First-Line Hormonal Manipulation of Prostate Cancer

18

Suresh Venugopal and John Anderson

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S. Venugopal, M.S., MRCS • J. Anderson, ChM, FRCS (✉)
Department of Urology, Royal Hallamshire Hospital, Sheffield, UK
e-mail: john.anderson@sth.nhs.uk; johnanderson@clara.co.uk

18.1 History of Hormone Manipulation

Little did the Flemish anatomist Andreas Vesalius know that the prostate gland he had illustrated for the first time in 1543 in De humani corporis fabrica would assume such importance. In 1853, the British surgeon John Adams described 'A case of scirrhus of the prostate gland with a corresponding affection of the lymphatic glands in the lumbar region and in the pelvis' and had judged this to be a rare disease (Denmeade and Isaacs 2002). Prostate cancer is now recognised to be the most common cancer in men with 258,000 men dying worldwide from the disease in 2008 (Ferlay et al. 2010).

The dependence of the prostate gland on testosterone had been first recognised in 1786 by John Hunter who found removing the testicles from young male animals prevented growth of the prostate (Hunter 1786). In 1941, Charles Huggins and Clarence Hodges confirmed that prostatic cancer is dependent for its growth on androgen activity in the body and that disseminated carcinoma of the prostate could be inhibited by eliminating androgens, either through surgical castration or neutralisation of their activity by oestrogen injection (Huggins and Hodges 1941). It was not until 1971, however, that Andrew Schally identified the complete peptide sequence of endogenous leutinising hormone-releasing hormone (LHRH) which is produced in the hypothalamus (Schally et al. 1971) and responsible for luteinising hormone (LH) secretion in the anterior pituitary which prompts the Leydig cells in the testis to produce testosterone.

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From there, he went on to develop synthetic analogues which formed the basis for medical castration therapies. Achieving these two important milestones resulted in Charles Huggins and Andrew Schally each being awarded the Nobel Prize for Medicine and Physiology in 1966 and in 1977, respectively, and, to date, they remain the only Nobel Prizes awarded in the field of urological practice. Today, in 2012, hormone manipulation remains the first line and mainstay of treatment for men with metastatic prostate cancer (Baker et al. 2008; Heidenreich et al. 2011).

18.2 Physiology of Hormone Manipulation

A full understanding of the hypothalamic–pituitary–gonadal axis has allowed different means of testosterone suppression or control to be developed for the treatment of prostate cancer. LHRH is produced by the neuroendocrine cells in the hypothalamus and stimulates the anterior pituitary gland to release LH. This in turn stimulates the Leydig cells in the testis resulting in the secretion of testosterone. Testosterone production acts as negative feedback on the hypothalamus to maintain normal testosterone levels in the body. Thus, manipulation of testosterone levels to control prostate cancer growth can be achieved in one of the three ways (Fig. 18.1) (Anderson 2003):

1. Surgical removal of the testes where the testosterone is produced
2. Disruption of the hypothalamic–pituitary–gonadal axis to reduce testosterone secretion by the testis
3. Direct block of the androgen receptors in the prostate itself to counteract the effects of circulating testosterone

