Managing locally advanced prostate cancer: a urologist's and a patient's perspective

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A 60-year-old man presented to his general practitioner with prostatic symptoms and high blood pressure. Based upon a prostate-specific antigen level of 44 ng/ml and further investigations (digital rectal examination, transrectal ultrasound-guided needle biopsy, and magnetic resonance imaging, ultrasound and bone scans), the patient was diagnosed with locally advanced (cT3, N0, M0) prostate cancer. Here, the urologist and the patient describe treatment from their respective viewpoints. Following discussion of the advantages and disadvantages of the various therapeutic options, radiotherapy plus hormonal therapy (bicalutamide 150 mg) was chosen as the approach that best suited the patient's lifestyle. In this review, the patient and the urologist consider the impact of the chosen treatment in terms of efficacy, tolerability and quality of life. ***Anti-Cancer Drugs*** **17:245–250 © 2006 Lippincott Williams & Wilkins.**

Anti-Cancer Drugs 2006, **17**:245–250

Keywords: adjuvant hormonal therapy, bicalutamide, locally advanced, prostate cancer, radiotherapy

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Sponsorship: Financial support was provided by AstraZeneca (Casodex and Zoladex are trademarks of the AstraZeneca group of companies).

Received 7 October 2005 **Accepted** 11 November 2005

Urologist's perspective

I first met Nigel, a 60-year-old hospital manager and former surgeon, when his general practitioner (GP) referred him to me in 2004. Prior to this, he had a 2-year history of lower urinary tract symptoms (increased frequency, reduced flow, urgency, with occasional incontinence) and perineal discomfort, which he had assumed was due to chronic prostatitis and had tried to ignore. However, the discovery of signs of raised blood pressure during a routine ophthalmological examination eventually prompted him to visit his GP. In addition to his raised blood pressure (145/95 mmHg), he was found to have a prostate-specific antigen (PSA) level of 44 ng/ml. By the time he saw me, he had undergone further investigations (digital rectal examination, transrectal ultrasound-guided needle biopsy, and magnetic resonance imaging, ultrasound and bone scans) which revealed cT3, N0, M0 prostate cancer with a Gleason score of 7 (4 + 3), determined from four (of eight) positive biopsy cores.

For patients with a diagnosis of clinically locally advanced prostate cancer, as in Nigel's case, the 15-year disease-specific survival rate is 57% [1]. Such patients are therefore generally offered treatment to improve their prognosis. A number of treatment options are available, each of which can impact very differently on the patient's quality of life. When making treatment decisions, it is therefore important to consider not only the patient's risk profile, but also factors such as his age, life expectancy, level of sexual and physical activity, lifestyle, and treatment preference. To promote long-term adherence to therapy, the patient should be encouraged to play an active role in the treatment decision-making process, and should be made aware of the advantages and disadvantages of each treatment option. Nigel's treatment options and choices are summarized in Fig. 1.

After I explained to Nigel that he had locally advanced prostate cancer, we talked through the available treatment options. Active surveillance/watchful waiting is a choice for asymptomatic patients with well or moderately differentiated locally advanced disease and a short life expectancy [2], but was not, in my opinion, suitable for a symptomatic, relatively young patient such as Nigel. We discussed radical prostatectomy, which is an option for patients with long life expectancy, limited extracapsular extension, Gleason score < 8 and PSA level < 20 ng/ml [2]. However, given Nigel's high PSA level, I could not recommend surgery as the best option in his case, because of the low probability of cure. Radiotherapy has traditionally been the mainstay of treatment for locally advanced disease, but 22–64% of patients who receive radiotherapy alone experience clinical progression and 32–43% die within 5 years of treatment [3–5]. Although techniques such as three-dimensional conformal radiotherapy have resulted in improved outcomes and reduced treatment toxicity [6], it is now widely accepted that the addition of hormonal therapy to radiotherapy (irrespective of the dose and technique used) provides improved outcomes in patients with locally advanced disease [2].

