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EDITORIAL

Long-Term Active Surveillance for Prostate Cancer: Answers and Questions

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In recent years, active surveillance has evolved from an experimental protocol to a broadly accepted—in fact, preferred—management strategy for men diagnosed with low-risk prostate cancer.[1] Active surveillance is a crucial aspect of efforts to solve the prostate-specific antigen (PSA) –based early detection conundrum without sacrificing the tremendous gains that have been realized in mortality rates.[2,3] Cohort studies of active surveillance, primarily from academic institutions, have collectively reported short- to intermediate-term outcomes on thousands of men, generally supporting the safety and efficacy of the approach over the first years of follow-up.[4] This conservative approach to low-risk disease appears to be making recent inroads even outside of academia, at least in limited settings.[5] The problem has been that the natural history of low-risk prostate cancer is measurable over years and decades, and short-term disease stability does not reliably predict long-term survival.

In the article accompanying this editorial, Klotz et al[6] report the longest follow-up to date in one of the largest extant active surveillance cohorts. The median follow-up in the Sunnybrook cohort of 993 men stands at 6.4 years, notably longer than most other centers, but still short in the context of prostate cancer's typical course. Over 200 of the men had 10 years or more of follow-up, which begins to be sufficient to identify true clinical progression events. Of those with adequate follow-up, more than 75% of the men remained on surveillance at 5 years—higher than in most cohorts—and over half beyond 15 years.[6]

In total, 149 men died during active surveillance; 15 of these died of prostate cancer, and another 13 developed metastatic disease. These figures highlight the extent to which competing morbidities are salient for men with low-risk prostate cancer, and it is notable than even among those with metastatic disease four died of other causes rather than of prostate cancer. Klotz et al[6] report an overall rate of metastasis of 2.8%, occurring at a median of 9.6 years after diagnosis. Before this figure is argued by proponents of immediate treatment for low-risk disease to represent the risk of active surveillance, it should be stressed that it is not dissimilar from the risk of lethal disease among men treated immediately for low-risk tumors (ranging from 1.4% to 5.9% at 10 years depending on primary treatment in one large, multicenter series).[7]

The last time the Sunnybrook surveillance experience was reported, in 2010, the cohort was less than half as large (N = 450) and median follow-up was similar. At that point, five men had died of prostate cancer, and Klotz et al[8] provided details on their clinical courses. All five had been identified with rapid PSA kinetics and were advised to undergo treatment; two refused, and two had rapidly progressive disease that likely was present at diagnosis. The authors concluded that only one man died after treatment delayed by at least 2 years of surveillance.[8]

The current article provides only cursory detail on the men progressing to lethal disease: about half were treated with radiation, only two with surgery, and rest with androgen ablation or no treatment.[6] These latter men in point of fact should be considered to have been on watchful waiting, not active surveillance. The article therefore does not yet answer the critical question: not how many men die of prostate cancer in a surveillance cohort, but how many ultimately succumb specifically because they chose surveillance and thereby missed the window of opportunity for cure.

Whatever this number truly is, it is greater than zero. These deaths by definition are preventable, and as sins of omission are particularly galling to cancer-focused clinicians. But in the alternative paradigm of immediate intervention for all low-risk tumors, they are vastly outnumbered by men harmed substantially by entirely avoidable treatments.[9,10]

The way forward for active surveillance, then, must be lighted by improved tools for risk stratification at diagnosis and for early identification of progressive disease. The first key question is who should be eligible for active surveillance. Various surveillance cohorts use criteria of varying stringency to select men for surveillance. Klotz et al[6] note that their inclusion criteria were made more restrictive as of 2000, including men with Gleason 3 + 4 tumors only in the setting of limited life expectancy. Yet over a quarter of the men who developed metastases met the strictest criteria for very low–risk disease, those proposed by Johns Hopkins University.[6,11] While a number of nomograms have been proposed to predict indolent prostate cancer, these actually only have been shown to predict small, low-grade tumors at prostatectomy, and none has proved reliably predictive in the setting of active surveillance.[12]

Conversely, the experience at University of California, San Francisco, which has offered active surveillance to a growing number of men with high-volume Gleason 3 + 3 and low-volume Gleason 3 + 4 tumors, has shown that such men are no more likely to progress, at least in the short term, than those with lower-risk tumors.[13] Recent articles have argued that Gleason 3 + 3 cancer does not metastasize no matter what volume of tumor is present,[14] and Gleason 3 + 4 tumors

with low proportions of pattern 4 may be similar biologically to pure Gleason 3 + 3 tumors.[15] Driving this finding in part may be the fact that even expert genitourinary pathologists often disagree on Gleason grading small cancers in prostate biopsy tissue.[16]

Following the question of eligibility is the closely-related question of how best to follow men on active surveillance. Most protocols entail relatively frequent PSA testing and prostate biopsies every year or two. This schedule is relatively intense, involves frequent visits, risks infection associated with biopsy,[17] and accumulates significant costs over time.[18] Moreover, outside the Sunnybrook cohort PSA kinetics have been found frequently noninformative in the first years of surveillance,[19,20] and change in grade or tumor volume is as likely to reflect resampling as true aggressive biology.[21] Progression to active treatment is certainly not reliable as an end point, as it reflects psychological and other factors at least as much as tumor biology.[22]

Multiple lines of research over the past several years have focused on developing and validating novel tests which can improve on clinical parameters in predicting tumor aggressiveness and prognosis. Prominent among these are genomic signatures based on RNA expression in tumor tissue[23,24] and multiparametric magnetic resonance imaging.[25] These tests are all expensive, but their costs pale in comparison to novel forms of radiation therapy and other active treatments for prostate cancer.[26] For the most part emerging tests have not yet been validated in large, prospective active surveillance cohorts with even intermediate-term follow-up, but such studies are presently underway.

Hopefully in the relatively near future, such adjunctive risk stratification tools will allow not only better identification of candidates for active surveillance, but also tailoring of the intensity of surveillance according to the risk of progression. Men with clinically low-risk disease but concerning imaging or genomic findings might be encouraged to undergo immediate treatment or at least close surveillance. On the other hand, those with low-risk clinical characteristics and molecular features suggesting indolence could follow a less-intensive protocol more akin to watchful waiting. Perhaps at least a subset of these men could be spared the diagnosis of cancer entirely.[27]

It is a relatively small minority of men with prostate cancer who eventually die of the disease,[28] so a future goal for the field must be to identify more men who can safely defer or avoid treatment. Policymakers and primary care opinion leaders are increasingly impatient with overtreatment of low-risk prostate cancer, and overtreatment provides ammunition for strident opponents of all PSA-based early detection efforts.[29] There is little question that abandoning early detection would engender a public health disaster,[30] but the current tenor of policy discussions is such that unless the community of prostate cancer clinicians moves aggressively to address overtreatment, we are unlikely to reclaim the terms of the debate on early detection.[31]

Alongside the goal of curbing overtreatment is the concurrent need to identify those with potentially lethal tumors when they are still at a curable stage. These aims are not at cross-purposes; indeed, they are entirely complementary. Therefore the future of active surveillance—and of prostate cancer treatment in general—must be found at the frontiers of precision medicine. Both the timing and intensity of intervention should be customized based on maximal information reflecting clinical tumor characteristics; patient health and comorbidity; and, where appropriate, novel imaging and genomic assessment. Prostate cancer has evolved to a diagnosis now recognized to reflect an extraordinary range of biology and prognostic risk, and its management must reflect this diversity.

AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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