Clinically Relevant Prognostic Markers for Prostate Cancer: The Search Goes On

The management of early-stage prostate cancer continues to present both diagnostic and therapeutic dilemmas to primary care physicians and specialists alike. Prostate cancer alone accounted for about 25% of incident cancer cases in men in the United States in 2008 (1). Based on cases diagnosed from 1996 to 2003, an estimated 91% of these men with newly diagnosed cases are likely to have stage 1 or 2 disease, for which 5-year relative survival chances approach 100%. With such a favorable prognosis, some question the benefit of exposing men with early-stage and low- or moderate-grade prostate cancer to radical therapy (2). Although a Scandinavian randomized trial showed that radical prostatectomy may lead to better overall survival among men with well and moderately differentiated prostate cancer, few of the cases in the trial were detected by screening (3). In the United States, where most cases are screening-detected, the relevance of these trial results to most cases is uncertain.

We now have the recently published 10-year mortality results of the Prostate, Lung, Colon, and Ovarian Cancer Screening Trial and the European Randomized Study of Screening for Prostate Cancer. Within 10 years of trial entry, screening increases the number of cancer cases diagnosed but has no effect on cause-specific mortality. These data suggest that a large fraction of prostate cancer diagnosed by prostate-specific antigen (PSA) screening (stage T1c) represents overdiagnosis, defined as screening detection of cancer that will have no long-term clinical effect (4, 5). However, even when localized prostate cancer is detected early and treated with curative intent, 15% to 20% of patients will have biochemical (PSA) recurrence within 5 years (6). Not all of those who have relapse will die of prostate cancer. The European study shows a small mortality benefit for screening at 10 to 13 years. Thus, the 2 screening trial reports are interim accounts and are not definitive. Therefore, physicians probably will continue to screen and make early diagnoses of prostate cancer until longer-term trial results are available. We would like to identify men whose early-stage prostate cancer is destined to be fatal and who may benefit from early aggressive therapy (7, 8).

In this era of genome-wide, high-throughput technologies, the application of molecular markers to clinical decision making for cancer treatment seems to have a bright future. To identify men with screening-detected prostate cancer who are candidates for aggressive therapy, we need prognostic markers that we can apply to biopsy specimens. However, histologic findings for prostate cancer can be heterogeneous, which presents a substantial barrier to the widespread application of molecular prognostic and predictive markers in cancer tissue. For example, we know that needle biopsy may underestimate histologic grade (Gleason score) in a large proportion of patients who subsequently undergo prostatectomy (9, 10). Gleason score is one of the most reliable prognostic markers yet approximately 30% of the time, the Gleason score of the biopsy samples underestimates the highest score found when the entire gland is removed. Some cases are easy: Extensive involvement of both lobes by histologic grade (Gleason score 5)—which would have the highest scores of 9 or 10—may obviate a recommendation for radical prostatectomy. Other cases are difficult: We have no clinically useful markers to help decide whether we should do radical prostatectomy or use watchful waiting for patients whose biopsy specimens contain small amounts of cancer (Gleason score, 4). Moreover, although prostates typically contain several foci of cancer, only 1 focus generally progresses to clinical disease (11). Therefore, because of sampling error, needle biopsy may miss the cancer focus that will develop into clinical disease, which means that molecular prognostic marker analysis of the core biopsy samples may be misleading.

Concato and colleagues, whose findings appear in this issue (12), had access to a remarkable panel of prostate biopsy specimens for which clinical outcomes were available. Despite the availability of modern high-throughput technologies for analysis of molecular markers, the authors took a candidate gene approach to evaluate needle biopsy specimens for molecular markers of apoptosis, cell adhesion, and angiogenesis. They concluded that BCL2, p53, or high microvessel density in prostate cancer biopsies is associated with increased risk for death from prostate cancer. In using the candidate gene approach, the authors used published correlative studies that suggested the importance of BCL2, p53, and microvessel density in prostate cancer prognosis as a guide. In prostate cancer, these 3 markers correlate well with tumor grade, tumor stage, or both. However, each has problems as a marker of prognosis.