I therefore advised Nigel to undergo external-beam radiotherapy in combination with neoadjuvant hormonal

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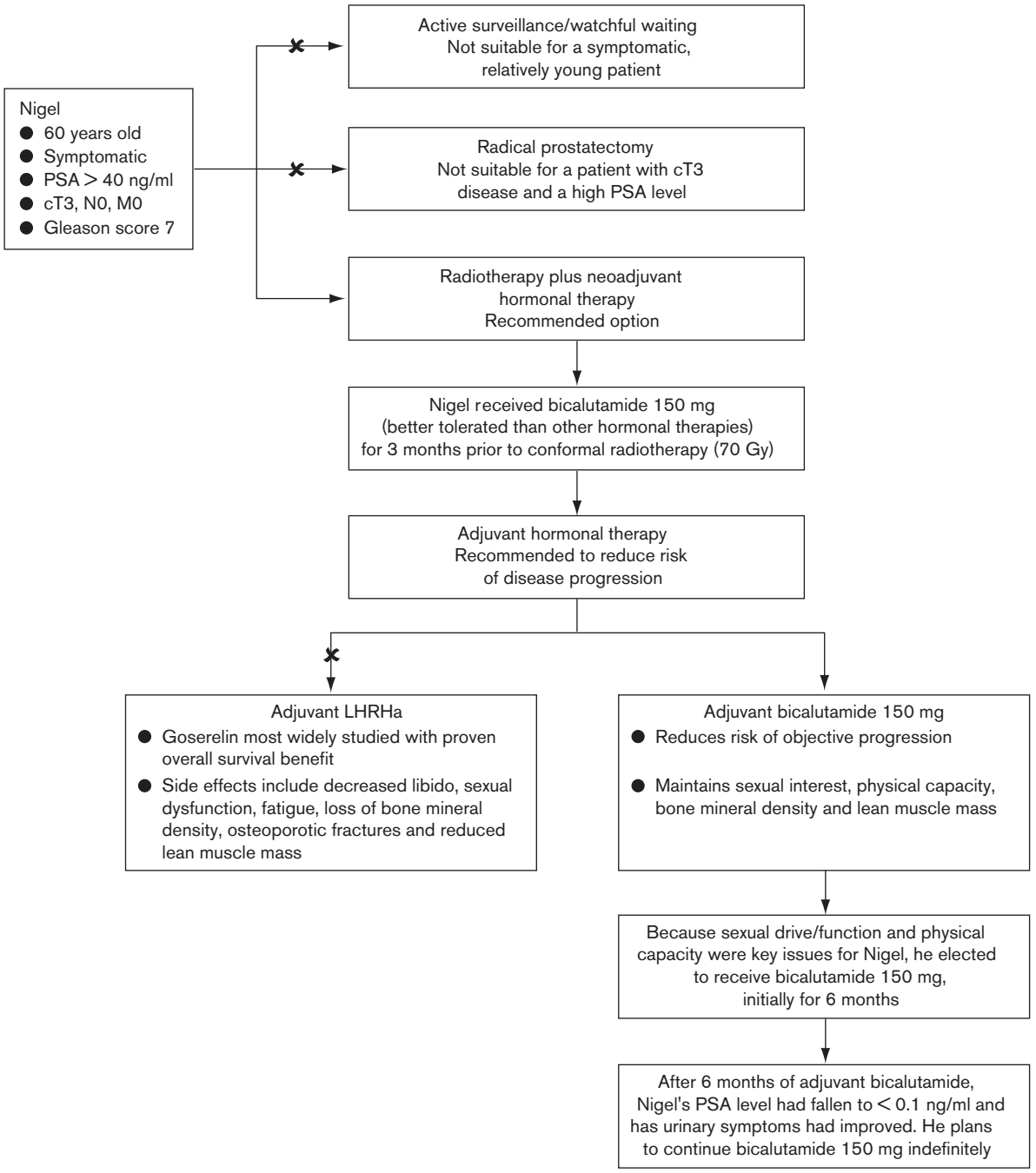
Fig. 1



