Is Low-Risk Prostate Cancer More Indolent in Younger Patients?

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The paradox of prostate cancer has been thoroughly debated in the medical literature over the past several decades. Although prostate cancer is the most incident visceral tumor of men living in the Western hemisphere; it is fatal in a relatively small fraction of those in whom it is detected. Improving patient selection for radical therapy through a personalized approach on the basis of tumor and patient characteristics has been the charge of several contemporary expert panels. In 2011, a National Institutes of Health panel endorsed active surveillance as a primary option for low- and very low-risk prostate cancer and it is the preferred option for men with shorter life expectancies. The National Institutes of Health and National Comprehensive Cancer Network have each called for more research in this evolving treatment area with the goals of developing evidence-based decision tools and the identification of biomarkers indicative of early-grade progression in patients on active surveillance.

In the article that accompanies this editorial, Leapman et al studied whether decreased age reduced the risk of cancer progression in an institutional active surveillance cohort. Reducing treatment-related morbidity could have substantive effects on health-related quality of life in younger men, considering their relatively high functional status at baseline combined with the additional expected longevity. Also, a key proviso of active surveillance is that patients remain at risk for death from competing morbidities, which can readily negate the perceived net benefit of early treatment a decade or more earlier. To this point, in a prospective, single-arm active surveillance study by Klotz et al with up to 20 years of follow-up, the ratio of death from nonprostate to prostate cancer was 9.2 to 1. The importance of competing morbidities in a prostate cancer cohort was also demonstrated in Prostate Cancer Versus Observation Trial (PIVOT). In subjects randomly assigned to either surgery or observation, nearly 50% of men in both arms died of competing morbidities within 10 years of trial enrollment. Conversely, the downside of widening access to active surveillance for younger men is that, invariably, some men will progress to an incurable state while being monitored closely. In the study by Klotz et al, with long-term follow-up, 45% of the surveillance cohort underwent treatment with curative intent and 22% of this group subsequently experienced recurrence of prostate cancer. To what degree these recurrences could have been prevented by early treatment is unknown.

There is certainly a strong biologic plausibility to justify the study of a possible protective effect of decreased age in prostate cancer. Cancer-predisposition factors associated with aging include cumulative toxin exposure, obesity, DNA alterations, decreased immune surveillance, and signal-pathway alterations. However, once a tumor is established and the clinical phenotype is determined, it is not clear that these predisposition factors will add prognostic or predictive information beyond current risk-stratifying methods.

The primary end point of the current study was to evaluate the effect of age on biopsy grade progression. The study findings presented herein showed that compared with the age > 60 years group, the age ≤ 60 years group had a 7% reduction (55% vs 48%) in rate of grade progression on surveillance biopsy at 5 years (hazard ratio per 1-year of age decreased, 0.97; 95% CI, 0.96 to 0.98). Several additional clinical factors were highly predictive of biopsy progression, including prostate-specific antigen (PSA), Gleason score, core involvement, PSA density, and number of monitoring biopsy procedures consistent with prior study findings in active surveillance cohorts. There were significant baseline differences in the younger patient group that are worthy of mention, including lower PSA values, lower Gleason scores, and lower Cancer of the Prostate Risk Assessment scores. The younger patients did undergo more surveillance biopsies (three v two) but had an equal number of PSA tests as older patients. When age was examined as a component of multifactor models, the authors state that it improved model performance “marginally.” Hence, use of younger age in risk assessment may ultimately be better for individual patient prediction rather than model inference. Importantly, 74% of the entire surveillance cohort was referred to the authors’ institution for disease follow up and external referral was associated with a lower rate of cancer progression (hazard ratio, 0.754; 95% CI, 0.60 to 0.95). Younger patients were more likely to have been referred to the tertiary care center for continued surveillance after having the initial diagnostic biopsy performed extramurally. Thus, it is not clear if these externally diagnosed patients are representative of a random sample of the population at large or if they represent a highly selected group with more favorable underlying risk features. Only having full information on the population from which they were drawn would allow for this
analysis. Another explanation for finding age as a negative predictor on progression may be that it is collinear with other factors. As such, age may be a convenient, easily identifiable numeric factor that encompasses both known and unknown covariates. Finally, because the younger patients had lower-volume cancers with lower PSA values, it is possible that lead-time bias may account for some group differences in progression between younger and older patients.

Important implications about age have been drawn from several studies that systematically examined age in the context of outcomes for prostate cancer. The effect of younger age in the clinical progression of prostate cancer has been studied in two population-based studies. These both demonstrated that younger men are potentially more susceptible to aggressive cancers than older patients. Recently, it was shown that men with prostate cancer diagnosed with metastases before the age of 50 years were 28% more likely to die of prostate cancer than men older than age 50 years. The role of age on prostate cancer-specific survival was reported in a Swedish trial in which subjects were randomly assigned to surgery versus watchful waiting and followed for a mean of 18 years. In a prespecified analysis, there were robust clinical benefits to patients younger than 65 years of age in the early treatment arm compared with observation. Furthermore, there were higher rates prostate cancer mortality, metastases, and use of androgen deprivation in the younger patients compared with older men, suggesting that younger patients were not protected from clinical progression. In the PIVOT trial, the incidence of death resulting from prostate cancer was compared by age group and found to be 7.6% versus 7.2% (nonsignificant) in younger and older subjects, respectively. Similarly, in the ongoing Prostate Cancer Testing and Treatment (ProtecT) randomized trial of active monitoring versus radical treatment, there was no association between decreased age and reduced prostate cancer mortality with up to 10 years of follow-up. Although these trials provide important information about the relationship of age to treatment, there may be unique differences in cohorts selected for active surveillance that cannot be detected in studies involving subjects selected for treatment. Further study in this area is clearly warranted.

Increasing the thoughtful application of active surveillance in patients with low-risk prostate cancer has the potential for benefits to health-care systems as a whole, including improved health-related quality of life, reductions in treatment burden, and reduced costs. Patients should be evaluated based on current health status, with known risk factors for progression and age taken into consideration. It is important for clinicians to understand and explain to the younger patient that he concurrently has both the most to gain and most to lose. Prior PSA-era studies have examined the safety of active surveillance in younger men and it seems efficacious in properly selected men. However, it is important to have clear and realistic expectations set for young men who choose to undergo active surveillance and, in turn, agree to undergo regimented monitoring of their condition. Future advancements in surveillance for disease progression will likely come from innovations in promising areas such as magnetic resonance imaging, blood, and tissue markers, which must then be prospectively validated in well-designed clinical trials.

**AUTHOR’S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

Disclosures provided by the authors are available with this article at jco.org.

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