Defining Clinically Significant Prostate Cancer: Pathologic Criteria Versus Outcomes Data

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During the past two decades, changes in therapeutic interventions and diagnostic testing have resulted in dramatic increases in the annual incidence rates of prostate cancer. During the 1980s, widespread use of transurethral prostatectomy yielded a significant increase in prostate cancer diagnoses (1). Clinicians divided these newly diagnosed tumors into two classes: 1) those involving less than 5% of the resected specimen, and 2) those infiltrating more extensive portions of the resected tissue. The former were labeled stage A1 and the latter stage A2 with the use of the Jewett/Whitmore classification system. A debate raged concerning the clinical significance of stage A1 disease. During the early 1990s, widespread use of prostate-specific antigen (PSA) testing fueled a new rise in the number of incident cases of prostate cancer detected annually (2). The large number of subclinical cancers identified by PSA testing necessitated a change in our classification scheme. We now refer to T1c disease and debate the clinical significance of this new category of cancers.

Physicians who encourage and support prostate cancer screening and aggressive treatment often define the clinical significance of resected specimens by specific pathologic features, such as tumor volume and tumor grade (3). Various therapies are administered on the basis of these pathologic findings, and treatment efficacy is often quantified by comparing cause-specific and all-cause survival curves with either historical controls or population-based survival curves (4,5).

The report by Helgesen et al. (6) in this issue of the Journal presents important data that challenge this approach. By comparing the long-term survival outcomes of men diagnosed in the late 1970s with men diagnosed in the early 1960s, the authors have demonstrated a significant relative survival improvement. These improvements occurred in an era that preceded the advent of PSA testing and the explosion of surgical intervention for localized disease. The authors suggest that the most likely explanation for their findings is an increase in the detection of

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nonlethal tumors coupled with the significant effect of lead-time bias. They caution clinicians and researchers that increases in relative survival must be taken into consideration when case series data are analyzed, since time trends can significantly confound nonrandomized comparisons.

These findings dramatize the important principles of epidemiology. Specifically, as we improve our ability to detect disease, we increase its prevalence. This effect, in turn, confounds our ability to assess how well our interventions alter the natural progression of disease. Black and Welch (7), in an elegant article titled *Advances in Diagnostic Imaging and Overestimations of Disease Prevalence and the Benefits of Therapy*, have commented that misperceptions of disease prevalence and therapeutic effectiveness can promote a cycle of increasing medical intervention. As our ability to detect prostate cancer has increased, first via transurethral resection, then by aspiration cytology, and now by PSA testing followed by transrectal biopsy, the number of incident cases has increased, including a subgroup of cases whose natural history and response to treatment is unknown. The enthusiastic support for prostate cancer screening provided by some professional organizations has encouraged increased testing, despite caveats that earlier detection may not improve clinical outcomes from a population perspective (8,9). Since in most reports the definition of "clinically significant" disease is based on pathologic criteria rather than clinical outcomes data, the increased case finding legitimizes the use of more sensitive tests that in turn leads to more case finding and treatment. Over time, as a result of this cycle, patients' outcomes will usually appear to improve, whether or not real improvement has actually occurred.

This is precisely the effect measured by Helgesen et al. (6) in their current publication. As the reported incidence and prevalence of prostate cancer increased in Sweden, patient outcomes appeared to improve, despite the absence of any effective intervention strategy. Lead-time bias and the increased prevalence of nonlethal tumors are the most likely explanations for their findings. Similar confounding issues have plagued other cancer interventions. Randomized trials evaluating screening for lung cancer, for example, initially documented higher rates of survival from the time of diagnosis but later failed to demonstrate any reduction in mortality from lung cancer.

As we debate the relative merits of free and bound PSA and the implications of detecting prostatic intraepithelial neoplasia in prostate biopsy specimens, we should be mindful of three important caveats. First, improvements in diagnostic testing and the expansion of pathologic criteria used to define clinically significant disease will increase the incidence and prevalence of disease in the absence of any change in its biological behavior. To date, despite aggressive prostate cancer detection efforts, the overall mortality rate from this disease remains unchanged. Before initiating aggressive screening and treatment efforts for subclinical disease, we should make an effort to understand its natural history. Second, as the incidence and prevalence of prostate cancer increases, therapeutic outcomes will appear to improve, even if the treatments offered are not effective. Lead-time and length-time biases are significant confounders of case series data. Therefore, clinicians should be cautious when interpreting results that are based on historical controls or other comparisons that do not adequately control for tumor grade, tumor stage, and other critical factors, such as patient comorbidities and the date of diagnosis. Real outcomes may, in fact, theoretically be worse because of complications associated with aggressive intervention. Finally, despite encouraging case series reports, well-designed randomized clinical trials remain the gold standard to judge treatment efficacy. Without these studies, we risk attributing improvements in cancer survival to the effects of treatment rather than seeing them as an artifact of increased cancer detection efforts.

References

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