Flow chart summarizing Nigel's treatment options and choices.

therapy for the first stage of his treatment. Neoadjuvant hormonal therapy has been shown to reduce the size of the prostate prior to radiotherapy, thus facilitating primary treatment by decreasing the amount of normal tissue irradiated [7,8]. Moreover, data from some randomized, controlled trials suggest that patients who receive neoadjuvant hormonal therapy [luteinizing hormone-releasing hormone agonist (LHRHa)-based therapy] may be more likely to remain free from clinical progression than those who receive radiotherapy alone [9,10]. Although non-steroidal anti-androgen monotherapy has not yet been investigated in the neoadjuvant setting, the non-steroidal anti-androgen bicalutamide has been shown to provide similar clinical benefits compared with castration as immediate therapy in patients with locally advanced disease [11].

Nigel received bicalutamide (Casodex) 150 mg/day orally for 3 months prior to radiotherapy. Bicalutamide was selected over other hormonal therapies due to its favorable tolerability profile, which will be discussed in detail later in this review. By the end of the neoadjuvant treatment period, his PSA level had decreased to 10 ng/ml, his prostate volume had decreased by 20% and his lower urinary tract symptoms improved. Conformal radiotherapy was then given every week day for 7 weeks (total dose 70 Gy). During radiotherapy, he again developed urinary problems including urgency and incontinence, which started to improve toward the end of the treatment course, and was also troubled by rectal symptoms (Common Toxicity Criteria grade 2) including tenesmus. Acute urinary and rectal symptoms are common in patients receiving radiotherapy, occurring in up to 80% of cases [12,13]. As Nigel showed signs of depression related partly to his diagnosis, he accepted the offer of counseling. It is not unusual for patients to develop depression when diagnosed with prostate cancer. Indeed, a study has found that 8–46% of patients report major depressive symptoms and 13–45% report anxiety reactions within the first few months after diagnosis [14].

Once Nigel had finished his radiotherapy treatment, we revisited his prognosis and the options available. There is now convincing evidence from randomized, controlled trials that adjuvant hormonal therapy provides clinical benefits and improved survival in patients who have received radiotherapy for locally advanced disease [15–18] (Table 1). Options for adjuvant hormonal therapy include either a LHRHa or the non-steroidal anti-androgen, bicalutamide 150 mg. Of the LHRHas, goserelin (Zoladex) is the most widely studied in this setting. Long-term data from the Radiation Therapy Oncology Group (RTOG) 85-31 trial, involving nearly 1000 patients with locally advanced prostate cancer, have shown that adjuvant goserelin continued until disease progression plus radiotherapy significantly improves overall survival and clinical progression-free survival compared with radiotherapy alone [16] (Table 1 and Fig. 2). These findings are supported by results from a second large study in which adjuvant goserelin was given for 3 years following radiotherapy [15] (Table 1). Moreover, a third relatively large study indicated that adjuvant goserelin significantly improved clinical progression-free survival compared with no adjuvant therapy in patients who had received radiotherapy and neoadjuvant hormonal therapy (goserelin plus flutamide for 2 months before and 2 months during radiotherapy) [17] (Table 1). Data from the Early Prostate Cancer (EPC) program support bicalutamide 150 mg as a possible alternative to castration in the adjuvant setting. In an analysis of the 305 patients with locally advanced disease who received radiotherapy in the EPC program, adjuvant bicalutamide significantly reduced the risk of objective progression by 42% versus radiotherapy alone (hazard ratio 0.58; 95% confidence interval 0.41–0.84; $P = 0.0035$; Table 1 and Fig. 3) [18]. Overall survival data for these patients are currently immature.

