Do Not Count Out External-Beam Radiation Therapy for High-Risk Prostate Cancer

To the Editor: We read with concern the recent article entitled “Metastasis After Radical Prostatectomy or External-Beam Radiotherapy for Patients With Clinically Localized Prostate Cancer: A Comparison of Clinical Cohorts Adjusted for Case Mix” by Zelefsky et al. The authors analyzed 1,318 patients after primary radical prostatectomy and 1,062 patients after primary radiation therapy (RT) between 1992 and 2002. Surgery was performed by one of two experienced surgeons at either the Memorial Sloan-Kettering Cancer Center or Baylor College of Medicine, and RT was delivered at Memorial Sloan-Kettering Cancer Center to ≥ 81 Gy using external-beam RT (EBRT). Of note, RT patients received at most short-term androgen-deprivation therapy (STAD), and no patients received long-term androgen-deprivation therapy (LTAD). In addition, no patients had RT to the pelvic lymph nodes.

Not surprisingly pretreatment risk factors were significantly greater in the RT group compared with the surgical group, including higher prostate-specific antigen (PSA), higher clinical stage (cT3, 9% vs 4%, respectively), higher Gleason scores (Gleason score of 8 to 10, 13% vs 4%, respectively), and a lower likelihood of remaining disease free based on the preoperative Kattan nomogram (all P < .001). Therefore, it also was not surprising that there was a slightly higher rate of metastasis at 8 years in patients treated with RT than in patients treated with a primary surgical treatment (7% vs 3%, respectively). The authors subsequently attempted to adjust for pretreatment characteristics and concluded that there were minimal differences in metastasis between treatment modalities in patients with low-risk disease but that in those with intermediate- and high-risk prostate cancer by National Comprehensive Cancer Network criteria, treatment with RT was associated with a 3.3% and 7.8% increased risk, respectively, of metastatic disease compared with primary surgical treatment.

The authors do mention several limitations of their study, which all bias against the RT outcomes, including the lack of any adjuvant therapy in the RT group but judicious (albeit limited) use of adjuvant therapy in the surgery group, the lack of pelvic lymph node RT (but the use of extensive pelvic dissections in the high-risk surgical group), the lower rate of salvage treatment in the RT cohort compared with those treated with surgery (43% vs 76%, respectively), and the longer delay to salvage treatment in the RT cohort compared with those treated with surgery (69 v 13 months, respectively). Any one of these factors could potentially explain the differences in outcome. Nevertheless, for high-risk prostate cancer, the authors went on to advocate that either surgery followed by planned adjuvant RT or combined EBRT and brachytherapy would be the preferred treatment compared with EBRT plus STAD.

How do these conclusions compare with the published literature? It certainly is worth pointing out that the two treatments that the authors propose have never been demonstrated to be superior to the current best proven treatment option involving RT for men with high-risk prostate cancer, which is the combination of LTAD (for 28 to 36 months) plus RT of the pelvic lymph nodes followed by further RT to the prostate gland. In two randomized trials, this treatment was associated with a 40% to 50% reduction in the rate of metastasis compared with conventional-dose EBRT delivered with STAD. Furthermore, although four randomized trials have now demonstrated improved biochemical control with higher dose EBRT (74 to 79.2 Gy) compared with lower dose RT (64.8 to 70.2 Gy), none of these trials demonstrated any decline in metastasis even if delivered with STAD. Therefore, the ≥ 81 Gy RT with STAD that Zelefsky et al used most likely resulted in higher metastasis, particularly in the highest risk group where they observed the greatest differences between patients treated with surgery or RT.

How does the actuarial rate of metastasis for the patients treated in this series compare with that of LTAD with conventional-dose RT or other surgical series? Unfortunately, because the authors only reported actuarial metastasis rates for the entire population and not broken down by risk groups, it is impossible to say. The Radiation Therapy Oncology Group (RTOG) 9202 study involved patients with locally advanced prostate cancer, and as such, patients had to have clinical T2c or bulky T2 disease (with ≥ 25 cm² prostate cancer on physical examination). These patients had a median PSA of more than 20 ng/mL, and more than 55% had Gleason scores ≥ 7. This clearly was a far more advanced group of men than those treated by Zelefsky et al, where 75% of patients had T1-2a disease and the median PSA was less than 8 ng/mL. Nevertheless, the 10-year rate of metastasis on RTOG 9202 was 15%, and even if restricted to only patients with Gleason scores of 8 to 10, the 10-year metastasis rate was 26%. For comparison, in their discussion, Zelefsky et al point out that, in a previous publication from the same two institutions, when restricted to men with high-risk disease by National Comprehensive Cancer Network criteria (although not locally advanced) who underwent radical prostatectomy between 1985 and 2002, there was a 22% risk of metastasis at 10 years and this rate was 24% if limited to patients with Gleason scores of 8 to 10. Therefore, it seems that the largest reason for the lower rate of metastasis in the surgical group in the current report is a result of patient selection for their own as well as other surgical series, supporting higher rates of metastasis after surgical treatment for advanced prostate cancer.

Finally, no large prospective studies to date have assessed surgery for locally advanced or high-risk prostate cancer with planned adjuvant RT. The Southwest Oncology Group (SWOG) did evaluate adjuvant RT for patients with pathologic T3 or margin-positive disease, but these patients were not necessarily high risk or locally advanced before surgery; they simply were found to meet pathologic enrollment criteria after surgical resection. The 10-year rate of metastasis was 39% in patients who received surgery with or without salvage RT and was decreased to 29% in patients who received immediate adjuvant RT. It is difficult to compare patient populations simply based on clinical characteristics; however, it seems that patients enrolled onto the RTOG and European Organisation for Research and Treatment
of Cancer2 studies of LTAD with RT had, on average, substantially higher clinical stage, PSA values, and Gleason scores compared with patients in the SWOG study. In addition, because patients on the SWOG study had pathologic T3 disease, it is impossible to compare this feature with the RT studies where surgery was not used. Nevertheless, despite these differences, the 10-year rate of metastasis on the SWOG study with adjuvant RT of 29% was twice that on both the RTOG and European Organisation for Research and Treatment of Cancer studies (at approximately 15% for both studies).

Therefore, the authors’ hypotheses that either EBRT along with brachytherapy or surgery followed by planned adjuvant RT is better than dose-escalated RT with STAD may be true. However, it is premature to presume that these treatments will result in better outcomes than the combination of LTAD and RT, which has been clearly evaluated in large prospective randomized studies in both North America and Europe. Instead, the authors have simply confirmed what four randomized trials have already demonstrated: moderate dose escalation of RT with or without STAD does not decrease overall metastatic rates for high-risk prostate cancer. However, they have not demonstrated a superior outcome for a predominantly surgically based treatment regimen for men with high-risk prostate cancer.

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