Identification of Candidates for Active Surveillance: Should We Change the Current Paradigm?

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Abstract

Active surveillance (AS) has been claimed to avoid overtreatment of prostate cancer (PCa). It remains unclear which patients may benefit from AS. One way to clarify this is to improve the definition of insignificant PCa. PSA and Gleason score—the basic instruments used to select patients for AS—suffer from systematic errors. The nomograms used to define insignificant PCa are based on patients whose disease was classified before changes were introduced in the 2005 Consensus Conference on Gleason Grading; thus, the experience obtained cannot be directly applied to today's patients. Additionally, despite the standardization of prostate-specific antigen assays promoted by the World Health Organization, differences persist and could lead to misclassification of patients. These factors lead to an incorrect classification of patients into risk groups. Although new variables would increase risk group classification, the necessary first step is to optimize the use of both prostate-specific antigen serum levels and Gleason score.

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Current Situation: Overdiagnosis and Overtreatment of Prostate Cancer

The incidence of prostate cancer (PCa) in the European Union is 78.9 per 100,000. It is the most commonly found cancer for men, with a mortality rate of 30.6 per 100,000 men per year. Although levels of incidence and survival rates may vary greatly from one region to another, no correlation has been observed between incidence and mortality.[1-3] Aside from known geographical and inter-ethnic differences, the different levels of incidence found between one country and another may be attributed to greater diagnostic pressure being applied in some of them. An initial reading of the data could lead one to understand that a significant number of the new diagnoses made play an important role in terms of the incidence and survival rates for PCa, but without affecting mortality rates—or, if this is so, only slightly, implying that said diagnoses had probably been none too opportune. In this sense, the Surveillance, Epidemiology, and End Results incidence rate increased from 94.0 to 150.5 between 1975, in the pre–prostate-specific antigen (PSA) era, and 2005, while the death incidence along these years decreased from 31.0 to 24.6.[4]

The probability that the number of diagnoses of PCa continues to rise is, without a doubt, high, as is made apparent by the difference between the number of men diagnosed with cancer in screening (5%-10% during the course of a man's life) and the number of patients who died is 55% for men in the sixth decade of life and 64% for men in the eighth decade of life.[5]

Approximately 50% of the cases of PCa currently diagnosed possess the same pathologic characteristics as the cases of incidental PCa identified in autopsies.[6] Those individuals diagnosed with PCa, but for whom it would have been better never to have done so because the disease would never have come to interfere in their normal, everyday lives, are referred to as overdiagnosed. Aside from the serious psychologic disturbance caused by receiving the diagnosis of cancer, the patient is further at risk of being treated unnecessarily with the statistically inexorable consequences thereof: overtreatment.[7]

The heterogeneity of PCa was studied by D'Amico et al,[8] who proposed its classification in risk groups. The D'Amico classification was, and is still today, the most broadly applied. The stratification proposed by D'Amico et al is based on Gleason score, PSA, and

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clinical stage; it classifies patients into 3 groups: low risk (Gleason score $\leq$ 6, PSA $<$ 10, clinical stage $\leq$ T2a), intermediate risk (Gleason score $\leq$ 7, PSA 10-20, clinical stage $\leq$ T2b), and high risk (Gleason score $>$ 7, PSA $>$ 20, clinical stage T2c). The authors did not suggest that low risk implies therapeutic abstinence, even when they found great differences in the evolution of the patients.

Overdiagnosis is particularly dangerous when followed by radical treatment because it is a potentially harmful treatment applied to a diagnosis that would not have affected the patient's normal, everyday life. The Prostate Cancer Outcomes Study, which enrolled 1291 patients who had received radical prostatectomy and follow-up of 2 years, found that 60% of patients presented erectile dysfunction, 43% reported problems in the sexual sphere, 42% occasional urine leakage, 7% frequent urine leakage, and 1.6% total urinary incontinence.[9] With regard to the adverse effects attributed to radiotherapy, mention should be made of the 40% to 50% of patients with impotence, the 2% to 39% with proctitis, and 5% with symptoms of irritating micturition syndrome.[10] Brachytherapy, especially indicated for low-risk tumors, also implies certain adverse effects,[11] from prostatourethral-rectal fistulas (2.7%)[12] to intermittent rectal bleeding (6.6%).[13]