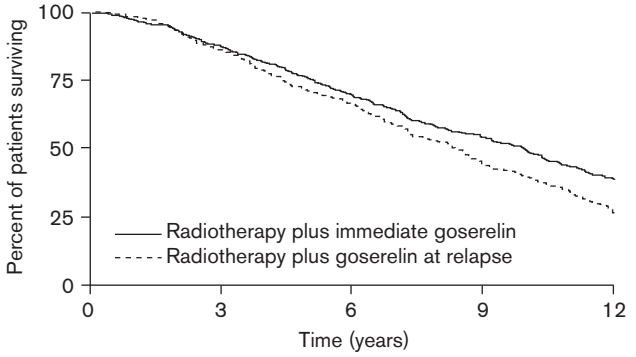
When deciding which type of hormonal therapy to take on a long-term basis, many patients prefer to weigh up the potential efficacy benefits of a particular agent against the risk of adverse effects. Goserelin is the only hormonal therapy with proven survival benefits as adjuvant to radiotherapy in patients with locally advanced disease. Castration, however, can be associated with adverse effects including decreased libido, sexual dysfunction, fatigue, hot flushes, loss of bone mineral density, osteoporotic fractures and reduced lean muscle mass [19–21]. Unlike castration, non-steroidal anti-androgens such as bicalutamide 150 mg do not suppress testosterone production and, therefore, offer potential quality-of-life benefits. Bicalutamide 150 mg has demonstrated statistically significant advantages over castration in terms of maintaining sexual interest ($P = 0.029$) and physical capacity ($P = 0.046$) [11]. There is also evidence that bicalutamide 150 mg preserves bone mineral density, lessens fat accumulation and has fewer adverse events, such as hot flushes, compared with castration [11,22]. Furthermore, bicalutamide 150 mg may have a more

Table 1 Randomized trials evaluating the addition of adjuvant hormonal therapy to radiotherapy in patients with locally advanced disease

Hormonal therapy	Type of patients	No. patients	Treatment duration (years)	Median follow-up (years)	Treatment difference: hormonal therapy versus control [% (*P* value)]	
					Clinical progression	Overall survival
Adjuvant goserelin 3.6 mg/4 weeks [15]	cT1–2, M0, N0–1 or cT3–4, M0, N0–1	415	3	5.5	26 vs 60[a] ($P<0.0001$)	78 vs 62[a] ($P=0.0002$)
Adjuvant goserelin 3.6 mg/4 weeks [16]	cT1–2, M0, N+ or cT3, M0, any N	977	until progression	7.6	63 vs 77[b] ($P<0.0001$)	49 vs 39[b] ($P=0.002$)
Neoadjuvant goserelin + flutamide then adjuvant goserelin 3.6 mg/4 weeks [17]	cT2c–4, M0, N0–1	1554	2	5.8	54 vs 72[b] ($P<0.0001$)	80 vs 79[b] ($P=0.73$)
Adjuvant bicalutamide 150 mg/day [18]	cT3–4, M0, any N or any T, M0, N+	305	≥ 2	5.4	34 vs 49 ($P=0.0035$)	not reported[c]

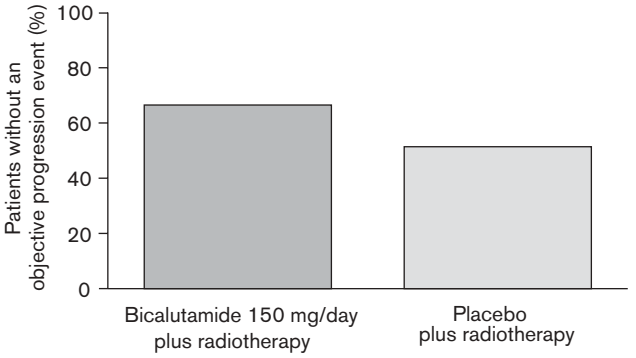
[a]Estimated 5-year rate.
[b]Estimated 10-year rate.
[c]Subgroup size insufficient.

Fig. 2



Kaplan–Meier curve of overall survival in patients with locally advanced prostate cancer who received goserelin adjuvant to radiotherapy or radiotherapy alone followed by goserelin at disease progression as part of the RTOG trial 85-31 ($n=977$). Estimated 10-year overall survival: 49 versus 39%; $P=0.002$. Adapted with kind permission from [16].

