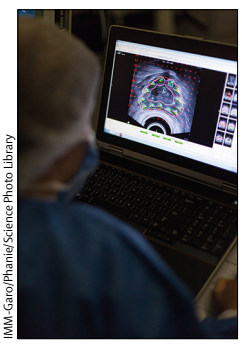
Androgen deprivation therapy in prostate cancer: new findings and questions for the future



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Since the seminal 1997 European Organisation for Research and Treatment of Cancer (EORTC) study by Bolla and colleagues,[1] which showed that men with locally advanced prostate cancer lived longer when external-beam radiotherapy and androgen deprivation therapy are combined, the interactions between prostate-directed external-beam radiotherapy and androgen deprivation therapy have been studied intensively. What have we learned so far? And what are the next steps in this quest of more than 20 years to optimise external-beam radiotherapy for men with localised prostate cancer?

In the original trial by Bolla and colleagues,[1] the comparison was between 0 and 36 months of androgen deprivation therapy. Given the significant improvement in overall survival with androgen deprivation therapy, the standard of care in this setting subsequently changed to include hormonal therapy. However, the shortcomings of a trial comparing 0 and 36 months of androgen deprivation therapy (plus external beam radiotherapy) are readily apparent. Is it necessary to give 36 months of a treatment that men would prefer not to receive? Castration is clearly deleterious to men's quality of life. Additional EORTC studies in men with high-risk (locally advanced) prostate cancer treated with external-beam radiotherapy plus 6 months or 36 months of androgen deprivation therapy found that 36 months was superior.[2] These studies established that 6 months of androgen deprivation therapy was inadequate in this setting.

The next series of prostate cancer trials with androgen deprivation therapy and radiotherapy focused on the duration of androgen deprivation therapy in various subsets of patients. Patients with high-risk localised disease and those with low-risk disease are obviously very different patient populations, and understanding the interplay between prostate cancer risk category and androgen deprivation therapy duration is clearly important. For patients with predominately intermediate-risk disease, D'Amico and colleagues[3] studied 0 months versus 6 months of androgen deprivation therapy, and established that 6 months of ADT was life-prolonging. Further studies from RTOG (94-08) confirmed that short-course androgen deprivation therapy (4 months) improved overall survival in intermediate-risk but not low-risk disease.[4]

Taken together, these large pivotal trials established that when using external-beam radiotherapy in high-risk or locally advanced prostate cancer, longer courses of androgen deprivation therapy are preferable (36 months) whereas for intermediate-risk disease, 4–6 months of androgen deprivation therapy combined with radiotherapy will suffice. For low-risk disease (in the prostate-specific antigen [PSA] era), we remain uncertain about whether any therapy is better than surveillance.

A Canadian trial recently reported that 18 or 36 months of androgen deprivation therapy plus external-beam radiotherapy yielded similar survival outcomes in patients with high-risk prostate cancer.[5] Ideally, this study would have been designed as a non-inferiority trial, better facilitating comparisons between the treatment groups. Instead, the investigators concluded that 36 months of androgen suppression was not superior to 18 months. For many clinicians, this finding has changed practice, but purists point to the trial design and question whether "not superior" is the same as "non-inferior".

The article by James Denham and colleagues in *The Lancet Oncology*[6] describes a trial (TROG 03.04) that enrolled men with T2b–4, N0 M0 prostate cancer, or T2a, N0 M0 tumours provided the Gleason score was 7 or higher and baseline PSA concentration was at least 10 µg/L. These inclusion criteria resulted in enrollment of a hybrid of intermediate-risk and high-risk patients. These patients were treated with external-beam radiotherapy and either 6 or 18 months of androgen deprivation therapy, with or without the addition of zoledronic acid. After 10 years, the primary endpoint (prostate cancer-specific mortality) was significantly improved with 18 months of androgen deprivation therapy compared with 6 months (sub-hazard ratio 0·70 [95% CI 0·50–0·98], adjusted p=0·035). The addition of zoledronic acid was inconsequential. The results also suggested some improvement in overall survival with 18 months of androgen deprivation

compared with 6 months, but statistical significance was not reached.

Where do we go from here? The older classic classification of low-risk, intermediate-risk, and high-risk localised prostate cancer is being supplemented with new molecular classifications.[7] The question of how to optimally classify patients is a key one, and the addition of genomic methods seems to be an improved approach. If one can classify risk better with newer technologies, then risk-adjusted escalation and de-escalation of systemic therapies should be considered as these new categories emerge.

Molecular imaging is now upon us.[8] CT and bone scans are far less sensitive than prostate-specific membrane antigen, fluciclovine, and choline PET assessments. Newer treatment strategies addressing the findings associated with these newer molecular imaging are both timely and appropriate.

Better forms of androgen ablative therapy and more precision targeted approaches are intriguing. Agents such as abiraterone and enzalutamide have substantial activity beyond androgen suppression alone.[9] These agents need to be tested in men at high risk of treatment failure in hopes of increasing cure rates. Lutetium-177-labelled prostate-specific membrane antigen ligands and other targeted radiopharmaceuticals are intriguing possibilities.[10] Today, they are used in advanced disease. Tomorrow, these agents will likely move into use in earlier disease stages.

Change is coming, and is coming fast. Androgen deprivation therapies and external-beam radiotherapy are the standards of care today but newer forms of molecular imaging, newer forms of androgen ablation, and newer forms of targeted therapy will be the focus in the next decade. Cure is a worthy goal, as is better quality of life. Hopefully tomorrow we will be able to achieve both.

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Ramucirumab and the controversial role of α-fetoprotein in hepatocellular carcinoma

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In *The Lancet Oncology*, Andrew X Zhu and colleagues report the results of REACH-2, a placebo-controlled phase 3 trial of ramucirumab in patients with hepatocellular carcinoma and baseline α-fetoprotein concentrations of 400 ng/mL or greater, who had previously received sorafenib.[1] Median overall survival was significantly improved in the ramucirumab group compared with the placebo group (8·5 months [95% CI 7·0–10·6] *vs* 7·3 months [5·4–9·1]; hazard ratio 0·710 [95% CI 0·531–0·949]; p=0·0199) at a median follow-up of 7·6 months (IQR 4·0–12·5). This work comes at a crucial time in view of the advent