Active Surveillance
Pathologic and Clinical Variables Associated with Outcome

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• Prostate adenocarcinoma • Active surveillance • Gleason grade • PSA

ABSTRACT

Over the past 10 years, active surveillance has emerged as a primary management option for men diagnosed with low-risk prostate cancer. Given the morbidity associated with curative treatment, active surveillance maintains quality of life for men whose disease may never become symptomatic. In order to confidently and safely offer this approach to as many patients as possible, improved metrics are needed to fully assess risk. While pathologic and clinical variables currently help determine whether active surveillance is a reasonable approach, emerging biomarkers and imaging technologies demonstrate promise for more precise identification of ideal candidates.

OVERVIEW

Prostate cancer is exceedingly common among men in the United States. Autopsy series suggest that more than 50% of elderly men and as many as 30% to 40% of men in their 30s and 40s are harboring the disease.[1] Nonetheless, the vast majority of American men will experience no symptoms and will not succumb to the disease. With widespread adoption of prostate-specific antigen (PSA) screening in the early 1990s, many of these clinically occult cancers were revealed, and prostate cancer incidence dramatically increased.[2] This in turn has been associated with a marked increase in the procedures used to treat prostate cancer, such as radical prostatectomy and radiation therapy, and along with them, significant morbidity. It is now widely acknowledged that these aggressive treatments are often unwarranted, as each year thousands of men are needlessly exposed to life-altering side effects to cure prostate cancers that may never be destined to cause harm.

PSA testing has been held largely responsible for overdiagnosis and overtreatment of prostate cancer over the past 20 years. As a result, in the absence of clear evidence of a mortality benefit from PSA testing, the US Preventive Services Task Force released a level D recommendation against PSA screening (http://www.uspreventiveservicestaskforce.org/uspstf12/prostate/prostateart.htm). Accordingly, screening rates in the United States have declined.[3] However, the PSA screening controversy has not yet been settled. Despite waning enthusiasm for PSA testing, several lines of evidence, while not yet definitive, suggest that PSA screening saves lives.[4] There is a clear need for early detection of aggressive prostate cancer, as the disease remains the second-leading cause of cancer-related death among men in the United States.[5] An overarching goal in the detection and subsequent management of localized prostate cancer, therefore, is to identify aggressive disease early while avoiding overtreatment of indolent cancer.

Active surveillance addresses the issue of overtreatment of newly detected disease. The approach has proven successful in safely managing nonaggressive prostate cancers, allowing physicians to withhold definitive local treatment until it is clearly necessary. A decision-analysis study, carefully taking quality of life into consideration, favored this approach for the average 65-year-old diagnosed with low-grade disease, when compared with radical prostatectomy or radiation

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therapy.[6] Identifying ideal candidates for active surveillance is critical, and the pathologist plays a central role in this determination (see also Adeniran and Humphrey, Morphologic Updates in Prostate Pathology, Surgical Pathology Clinics, 2015, vol 8, issue 4).

Active surveillance entails close monitoring of a biopsy-proven prostate cancer, proceeding with definitive local treatment if and when the disease appears more aggressive than initially anticipated. Several series of active surveillance cohorts have been reported.[7] Although data suggest that active surveillance can successfully avoid or meaningfully forestall aggressive therapies, data are limited regarding its safety after 10 to 15 years of follow-up. This is an important limitation in our current understanding of the approach, given the long natural history of the disease and the long life expectancy of many newly diagnosed patients.

ACTIVE SURVEILLANCE OUTCOMES

Among the most extensively annotated cohorts is from the University of Toronto. In that cohort, 993 patients with Gleason score of 6 or lower and PSA of 10 ng/mL or lower (as well as patients with PSA 10–20 ng/mL and/or Gleason score 3 + 4 with a life expectancy of <10 years) have been followed with serial PSAs (every 3 months for 2 years, then every 6 months if stable), digital rectal examinations, and prostate biopsies (performed according to Vienna nomogram[8] within 1 year then every 3–4 years thereafter).[9] Patients have been referred for treatment due to any of the following factors: significant change in PSA kinetics (through 2008, PSA doubling time <3 years was an automatic trigger for treatment, although this is no longer an automatic trigger), histologic upgrade on repeat prostate biopsy, or development of a palpable prostate proven to represent progression.[9]

After median follow-up of 6.4 years from time of initial biopsy, including greater than 10 years of follow-up for 206 individuals, prostate cancer–specific deaths were rare. Among 993 patients, a total of 28 (2.8%) developed metastatic prostate cancer, and there were 15 (1.5%) prostate cancer–specific deaths. Of note, among the 28 who developed metastases, 12 were in the subset of 132 patients with Gleason 7 disease at diagnosis.[9] At 10 years' follow-up, approximately 38% of patients underwent definitive local treatment, most commonly due to a shortening PSA doubling time.[9]

Other series have reported active surveillance or watchful waiting outcomes, but information from these studies are generally limited because of relatively short follow-up time, inclusion of patients with higher-risk disease, or low proportion of patients undergoing definitive local treatment despite evidence of progression. A study from Sweden, for example, in which 223 men with localized disease underwent watchful waiting, showed a marked increase in mortality in the subset of patients reaching 15 years' follow-up.[10] However, only 70 of the 223 patients were considered low risk at the time of diagnosis and patients were not followed closely with intention of timely referral for curative treatment as in the Canadian cohort. In this series, patients were started on androgen deprivation therapy at the time of symptomatic progression.

PATHOLOGIC AND CLINICAL VARIABLES ASSOCIATED WITH OUTCOME

As active surveillance is increasingly adopted by urologists and medical oncologists as an attractive approach for localized disease, appropriate patient selection is critically important. This entails thorough and accurate characterization of a patient's disease at the time of diagnosis (see also Adeniran and Humphrey, Morphologic Updates in Prostate Pathology, Surgical Pathology Clinics, 2015, vol 8, issue 4). It is clear that Gleason 3 + 3 prostate cancer has extraordinarily little metastatic potential.[11] In retrospective series of 14,123 Gleason 3 + 3 radical prostatectomy cases in which lymph nodes were sampled, only 22 cases (0.1%) had lymph node involvement. Histopathologic analysis of the 19 cases available for review demonstrated higher grade than originally reported.[12] However, these series were able to clearly establish low-grade disease based on examination of the entire prostate gland. Biopsy is only a sampling and a diagnosis of Gleason 3 + 3 disease at biopsy does not guarantee indolent disease.

One approach to help ensure the safety of active surveillance is to use conservative criteria for initiating this approach. In a series at Johns Hopkins, 769 men with very low risk cancers, defined by clinical stage T1c, PSA density less than 0.15 ng/mL, biopsy Gleason score 6 or lower, 2 or fewer positive biopsy cores, and 50% or less cancer involvement of any core, were followed for a median 2.7 years (range, 0.01–15.0). No prostate cancer–specific deaths have been reported.[13] However, the data from the University of Toronto, in which 13% had Gleason 7 disease on screening biopsy and many more had greater than 2 cores positive, strongly suggest that many men not meeting these stringent criteria may safely pursue and benefit from active surveillance (**Box 1**).[9]