Fig. 3



Bar chart of objective progression-free survival in patients with locally advanced prostate cancer who received bicalutamide 150 mg or placebo as adjuvant to radiotherapy as part of the EPC program ($n=305$). Adapted with kind permission from [18].

favorable tolerability profile than other non-steroidal anti-androgens (flutamide and nilutamide), particularly in terms of a reduced risk of diarrhea and abnormal liver function [23].

Physical capacity and sexual drive and function were key issues for Nigel when making his treatment decision as he is relatively young, active, and was keen to return to work. After completing his radiotherapy treatment, he therefore requested to receive bicalutamide 150 mg/day, initially for 6 months to assess the efficacy and tolerability of treatment.

Compared with patients receiving castration, those receiving non-steroidal anti-androgens do have a higher incidence of gynecomastia (4.4 versus 49.4%, respectively) and breast pain (1.9 versus 40.1%, respectively), although these side-effects are generally of mild to moderate intensity in the majority of cases [11]. Nigel developed moderate gynecomastia and breast pain within 3 months of neoadjuvant bicalutamide treatment, which was successfully managed by a 5-day course of therapeutic radiotherapy to both breast areas at a total dose of 15 Gy. An alternative option would have been prophylactic radiotherapy or oral tamoxifen before starting neoadjuvant bicalutamide therapy, as studies have shown that these strategies are effective in preventing breast symptoms [24,25]. Six months after adjuvant bicalutamide treatment, Nigel's PSA level had fallen to below 0.1 ng/ml, and he described substantial improvements in his urinary symptoms and depression. Moreover, partly due to lifestyle changes, including taking regular exercise and eating more healthily, his blood pressure had normalized without the need for anti-hypertensive medication. Nigel has returned to work, and reports feeling optimistic, stronger and more positive. He now plans to continue bicalutamide 150 mg treatment indefinitely to reduce the risk of disease relapse.

Patient's perspective

The first indication that I had problems with my urogenital system was when I found myself wanting to go to the toilet frequently and urgently, sometimes with incontinence. At the time, however, my life was in turmoil as I was in the middle of a marriage breakdown and I pushed my symptoms to the back of my mind, convincing myself that they were due to chronic prostatitis. I should perhaps have known better, given my medical background and the fact that my father died from prostate cancer when he was in his 80s. Nonetheless I went into denial.

Many months later, during a routine eye examination, my optician noticed that I had signs of raised blood pressure and advised me to visit my GP. While visiting my GP on this matter, I finally mentioned that I had been having prostatic symptoms for some time. He arranged for me to have a PSA test, and when the results came back considerably higher than you would expect from a man of my age, he immediately referred me to see a specialist.

On hearing that my PSA level was abnormal, I was frightened at the prospect of facing a prostate cancer diagnosis on my own in view of my recent divorce, but still clung to the hope that it might be explained by other causes. However, additional diagnostic tests were performed prior to my appointment with the specialist, and with all the results available, it was confirmed that I did in fact have locally advanced prostate cancer.

Even if you have tried to prepare yourself for it, and I had, the diagnosis of cancer comes as something of a shock.

Having treated thousands of cases myself was of little relevance. I was somewhat relieved to hear that the tumor had not metastasized and was therefore 'locally advanced'. However, the knowledge that surgical removal was not really an option was in some ways disappointing, even though the thought of a major operation was somewhat daunting. The information that Professor Kirby gave me on the improved results with combined radiotherapy and hormonal therapy was heartening, as was his expressed view that a cure was possible. An immediate visit to a counselor, who incidentally also had the disease, was enormously helpful and very unexpected. At the end of the counseling session I left rather emotional, but was determined to get through the forthcoming treatment.

The various treatment options and the suitability of each approach in my particular case were explained. Watchful waiting/active surveillance and surgery were clearly not appropriate choices, and, after much discussion with my physician, I decided to undergo radiotherapy plus neoadjuvant hormonal therapy, as this combination offered me the possible chance of a complete cure. I was also offered counseling at this point, which I accepted and found helpful.

