Another Reason to Consider Active Surveillance

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Appropriate treatment of newly diagnosed, localized prostate cancer remains controversial. Men with poorly differentiated cancers face a high risk of disease progression and often require multiple treatments including surgery, radiation, and androgen deprivation therapy. Conversely, men with low-volume, well-differentiated cancers often require no intervention at all. Unfortunately, the uncertainty surrounding the likelihood of disease progression encourages most patients to seek some type of aggressive treatment [1]. Active surveillance is available for men who are willing to accept a small risk of disease progression to avoid the known complications associated with surgery and radiation.

How safe is this approach? We recently conducted a systematic review of the literature documenting outcomes following a delay in curative treatment for men with localized prostate cancer [2]. We identified 17 retrospective studies that included a total of 34,517 patients diagnosed between 1981 and 2009. As expected, there was substantial heterogeneity among the reports in the criteria used to classify patients, the reasons for any treatment delay, and the outcomes used to define success or failure. Seven studies suggested no significant impact of a treatment delay within ≤2.1 yr of diagnosis, and four studies showed no difference in outcome after multivariable adjustment. Two studies showed less adverse pathology among men undergoing delayed treatment, but this was attributed to selection bias. By contrast, four studies showed evidence of biochemical progression and/or more adverse pathology after a significant treatment delay.

Interpreting this literature is difficult. All of the studies analyzed were retrospective and nonrandomized. Reasons for delay were not always clear. As a consequence, these data are subject to significant biases. One particularly important bias is often termed the Will Rogers’ effect. This occurs when men with the worst prognosis (i.e., those with a rising prostate-specific antigen [PSA] level or pathologic disease progression) are removed from the active surveillance group and placed in the treatment group. The long-term outcome for the active surveillance group will improve along with that for the surgical intervention group. This effect will also explain large differences in Gleason upgrading among men undergoing immediate radical prostatectomy when compared to those having delayed surgery. Differences in comorbidity may also introduce potential biases among patients receiving immediate versus delayed surgery. Patients with more comorbidities may be preferentially steered towards active surveillance, under which they succumb to other disease hazards at an earlier stage in comparison to healthier men who opted for immediate surgery.

The report in this issue of European Urology by Tosoian et al [3] adds a significant new chapter to this body of knowledge. Utilizing the extensive Johns Hopkins prospectively maintained active surveillance database (n=1298), the authors conducted a retrospective analysis and identified a subset of 89 men who underwent a delayed radical prostatectomy. The authors were careful to include only those men who elected for surgery on the basis of anxiety or some other psychological factor, and excluded all men who had evidence of disease progression in terms of either a rising PSA level or Gleason score progression. This was a critical step in avoiding the selection bias involved in referring only men with disease progression for surgery and retaining only men who had stable disease on active surveillance. The authors established that a delay in prostatectomy by 2.0 yr from diagnosis resulted in comparable outcomes to those for men with low-volume, low-grade disease who elected for immediate surgery.
Similar proportions of men had evidence of Gleason pattern 4 for surgical specimens, and the incidence of positive lymph nodes and overall adverse pathology was comparable between the two groups. The authors concluded that among men with favorable-risk prostate cancer, delayed surgical intervention does not appear to have an adverse effect on clinical outcome.

Within the next year, more definitive data addressing this question will become available [4]. By then the ProtecT trial will have reached median follow-up of 10 yr. This prospective randomized controlled trial recruited 1643 men to the following three treatment alternatives: 553 to surgery, 545 to external beam radiation, and 545 to active monitoring. Some 77% of these men had Gleason 6 disease at diagnosis and 89% had a preoperative PSA of <10 μg/l. Trial findings should definitively determine whether a delay in performing radical prostatectomy will compromise prostate cancer–specific survival.

In the interim, the findings of Tosoian et al should encourage men to consider active surveillance as the preferred treatment for low-volume, low-grade prostate cancer. At a minimum, the data suggest that waiting 1–2 yr for the ProtecT trial findings will not compromise their clinical outcomes. Improvements in magnetic resonance imaging (MRI) have increased our confidence in diagnosing these men accurately. The UK National Institute for Health Care Excellence now recommends that multiparametric MRI should be performed after an initial decision to proceed with active surveillance to detect the presence of more aggressive disease not detected during the initial biopsy [5]. New serum markers including the Prostate Health Index and a panel of four kallikreins will also help to identify men who are good candidates for active surveillance [6,7].

According to several previous studies and the current report by Tosoian et al, men with low-volume, low-grade prostate cancer who delay surgery for several months or even years do not appear to compromise their long-term prostate cancer outcomes. Curative treatment for these men, if indicated at all, is not an urgent matter. This provides the necessary time for patients to carefully consider treatment alternatives and obtain follow-up studies such as serum markers, multiparametric MRI, and a confirmatory biopsy. Should these studies confirm low-volume, low-grade prostate cancer, men should feel confident that they can delay intervention for at least 2 yr if not much longer.

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References