Active Surveillance Not Only Reduces Morbidity, It Saves Lives

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The concept of active surveillance is based on the observation that Gleason 6 (pattern 3) prostate cancer is an indolent condition that poses little or no threat to the patient’s life. This view is supported by the molecular characteristics and clinical behavior of the disease. Conservative management is thus appropriate for these patients. Close and ongoing monitoring is required for two reasons: (1) to identify those patients initially diagnosed with Gleason 6 disease who harbor higher-grade cancer, and (2) to find the small proportion of patients who have true biological progression over time. Despite these two concerns, the majority of patients will remain unaffected and untreated, thereby avoiding the significant quality-of-life effects of radical intervention for prostate cancer. Those patients who are eventually reclassified as higher risk and who are subsequently treated have an extremely small likelihood of dying of prostate cancer.

Interest in, and support for, the concept of active surveillance has increased substantially in recent years. This is due to a number of factors. The problem of overtreatment of prostate cancer has been widely recognized. In particular, the US Preventive Services Task Force (USPSTF) recommendation against prostate cancer screening was based to a large degree on evidence that rates of overdiagnosis and overtreatment were unacceptably high.[1] For the USPSTF, the risks associated with overdiagnosis and overtreatment outweighed the evidence that screening was beneficial because of reduced prostate cancer mortality. A second factor has been an increased acceptance of surveillance as an antidote to overtreatment.[2] Selective therapy confined to patients with potentially aggressive disease will reduce the number needed to screen and treat to the point where the risk-benefit ratio of screening is palatable. A third factor is the mounting molecular and clinical evidence that Gleason 6 (pattern 3) disease lacks the hallmarks of cancer. The aberrant genes and pathways that induce the features typical of cancer have been characterized. With remarkable consistency, where a specific gene or protein alteration is linked to one of these aberrant pathways, the alteration associated with malignancy is absent in Gleason 3 pattern disease and present in Gleason 4 and 5 patterns. A confounder in determining the clinical outcome of Gleason 6 cancer has been the known rate of undergrading, which has been well documented as a feature of systematic biopsies. The rate of progression and metastases from pathologically confirmed Gleason 6 disease testifies to this. One would expect, if Gleason 6 cancer had even slight metastatic potential, that a few patients treated surgically would eventually fail—due to occult metastasis prior to surgery, or due to local failure from an incomplete resection with progression to metastasis—and that these patients would eventually die of the disease. In fact, patients with surgically confirmed Gleason 6 disease do not die of prostate cancer. This has been confirmed in several large series involving more than 10,000 patients. Our understanding of the nature of occult high-grade disease in patients who had been classified as “low-grade” has improved since surveillance was introduced. Twenty-five percent of patients initially diagnosed with low-risk prostate cancer (Gleason 6, prostate-specific antigen [PSA] level < 10 ng/ml) harbor higher-grade disease. In 90% of cases, this higher-grade disease is Gleason 3+4—ie, at the low end of intermediate risk[3]; it is often indolent as well. A few men with only Gleason 3+3 cancer will dedifferentiate over time to higher-grade disease (just as some patients without prostate cancer will develop high-grade disease over time). We estimate that this occurs at a rate of 1% per
year, based on the relationship between the time since the diagnostic biopsy and the likelihood of upgrading in our cohort.[4] Thus, patients require long-term follow-up. Finally, the increasing use of multiparametric MRI is enhancing our ability to identify patients with large occult cancers early, and to reassure the remainder. Absence of an abnormality on multiparametric MRI has recently been reported to have a 96% to 100% negative predictive value for the presence of higher-grade disease in a surveillance cohort.[5] The urologist is the sole physician contact for many men on surveillance. This represents an opportunity to counsel these patients on other aspects of men’s health, including smoking cessation, dietary modification, weight reduction, and exercise. These recommendations, if followed, may have as much of a beneficial health impact as prostate cancer monitoring, or perhaps more.

The real debate in 2013 is not active surveillance pro or con, but the nuances of how to optimize this approach. Which favorable-risk patients (high-volume disease at a young age, for example) should be treated; which intermediate-risk patients are candidates for surveillance; how to use MRI and biomarkers to better risk-stratify; how often to biopsy; targeted vs template strategies; and when to intervene—there are an abundance of challenging research questions to address in this field. Financial Disclosure: Dr. Klotz has no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

References:

REFERENCES


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