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RESEARCH HIGHLIGHT

External-beam radiation therapy should be given with androgen deprivation treatment for intermediate-risk prostate cancer: new confirmatory evidence

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A newly published study, Radiation Therapy Oncology Group (RTOG) trial 94-08, has demonstrated that a short-course of neoadjuvant androgen deprivation therapy (ADT) given together with external-beam radiation therapy (EBRT) improves outcomes for men with intermediate-risk prostate cancer compared with EBRT alone.[1] The benefits of neoadjuvant ADT for men receiving EBRT have been recognized for years, but in light of growing concerns regarding potential long-term skeletal, metabolic and cardiovascular toxicities of ADT, the demonstration of benefits with only short-term treatment is timely.

Identifying appropriate and optimized treatment algorithms for clinically localized prostate cancer remains challenging. Given the generally prolonged natural history of the disease, among other considerations, clinical research on prostate cancer generally has been notable for a lack of high-quality randomized controlled trials to help guide physician–patient decision-making.[2] An important exception is the question of neoadjuvant ADT given before and/or continuing through and after EBRT. Three large, well-described trials,[3–5] initiated over 20 years ago, randomized men with locally-advanced or otherwise relatively high-risk disease to EBRT±ADT.

The European Organization for Research and Treatment of Cancer 22863 trial demonstrated a substantial survival benefit (58% *vs.* 40% overall survival, $P<0.001$), as well as improved local control and metastasis-free survival, among men with high grade and/or high stage prostate cancer who received 1 month of combined androgen blockade (a luteinizing hormone releasing hormone agonist plus an anti-androgen) followed by 3 years of luteinizing hormone releasing hormone agonist monotherapy.[3] The RTOG 85-31 trial randomized 977 men with stage T3 and/or N1 disease to EBRT with or without indefinite luteinizing hormone releasing hormone agonist therapy. This trial demonstrated improved local, biochemical and distant control, and cancer-specific survival for those with high-grade disease.[4]

Finally, the RTOG 86-10 study randomized men with bulky, local clinical stage ⩾T2b disease to EBRT±4 months of combined androgen blockade. This study again showed a benefit for combination therapy in terms of local, biochemical and distant control, and in cancer-specific but not overall survival.[5] A secondary analysis showed combination EBRT+ADT to be cost-effective over EBRT monotherapy for this patient population.[6]

The most recently reported RTOG study 94-08 was intended to determine whether short-course ADT can improve survival without causing undue morbidity among men with low- to intermediate-risk prostate cancer. In brief, 1979 men with prostate-specific antigen <20 ng ml^{-1} and clinical stage T1b-T2b were randomized between 1994 and 2001 to 67 Gy of radiation to the prostate (including 47 Gy to the pelvis for those with prostate-specific antigen >10 ng ml^{-1} and/or Gleason sum >7) with or without 4 months of combined androgen blockade starting 2 months before radiation. Eighty-four percent of patients across both arms were treated per protocol or with acceptable variation; 95% of ADT was administered per protocol or with acceptable variation.[1]

The mean age was 70 (range: 47–91) years. Twenty-seven percent of the tumors across both groups were Gleason 7, and 9% were Gleason 8–10. 90% had prostate-specific antigen levels between 4 and 20 ng ml^{-1}, though the specific breakdown between groups was not reported. Just over 50% were considered intermediate-risk; one-third were low-risk and 11% were high-risk. With median 9.1 years follow-up, relatively few men in either treatment arm had died of prostate cancer, but survival was better in the combination therapy arm (cancer-specific survival: 96% *vs.* 92% in the EBRT-only arm; hazard ratio: 1.87, 95% confidence interval: 1.27–2.74, $P=0.001$). Overall survival was also better in the EBRT+NADT arm: 62% *vs.* 57%; hazard ratio: 1.17, 95% confidence interval: 1.01–1.35, $P=0.03$.

Subgroup analysis indicated that the majority of the survival benefit for combined androgen blockade accrued to men with intermediate-risk disease. There was a trend toward improved survival for men with high-risk disease, while those with low-risk disease experienced no benefit with combined therapy compared to EBRT alone. The benefits for combination therapy were observed across age and racial groups.

Acute and delayed grade ⩾3 gastrointestinal toxicity was noted in 1% and 3% of patients; three men (0.15%) died of these complications. Acute and delayed grade ⩾3 genitourinary toxicity was identified in 2% and 7% of the men. Among the roughly half of patients with good pre-treatment erectile function, 58% noted worse function 1 year after treatment, with no significant difference between the two arms. Fifty-five percent of men on ADT experienced hot flashes, but other effects of ADT appeared minimal. No increase in other-cause mortality was noted in the ADT arm compared to the EBRT-only arm.

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Of note, persistent local cancer was identified in the prostate 2 years after treatment in 39% of the EBRT monotherapy group, *vs.* 20% of the EBRT+NADT group ($P<0.001$). This raises the concern that the dose of radiation therapy given in this study, over 10 years ago in all cases, would generally be considered suboptimal by contemporary standards. Intensity-modulated radiation therapy and brachytherapy allow delivery of higher doses of radiation to the prostate, and higher doses have been associated with better recurrence-free survival rates, albeit at the cost of greater toxicity.[7]

On balance, this study adds further support to the assertion that EBRT should be given with ADT for men with intermediate-risk disease, and that combination therapy is not needed for those with low-risk disease. A relatively short duration of treatment (6 months) appears to be adequate for intermediate-risk disease, though this study was not intended to compare short- to long-duration treatment explicitly. For men with locally advanced disease, the RTOG 92-02 and European Organization for Research and Treatment of Cancer 22961 studies have previously showed that longer-duration ADT yields superior outcomes compared to short-duration treatment.[8,9] (Of note, longer-term treatment was not associated with greater cardiovascular mortality.[10])

Ultimately, however, RTOG 94-08 does not answer the question of what is the optimal therapy for men with low- to intermediate-risk prostate cancer. Two recent studies comparing radical prostatectomy to EBRT found superior risk-adjusted, cancer-specific and overall survival outcomes in the surgical arms.[11,12] Of note, in one of these, the radiation was consistently given as intensity-modulated radiation therapy at 77 Gy,[12] a higher dose than in RTOG 94-08.[1] In both studies, however, most of the difference was seen for men with intermediate- to high-risk disease. Minimal differences were seen for those with low-risk disease. Very few men with low-risk disease in fact die of prostate cancer; most likely would have been well-served with active surveillance as an alternative to any local treatment.[13,14]

RTOG 94-08 thus confirms that for men with intermediate-risk prostate cancer, EBRT should be given with ADT, and that the toxicity of the combination compared to EBRT alone appears to be modest. However, whether short-course ADT is equivalent to long-term treatment, and whether EBRT is comparable to brachytherapy, surgery and other alternative modalities, must be the subject of future randomized controlled trials and other comparative effectiveness studies.

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