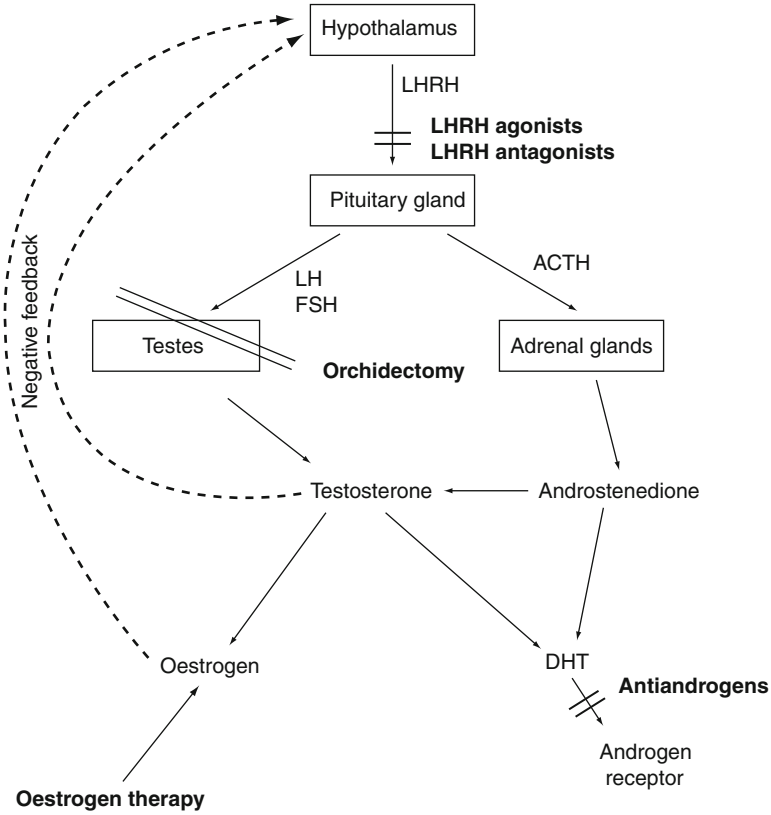

Fig. 18.1 The hypothalamic–pituitary–gonadal axis showing the site of action of the hormonal therapies for prostate cancer. *LHRH* luteinising hormone-releasing hormone, *LH* luteinising hormone, *FSH* follicle-stimulating hormone, *ACTH* adrenocorticotrophic hormone, *DHT* dihydrotestosterone

Table 18.1 Comparative studies of hormonal therapy in patients with metastatic prostate cancer (Anderson 2003)

Hormone therapy	Comparator	Patients	Duration of follow-up (months)	Overall survival outcome	Reference
Goserelin 3.6 mg per 28 days	Bilateral orchidectomy	358	Median 24	Median: 110 vs. 99 weeks	Kaisary et al. (1991)
Goserelin 3.6 mg per 28 days	Bilateral orchidectomy	283	Median 48	Median: 119 vs. 136 weeks	Vogelzang et al. (1995)
Bicalutamide 150 mg per day	Castration	852	Median 23	Median: 105 vs. 111 weeks	Tyrrell et al. (1998)
Flutamide 250 mg tds	Bilateral orchidectomy	104	Minimum 36 (median 69)	No difference	Boccon-Gibod et al. (1997)
Polyoestradiol phosphate	MAB	915	Median 18.5	Deaths: 58.1% vs. 58.9%	Hedlund and Henriksson (2000)

18.3 First-Line Hormone Manipulation of Prostate Cancer: The Therapeutic Options

18.3.1 Surgical Castration

Bilateral orchiectomy removes the testicular source of androgens and rapidly leads to castrate levels of testosterone. It is considered the gold standard therapy for hormone manipulation against which all other modalities of treatment are judged (Griffiths 1993) (Table 18.1). Surgical castration is the preferred therapeutic option in patients in whom the testosterone levels need to be rapidly lowered to avoid serious consequences from complications of advanced disease such as spinal cord compression or renal failure. This procedure rapidly lowers testosterone to very low levels (mean 15 ng/dL) (Oefelein et al. 2000) and not only reduces the painful symptoms of the disease but also slows overall cancer progression. Although orchidectomy may be reliable, economical, simple and safe to perform, it is not a popular option for men with prostate cancer due to the psychological effects associated with permanently losing one's manhood and the inevitable and irreversible adverse impact on libido and potency (Anderson 2003). Equivalent levels of testosterone suppression and oncological control by medically based castration therapies have resulted in limited use of orchidectomy in routine urological practice (Mcleod 2003).

18.3.2 Medical Castration

Medical castration is now the treatment of choice for men with advanced prostate cancer both by the patients themselves and by their doctors.

