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Does short-term ADT before and during radiation therapy improve outcomes in locally advanced prostate cancer?

Emmanuel S Antonarakis and Mario A Eisenberger*

ES Antonarakis is a Medical Oncology Fellow and MA Eisenberger is a Professor of Oncology at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins School of Medicine, Baltimore, MD, USA.

SUMMARY

This Practice Point discusses the 10-year data of the RTOG 8610 trial, published by Roach III and colleagues, which suggest that a short, 4-month course of neoadjuvant–concomitant androgen deprivation therapy (ADT) might be sufficient to improve clinically relevant long-term outcomes in men with bulky, locally advanced prostate cancer. The results show that patients randomized to receive short-term ADT before and during radiation therapy (RT), rather than RT alone, had improved long-term disease-specific mortality, freedom from distant metastases, disease-free survival, freedom from biochemical failure, and possibly even overall survival. Importantly, no increase in the risk of fatal cardiac events was seen. The study did not, however, address the issue of the optimum duration of ADT; recent data suggest that longer courses of ADT (2 years), when added to RT, might further improve disease-free and even overall survival, especially in patients with high-grade disease.

Keywords

androgen deprivation therapy; disease-free survival; locally advanced prostate cancer; overall survival; radiation therapy

COMMENTARY

The use of adjuvant androgen deprivation therapy (ADT) has improved the outcomes of patients with locally advanced or high-risk localized prostate cancer treated with curative radiation therapy (RT). The optimum role of ADT in this setting, however, is uncertain. Roach III *et al.*¹ report the 10-year data of the phase III Radiation Therapy Oncology Group (RTOG) 8610 trial, in which 456 men with T2b–T4 tumors, with or without pelvic lymph node involvement, were randomized to receive either 4 months of combined neoadjuvant and concurrent ADT plus RT, or RT alone. ADT consisted of goserelin (3.6 mg every 4 weeks) and flutamide (250 mg three times daily), starting 2 months before RT. Pretreatment PSA measurements were available for 64 of 224 patients in the combined-therapy arm and

67 of 232 patients who received RT alone (median 22.6 ng/ml and 33.8 ng/ml, respectively); 67% and 73% of patients had a centrally reviewed Gleason score of 7–10. Median follow-up durations were 11.9 years and 13.2 years in the ADT–RT and RT-alone groups, respectively, and the median survival times were 8.7 years in the ADT–RT group and 7.3 years in the RT-alone group. Similarly, the respective 10-year overall survival rates were 43% and 34%, although no significant difference in 10-year overall survival was detected between the two groups ($P = 0.12$). At 10 years, statistically significant benefits were seen in the ADT–RT arm in terms of disease-specific mortality (23% vs 36%; $P = 0.01$), rate of distant metastases (35% vs 47%; $P = 0.006$), disease-free survival (11% vs 3%; $P < 0.0001$), and rate of biochemical failure (65% vs 80%; $P < 0.0001$). A retrospective review of patient records revealed no significant increase in fatal cardiac events at 10 years in the ADT–RT group compared with the RT-alone group (12.5% vs 9.1%; $P = 0.32$).

Various prospective, randomized trials and a recent systematic review have shown that long-term ADT given to men treated with RT has clinically meaningful effects on prostate-cancer-specific end points.² The present study is important because it suggests that prostate-cancer-specific and overall survival benefits might still be seen even when the total duration of adjuvant ADT is as short as 4 months. The biological mechanism by which 4 months of ADT given before and during RT could have such a profound synergistic effect on long-term outcomes remains to be elucidated. ADT might cause a reduction in tumor volume before RT, or might sensitize tumor cells to the effects of radiation.³ In addition, some elderly men who receive 4 months of goserelin might have a slow gonadal recovery, although it seems unlikely that such a short course of ADT could result in long-term or permanent castration in the majority of these patients. While this study supports the use of a combined ADT–RT approach, it does not provide additional insight on the optimum timing or duration of ADT because it was not designed for this purpose. Other recent studies have, however, suggested that in patients with locally advanced prostate cancer, the addition of post-RT, long-term ADT (24 months) improves disease-free and overall survival in men with tumor Gleason scores of 8–10.^{4,5} By contrast, in patients with low-risk disease (Gleason score 7, PSA level <20 ng/ml), a short course of ADT is safe and might be sufficient to improve outcomes. Ultimately, the duration of ADT is often influenced by patient wishes, physician preferences, and the presence of cardiac risk factors.

Another significant effect of adjuvant ADT in this study is a decrease in the rate of distant metastases. Bone metastases are a major source of morbidity in men with prostate cancer, often leading to pain, fractures and epidural extension of disease. Although the median time to the development of distant metastases in the ADT–RT arm was greater than the duration of follow-up, the Kaplan–Meier curves show that 40% of men in the ADT–RT group had developed bone metastases at 13 years, whereas the same proportion had bone metastases at only 5 years in the RT-alone group. Finally, while RTOG 8610 did not show a statistically significant improvement in 10-year overall survival for the ADT–RT group, the trial was not powered to detect survival improvements smaller than 15% at 5 years.

Concerns over the long-term consequences of ADT and its association with non-prostate-cancer-related mortality have been raised.^{6,7} High rates of osteoporosis, fractures, diabetes, hyperlipidemia, obesity and depression have been observed in men receiving long-term

ADT. These disorders, in turn, most likely translate into increased cardiovascular mortality. The data in this study did suggest a slightly higher rate of fatal cardiac events in the ADT–RT group than in the RT-alone group, but this difference was not statistically significant. A small but real increase in cardiovascular mortality in the ADT–RT arm, undetected as a result of the small sample size, remains a possibility. To this end, men receiving ADT as part of their prostate cancer treatment might benefit from aggressive control of cardiovascular risk factors (by way of exercise, weight control, lipid lowering, and glucose management) in an effort to limit the long-term morbidity and mortality associated with hormonal therapy.

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PRACTICE POINT

In patients with bulky, high-risk locoregional prostate cancer, 4 months of androgen deprivation therapy, given before and during definitive radiation therapy, significantly improves clinical outcomes. Even with short-term treatment, however, patients might still benefit from aggressive control of cardiovascular risk factors to reduce the risk of fatal cardiovascular events.