Before I started radiotherapy, I was prescribed hormonal therapy for 3 months in the form of bicalutamide 150 mg/day, which has tolerability advantages over other hormonal therapies with regard to preserving sexual and physical activity. This had a dramatic effect, reducing my PSA level from 44 to 10 ng/ml, which was very reassuring. My urinary symptoms also began to improve towards the end of the treatment period although, initially, they worsened. I then started radiotherapy, and unsurprisingly had an initial increase in symptoms of incontinence and urgency; I also experienced some rectal symptoms. This was particularly difficult and embarrassing because I had to make a 1-h train journey into London each day and the toilet facilities *en route* were unreliable to say the least. Thankfully, my symptoms began to improve again about 2 weeks after the completion of radiotherapy.

Based on my experiences, and if I were responsible for managing men with prostate cancer, I would advise my patients to arrive at the clinic early with an empty bladder. If a full bladder was subsequently required during the appointment, then the patient would have time to drink several glasses of water upon arriving at the clinic. Similarly, as a result of treatment-related rectal symptoms, particularly immediately during and after radiotherapy, I would recommend that patients refrain from eating for at least 2 h before and after treatment.

Obviously, I was concerned about the possibility of the cancer returning after radiotherapy and understood that taking adjuvant hormonal therapy on a long-term basis could reduce this risk. As different hormonal therapies are available, the next step was to consider the advantages and disadvantages of each agent in order to select the approach that best suited my personal circumstances. I understand that men who undergo medical castration with goserelin after radiotherapy have improved survival compared with those who receive radiotherapy alone. However, castration is associated with side-effects including impotence, reduced libido, tiredness and loss of bone mineral density. Instinctively, I felt that medical castration was not something that I wanted. Although I am divorced with two grown up sons, I still hope to meet someone again and preserving my sexual capability was and still is very important to me. I also wanted to go back to my career as soon as possible and felt that side-effects such as tiredness would have restricted my ability to do so. An alternative to castration is a non-steroidal anti-androgen, e.g. bicalutamide 150 mg, which I understood provides quality-of-life advantages over castration in terms of maintaining sexual and physical activity. It was explained that men who take bicalutamide 150 mg after radiotherapy have a significantly reduced risk of disease progression, although no survival advantage has yet been demonstrated. I thought carefully about the clinical benefits and quality-of-life implications of each treatment option, and decided that I would much prefer to continue on bicalutamide 150 mg.

I had read about the possibility of developing male breast enlargement on non-steroidal anti-androgens. I began to feel some discomfort and breast swelling after taking bicalutamide 150 mg for the 3 months prior to my radiotherapy course. I therefore opted to undergo a 5-day course of radiotherapy (15 Gy) to the breast area during my radiotherapy to the prostate gland, which successfully prevented any further development of abnormal breast tissue. All things considered, I am quite prepared to live with this side-effect, which is relatively mild and easily managed, rather than compromise my sexual function. However, in retrospect, I would prefer to start the breast treatment when starting the bicalutamide, as the discomfort and swelling present before treatment persists, and is avoidable.

After continuing on adjuvant bicalutamide 150 mg for 6 months, I feel that my life is getting better and better. The urinary symptoms that I developed during treatment have disappeared. In addition, I have made lifestyle changes by walking regularly and making an effort to eat sensibly, and, as a result, feel virtually back to full fitness again. Having felt tired for a long time previously, I now have the energy to resume my hobbies such as gardening, and to become more involved in my social circle of family and friends. Furthermore, I have returned to my job and am thoroughly enjoying being back at work.

My self-image has improved immensely, and I am feeling much stronger and more positive about the future. Looking back, I am completely happy with the treatment choices that I made. My main regret is that I did not go for PSA screening earlier, when I experienced my initial urinary symptoms, particularly given my family history. Both my sons have promised that they will have PSA tests when they reach their 40th birthdays.

Acknowledgments

Editorial support was provided by Sharon Gladwin.

