Hot topics for debate in prostate cancer: part 1

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This report is based on a seminar held during the 8th Annual Meeting of the British Uro-oncology Group in York last September. Hot topics for debate covered in part 1 of this article are the use of active surveillance for intermediate-risk prostate cancer and cardiovascular risks in the hormonal management of locally advanced prostate cancer. All participants, most of whom were clinical oncologists, were invited to contribute and respond to set questions using a keypad voting system.

ACTIVE SURVEILLANCE FOR INTERMEDIATE-RISK DISEASE?

Dr Chris Parker showed interim data from the Prostate Cancer Intervention Versus Observation Trial (PIVOT), a multicentre, randomised controlled trial, initiated in 1994, comparing radical prostatectomy (RP) to watchful waiting in men with clinically localised prostate cancer.1 The interim results show no significant difference in prostate cancer mortality between patients who received RP and those managed through watchful waiting after a median follow-up of 10 years. These early results suggest that the benefit of treating low-risk disease through RP is very small, and that these patients can be managed through active surveillance (AS) without increasing the risk of adverse outcomes.

In the only trial so far to have studied AS in intermediate-risk prostate cancer, progression-free survival (PFS) in low- and intermediate-risk patients was compared following a period of AS.2 Within four years of the first positive biopsy, no significant difference was found between groups in the proportion of patients with PFS (54 versus 61 per cent for low and intermediate risk, respectively; \( p=0.22 \)) or in the proportion who underwent active treatment (30 versus 35 per cent for low and intermediate risk, respectively; \( p=0.88 \)).

These data suggest that managing selected intermediate-risk patients with AS seems a rational approach, and may provide an opportunity to reduce overtreatment of a disease that is unlikely to progress to advanced cancer.

The case

Dr Parker presented the case of a fit 63-year-old man with a clinical stage T1c, Gleason 3+4 adenocarcinoma in up to 4mm of 3/10 cores. Prostate-specific antigen (PSA) was 8ng/ml and the gland volume was 60cm³.

The debate

The group was asked to consider whether AS would be a reasonable option for this patient, using the keypad voting system to record their response.

Sixty-four per cent of clinical oncologists at the meeting responded that AS would be
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involves the patient in his own care. A positive way to extend patient choice and potentially fitter. This was seen as a intervention while he is younger and years, and to offer the option for early given risk that he will need RP within five years of AS, around 40–50 per cent of intermediate-risk patients had gone on to develop prostate cancer. The feeling was that surveillance seems to be moving away from PSA kinetics towards imaging protocols. In terms of biopsy, template biopsy was felt to be an improvement on transrectal ultrasound biopsy, but it was agreed that all biopsy procedures had shortcomings that would be circumvented only when improvements in imaging techniques rendered biopsy unnecessary.

A show of hands indicated that approximately equal numbers currently use and do not use MRI scans during AS. Dr Parker advocated the use of multi-parametric MRI integrating T2-weighted and diffusion-weighted imaging, possibly with dynamic contrast, as the best predictor of repeat biopsy results.

Additional unpublished data from the Royal Marsden NHS Trust presented by Dr Parker showed that after five years of AS, around 40–50 per cent of intermediate-risk patients had gone on to receive treatment for prostate cancer. This was discussed as an opportunity to explain to the patient on diagnosis that there is a given risk that he will need RP within five years, and to offer the option for early intervention while he is younger and potentially fitter. This was seen as a positive way to extend patient choice and involve the patient in his own care.

**Table 1. Response to question about active surveillance in the case presented**

<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
<th>% Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is active surveillance a sensible option?</td>
<td>Yes</td>
<td>64.4</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>13.3</td>
</tr>
<tr>
<td></td>
<td>Maybe</td>
<td>22.2</td>
</tr>
</tbody>
</table>

Locally Advanced Disease: Cardiovascular Risk and Hormones?

