitigated by the preponderance of men in this sample with PSA screening-detected cancers. To clarify, Wong and colleagues posit that the treatment and observation groups are likely to be innately similar insofar as screening practices in the United States

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reflect the judicious application of PSA testing following a priori clinical assessment of life expectancy and functional status. In fact, routine PSA screening is ubiquitous and indiscriminate.¹³⁻¹⁵ Accordingly, it is possible that the studied cohorts remain imbalanced with respect to frailty, cognitive function, and other important, albeit unmeasured, confounders.

Readers may note that these data contradict the findings in the Scandinavian trial³ that men younger than 65 years experienced most of the survival benefits attributable to surgical intervention; in fact, planned subgroup analyses demonstrated a statistically significant interaction between age and treatment group for both disease-specific and overall survival.³ That the Scandinavian trial was randomized and, hence, less likely to harbor residual confounding, suggests a more limited survival benefit for treated older men.

In many clinical scenarios, a survival benefit alone provides ample rationale for the widespread application of a therapeutic intervention. Among older men with early stage prostate cancer, however, a more nuanced risk-benefit assessment must consider the adverse consequences of local therapy, including the potential for treatment-related complications and impairments in health-related quality of life.^{16,17} Therefore, despite the important goal of preventing prostate cancer deaths, a clinical policy that interprets the current study as justification for universal aggressive treatment is premature.

Improvement in the quality of care for men with prostate cancer may best be achieved not by treating more patients but by treating them more discerningly. Clinicians must remain steadfast in their efforts to reduce overtreatment and undertreatment¹⁸⁻²⁰ by thoughtfully defining each patient's unique balance between the natural history of prostate cancer and that individual patient's life expectancy. To this end, an important recent advance is the development of refined strategies for active surveillance with selective, delayed intervention.^{21,22} As Whitmore²³ articulated more than 3 decades ago, the persistent clinical quandary is that "for men in whom cure is possible it may not be necessary, while for men in whom cure is necessary, it may not be possible."

The reported association between treatment and improved survival for older men with low- and intermediate-risk prostate cancer will be confirmed or refuted by the results of ongoing randomized controlled trials, including the Veterans Affairs Prostate Cancer Intervention vs Observation (PIVOT) study²⁴ and the United Kingdom's Prostate Testing for Cancer and Treatment (Protect) trial.²⁵ Until then, physicians should apply these provocative findings judiciously and continue their concerted efforts to help patients make informed treatment decisions based not only on survival predictions but also on health status, functional concerns, and—most importantly—personal preference.

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