EDITORIAL

Improved Therapy for PSA Recurrence after Prostatectomy

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In developed countries around the world, prostate cancer is the most common solid neoplastic disease. In the United States, approximately half the men with localized prostate cancer undergo radical prostatectomy.[1] Prostate-specific antigen (PSA) levels should be undetectable after surgery; a detectable PSA level usually indicates disease recurrence. Almost uniformly, patients who have progression to metastatic disease and subsequently die from prostate cancer present with a detectable PSA level as the first evidence of cancer recurrence.

In many patients, residual or recurrent disease is limited to the prostatic bed or pelvis, a phenomenon that has been confirmed by observations that adjuvant radiation therapy (in patients with high-risk cancer) or salvage radiation therapy (at the time of PSA recurrence) can result in long-term survival without evidence of disease. The prognosis for patients with PSA recurrence is related to the initial tumor characteristics — grade, volume, and local stage. Despite randomized trials showing benefits of radiation after prostatectomy, the disease may recur and patients may ultimately die from prostate cancer.

Shipley and colleagues report in this issue of the *Journal* the long-term outcomes of a randomized trial comparing pelvic radiation therapy plus 2 years of antiandrogen therapy with pelvic radiation therapy plus placebo in high-risk patients who have PSA recurrence after surgery.[2] Using a moderate dose of radiation and high-dose (150 mg) bicalutamide as the androgen-deprivation therapy, the investigators found a 23% higher rate of overall survival and a 51% lower rate of death from prostate cancer in the bicalutamide group than in the placebo group. The number needed to treat with the nonsteroidal antiandrogen drug bicalutamide to prevent one death from prostate cancer was 20. By comparison, the number needed to treat (surgery or radiation therapy) to prevent one death from prostate cancer has been estimated to be 27, which shows the magnitude of the benefit of antiandrogen therapy.[3] As expected, the primary side effect of bicalutamide was gynecomastia, which was seen in 70% of the men treated. This side effect can be distressing but can be mitigated by prophylactic radiation of the breast or by the administration of tamoxifen.[4]

Androgen-deprivation therapy with high-dose bicalutamide may be used in place of luteinizing hormone–releasing hormone–based (LHRH) therapy to reduce sexual and bone side effects. More commonly, contemporary trials of adjuvant therapy have used LHRH-based agents; most data suggest that LHRH-based agents have a similar effect as bicalutamide.[5] Higher contemporaneous doses of radiation, delivered with intensity-modulated radiation therapy or other techniques, may have greater efficacy than the dose prescribed in the trial conducted by Shipley et al. Given the magnitude of benefit that was seen with bicalutamide in this trial, it is unlikely that higher doses of radiation would reduce this benefit, but the treatment outcomes would probably be even better.

Despite evidence supporting and guidelines calling for the use of salvage radiation therapy at the time that PSA becomes detectable, in clinical practice, radiation therapy is often not administered or treatment may be delayed until the PSA level continues to rise.[6] The benefit of the conclusions of this trial can be accrued only if salvage radiation therapy is administered appropriately; this is clearly an opportunity for national quality-improvement initiatives.

Androgen-deprivation therapy in combination with radiation therapy is worth serious consideration in high-risk patients with PSA recurrence. Nonetheless, in the era of precision medicine, it is our ultimate goal to administer this therapy to patients who are likely to benefit. The RADICALS (Radiation Therapy and Androgen Deprivation Therapy in Treating Patients Who Have Undergone Surgery for Prostate Cancer) trial (ongoing in Europe and Canada; ClinicalTrials.gov number, NCT00541047) will help to address this issue by investigating two critical questions. With evidence that adjuvant radiation therapy significantly reduces the risk of disease recurrence and, in the National Cancer Institute clinical trial,[7] reduced the risk of metastases and prolonged survival, the RADICALS trial is comparing adjuvant radiation therapy (in high-risk patients after surgery) with salvage radiation therapy (at the time of PSA recurrence). The other question that is addressed is the duration of androgen-deprivation therapy: none, 6 months, or 24 months. A recent secondary analysis of a randomized trial of androgen-deprivation therapy showed that the benefit of 6 months of androgen-deprivation therapy added to radiation therapy was seen only in men with no or minimal coexisting conditions.[8] Given the range of side effects of androgen deprivation in older men with coexisting conditions, especially in those with early cognitive decline or with the metabolic

syndrome, the use of antiandrogen therapy in lieu of LHRH-based therapies or the omission of hormonal therapy entirely may be considered.[9]

This remarkable contribution by the National Clinical Trials Network of the National Cancer Institute shows the importance of randomized clinical trials with very long follow-up. Studies that incorporate interventions without proprietary intellectual property (e.g., surgery or radiation therapy) or pharmaceutical agents whose patents often expire before the study is completed can be achieved only with the use of this invaluable national resource.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

SOURCE INFORMATION

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