The following drugs are available to use in this context:

18.3.2.1 Diethyl Stilbesterol (DES)

The mechanism of action of oestrogens is complex. They act not only by reducing the secretion of LHRH, and thereby LH and testosterone (Fig. 18.1), but also by androgen inactivation and by direct suppression of Leydig cells. In addition, synthetic oestrogens have a suppressive effect on dihydroepiandrosterone sulphate (DHEA), which is the precursor for adrenal androgen production (Kitahara et al. 1997; Miyamoto et al. 1998) and may also be directly cytotoxic to the prostatic epithelium as noted in in vitro studies (Oh 2002). The Veterans' Administration Cooperative Urological Research Group studies in the 1960s showed that oestrogens achieved comparable cancer control to surgical castration but, at a dose of 5 mg/day, DES is likely to cause significantly more cardiovascular morbidity and even mortality (Byar 1973). With the advent of LHRH analogues and antiandrogens which do not carry the same risk of cardiovascular toxicity, the use of oestrogens has fallen out of favour.

Despite various attempts to overcome the cardiovascular toxicity of oestrogens, including parenteral administration of polyoestradiol phosphate

(PEP) and the use of antithrombotic medication such as low-dose aspirin or warfarin, ongoing concerns regarding cardiovascular complications have prevented the return of oestrogens into mainstream practice (Hedlund et al. 2008; Heidenreich et al. 2011; Seidenfeld et al. 2000).

18.3.2.2 LHRH Analogues

Buserelin was the first LHRH analogue to be used to treat prostate cancer. It is administered by subcutaneous injection for the first week followed by intra-nasal spray every 4 h but rapidly fell out of favour due to the frequency and less than optimal route and frequency of administration (Mcleod 2003). The newer LHRH analogues have the convenience of monthly or three monthly (goserelin, leuprorelin, triptorelin) or in some cases half-yearly (leuprorelin) and annual (histerelin) depot preparations. Their efficacy has been found to be to be equal to surgical castration or that of DES (Anderson 2003; Kaisary et al. 1991; Vogelzang et al. 1995).

Synthetic LHRH analogues work by acting as a competitive agonist at the LH receptors in the pituitary, and before they saturate the receptors, they initially stimulate the production of LH from the pituitary gland. Administration of LHRH analogues therefore causes an initial rise, or 'surge', in serum testosterone levels which can result in a 'flare' in clinical symptoms (Waxman et al. 1985). This effect can be minimised by the concurrent administration of antiandrogens started prior to the first injection of the LHRH analogue and continued for 1–2 weeks thereafter. Whilst the significance of this clinical flare in patients with extensive disease, or in those with significant back pain or early neurological sequelae, is undoubted (Thompson 2001; Waxman et al. 1985); we also need to consider whether this surge in the testosterone levels may also cause a subclinical stimulus to cancer growth.

18.3.2.3 GnRH Antagonists

Gonadotropin-releasing hormone (GnRH) antagonists are a more recent development, and their mechanism of action is quite different to that of the analogues. Rather than act as competitive agonists with the endogenous LHRH in the pituitary, they are genuine antagonists which immediately block the receptors, thereby blocking LH release and testosterone production and avoiding the initial testosterone surge seen with the LHRH agonists. Unlike the analogues, these agents also cause a reduction in FSH secretion from the pituitary, the significance of which is uncertain. GnRH blockers cause a rapid and profound fall in the testosterone levels, comparable with surgical castration, something which is not achieved by LHRH analogues for up to 28 days. The adverse event profile for these agents is small (Klotz et al. 2008) and whilst the use of the GnRH blocker abarelix has been restricted because of potential hypersensitivity reactions (Trachtenberg et al. 2002), degarelix has been licensed for use in the treatment of metastatic and symptomatic prostate cancer (Klotz et al. 2008) both in Europe and North America.

18.3.2.4 Antiandrogens

Steroidal antiandrogens such as cyproterone acetate and nonsteroidal agents such as flutamide, bicalutamide or nilutamide may be used either as monotherapy or else as part of a combined treatment regime together with an LHRH agonist. The nonsteroidal drugs are purely antiandrogenic and only block the androgen receptors in the prostate. When used on their own, nonsteriodal antiandrogens ensure preservation of normal circulating levels of testosterone and therefore have potential quality of life benefits in terms of maintaining potency and libido (Iverson et al. 2001). In addition to their antiandrogen properties, the steroidal antiandrogens also have central progestational effects, resulting in suppression of LH and thereby resulting in lower circulating testosterone levels leading to impotence and loss of libido (Anderson 2003). Their use has been limited by their liver (Parys et al. 1991) and possible cardiovascular toxicity (Seaman et al. 2007).

