EDITORIAL

Localized Prostate Cancer — Then and Now

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Between 1999 and 2009 in the United Kingdom, 82,429 men between 50 and 69 years of age underwent prostate-specific antigen (PSA) testing as part of the Prostate Testing for Cancer and Treatment (ProtecT) trial. After a median follow-up of 15 years, we can now review the results of this herculean task.[1] Of the men who first joined the trial, 2664 (3.2%) received a diagnosis of localized prostate cancer. A total of 1643 men (61.7%) were randomly assigned to undergo active monitoring, prostatectomy, or radiotherapy plus a short course (3 to 6 months) of androgen-deprivation therapy. Treatments were originally stratified according to age, Gleason score (<7, 7, or 8 to 10), and PSA level.

At 15 years, follow-up data were available for a remarkable 98% of the men who had enrolled in the trial. The incidence of death was low and similar in the three groups. Overall, 21.7% of the men had died from any cause and 2.7% from prostate cancer. The incidence of metastasis was 9.4% in the active-monitoring group and approximately half that in the prostatectomy and radiotherapy groups. The incidence of clinical progression was also higher in the active-monitoring group than in the other two groups, but that end point was quite heterogeneous and represented a somewhat nebulous measure of outcome.

The authors conclude that the choice of therapy for men with localized prostate cancer involves weighing trade-offs between benefits and harms of treatment — perhaps not the hoped-for conclusion for treatment advocates, given the duration and size of the trial. The side effects of radical prostatectomy and radiation therapy are well annotated, and many men have substantial sexual or urinary dysfunction after definitive local treatments.[2,3] Today, as ever, less intensive approaches to the treatment of prostate cancer are clearly needed.

When the ProtecT trial was initiated, the typical approach of screening men for prostate cancer was to assess the PSA level, biopsy those with an elevated PSA, and treat the cancer. That simplistic approach has dramatically changed in the wake of evidence that has been gathered since 1999. PSA testing is no longer the norm. In many clinics, PSA testing is not done at all, and the legal consequences of not testing are diminished, given that guidelines now embrace patient-centric informed decision making.[4] Unfortunately, such an evaluation is often problematic at best, given that busy primary practitioners are faced with an array of issues and have only limited time to discuss the nuances of the decision and the possible outcomes.

Today, if a patient has an elevated PSA level, data suggest that the clinician may use multiparametric magnetic resonance imaging (MRI) to selectively biopsy only patients with a score of 3 to 5 on the Prostate Imaging Reporting and Data System (PI-RADS), which classifies a lesion on a scale from 1 to 5, with higher scores indicating a higher suspicion of cancer. A targeted biopsy appears to be sufficient to diagnose tumors in grade groups 3 to 5.[5] Additional risk-stratification methods beyond clinical stage, PSA level, and Gleason score are also readily available. Transcriptomic assays (also known as genomic classifiers) can provide important prognostic information and help guide treatment decisions.[6] Germline genomic assessments are also endorsed by expert groups in patients with higher-grade tumors or selected family histories. Prostate-spe-

cific membrane antigen (PSMA) positron-emission–tomographic (PET) scans are now approved to better assess staging in patients with unfavorable intermediate or high-risk localized disease. In certain circumstances, PSMA PET scans may also be useful in determining appropriateness for biopsy.[7] Once risk stratification regarding the tumor is complete, clinicians can undertake appropriate action on the basis of additional factors, such as age, family history, coexisting conditions, and (possibly most important) patient preference.

Despite the laudatory nature of the ProtecT trial and the long-term follow-up, certain issues deserve further scrutiny. The median PSA was quite low among randomized patients (4.6 ng per milliliter). Of the 1643 patients, 1268 (77.2%) were in grade group 1 (Gleason score of 6), and only 169 (10.3%) had a PSA level of 10 or higher. Although subclassification of intermediate-risk patients was not performed, only 99 patients (6.0%) had grade group 3 disease (Gleason score of 7 [4+3]) or higher. The vast majority of the trial patients were at low risk or favorable intermediate risk and would today be considered appropriate candidates for active surveillance. The patients who were at unfavorable intermediate risk or high risk represent an underpowered subgroup. Conclusions regarding underpowered subgroups are not appropriate on the basis of the ProtecT data, especially when numerous excellent guidelines are available to guide appropriate decision making.[8]

Active monitoring as performed in the ProtecT trial should not be used today. We can do better by adding serial multiparametric MRI assessments.[9] The increased rate of metastasis that was noted in the active-monitoring group would likely be diminished with the active surveillance protocols that are being used today.[9] Surveillance for low-risk prostate cancer is more accepted today than in 1999, although at times patients remain anxious about leaving a cancer untreated. However, treating anxiety by removing a prostate often creates larger problems. Various forms of focal therapy are increasingly being used, especially now that tumors can be better visualized and potentially targeted with the use of advanced imaging techniques.[10] Taken together, the management of localized prostate cancer has undergone a wholesale change since 1999 when the ProtecT trial was started. Even so, the results of this trial provide valuable data to inform decision making in the large group of men with low- or intermediate-risk prostate cancer.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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