Dr Zafar Malik described the current controversy surrounding whether the use of hormonal treatment, in particular treatment with luteinising hormone-releasing hormone (LHRH) analogue therapy, increases the risk of cardiovascular (CV) morbidity and mortality in patients with locally advanced prostate cancer.

Treatment with LHRH analogues can give rise to a condition known as pseudo-metabolic syndrome, which differs in a number of important ways from the classical metabolic syndrome typically associated with obesity. For example, pseudo-metabolic syndrome tends to lead to sarcopenic obesity, in which lean muscle mass is lost from key areas such as the shoulders and paravertebral musculature, and fat tends to be deposited peripherally rather than centrally. Variations are also observed in terms of some laboratory parameters. For example, C-reactive protein levels are elevated in classical metabolic syndrome but not in pseudo-metabolic syndrome, while some studies have suggested that high-density lipoprotein levels actually rise with LHRH analogue therapy. However, changes in other parameters such as fat mass and total cholesterol appear to be consistent across both syndromes.

The clinical effect of pseudo-metabolic syndrome is not clear, with a large number of small studies offering apparently contradictory findings. In an observational study conducted by Keating in a population-based cohort of more than 70,000 patients aged 66 years or older, the hazard ratio for developing diabetes mellitus was shown to increase significantly by 44 per cent in patients who received LHRH analogue therapy compared with those without hormonal therapy (p<0.01), while the risk of coronary heart disease, myocardial infarction and sudden death increased significantly by 16 per cent (p<0.01), 11 per cent (p=0.03) and 16 per cent (p<0.01), respectively. A later update by Keating showed a similar effect was repeated among patients of all ages.

The results reported by Keating, however, are contrasted by a number of smaller studies in locally advanced prostate cancer, which showed no effect of androgen deprivation therapy on the risk of CV morbidity or mortality. The discrepancy between reported findings lies at the route of the controversy in this area.

Dr Malik concluded that any potential increased risk of CV events associated with hormone therapy cannot be considered in isolation but should be viewed within the context of the typical patient who may have independent competing risk factors. Furthermore, it should be considered that CV events in these patients can be managed medically and should not necessarily preclude the use of androgen deprivation therapy.

The case

Dr Malik presented the case of a 67-year-old obese man presenting with T3b N0, a Gleason score of 5+4, and a PSA of 17ng/ml. Comorbidities were type 2 diabetes mellitus, hypertension and a previous myocardial infarction, for which he had received a coronary artery bypass graft. Angina on exertion was controlled with medication. The patient had declined radiotherapy.

The debate

The group was asked to consider whether they would treat this man with hormonal therapy, whether the treatment given would be intermittent or continuous, and whether further monitoring (blood
pressure, lipid levels, fasting blood sugar, and weight) would be requested. The responses are summarised in Table 2.

It was observed that there is no randomised evidence to show that LHRH increases CV risk, with all evidence available being retrospective and open to potential bias. It was further queried whether hormonal therapy should even be given in these patients in the long term, as there is good level 1 evidence from a large multicentre study, EORTC 30981 (2006), in patients with newly diagnosed prostate cancer (T04 N02 M0), that immediate androgen deprivation offers no benefit in prostate cancer mortality or symptom-free survival over treating on disease progression.13

It was also observed that this population cannot be treated as a homogeneous group and that the patient’s comorbidities should be optimised and lifestyle choices improved. Finally, it was suggested that this issue will become less of a problem as we learn how to give intermittent androgen blockade therapy and as our experience grows with the next generation of androgen-depriving therapy.11

The discussion concluded with a presentation of guidelines from the American Heart Association, American Cardiac Society and American Urology Association, which recommend that patients should be referred to primary care for periodic follow-up and treatment, while men with pre-existing CV disease should have their secondary prevention treatment optimised.

**Declaration of interests**

The British Uro-oncology Group seminar ‘Hot topics for debate in prostate cancer’ was sponsored by Takeda. Takeda selected and briefed the speakers on the content of the session and they were paid an honorarium by Takeda. Takeda have had no editorial control over any publications arising from the meeting.

**REFERENCES**