Improving the awareness and understanding of modern prostate cancer management

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The choice of treatment options for prostate cancer continues to expand, particularly for advanced disease, where the options range from chemotherapies through to new biological approaches. Nevertheless, doctors are still faced with the dilemma of deciding which cancers at an earlier disease stage are of clinical significance and require treatment.

Hormonal therapy for prostate cancer is an evolving treatment, with common usage of luteinising hormone-releasing hormone (LHRH) agonist depot formulations and their accepted use both for advanced disease and as neoadjuvant or adjuvant therapy with radiotherapy. Another issue facing healthcare professionals in this area is the question of who manages the patient with advanced prostate cancer: the urologist or the oncologist?

ROLE OF ACTIVE SURVEILLANCE

With a focus on reducing the risk of overtreatment, a number of national and international guidelines proposed active surveillance as an alternative management strategy that can be considered in appropriate patients with low- and intermediate-risk localised prostate cancer (Figure 1). Low-risk prostate cancer is defined as stage cT1–T2a and PSA <10ng/ml and Gleason score ≤6,6,7 while intermediate-risk prostate cancer is defined as stage T2b–T2c, or PSA >10 to ≤20ng/ml, or Gleason score 7.1,7

The European Association of Urology (EAU) prostate cancer guidelines suggest that patients with low- and intermediate-risk, localised prostate cancer should be informed about the results of the randomised trial comparing radical prostatectomy with watchful waiting in localised prostate cancer.2 The study showed that the survival benefit was similar before and after nine years of follow-up and was confined to men <65 years of age.5 The number needed to treat to avert one death was 15 overall and seven for men aged <65 years. The National Comprehensive Cancer Network recommends active surveillance for prostate cancer patients with clinically localised disease that is at very low (T1c, Gleason score ≤6, PSA <10ng/ml, fewer than three biopsies positive with ≤50 per cent cancer in any core, PSA density <0.15ng/ml per g) or low (T1–T2a, Gleason score ≤6, PSA <10ng/ml) risk of recurrence.6 According to the NICE guidelines, active surveillance can also be discussed as an option for men with intermediate-risk localised prostate cancer.1

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Active surveillance involves follow-up with digital rectal examination, PSA and potentially repeat imaging and biopsies, although the optimal timing of follow-up is still unclear. Certain protocols recommend an initial frequency of three months and six months thereafter. In addition, the stimulus for patients moving off active surveillance to active treatment is primarily based on PSA progression (although this remains controversial), grade progression on repeat biopsy or progression on imaging.

**ROLE OF HORMONAL THERAPY ADJUVANT TO RADICAL RADIOTHERAPY**

High-risk, non-metastatic prostate cancer is defined as stage T3 or T4 (locally advanced) or localised disease (T1/T2) with a Gleason score 8–10 or PSA >20ng/ml. Active surveillance is not recommended in this patient group. NICE guidelines recommend adjuvant hormonal therapy for a minimum of two years in men receiving radical radiotherapy for locally advanced or high-risk localised prostate cancer. The EAU guidelines recommend hormonal therapy for three years in men receiving radical radiotherapy for high-risk localised (T1 or T2 with Gleason 8–10 or PSA >20ng/ml) and locally advanced prostate cancer (T3–T4 N0 M0).

The European Organisation for Research and Treatment of Cancer (EORTC) study 22863 demonstrated that immediate androgen suppression given during and for three years after external irradiation improved disease-free and overall survival of patients with locally advanced prostate cancer at 10 years. The benefits for overall survival of long-term adjuvant androgen deprivation therapy with radiotherapy have also been shown in the Radiation Therapy Oncology Group protocols 85-31 and 92-02. More recently, the EORTC 22961 trial provided a definitive observation that six months of androgen suppression in association with three-dimensional conformal radiotherapy resulted in inferior survival compared with...
Radical prostatectomy can be considered in these patients with low tumour volume provided that the tumour is not fixed to the pelvic wall, or if there is no invasion of the urethral sphincter. Adjuvant hormonal therapy may be considered in patients where nodal involvement has been detected after surgery.

**LUTEINISING HORMONE-RELEASING HORMONE AGONISTS**

In addition to its role in adjuvant therapy for locally advanced or high-risk localised prostate cancer, hormonal therapy is the mainstay of treatment for advanced prostate cancer and the first-line choice, as an alternative to bilateral orchidectomy, for newly diagnosed patients or those with relapsing metastatic prostate cancer.