The use of flutamide is limited by excessive gastrointestinal side effects, but bicalutamide monotherapy has been extensively investigated and is known to have equivalent efficacy to LHRH agonists at a dose of 150 mg/day for patients with locally advanced prostate cancer (Iversen et al. 2000). Despite the better quality of life offered by bicalutamide, however, patients with metastatic prostate cancer have a reduced overall survival by

42 days compared to those treated with LHRH agonists, and for this reason, bicalutamide is not licensed for treating patients with metastatic disease.

18.3.3 Combined Androgen Blockade (CAB)

The persistence of low levels of circulating androgens from the adrenal glands was thought to be responsible for prostate cancer progression despite castration by surgical or medical means, and combining orchidectomy or LHRH analogues with an antiandrogen was considered to be the most effective means to combat the effects of these androgens at the level of androgen receptor in the prostate gland (Akaza 2011; Schmitt et al. 2001). Many randomised trials have sought to clarify the validity of this assumption and have compared either orchidectomy or LHRH analogues in combination with an antiandrogen or placebo (Eisenberger et al. 1998; Prostate Cancer Trialists' Collaborative Group 2000). A large meta-analysis of 8,275 patients from 27 studies concluded that CAB has a minimal overall 5-year survival benefit of between 2% and 5% (Prostate Cancer Trialists' Collaborative Group 2000). The side effects from combination therapy are increased due to the addition of antiandrogens and against this have to be balanced the benefit to be derived after 5 years of therapy. The number of men who have to be treated with combined androgen blockade for 5 years to prevent one additional death from prostate cancer is between 20 and 100, and this is at a cost of more than US$1 million per quality-adjusted life-year for CAB over orchidectomy alone (Loblaw et al. 2007), and it has been suggested that CAB is not used as standard therapy for first-line management of advanced prostate cancer but reserved for the failures of initial monotherapy (Miyamoto et al. 2004).

18.3.4 Intermittent Androgen Deprivation Therapy (IAD)

It has been hypothesised that if an androgen-dependent tumour which regressed following androgen withdrawal was re-exposed to androgens again, it would regain its potency for apoptosis, thereby retaining its androgen-dependent status for longer (Akakura et al. 1993; Klotz et al. 1986; Suzuki et al. 2010). Animal studies have certainly shown that androgen dependency was maintained for longer using intermittent androgen deprivation therapy (Akakura et al. 1993).

Quite apart from the theoretical advantage of prolonging androgen dependence, there can also be a very real advantage to intermittent therapy by reducing the adverse effects associated with that treatment. Whilst the long-term side effects of ADT such as osteoporosis, metabolic syndrome, cardiovascular toxicity, hot flashes and fatigue can be minimised, 'holidays' from treatment may also allow men to recover sexual function, during periods off treatment (Suzuki et al. 2010). In a recent review, 19 phase two studies and 8 phase three studies were analysed for quality of life issues and the potential benefits of intermittent androgen deprivation therapy. It was found that the oncological outcomes for intermittent ADT were at least as good as continuous ADT, but when it came to quality of life (QoL), especially recovery of sexual function, intermittent therapy was superior to continuous treatment (Abrahamsson 2010).

Although the superiority of IAD over continuous ADT, in terms of oncological control, may never be demonstrated, the results of two large randomised controlled trials (NCIC PR7 and SWOG 9346) are awaited to ascertain the quality of life benefits of intermittent therapy (Buchan and Goldenberg 2010).

18.4 When Is It Right to Commence Hormone Therapy?

18.4.1 Symptomatic Metastatic Disease

Symptomatic metastatic prostate cancer remains an absolute indication for immediate hormone manipulation, and successful outcomes for such patients treated with immediate ADT were confirmed from the VACURG studies nearly five decades ago (The Veterans Administration Cooperative Urological Research Group 1967).

