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Is It Time to Reevaluate Definitive Therapy in Prostate Cancer?

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In this issue of the Journal, Hoffman et al. (1) explore one of the many unanswered questions confronting newly diagnosed prostate cancer patients: Which definitive treatment is superior—radical prostatectomy (RP) or external beam radiotherapy (EBRT)? The authors analyzed an observational cohort from the population-based Prostate Cancer Outcomes Study treated in the mid-1990s, and the resulting data suggested a survival benefit associated with RP over EBRT (1). A propensity score analysis was used to adjust for treatment selection bias in this cohort of men aged 55 to 74 years with clinically localized disease. In men with high-risk tumors (Gleason score ≥ 8 or prostate-specific antigen > 10), both overall and prostate cancer–specific mortality were statistically significantly lower in the group that received RP than the group that

received EBRT. In men with low-risk tumors (Gleason score ≤ 6 and prostate-specific antigen ≤ 10), there was no difference in prostate cancer mortality and a modest but statistically significant difference in overall mortality. Notably, this analysis did not include intermediate-risk patients. It is also interesting to note that acceptance of active surveillance as a treatment option for most, if not all, patients with low-volume, low-risk disease is much greater now than it was when this study was initiated.

Although this analysis is provocative, it has several limitations. First and foremost, as in most studies comparing RP and EBRT, there is substantial concern that patients who receive EBRT have far more serious comorbidities and potentially more advanced local disease. Although this analysis employed propensity scoring

to control variations within the study groups, inherent imbalances undoubtedly existed (2). Of greater concern in interpreting these data are the evolution in the use of androgen-deprivation therapy (ADT) in combination with EBRT and the demonstrated importance of radiation dose. Multiple randomized trials have demonstrated a clear survival benefit for men with high-risk disease who received EBRT followed by prolonged ADT over EBRT alone or EBRT with shorter-term ADT (3,4). Thus, although these data appear to show a better outcome with RP than with EBRT, particularly in high-risk patients, the data do not address whether RP is superior, equivalent, or inferior to EBRT combined with prolonged ADT. Furthermore, accumulating data on the importance of dose in radiation therapy and improvements in targeted delivery of radiation render data from nearly 20 years ago increasingly irrelevant clinically (5,6).

Beyond the nuances of this analysis, however, lies a broader need to reevaluate the long-standing dogma that RP and EBRT are equivalent and that no prospective study will either confirm or refute this assessment. Although EBRT can be used in some cancers such as early-stage squamous and basal cell carcinomas and in cervical and head/neck cancers, surgery is generally the preferred option (7). Prostate cancer is the only major solid tumor for which radiation without chemotherapy or surgical resection is routinely used in patients in whom primary surgery is feasible. In patients with low-risk disease, there is little doubt that EBRT, RP, and active surveillance will likely lead to approximately equivalent long-term outcomes. However, although largely flawed by potential biases in the data, some studies suggest that treatment with EBRT and RP in more aggressive disease may not always be equivalent. In the last decade, at least seven observational or retrospective studies have suggested that RP yields better disease-specific survival than EBRT (8–14). In addition, two randomized studies done before

the prostate-specific antigen era suggested that RP resulted in improved disease-specific survival (15,16). Although those studies share many of the flaws and biases of the Hoffman et al. analysis, perhaps the activity of RP relative to EBRT (based on older standards) in high-risk disease merits further consideration.

Beyond standard concerns that the EBRT approach used in this study was anachronistic in terms of dose or lack of combination with ADT, there are other plausible explanations for the resulting data. Is maximal tumor debulking essential to a good outcome? If so, is the effectiveness of EBRT limited by the density of tumor (17)? Radiation oncologists on our multidisciplinary tumor board often discourage the use of EBRT for patients with large tumors and clinically significant obstructive symptoms, with their concern being not only residual fibrosis but also the ability of EBRT to safely eradicate all local disease. Furthermore, patients are likely to receive adjuvant or salvage local therapy after RP, especially for high-risk disease (11,12,18). This may not actually confound a comparison of RP with EBRT but rather be an integral component of a therapeutic approach. In addition, surgery that includes sampling of lymph nodes and exploration of margins and capsular extension may enhance staging of disease, allowing for earlier (adjuvant) EBRT and/or hormonal treatment. This raises the intriguing possibility that in appropriately selected patients, RP may result in expedited use of secondary interventions that improve long-term outcomes (13,19,20). This multimodality approach has been the standard model for treatment of breast cancer for more than three decades.

Perhaps the missing component in the breast cancer analogy has been imaging, as there is no standard equivalent to mammography to allow for accurate identification of the volume and location of disease within and extending from the prostate. As with the increasing therapeutic options in advanced prostate cancer, prostate cancer imaging is also evolving significantly. Modern endorectal,

Figure 1. Emerging magnetic resonance imaging (MRI) techniques can be used to localize individual tumors within the prostate. **A)** Axial T2W MRI shows a low signal intensity lesion in the left midbase peripheral zone (arrow). **B)** Apparent diffusion coefficient map obtained from diffusion-weighted MRI shows restricted diffusion within the left midbase peripheral zone lesion (arrow). **C)** Dynamic contrast-enhanced

MRI demonstrates early and intense enhancement within the same lesion (arrow). **D)** Kep (reverse contrast rate constant) map obtained after processing of dynamic contrast-enhanced MRI also localizes the left midbase peripheral zone lesion (arrow). This lesion was biopsied by transrectal ultrasound-MRI fusion biopsy platform, and histopathology revealed Gleason 3+4 tumor within the left midbase peripheral zone.

multiplanar magnetic resonance imaging can potentially detect clinically important tumors within the prostate, allowing for targeted ultrasound-guided biopsy to specifically diagnose and grade individual lesions (21,22) (Figure 1). Although this technology is currently available in only a few research institutions, as it becomes more widely available, it could lead to more accurate staging and grading of prostate cancer.

The future of treatment for localized prostate cancer offers tantalizing possibilities. If a tumor could be mapped to specific, limited regions of the prostate, could we then, like our colleagues in breast cancer, use multimodality strategies to minimize the morbidity associated with complete resection of the prostate? Could focal therapies such as laser ablation be employed in some patients? Could current technology for treating localized prostate cancer evolve to the point where “prostate cancer lumpectomy” is feasible? In the years to come, renewed efforts must be made to answer these quandaries as we move beyond the simple question, “What is better: surgery or radiation?”

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