However, according to the European Randomised Study of Screening for Prostate Cancer (ERSPC) trial, it requires 1410 men to be enrolled in the screening program and 48 of them to be treated to be able to prevent 1 cancer death.[14] Likewise, the application of a mathematical model, MISCAN (MIcrosimulation for SCreening ANalysis), to the ERSPC data revealed overdiagnosis in 56% of the cancers detected by the annual screening program for men aged 55 to 67 years.[15] Similarly, the recently published data from the PIVOT Trial (Prostate Cancer Intervention vs. Observation Trial), including patients enrolled from 1994 to 2002 period with a follow-up of 12 years, showed that patients with localized low-risk PCa followed but not treated in any way had a slightly lower rate of cancer-specific mortality (1.4%) than those from the same group treated with radical prostatectomy.[16] Further data along similar lines were recently presented by Carter et al,[17] who had questioned whether or not PCa with a Gleason score of 6 should still be labeled as cancer. This fresh approach, for which data can be found for both pros and cons, seeks to facilitate the decision not to treat, or to delay the treatment, because that is what would prove best for the patient.

Active Surveillance

Because not all the cancer diagnosed requires treatment, and given that all radical treatment significantly worsens the quality of life of the patient, there is great interest today to find a way to determine which patients require treatment and which could follow an active surveillance (AS) protocol. On the basis of the European Screening Study, the European Association of Urology has made an institutional statement in which it calls for the development of safe methods of AS to palliate the negative effects of overdiagnosis and overtreatment.[18] For men diagnosed with PCa, AS is a way to delay any kind of definitive treatment—a resource that would only be used if there were firm evidence showing increased risk of progression. In this light, AS could be considered for cases of localized, well-differentiated PCa that shows low risk of progression. As opposed to watchful waiting, AS means delaying treatment only to the point at which there is still no significant decrease in the likelihood of being cured.

The PCa that without treatment will not prove clinically significant during the lifetime of the patient is called indolent PCa. We have evidence that supports the idea that many of the men with PCa have indolent cancer that does not require immediate treatment. It is a well-known fact that autopsy studies detect a high percentage of PCa that were not clinically evident during the lifetime of the subject (indolent), and there is at least one study that shows that the number of such hidden cases of cancer has been falling since the introduction of PCa screening.[19] It is probably the origin of a large number of newly diagnosed PCa. On the other hand, epidemiologic studies show that since the introduction of PSA-based screening, the number of PCa diagnosed has been far higher than prescreening, without observing a corresponding increase in mortality. Finally, up to 15% of men without high PSA levels and normal digital rectal examination who received placebo during the Prostate Cancer Prevention Trial were found to have cancer at the routine biopsy performed at the close of the trial.[20]

The first to use the concept of insignificant PCa was Stamey et al in 1993,[21] in a study on incidental cancer found in cystoprostatectomy specimens. These authors proposed a limit of 0.5 mL, corresponding to the largest tumor found in the specimen, as the cutoff limit for the definition thereof. In 1994, Epstein et al[22] validated this data with a series of patients on whom a radical prostatectomy had been performed, initially establishing 0.2 mL as the largest tumor to be considered insignificant since, when the size of the tumor was between 0.2 mL and 0.5 mL, according to the authors, "cases of capsular penetration were found." The criteria most broadly applied when defining insignificant cancer are based on the pathologic findings from radical prostatectomy specimens and include 3 prognostic factors: Gleason score $\leq$ 6, without pattern 4 or 5; organ-confined disease; and dominant tumor volume of under 0.5 mL.[22-24]

From a terminological point of view, there are 2 definitions that are broadly used to define similar, though not identical, concepts: indolent PCa and insignificant PCa. Indolent cancer is defined by its pathologic characteristics, avoiding attending the circumstances of the patient (such as age and comorbidities),[25] while insignificant cancer includes, in addition to indolent cancers, cases of cancer diagnosed in patients of advanced age or with significant comorbidity. Thus, cancer considered insignificant, either for the nature of the tumor or of the patient, should not lead to cancer-specific morbidity or mortality during the lifetime of the patient who has remained untreated.[26,27] Despite the aforementioned terminological distinction, the 2 terms—indolent cancer and insignificant cancer—are often used indistinctly, and in order to fall in line with the majority of authors, in the present review, we use the term "insignificant cancer."

The next step required to make the concept useful was to attempt to predict the existence of insignificant PCa from clinical information and data obtained from a prostate needle biopsy. In the way of avoiding unnecessary radical treatment, in 1994, Epstein et al[22] defined criteria to predict, before performing radical therapy, those cancers that could be considered insignificant. This study included 157 men with cases of nonpalpable PCa (T1c), diagnosed by needle biopsy and treated with radical prostatectomy between 1989 and 1992. The best model for predicting insignificant PCa was defined as PSA density (PSAD) $<$ 0.1 μg/L/g, Gleason score $\leq$ 6, fewer than 3 cores affected, no single core with over 50% positivity; or also PSAD of between 0.1 and 0.15 μg/L/g, Gleason