Adjuvant treatments for locally advanced prostate cancer

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There is no standard definition of 'locally advanced prostate cancer'. In surgical series, this usually refers to patients with extracapsular extension or evidence of nodal involvement. However, the implication of the definition is an increased risk of recurrence and for localised prostate cancer, risk models usually incorporate factors such as Gleason score and PSA. The National Comprehensive Cancer Network has defined "high-risk" prostate cancer as extension through the capsule, Gleason score 8–10, or PSA >20 ng/ml. If the tumour has multiple adverse factors or there is extension to the seminal vesicle or to an extra-prostatic organ or nodal involvement, the classification is "very high-risk" disease.

Generally, patients with locally advanced disease are treated with radiotherapy using an external beam technique although some patients with more localised disease with high-risk features are treated by prostatectomy. If local extracapsular extension is seen, adjuvant radiotherapy will reduce the recurrence risk after prostatectomy. Overall, patients treated only with local treatment modalities for "advanced" disease have a biochemical (PSA) failure rate of about 50% at five years and in this group adjuvant systemic therapy should be considered.

The extreme androgen dependence of prostate cancers has led to extensive study of the role of hormone therapy in localised disease. Potential benefit must be balanced against toxicity risks, including not only the more obvious loss of libido and erectile function, but also, the discomfort of hot flushes and the risk of fatigue syndrome, loss of muscle mass, insulin resistance, cardiovascular effects and decreased bone mineral density. Thus, it is important to judge the role of hormone therapies in the context of the particular risk offered by the patient's prostate cancer and the prognosis of a patient who may have comorbid conditions. To mitigate risks, it is important that those starting androgen deprivation therapy have any cardiovascular risk factors addressed, including possible treatment for diabetes, hypocholesterolemia and hypertension. An exercise programme should be recommended to maintain muscle mass and strength and the use of low-dose aspirin should be considered. Although adjuvant hormone therapy has been shown to improve radiotherapy outcomes, questions to consider should include duration of hormone therapy, whether to use hormone deprivation or an anti-androgen, whether radiotherapy is beneficial in patients who have been treated anyway on long-term hormone therapy, and whether in some circumstances, hormone therapy can be given intermittently.

The most convincing evidence for the benefit of adding androgen deprivation to local radiotherapy for locally advanced prostate cancer came initially from an EORTC trial. The trial administered concurrent and adjuvant hormones for a period of three years starting on the first day of radiotherapy. The hormone therapy led to a significant improvement in five-year overall survival compared with radiotherapy alone (78% vs. 62%; $P = 0.0002$). The clinical disease-free survival was 74% with hormone therapy compared with 40% with radiotherapy alone. Similarly, an RTOG trial in patients with clinical T3 tumours or smaller tumours with regional lymph node involvement demonstrated the benefit of androgen deprivation in terms of reduced local failure rate, reduced incidence of distant metastasis and increased survival. A Swedish trial also showed a survival advantage in node-positive patients for those receiving hormone therapy.

It can be considered that the benefit of hormone therapy is largely through improving local control by radiotherapy. In that setting, hormone therapies would be administered either before or during radiotherapy in order to improve the cure rate of the primary tumour. For example, the RTOG 86–10 trial compared short-term neoadjuvant androgen deprivation therapy plus external beam radiotherapy compared with external beam radiotherapy alone in locally advanced tumours. 465 men were randomised and those receiving radiotherapy had four months of hormone therapy before and during radiotherapy. This showed significant benefits in terms of reducing the 10-year PSA failure rate from 80% to 65% and the distant metastasis rate from 47% to 35%. The ten-year disease-specific mortality was also significantly improved from 36%

to 23%. Long-term follow-up of TROG 96.01 showed a survival advantage for six months of neoadjuvant hormone therapy.

A number of trials have gone on to investigate the duration of hormone therapy when combined with radiotherapy. In the EORTC 22961 trial, 970 men were randomly assigned either to short-term androgen suppression for six months or to continue to a total of three years' androgen suppression. After a median follow-up of 6.5 years, the five-year overall mortality was 15.2% in those receiving long-term hormones and 19% for the short-term group. For prostate cancer-specific mortality, the five-year cumulative rate was 4.7% in the short-term group and 3.2% in the long-term group. There was no significant difference in the cumulative incidence of fatal cardiac events at five years, 4% in the short-term group and 3% in the long-term group.

Men with locally advanced prostate cancer have in the past been treated with endocrine therapy alone. However, two trials have now shown that the addition of local radiotherapy reduces prostate cancer-specific mortality and overall mortality. A Scandinavian trial randomised 875 patients with locally advanced node-negative prostate cancer to endocrine treatment alone vs. the same combined with radiotherapy and after a median follow-up of more than seven years, the cumulative prostate cancer-specific mortality at ten years was 23.9% in the endocrine group and 11.9% in the endocrine + radiotherapy group. Similarly, the NCRI PR3/MRC PR07 trial was recently reported in abstract form. This randomised 1200 patients to hormone therapy alone vs. hormone therapy + radiotherapy to prostate and pelvis. The addition of hormone therapy improved the seven-year overall survival from 66% to 74% and improved the seven-year cause-specific survival from 79% to 90%.

Hormone therapy clearly benefits patients at significant risk of recurrence after local treatment for locally advanced prostate cancer. There have been a number of approaches to reducing hormone toxicity that may be relevant in this setting, including the use of an anti-androgen such as bicalutamide rather than androgen deprivation, and this was an effective adjuvant compared with radiotherapy alone. The evidence for adjuvant hormone therapy after prostatectomy is less clear-cut. It may benefit those with surgical evidence of nodal involvement. However, adjuvant bicalutamide did not influence overall survival after prostatectomy. Intermittent therapy appears equivalent to continuous hormone therapy in studies that included patients with locally advanced disease being treated with hormone therapy alone.

It may be the case that the benefits of adjuvant hormone therapy would be enhanced if combined with other well-tolerated systemic agents. A current trial entitled 'Stampede' is using a multi-arm, multi-stage method to assess the five research arms against the control arm of hormone therapy alone, and this trial also includes patients with locally advanced disease. The trial originally included the addition of zoledronic acid or of docetaxel or of the combination of the two, or celecoxib, or the combination of celecoxib with zoledronic acid. The two arms of the trial that used celecoxib recently halted recruitment when an interim analysis found that there was lack of sufficient evidence of benefit.

New approaches to improving the adjuvant therapy of localised prostate cancer include investigation of docetaxel chemotherapy, and future opportunities include combining radiotherapy with a CYP17 inhibitor such as abiraterone acetate or TAK-700. Additionally, more effective anti-androgens such as MDV3100 will be investigated in locally advanced disease. The challenge is to improve cancer control rates with a lower risk of toxicity.

Conflict of interest statement

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