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RESEARCH HIGHLIGHT

The opportunity cost of androgen suppression in locally advanced prostate cancer

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The use of androgen suppression therapy (AST) and radiotherapy for locally advanced prostate cancer has become the standard of care worldwide. At the same time, it has become clear that AST carries significant risk for side effects. Recently, Denham and colleagues have reported initial quality of life (QoL) results from the TROG 03.04 RADAR trial. The authors identify clinically meaningful decrements in patient-reported QoL for those treated with 18 months of AST *vs.* 6 months but only marginal differences at 36 months. Once survival data becomes available, these data will help to frame any benefits seen for longer courses of AST.

The use of AST and radiotherapy for the treatment of locally advanced prostate cancer has become the *de facto* standard of care based on a rapidly accumulating body of evidence pointing to superior outcomes when the treatments are combined rather than offered in isolation.[1–6] As these trials have progressed, it has become equally clear that AST carries with it a significant risk of toxicity. While some data has indicated that AST is associated with a modest increased risk in cardiovascular events, recent reports have suggested that this is unlikely to affect rates of cardiovascular death for those receiving androgen suppression as part of a curative combined-modality approach.[7–9] Recent studies have focused on the QoL effects associated with such therapy including fatigue, emotional dysfunction or sexual dysfunction. Such endpoints are often difficult for physicians to measure and so collecting patient-reported QoL information has become the preferred method for assessing such toxicity.

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In the December 2012 edition of *Lancet Oncology,* Denham and colleagues reported initial results from the TROG 03.04 RADAR trial.[10] This trial is a natural extension of the earlier TROG 96.01 trial which demonstrated the superiority of six months of AST combined with radiotherapy over 3 months or radiotherapy alone for locally advanced prostate cancer.[5] The RADAR trial adopted a more complex approach, randomizing 1071 men with locally advanced prostate cancer to radiation plus short-term androgen suppression (6 months) or intermediate-term androgen suppression (18 months)±zoledronic acid using a 2×2 factorial design. A full analysis of survival-related outcomes will not be performed until 2014 and so in this first report, the authors present patient-reported outcomes data collected using two validated metrics (EORTC QLQ C-30 and PR-25).

As would be expected, all patients receiving treatment with neoadjuvant androgen suppression and radiotherapy reported significant decrements from baseline in their global QoL due to side effects related to their treatment. For the months following treatment, however, significant differences emerged between patients treated with short-term *vs.* intermediate-term androgen suppression. At 12, 18 and 24 months from enrollment, patients treated with intermediate-term hormones reported, on average, significantly worse QoL in the domains of fatigue, emotional function, sexual function and hormone treatment-related symptoms (including such things as hot flashes, weight gain and breast tenderness). At 18 months, the differences between the two groups reached both statistical significance and crossed a threshold of clinical relevance (defined as a score change of >10 from baseline). By 36 months, however, only marginal differences in patient-reported QoL were apparent between the two groups. The addition of zoledronic acid appeared to have no effect on QoL.

These data confirm the work of others who have studied the effect of AST on patient-reported QoL.[11,12] Though treatment-related toxicity can be a significant burden for patients, it must be weighed in the context of mounting data pointing to improved outcomes with longer courses of AST.[11,13] As such, this toxicity may be viewed as the opportunity cost of selecting a treatment approach with a potential higher chance for cure and long-term survival. Given the apparent time-limited nature of these toxicities, as demonstrated by these initial results from the RADAR trial, this cost seems reasonable.

Several lingering questions remain given the preliminary nature of these data. First, this trial was conducted during an era in which the benefits of radiation dose escalation were just being realized. Indeed, randomization in the RADAR trial was stratified by treatment center and each center was asked to select a dose of 66, 70 or 74 Gy (with a fourth subgroup receiving 46 Gy with a 19.5 Gy high dose rate brachytherapy boost). As previous studies demonstrating the superiority of longer courses of androgen suppression used relatively low doses of radiotherapy, the benefit in the era of dose escalation remains a topic of debate and ongoing clinical trials. Additionally, higher doses of radiotherapy may affect the interpretation of patient-reported QoL differences between the arms, though such differences would be expected to be of a lower magnitude than those induced by longer courses of androgen suppression.[14]

Second, longer follow-up is needed to fully explore the true effects of intermediate-term androgen suppression on patient QoL. Though differences between the arms were minimal at 36 months, the authors noted that, in their exploratory investigations, patients identified to have persistent low testosterone and hemoglobin levels were twice as common among those treated with intermediate-term androgen suppression. These

patients were also much more likely to report consistently lower QoL in the long term. Such findings are common in the elderly and in those with low baseline testosterone, thus for these or other subgroups (such as those with significant comorbidities) the opportunity cost of such therapy may in fact be much higher than expected.

Finally, a full report of outcomes for this population are needed before final conclusions can be made. Will this study confirm the advantages of longer course androgen suppression seen in other trials?[11,13] Despite this unanswered question, the authors should be commended for their choice to release the analysis of this secondary endpoint before the results of the primary endpoint become available. Given the long natural history of prostate cancer, trials with primary endpoints of overall or cancer-specific survival can take years to mature. As the number of novel therapies increases over the coming years, the length of time needed to find significant differences in survival will only grow. Patient-reported QoL is an extremely valuable endpoint and one which can mature within a much shorter period of time. Such early publication allows for the final data to be understood within this important context and provides patients and providers with timely information to inform their therapeutic decisions.

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