The choice of ADT when treating patients with serious complications such as impending spinal cord compression or pathological fracture is determined by the requirement for a very rapid reduction in the levels of serum testosterone, and this can be achieved most effectively either by surgical castration (with castrate testosterone levels achieved at a mean 8.3 h) (Lin et al. 1994) or GnRH antagonists (Klotz et al. 2008). Whilst randomised controlled trials to confirm the benefits in this setting would be clearly inappropriate, we know that immediate hormonal therapy helps to achieve the best and quickest palliation of symptoms in patients with symptomatic metastases and reduces their risk from complications of the disease (Heidenreich et al. 2011).

18.4.2 Asymptomatic Metastatic Disease

The best time to commence ADT in men with metastatic disease who are asymptomatic is the night before they develop symptoms, but this is clearly impossible to predict (Kirk 2000). Although the outcomes in terms of overall survival have not been shown to be inferior to those in whom treatment was deferred until they become symptomatic (Nair et al. 2002; Walsh et al. 2001), patients commenced on ADT at the time of diagnosis went on to develop fewer complications such as pathological fractures, cord compression, ureteric obstruction or the need for TURP for bladder outflow obstruction (Kirk 2000). The choice of ADT in this group of patients, as well as the merits of continuous or intermittent treatment, has already been discussed in Sects. 18.3.3 and 18.3.4.

18.4.3 Lymph Node Only Metastatic Disease (M0 N1-3 Any T)

The pathological detection of lymph node metastases in men undergoing radical prostatectomy with curative intent has decreased over the years (Haese et al. 2002). Evidence to support the optimal management of this group is necessarily limited and was provided by the ECOG trial from 36 institutions in the United States where 100 patients with positive lymph nodes identified after radical prostatectomy for clinically localised prostate cancer were assigned to receive either immediate ADT (medical or surgical castration) or their treatment was deferred until they developed metastases confirmed on a bone scan. With a median follow-up of 11.9 years, this trial showed better outcomes for those treated at diagnosis in terms of overall, cancer-specific and progression-free survival (Messing et al. 2006). By contrast, another retrospective analysis showed no difference in overall survival between those who started immediate ADT after surgery, compared to those who received salvage ADT based on biochemical failure or disease progression (Gjertson et al. 2007), whilst in the EORTC 30846 study, patients confirmed to be node positive, and in whom no primary treatment was given to the prostate, no significant difference was identified between those receiving immediate versus delayed ADT with 13 years of follow-up (Schröder et al. 2009).

18.4.4 Locally Advanced Nonmetastatic Disease (M0 N0 T3/4)

The gold standard for treatment in patients with locally advanced disease but no evidence of nodal or skeletal spread is radical external beam radiotherapy in conjunction with 3 years of ADT (Bolla et al. 2010; Pilepich et al. 2005; Widmark et al. 2009).

In conjunction with radiotherapy, the use of ADT has unequivocally been shown to improve outcomes for patients on all counts in several trials (Bolla et al. 2010; Pilepich et al. 2005; Widmark et al. 2009). In the EORTC 22863 trial of external beam radiotherapy (ERBT) versus ERBT and ADT in patients with locally advanced prostate cancer, the 10-year clinical disease-free survival was 22.7% in the ERBT group and 47.7% in the combined treatment group, whilst prostate cancer mortality was 30.4% versus 10.3%, overall survival was 39.8% versus 58.1% with no evidence of increasing late cardiovascular toxicity

related to the ADT component of treatment (Bolla et al. 2010).

The Scandinavian prostate cancer group trial (SPCG7) specifically questioned the benefits of adding radiotherapy to immediate ADT. The prostate cancer-specific mortality at 10 years was 23.9% in the ADT alone group and 11.9% in the combined ADT and ERBT group with similar results for the overall mortality (39.4% versus 29.6%). Although urinary, rectal and sexual complications were slightly more common in the combined treatment group after 5 years, the addition of local radiotherapy to immediate ADT halved the 10-year prostate cancer-specific mortality and substantially decreased overall mortality with fully acceptable risk of side effects compared with immediate ADT alone (Widmark et al. 2009).