One of the key treatments is the LHRH agonist. There are a number of different LHRH agonists available in the UK as one-, three-, six- or 12-monthly formulations, although the majority are prescribed as three-monthly injections. There is reasonable consensus demonstrating that longer-acting LHRH agonist formulations offer convenience to patients and physicians by reducing the injection frequency and, therefore, improving patient acceptability and treatment compliance. There are potential additional benefits to the use of the longer-acting formulations, for example in reducing the number of patient appointments, so releasing valuable clinical time.

The question of where the long-acting LHRH agonists are used in the management of prostate cancer patients remains an evolving concept. One UK patient survey conducted in 165 men with prostate cancer questioned patients’ preferences for the use of LHRH agonist depot. The six-month depot was the most popular choice in 104 (63 per cent) patients, followed by the three-month depot in 36 (21.8 per cent) patients and the yearly injections in 25 (15.2 per cent) patients. The EAU guidelines recommend that, following the initiation of hormonal treatment, patients are followed up at three months and then subsequently at six-monthly intervals for those with a good treatment response. Consequently the six-month depots might be considered the treatment of choice for patients with stable disease.

One area of controversy with the LHRH agonist is the definition of castrate levels of testosterone. The standard determination of castrate levels was defined as ≤0.5ng/ml more than 40 years ago, at a time when the sensitivity of available testosterone assays was limited. Currently unknown is the absolute minimal effective level of testosterone necessary to prevent prostate cancer growth and progression by the LHRH agonists. Current techniques using chemiluminescent assay methodology have reported a testosterone value of 0.15ng/ml after bilateral orchidectomy. The lowest level reported was 0.10ng/ml after medical castration.

There is expanding evidence from a number of studies to support resetting castrate levels to 0.2ng/ml. Perachino and co-workers presented a retrospective case series analysis of 129 consecutive patients with metastatic prostate cancer, which suggested a correlation between six-month serum testosterone level and the risk of death. Testosterone levels were measured every three months for the duration of the follow-up; mean follow-up was 47.5 months. Statistical analysis showed that in these patients the risk of death was directly correlated not only to Gleason score (p<0.01) and to the six-month PSA level (p<0.01), but also to the six-month serum testosterone level (hazard ratio 1.33, p<0.05). The authors concluded that lowering the testosterone level as much as possible should be the objective in patients with metastatic prostate cancer in order to maximise survival.

**MANAGING PATIENT CARE: THE TEAM APPROACH**

Treatment decisions for patients with metastatic prostate cancer are frequently based on the patient’s response to previous therapy, the number and duration of previous therapies and the speed of progression. There is, however, a lack of a standard approach to therapy, particularly for those with castrate-resistant prostate cancer. This topic is gaining in importance in light of the number of new agents that are becoming available for metastatic prostate cancer, including biological and chemotoxic treatments. This raises the important issue of who should manage the patient at this stage of his disease; whether his care remains under the control of the urologist or moves to an oncologist, or whether a team approach should be adopted to maximise the quality of care.

A postal survey of 51 oncologists and 63 urologists was conducted in 2010 by the British Uro-Oncology Group and the British Association of Urological Surgeons Section of Oncology to determine the management practices and the involvement of multidisciplinary teams (MDTs). Although most responses to the survey indicated that decisions were made jointly by the two specialties, it appeared that most oncologists expected the sole responsibility to lie within their own specialty. In contrast, it was the opinion of 70 per cent of urologists that joint responsibility was needed.

The NICE prostate cancer guidelines also recommend that when men with prostate cancer develop biochemical evidence of castrate resistance, their treatment options should be discussed by a urological cancer MDT, which includes urologists, oncologists and specialist nurses, with a view to seeking an oncological and/or specialist palliative care opinion, as appropriate.
**Declaration of interests**

Ipsen Ltd provided financial sponsorship for this article but had no editorial control over the content. Editorial support was provided by Medscimedia Ltd. Heather Payne has attended and received honoraria for advisory boards and served as a consultant for Teva, Astra Zeneca, Janssen, Johnson and Johnson, Sanofi Aventis, Takeda, Ferring and Novartis. Mike Kirby has received funding from the pharmaceutical industry for research, lecturing, conference attendance and advice.

**REFERENCES**


**KEY POINTS**

- Prostate cancer treatment is an evolving process at all stages of the disease. Nevertheless, active surveillance is a recommended treatment option for low- and intermediate-risk localised prostate cancer
- Advances have been made in the management of locally advanced disease with the recommendation of hormonal therapy as adjuvant to radiotherapy for a minimum of two years
- Depot formulations of the luteinising hormone–releasing hormone agonists are routinely used and offer convenience to both patient and physician.
  Survey results indicate patient preference for the six-month depot
- The multidisciplinary team approach to prostate cancer treatment is recommended by NICE and the British Uro-Oncology Group, with the involvement of urologists, oncologists and specialist nurses


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