Harms versus benefits with duration of androgen suppression

The decades of debate about the optimum duration of androgen suppression with radiotherapy for prostate cancer have been informed by the results of landmark randomised trials that have identified, with some overlap, durations that were proven more efficacious (4 months, 6 months, 28 months, and 36 months) versus less efficacious (no androgen suppression, 3 months, 4 months, and 6 months).[1–7] The arguments thus far have focused on the magnitude of the benefit from the longer-course regimens of androgen suppression, and which patients are likely to need the 28 month and 36 month regimens (mainly those with locally advanced disease) and which patients could be adequately treated with 4 month and 6 month regimens (mainly those with intermediate and high-risk localised disease). In *The Lancet Oncology*, James Denham and colleagues[8] remind us of the equal importance of considering the harms versus the benefits of androgen suppression for locally advanced prostate cancer in their study of patient-reported quality-of-life outcomes, which is being released 2 years before they report the oncological outcomes of the RADAR trial.

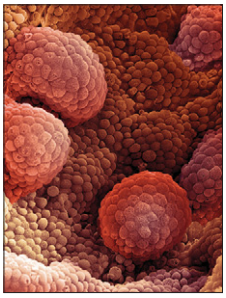
In Denham and colleagues' trial, hormone-treatment-related symptoms (HTRS), sexual activity, social function, fatigue, and financial problems were significantly worse at 18 months in patients who received 18 months of androgen suppression than in those who only had 6 months of androgen suppression. However, most of the differences from the baseline measures resolved by 36 months in both groups, unlike in the EORTC 22961 6 month versus 36 month trial in which sexual symptoms and HTRS seemed to remain qualitatively worse for the 36 month group at 3·5 years.[1] In Denham and colleagues' trial, there were still small differences in HTRS at 36 months, possibly caused by the much higher proportion of men who remained hypogonadal (23% *vs* 5%) in the 18 month group than the 6 month group, 2 years after completing androgen suppression. What the results of this study clearly provide is a measure of the harms men will have to endure for the oncological benefit, if there is any, with the additional 12 months of treatment that Denham and colleagues will report in 2014.

If the results for the oncological outcomes are negative then there will be no reason to use 18 months of androgen suppression, and the optimum regimens will still be 4 months, 6 months, 28 months, and 36 months. However, if 18 months is better than 6 months, then two questions will remain. First, is the benefit worth the short-term reduction in quality of life? This is a question that patients and providers will need to address individually with the data from this study. Second, will 18 months become a new standard?

Although purists might argue that 18 months of androgen suppression will need to be tested against 28 months or 36 months in a randomised trial before it is accepted, practicality and history suggest that such a trial will probably not be done. Currently, 2 years or 3 years of androgen suppression are judged to be acceptable long-course options because they have shown benefits in randomised trials, even though the 2 years (actually 28 months) of treatment in the RTOG 92-02 study[1] has not been compared with 3 years of treatment in the EORTC 22961 trial.[5] Assuming 18 months of androgen suppression shows an overall survival benefit over 6 months, it is likely to become a longer-course standard as well.

Although it is not ideal to draw conclusions from the results of separate trials, compared with no androgen suppression, only 6 months of treatment improved overall survival by 10% at 5 years in the Dana-Farber trial,[3] whereas 30 months of treatment added to 6 months in EORTC 22961 only improved survival by 3·8% at 5 years.[1] This difference in outcomes suggests that the most important period of androgen suppression is the first few months, and with additional months beyond a certain threshold the benefits start to diminish. If the results of Denham and colleagues' trial are positive, 18 months might indeed be a worthwhile trade off in harms versus benefits. A further important question is whether 18 months would be needed for all patients included in the trial, or whether the 63% of patients with localised disease could do equally well with only 6 months of androgen suppression. Because the investigators have stratified by stage, this subgroup analysis should be possible and will be much anticipated. Age and comorbidity will also need to be considered to optimise duration of androgen suppression for each individual.

Irrespective of the ultimate oncological outcomes of Denham and colleagues' trial in 2014, the authors are to



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be commended for putting equal emphasis and care on measuring the effect of the treatments on the quality of the lives of the patients so that we may all make more informed decisions. Quality of life should continue to be key components in all future prostate cancer trials.

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