Many articles have shown that *P53* expression and gene mutation occur focally in prostate cancer. Their confinement to selected regions of a prostatectomy specimen means that they are difficult to analyze in needle biopsies because of sampling error. The relatively few analyses of *BCL2* expression in prostate cancer specimens reported that it is rarely overexpressed in localized prostate cancer, a finding confirmed in the study by Concato and colleagues (12), where only 6% of cancers stained for BCL2. Analysis of microvessel density in needle biopsy specimens depends on identification of factor VIII staining vessels within the regions of malignant foci. In narrow-needle biopsy specimens, scoring for microvessel density tends to be subjective, which suggests possible biased interpretation in the current study because the pathologist who read all of the

slides could not be blinded to histologic grade. Automated image analysis to validate at least a subset of the microvessel density interpretations would have been an important check on the pathologist's interpretations (13).

A shortcoming of the study was the choice of molecular markers to test. The published literature strongly suggests that these markers would have limited clinical effect. The authors themselves have commented on the hundreds of articles evaluating correlations of *P53* and *BCL2* expression and microvessel density with prostate cancer progression (14). Although Concato and colleagues (12) show that p53 and BCL2 detection and microvessel density are statistically associated with a worse prognosis, the authors themselves describe the advance made by their study as "incremental." We agree. We doubt that their findings will have any effect at all on clinical practice for several reasons. First, the hazard ratios are of insufficient magnitude for the markers by themselves to influence clinical decisions. Based on these results, it would be difficult for pathologists to justify performing these immunohistochemical studies routinely for prognostic purposes. Of the 3 markers that were statistically significantly associated with prognosis, BCL2 expression in early-stage prostate cancer may be particularly important, but because this finding was infrequent, the 95% CI around the hazard ratio is wide, diminishing its clinical applicability. Another major issue is the challenge of translating a multiplex immunohistochemical assay for use in routine clinical practice. Standardization would be difficult because a single pathologist did all of these analyses and, in the case of p53 and BCL2, relied on a subjective measurement of the staining intensity. The authors do not provide details of immunohistochemical staining or of sample preparation using antigen retrieval techniques. Differences in application of these technical variables between laboratories can result in large differences in sensitivity.

Another important consideration is the applicability of their findings to most patients with newly diagnosed disease who present with screening-detected, early-stage, localized disease. Among the 1172 men in the analysis, 181 (15%) died of prostate cancer and 26% presented with a baseline PSA level of at least 20 μg/L. This profile is different from most contemporary screening-detected prostate cancer cohorts. Although men with low-risk clinical status had a larger hazard ratio for the association of BCL2, p53, or microvessel density and death from prostate cancer, the CI was too wide to be sure of the prognostic value of these markers in low-risk patients.

Of what value is this information in light of recently published randomized trials of radical prostatectomy and PSA screening, which show that the risk for illness from treating screening-detected prostate cancer far outweighs the potential advantage in long-term survival? The 2 trials show that most cases of screening-detected prostate cancer diagnosed today are overdiagnosed. These observations suggest that screening and aggressive treatment has little value for most men. If screening frequencies declined, we would have less use for markers designed to identify high-risk cancer in biopsies. However, many believe that the trial results will not slow the demand for prostate cancer screening (15). Therefore, physicians will continue to face the challenge of advising patients who have newly diagnosed, screening-detected prostate cancer. The physicians and their patients need reliable markers that can identify cancer that requires immediate and aggressive therapy. Until we have sufficiently discriminating markers to inform treatment decisions, the problem of whom to treat will continue to grow exponentially as the number of cases of screening-detected, low-risk cancer increases. The dilemma of treating localized prostate cancer, as verbalized by Willet Whitmore, still remains, "If cure is necessary, is it possible, and if it is possible, is it necessary?"

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