There is increasing interest in radical surgery as part of a multimodality approach to treatment in patients with locally advanced prostate cancer but a relatively low PSA and Gleason score. As with those patients treated with ERBT, these cases have also been shown to benefit from adjuvant ADT following surgery (Freedland et al. 2007; Schreiber et al. 2011).

ADT alone for men with locally advanced non-metastatic disease is best reserved for those who are not fit for radiotherapy, those who have bulky disease with a high PSA and a PSA doubling time of less than 1 year or in those who are symptomatic from the disease (Heidenreich et al. 2011).

18.4.5 Localised Disease (M0 N0 T1/2)

Despite the evidence to suggest that androgen deprivation is not the treatment of choice for men with localised prostate cancer, there has been a two- to threefold increase in the frequency of administration of ADT in this group of men over the last two decades (Cooperberg et al. 2003). There is no survival advantage for using primary ADT, with its unwanted systemic effects and side effects over local treatment such as radical prostatectomy or radical radiotherapy (Akaza 2006; Messing et al. 2006). Nevertheless, patients with localised disease who are deemed unsuitable for treatment with curative intent for whatever reason may eventually become a suitable candidate for ADT if symptoms develop or if their cancer progresses. The question which has to be addressed therefore is the ideal time when this treatment should be initiated. A population-based study of 19,271 men with localised prostate cancer comparing those who received ADT to those who were monitored until symptomatic progression showed that in men with poorly differentiated tumours, cancer-specific survival, but not overall survival, was improved with primary ADT (Lu-Yao et al. 2008). This benefit could not be demonstrated in patients with low-risk cancers (Messing et al. 2006). Considering the potential adverse effects associated with ADT, one should be mindful that any such treatment in this patient group should be individualised, and wherever possible, they should be offered a treatment with curative intent.

Again, the decision as to when to initiate ADT in men with a rising PSA after failed primary treatment can be a difficult one. The evidence to help us guide patients for the best depends on the grade and stage of the original tumour and the PSA kinetics following treatment (Anderson 2008; Studer et al. 2008), but the wishes of the patients can often confound this evidence-based approach to treatment.

Neo-adjuvant ADT in conjunction with radical prostatectomy has not shown any reduction in cancer recurrence rates after surgery although the positive surgical margin rates are reduced (Soloway et al. 2002). Adjuvant ADT for adverse histopathological findings following prostatectomy confers no survival advantage as noted in a recent Cochrane review (Kumar et al. 2006). By contrast, in conjunction with radiotherapy for localised prostate cancer, ADT is used both in the neo-adjuvant and adjuvant settings, and EORTC 22961 results have shown a definite overall survival advantage for both short- and medium-term ADT with the 3-year medium-term treatment providing superior outcomes (Bolla 2010; Poppel 2008).

Even after definitive curative treatment, pathologically confirmed stage T1 and T2 disease can

be associated with biochemical or clinical recurrence in up to 35% of patients (Freedland et al. 2005).

18.4.6 Summary

For patients with asymptomatic metastatic or locally advanced prostate cancer, the important question is: when should one initiate ADT? Information from the EORTC 30891 study of immediate versus deferred ADT in patients with advanced nonmetastatic prostate cancer provides helpful guidance for doctors and patients alike and can be extrapolated to guide the management of patients with a rising PSA after failed local treatment depending on the stage and grade of the primary tumour.

- Patients with a PSA at diagnosis of >50 ng/mL are likely to eventually die of prostate cancer and are therefore appropriate candidates for immediate ADT to prevent complications from progressive disease.
- Patients with a baseline of <8 ng/mL are at very low risk of dying from prostate cancer within 7 years of diagnosis and may never require ADT.
- For those with a PSA between 8 and 50 ng/mL, ADT should be initiated as soon as a PSA doubling time of <12 months is identified (Anderson 2008; Studer et al. 2008).

