Waiting Time in Prostate Cancer

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THE STUDY FROM JOHANSSON AND COLLEAGUES[1] PUBlished in this issue of THE JOURNAL illustrates why oncologists often substitute the jargon of survival rates to sidestep using the magic word *cure*, which is really what's on every patient's mind.[1] In this well-conducted investigation, the researchers complete more than 2 decades of follow-up for a cohort of more than 200 Swedish men with early-stage prostate cancer from before the prostate-specific antigen (PSA) era who were treated with watchful waiting. Earlier reports by Johansson et al documented the relatively high rates of recurrence and mortality for those with high-grade tumors and the relatively lower rates among those with low-grade tumors, extending up to about 15 years of follow-up.[2-8] In the current article, the authors extend their follow-up to more than 20 years and find a surprising acceleration in the recurrence and mortality rates of the patients with low-grade tumors.[1] The result is that more aggressive disease indeed occurs after 15 years of follow-up for these patients.

One lesson, of course, is that cure is only an abstract concept in certain types of cancer. Clearly, prostate cancer joins breast cancer in this arena. It is well known that 5-year survival in breast cancer is not adequate and that even after 10 and 20 years, women continue to experience recurrence, with no plateau in the survival curves.[9] Prostate cancer, similar to breast cancer in many other respects, shares this common feature.

What is unusual, however, is not the continued progression to recurrence and mortality, but the acceleration. Why did this occur? One possibility is that new technology was introduced, including the use of PSA testing and computed tomography or magnetic resonance imaging,[10] and so more prostate cancer recurrence was recognized than in prior years, a variant on the Will Rogers phenomenon.[11] Because PSA testing became available with these radiologic techniques, disease that would have been unrecognized in the first 10 to 15 years (up to 1985 or 1990) of cohort follow-up would have remained unrecognized while becoming recognized in the final 5 or more years of the study. Thus, there is not truly an acceleration in the occurrence of recurrence, simply an increased rate of its detection and diagnosis. Another possibility is that the recurrences represent a different clone of prostate cancer within the prostate, and not simply recurrence of the original prostate cancer. Since this initially untreated cohort of patients, followed up for 20 years, was treated for symptomatic progression of cancer with either estrogen therapy or orchiectomy,[1] dedifferentiation of hormone-resistant cancers may have occurred.[12] Furthermore, the use of estrogen therapy may have led to cardiovascular disease or thrombophlebitis,[13] potentially fatal adverse effects of therapy that would have been attributed to prostate cancer.

Whatever the reason for the acceleration, this is the first study to have such long follow-up of a cohort with prostate cancer. As such, it has some relevance, as the authors state, for treatment. Although the 5-year survival rate is a valid metric for comparing the results of randomized clinical trials, the use of this outcome for a cohort of untreated patients across time or place may be misleading.[14] The randomized trial of radical prostatectomy, also conducted in Sweden, had a 50% reduction in prostate cancer-specific mortality for the radical prostatectomy group compared with the watchful waiting group, with no significant improvement in overall mortality.[15,16] However, the short follow-up time of this trial (ie, only 6.2 years) is not sufficient for the assessment of prostate cancer outcomes. Longer follow-up beyond 5-year survival is needed in this trial and in other studies to fully assess the real benefits of radical prostatectomy.

Also, the patient population in the current study by Johansson et al is, on average, 70 years or older.[1] Younger patients will need more aggressive treatment, particularly given the poor long-term outcomes and the increasing survival that they will have from other causes. Furthermore, because of their increased age and longevity, there may also be a survival bias because they have survived competing causes of mortality. As a consequence, all age-dependent causes of death will increase, especially for a disease such as prostate cancer.

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Most important, this cohort was assembled prior to the advent of widespread PSA testing. What relevance and what implications do the findings have in the current era of PSA screening? Two ongoing studies of watchful waiting for patients with localized low-risk prostate cancer are measuring PSA levels and using PSA doubling times as an indication for therapeutic intervention.[17,18] Screening, of course, adds lead time to the follow-up and thus the extent of follow-up before progression and mortality potentially will be even longer than this study shows.

These studies remain confusing in terms of their overall implications for prostate cancer screening. After all, one of the key questions in prostate cancer remains: Why isn't it obvious that prostate cancer screening with PSA works? Many of the ingredients for successful screening have always been present in prostate cancer, such as an excellent potential screening test, good stage-specific survival, and down staging with use of the screening test. The incidence of prostate cancer increased dramatically in the United States starting in 1988, with a peak around 1992, but no clear-cut subsequent decline in prostate cancer mortality has occurred.[19] The study by Johansson et al adds one more datum: the fact that long follow-up may be necessary to observe the full benefits of earlier diagnosis and treatment.

A major question has been whether the use of radical prostatectomy improves survival, a question addressed by the recent radical prostatectomy randomized trial from Sweden[15] and by the Prostate Cancer Intervention Versus Observation Trial (PIVOT), now in progress.[20] But perhaps one of the key problems is the one raised in this study,[1] ie, the length of follow-up necessary to demonstrate a survival benefit. It is difficult to think in terms of conducting a randomized trial for screening with a horizon of 15 to 20 years, but perhaps that is exactly what will be necessary to really observe the impact of PSA screening on prostate cancer.

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