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RESEARCH HIGHLIGHT

High-risk prostate cancer: is androgen deprivation monotherapy still appropriate?

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The optimal management of high-risk prostate cancer, defined by tumor stage T3a or higher, a Gleason score of 8–10 or a prostate-specific antigen level >20 ng ml^{-1}, is unclear, and continues to be a source of substantial controversy.[1] Though now much less common with the widespread adoption of prostate-specific antigen screening, it remains important as a cause of prostate cancer death. In large clinical trials, it has already been established that androgen deprivation therapy (ADT) added to external beam radiation therapy improves overall survival when compared to radiation alone.[2,3] Although this clarifies the best approach for men choosing radiation therapy, it leaves open the question of the value of androgen deprivation monotherapy (i.e., as primary therapy). In the United States and elsewhere, primary ADT is still very commonly used for high-risk disease,[4] perhaps due to patient perceptions that radiation treatment may be too aggressive and fears of its adverse effects. Furthermore, in one of the only clinical trials of relevant design, comparing orchiectomy alone, radiation alone and the combination of the two, the orchiectomy alone and combination groups were similar in their ability to delay progression to metastases, and superior to radiation alone.[5] Although that trial was small and underpowered to examine overall survival, the results suggested that the benefits of combination therapy may be predominantly derived from the androgen deprivation.

Shedding new light on this issue is a recent study by Warde *et al.*[6] reporting on the planned interim analysis of a clinical trial examining the effect of radiation plus ADT versus ADT alone in men with high-risk prostate cancer (the majority of whom had locally advanced disease). The unblinded study randomized a total of 1205 men with prostate cancer diagnosed from 1995 through 2005. Androgen deprivation was lifelong, and given in the form of gonadotropin-releasing hormone agonists or bilateral orchiectomy. Radiation doses used over the study period were 65–69 Gy. The primary end point was overall survival, and effects on health-related quality of life as well as gastrointestinal and genitourinary toxicities were assessed using the Functional Assessment of Cancer Therapy-Prostate and European Organization for Research and Treatment of Cancer QLQ-C30 with PR13 prostate cancer-specific module instruments. Over a median of 6 years of follow-up, 175 men died in the ADT alone group versus 145 in the radiation plus ADT group, resulting in a clear overall survival benefit with the addition of radiation therapy (hazard ratio: 0.77, 95% CI: 0.61–0.98). The difference was driven predominantly by prostate cancer deaths, with disease-specific mortality of only 9% at 7 years in the ADT plus radiation group versus 19% in the ADT-alone group (P=0.0001). There were slightly more non-cancer deaths in the combined treatment arm, but this was not statistically significant. The cause-specific mortality results should be viewed with some caution however, given that assessors were not blinded to treatment assignment. The survival benefit of adding radiation appeared to come at little cost in terms of adverse effects. The impact of radiation on symptom burden and toxicities was very modest, and limited to the short term (6 months), with virtually no differences between the treatment arms at 36 months.

The results essentially duplicate those of the Swedish SPCG-7 trial which also examined the value of adding radiation therapy to androgen deprivation in high-risk disease.[7] However, the study by Warde *et al.* improves on it as it is larger, and was powered to examine overall survival (as opposed to disease-specific) as the primary end point. In addition, the SPCG-7 study used anti-androgen monotherapy (after 3 months of combined androgen blockade), which would not be considered standard or sufficient for androgen deprivation therapy in the current era.

Despite the impressive results, several unanswered questions and concerns remain. As is typical of prostate cancer trials, which by necessity have relatively long follow-up, protocols often become obsolete by the time the results are mature. Standard radiation doses applied in the current era are substantially higher than those used over the study period, and could further improve the efficacy of the regimen.[8] The advent of more conformal radiation delivery methods, such as intensity-modulated radiation therapy, may also reduce toxicity, though definitive evidence of enhanced safety of the newer technologies is as yet lacking.[9] The instruments used to assess symptom burden in the study are not as sensitive as more recently developed measures,[10] possibly leading to an underestimation of the impact of radiation related toxicity. In addition, data on some potentially important adverse effects were not reported at all. Cardiovascular complications have apparently been assessed and will be reported when the results of the final analysis are published. Unfortunately, data on skeletal events were not collected, which would have been of particular interest as radiation and ADT appear to have additive effects on the risk of hip fracture.[11] Though not addressed in this study, the issue of the optimal duration of ADT has been previously examined. At least for high-risk disease, longer is better, with 3 years of ADT following radiation improving overall survival when compared with 6 months.[12] Whether moving beyond 3 years, or even providing lifelong therapy as was done in this study, leads to additional benefit is not clear and may expose men to greater

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risks of adverse effects from ADT. Finally, there is increasing acceptance of radical prostatectomy as an approach for high-risk disease, bolstered by observational studies showing improved outcomes as compared with radiation-based regimens.[13,14] However, residual confounding by indication is likely to be a major problem in those studies despite statistical adjustments, making a clinical trial comparing the two approaches necessary in order to draw definitive conclusions.

Ultimately, the results of this trial push the use of androgen deprivation as monotherapy for high-risk disease further into a therapeutic limbo, rendering its appropriate use unclear. Although early use of primary ADT appears to improve prostate cancer-specific survival, it does not clearly improve overall survival,[15] perhaps related in part to adverse effects of the ADT. On the one hand, for men who wish to adopt a conservative approach, such as those with limited life expectancy due to age or comorbidities, it may be most reasonable to defer initiation of any therapy until they develop symptomatic progression. On the other hand, for men wishing to treat their cancers aggressively, the study results imply that combining radiation with ADT is clearly the superior approach, and failure to do so will be denying them a substantial overall survival benefit.

COMPETING FINANCIAL INTERESTS

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