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Prostate cancer: Too much dogma, not enough data

THE ARTICLE ON PROSTATE-SPECIFIC ANTIGEN (PSA) testing from Drs. Jones and Klein¹ in this issue of the *Cleveland Clinic Journal of Medicine* illustrates an important phenomenon in our recent approaches to management of prostate cancer: dogma often outweighs real data.

■ DOGMA 1: PSA \leq 4 IS NORMAL AND PSA $>$ 4 IS ABNORMAL

As Drs. Jones and Klein emphasize, a single PSA value does not necessarily indicate cancer is present or absent, although we should note that they are speaking predominantly of PSA values lower than 10 $\mu\text{g/L}$.

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In reality, however, a confirmed blood PSA concentration of 100 $\mu\text{g/L}$ is effectively diagnostic of prostate cancer, and I would be quite prepared to treat a patient for prostate cancer in an urgent setting (eg, spinal cord compression from sclerotic bone metastases) based on that confirmed PSA level without a tissue diagnosis. It is important to consider the costs and benefits of treatment and the impact of delay when making decisions of this type. In the setting of imminent spinal cord compression, the results of waiting for a diagnosis by conventional means (ie, by biopsy) are disappointing,² and delay in care can be an important factor. Thus, we should not ignore the implications of a *markedly* raised PSA level when the clinical context is appropriate. The conundrum is determining at what cutoff the PSA allows that type of decision to be made without a tissue diagnosis.

■ DOGMA 2: PROSTATE SCREENING IS BENEFICIAL

An equally vexing issue is community-wide screening for prostate cancer. Screening is the assessment of

symptom-free people in the general population for a particular disease, and for it to be successful, it must identify disease early in its course, and early identification of the disease must result in decreased morbidity of treatment or a reduced overall mortality rate. Current dogma is that prostate cancer screening is good for the community at large.

It seems intuitively sensible and logical that assessing healthy, symptom-free men for prostate cancer should be a good idea and should lead to earlier diagnosis and an increased chance of cure. The evidence in favor of routine screening includes “first principles,” common sense, the suggestion that death rates from prostate cancer have fallen in various countries since such approaches have been introduced, and the observation of stage migration (with a greater proportion of initial presentations with earlier-stage disease) in association with these screening exercises.

However, level-1 evidence to support this hypothesis is simply nonexistent—there have been no completed, well-designed randomized trials that demonstrate improved survival from the introduction of routine community screening for prostate cancer with digital rectal examination or PSA measurement. To know the true usefulness of community screening for prostate cancer, we must wait until the ongoing European randomized trial of screening is completed.

■ DOGMA 3: PROSTATE SCREENING IS WORKING

Although the concept of screening for prostate cancer is very appealing, we should not lose sight of the fact that absolute death rates from prostate cancer have fallen remarkably little in the United States since the introduction of our current screening techniques.

The absolute number of deaths from prostate

cancer in the United States has hovered in the range of 26,000 to 30,000 per year since the 1980s, when PSA testing became widespread. In 1985, the American Cancer Society estimated that there were 25,500 deaths from prostate cancer³; in 2007, the estimate was 27,050 deaths,⁴ hardly a quantum leap forward!

In addition, even if one introduces changes in the incidence of prostate cancer and the aging of the community into the argument and thus increases the denominator for calculation of death rates, the diagnosis and treatment of prostate cancer have improved in many other ways besides screening, including better noninvasive imaging and staging techniques, refined methods for pathological classification, advances in surgery and radiotherapy, hormonal adjuvant therapy for locally advanced tumors, improved chemotherapy, and better support technologies. Thus, it is difficult to attribute any perceived major improvement only to screening.

■ DOGMA 4: SURGERY IS BETTER . . . OR . . . RADIOTHERAPY IS BETTER

One of the tantalizing dogmas of prostate cancer management is the myth that surgery is vastly superior to radiotherapy, or vice versa.

In reality, most of the comparisons of surgery vs radiotherapy constitute comparisons of apples and oranges—surgical staging vs clinical staging, careful case selection, historical comparison, or single-center vs collaborative group outcomes. Once again, few well-constructed randomized trials have attempted to address this question, and most have closed prematurely because of poor accrual. In fact, most clinicians evolve a case-based and intuition-based experience, which is colored to varying extents by their medical school teaching and the medical literature,⁵ and really believe in the dogma and opinions that they quote. When one takes a step back and considers the true long-term outcomes, balancing inaccuracies of definition and documentation of the side effects of treatment,⁶ the variables outlined above, and the heterogeneity of salvage therapy, it is hard to make a strong case that only one therapeutic option reigns supreme.

■ DOGMA 5: CHEMOTHERAPY NEVER WORKS

Similarly, the view prevailed for many years that cytotoxic chemotherapy had no role in the management of hormone-refractory prostate cancer. With improved

clinical staging and assessment, the introduction of serial PSA measurement as a surrogate of response, better definition of the indices of quality of life, and the completion of large randomized trials, it has become clear that the use of chemotherapy improves quality of life,⁷ that survival can be prolonged by the use of cytotoxic drugs,⁸ and that it might even be worth testing the utility of chemotherapy in the adjuvant setting, in combination with hormonal therapy, as is done in locally advanced breast cancer.⁹

■ EVIDENCE-BASED MEDICINE: THE CURE FOR DOGMA

Ultimately, we have one major tool to help us resolve challenges to dogma, and it is neither rhetoric nor more dogma. Our ultimate weapon is data, and data are best gleaned from well-designed and well-supported randomized clinical trials.

Today, in the United States, fewer than 10% of patients with cancer enter structured clinical trials, reflecting the ennui of government, the medical profession, and patients themselves, as well as the downstream products of disbursement of dogma.¹⁰ As a community we need to address these issues for a broad range of medical conditions beyond cancer by using evidence gained from clinical trials, and by practicing evidence-based medicine. ■

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