18.5 Side Effects and Quality of Life Issues

The first commandment for us as doctors is 'Primum non nocere' – 'First do no harm'. Despite the beneficial effects in terms of oncological control for ADT, one must be mindful of the potentially deleterious consequences and side effects of this form of treatment. The side effect profile of any form of hormonal manipulation in the short term is predictable and includes reduction in libido and sexual function. Of the various forms of therapy, nonsteroidal androgen monotherapy with bicalutamide would seem to provide the best chance at minimising these effects (Heidenreich et al. 2011; Iverson et al. 2001). Less predictable side effects such as hot flashes with LHRH analogues can be countered by the use of a progestational agent such as CPA or medroxyprogesterone (Irani et al. 2010). Patients on antiandrogens report breast swelling in up to 71% of cases (Higano 2003). This can be managed by tamoxifen or radiotherapy to the breast tissue prior to the initiation of treatment (McLeod and Iversen 2000).

In the longer term, side effects of ADT include osteoporosis, obesity, hyperlipidemia, insulin resistance, metabolic syndrome, diabetes and cardiovascular disease (Isbarn et al. 2009). The loss of bone mineral density is associated with an increased risk of osteoporotic fracture in up to 45% of patients (Smith et al. 2006), and this can have major significance as hip fractures in men are associated with a significant risk of death (Cree et al. 2000). The risk can be minimised by increasing physical activity, resistance-based exercise and the use of bisphosphonates or the monoclonal antibody denosumab (Heidenreich et al. 2011). Furthermore, metabolic syndrome (waist circumference >102 cm, serum triglyceride >1.7 mmol/L, blood pressure >130/80 mmHg, HDL cholesterol <1 mmol/L and glycaemia >6.1 mmol/L) has been identified in up to 50% of men on ADT, and this is thought to be one of the factors contributing to the possible increased cardiovascular comorbidity associated with ADT (Braga-Basaria et al. 2006). Whilst cardiovascular comorbidity with DES usage is well recognised, there is now increasing evidence to suggest that other forms of ADT may have similar consequences (Jones 2011; Saigal et al. 2007).

Any reduction in the overall QoL with ADT can be responsible for patients discontinuing ADT, and a lower QoL is reported in patients on therapy even after only 6 months of treatment (Saylor and Smith 2010). Although there are clear benefits in terms of better oncological outcomes with different types of ADT, more research is required to evaluate the full implications of the side effects of treatment so that we can recommend the right form of ADT for the right patient at the right time.

Indications for hormonal therapy: EAU guidelines (Hedlund and Henriksson 2000)

Hormonal therapy Indications for castration	Benefits
M1 symptomatic	To palliate symptoms and to reduce the risk for potentially catastrophic sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction, extra-skeletal metastasis) Even without a controlled randomised trial, this is the standard of care and must be applied and considered as level 1 evidence
M1 asymptomatic	Immediate castration to defer progression to symptomatic stage and prevent serious disease progression-related complication An active clinical surveillance protocol might be an acceptable option in clearly informed patient if survival is the main objective
N+	Immediate castration to prolong progression-free survival and even overall survival Might be questioned in single micrometastasis after extended lymph node dissection and radical prostatectomy
Locally advanced M0	Immediate castration to improve cancer-free survival
Locally advanced disease treated with radiotherapy	High risk d'Amico: combined and prolonged ADT Intermediate risk d'Amico If low dose (<75 Gy) RT: 6 months ADT If high dose (>75 Gy) RT: ADT questionable
Locally advanced asymptomatic unfit for local definitive treatment	Limited overall survival improvement not related to a cancer-specific survival benefit
Antiandrogens	
Short-term administration	To reduce the risk of 'flare' phenomenon in patients with advanced metastatic disease who are to receive an LHRH agonist
Nonsteroidal antiandrogen monotherapy	Primary monotherapy as an alternative to castration in patients with locally advanced prostate cancer (T3–4, any N or any T) No place in localised disease as a single treatment modality Combined with radiotherapy: no clear recommendation is possible at the present time Combined with radical prostatectomy: no place so far in an adjuvant setting

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