Timing of Androgen Deprivation Therapy: Some Questions Answered, Others Not

Paul F. Schellhammer

The objective of the article by Shahinian et al. (1) in this issue of the Journal was to determine the factors involved in the use of androgen deprivation therapy—specifically, to distinguish patient and tumor characteristics from physician decision making as a determinant for the use of androgen deprivation therapy. For this retrospective study, they linked the Surveillance, Epidemiology, and End Results (SEER) and Medicare databases to identify 1802 urologists who provided care within 1 year of prostate cancer diagnosis for 61,717 patients who were older than 66 years.

Of the 61,717 patients, 31.4% received androgen deprivation therapy within 6 months of diagnosis. The study population was chronologically divided into two cohorts: those patients diagnosed in the years 1997–1999 and those diagnosed between January 1, 1992, and January 1, 1997. This division was made because information from randomized control trials became available in 1997 that showed a survival advantage was associated with the addition of androgen deprivation therapy to radiation therapy, compared with radiation therapy alone. The 1997–1999 cohort was further divided into a high-risk or “evidence-based” group that included patients with clinical stage T4 tumors and patients receiving radiation therapy who had either T3 or T2 tumors with high-grade histology, defined as having a Gleason score of 8–10. Receipt of androgen deprivation therapy by such patients was considered to be evidence based, according to the results of the randomized control trials available in 1997. The other patients, whose tumor characteristics did not fall into the advanced-stage or grade criteria, were categorized in an uncertain-benefit group for androgen deprivation therapy.

The overall variance for identifying the urologist as the determinant for androgen deprivation therapy, as opposed to the important factors associated with patient and tumor characteristics, was 20.63%. This value was 26.55% when the analysis was limited to patients diagnosed between 1997 and 1999. When patients were divided into evidence-based and uncertain-benefit groups, the values were similar at 29.09% and 25.48%, respectively. The variance attributed to the physician was higher for androgen deprivation therapy than for other diseases or physician practices studied, such as care of diabetic patients or prescription of beta-blockers. It is also important that the decision to use androgen deprivation therapy be appropriate because androgen deprivation therapy is the second highest Medicare Part B expenditure ($1.2 billion in 2003) and because adverse effects of this treatment reduce quality of life. If urologists direct use of this therapy, their decisions should be appropriate and evidence based.

My discussion will address two issues. The first issue provides a rationale or explanation as to how urologists might play a more clinically important role in directing androgen deprivation therapy. The second issue deals with my concerns about the accuracy of assumptions concerning grade and prostate-specific antigen (PSA) made in the analysis of the database-derived information. When discussing androgen deprivation therapy, it must also be recognized that there are few strategies for the treatment of non–germ-cell solid tumors that can so rapidly lower a disease-related serum marker (such as PSA) to undetectable levels and that can produce such dramatic subjective and objective responses for as long as a decade.

The timing of androgen deprivation therapy in the absence of symptoms presents the urologist with the following dilemma: Should androgen deprivation therapy be withheld because of the paucity of evidence-based trials demonstrating survival benefits, or should it be administered because it could provide, at the minimum, a temporary dramatic biochemical, radiologic, or clinical response? Prostate cancer mortality has decreased over the last 5 years (2). Potential explanations that have been proposed include screening, early detection, earlier and better definitive local therapy, and the increased and earlier use of androgen deprivation therapy. Randomized trials have supported the benefits of therapy (3–8), as has a meta-analysis.

When the authors evaluated the delivery of androgen deprivation therapy between 1997 and 1999 (after the publication of results from a phase III trial showing survival advantage for androgen deprivation therapy in conjunction with radiation therapy for patients with high-grade or end-stage T3, T4 disease) (3), they found an upswing in the use of androgen deprivation therapy for patients meeting the same stage and grade criteria. Evidence-based medical therapy was penetrating clinical practice. But they also noted a similar increase in the use of androgen deprivation therapy for patients without these criteria. Is this trend really unexpected? A trial had reported groundbreaking news—that a combination of radiation therapy and androgen deprivation therapy was associated with a survival benefit. The information was available not only to physicians but also to patients.

Although not valid, a not unexpected extrapolation might follow—that hormone therapy in conjunction with radiation therapy for all patients would provide a benefit. In fact, one could argue the premise that, because the combination therapy proved a survival benefit in more advanced disease, it might be even more beneficial for patients with less advanced disease. Admittedly, this was and remains an unproven assumption.

Weinberg’s practice style hypothesis (9) that “intervention is determined by characteristics of the physician” was published in 1982 before the Internet revolution and before PSA measurements became available. Today, patients have access to more information, and PSA levels can be monitored by physicians and patients as an indication of biochemical disease progression. Androgen deprivation therapy is available to silence the ticking PSA clock of disease progression in the short-to-intermediate term. Under these circumstances, the patient who focuses on achieving a lower PSA level may seek a physician who will administer androgen deprivation therapy. The challenge for urologists is to...
offer men with high-risk, potentially lethal prostate cancer androgen deprivation therapy early in their course of treatment and to avoid the unnecessary risks of androgen deprivation therapy among men with low-risk indolent disease.

My concerns about the accuracy of the assumptions made about grade and PSA are as follows. The authors note that their grade distributions are obtained from the patient’s records, in which tumor grade is recorded as a Gleason sum. A Gleason sum of 2, 3, or 4 is translated to a well-differentiated tumor; a sum of 5, 6, or 7 to a moderately differentiated tumor; and a sum of 8, 9, or 10 to a poorly differentiated tumor according to the protocol of the SEER database. The translation of a Gleason sum of 5, 6, or 7 to a moderately differentiated or intermediate-risk category may be problematic because it mixes clearly low-risk disease (represented by a Gleason sum of 5 or 6) with more aggressive disease (represented by a Gleason sum of 7). A Gleason sum of 7 can trend to intermediate or high-risk disease, depending on the preponderance of pattern 4. Therefore, the SEER intermediate or moderately differentiated category—indeed, 35,536 case patients in this study—could, depending on its composition, be a high-risk cohort (Gleason sum of 4 + 3) that may be appropriate for androgen deprivation therapy or to be a low-risk cohort (Gleason sum of 5 and 6) for whom evidence for a benefit associated with androgen deprivation therapy is lacking.

The authors could not use PSA data, which were unavailable, to define risk categories. PSA data can move a patient to a high-risk category, specifically, if his PSA level is greater than 20 ng/mL. They state that, because neither grade nor stage influenced their variance analysis, they assumed that PSA data would not either. I disagree. I have discussed the grade problem—namely, that including disease with a Gleason sum 7 and disease with a Gleason sum of 5 and 6 in the same intermediate category clouds the discriminatory potential of the Gleason sum of 7. PSA data may have provided information to expand the high-risk evidence-based cohort and thus decrease the variance attributed to the urologist.

The last sentence of the report conveys an interesting admonition, but one that may not be practical in the real world setting regarding decisions about androgen deprivation therapy. “The primary care physician should carefully consider the choice of urologist for their patients.” There may be a unique set of primary-care physicians who are aware of the evolving nuances associated with evidenced-based data associated with androgen deprivation therapy. If so, it is unclear how they should assess the practice patterns of an individual or group of urologists. This very concept of monitoring evidence-based and/or guideline-based delivery of care by other physicians is a black hole that challenges the practice of medicine in general and that places initiatives such as pay for performance on shaky and uncertain grounds.

REFERENCES