References

1 Johansson J-E, Holmberg L, Johansson S, Bergström R, Adami H-O. Fifteen-year survival in prostate cancer. A prospective, population-based study in Sweden. *JAMA* 1997; **277**:467–471.
2 Aus G, Abbou CC, Pacik D, Schmid H-P, Van Poppel H, Wolff JM, *et al. Guidelines on prostate cancer.* Arnhem: European Association of Urology; 2004. http://www.uroweb.org/files/uploaded_files/prostatecancer.pdf.
3 Chuba PJ, Moughan J, Forman JD, Owen J, Hanks G. The 1989 patterns of care study for prostate cancer: five-year outcomes. *Int J Radiat Oncol Biol Phys* 2001; **50**:325–334.
4 Vicini FA, Martinez A, Hanks G, Hanlon A, Miles B, Kernan K, *et al.* An interinstitutional and interspecialty comparison of treatment outcome data for patients with prostate carcinoma based on predefined prognostic categories and minimum follow-up. *Cancer* 2002; **95**:2126–2135.
5 Roach III M, Lu J, Pilepich MV, Asbell SO, Mohuiddin M, Terry R, *et al.* Four prognostic groups predict long-term survival from prostate cancer following radiotherapy alone on Radiation Therapy Oncology Group clinical trials. *Int J Radiat Oncol Biol Phys* 2000; **47**:609–615.
6 Hanks GE, Hanlon AL, Pinover WH, Horwitz EM, Schultheiss TE. Survival advantage for prostate cancer patients treated with high-dose three-dimensional conformal radiotherapy. *Cancer J Sci Am* 1999; **5**:152–158.
7 Yang FE, Chen GT, Ray P, Vaida F, Chiru P, Hamilton RJ, *et al.* The potential for normal tissue dose reduction with neoadjuvant hormonal therapy in conformal treatment planning for stage C prostate cancer. *Int J Radiat Oncol Biol Phys* 1995; **33**:1009–1017.
8 Shearer RJ, Davies JH, Gelister JSK, Dearnaley DP. Hormonal cytoreduction and radiotherapy for carcinoma of the prostate. *Br J Urol* 1992; **69**:521–524.
9 Pilepich MV, Winter K, John MJ, Mesic JB, Sause W, Rubin P, *et al.* Phase III Radiation Therapy Oncology Group (RTOG) trial 86-10 of androgen deprivation adjuvant to definitive radiotherapy in locally advanced carcinoma of the prostate. *Int J Radiat Oncol Biol Phys* 2001; **50**:1243–1252.
10 Laverdière J, Nabid A, De Bedoya LD, Ebacher A, Fortin A, Wang CS, *et al.* The efficacy and sequencing of a short course of androgen suppression on freedom from biochemical failure when administered with radiation therapy for T2–T3 prostate cancer. *J Urol* 2004; **171**:1137–1140.
11 Iversen P, Tyrrell CJ, Kaisary AV, Anderson JB, Van Poppel H, Tammela TLJ, *et al.* Bicalutamide monotherapy compared with castration in patients with nonmetastatic locally advanced prostate cancer: 6.3 years of followup. *J Urol* 2000; **164**:1579–1582.
12 Beckendorf V, Guerif S, Le Prise E, Cosset JM, Lefloch O, Chauvet B, *et al.* The GETUG 70 Gy vs. 80 Gy randomized trial for localized prostate cancer: feasibility and acute toxicity. *Int J Radiat Oncol Biol Phys* 2004; **60**: 1056–1065.
13 Soffen EM, Hanks GE, Hunt MA, Epstein BE. Conformal static field radiation therapy treatment of early prostate cancer versus non-conformal techniques: a reduction in acute morbidity. *Int J Radiat Oncol Biol Phys* 1992; **24**: 485–488.
14 Manne S, Babb J, Pinover W, Horwitz E, Ebbert J. Psychoeducational group intervention for wives of men with prostate cancer. *Psychooncology* 2004; **13**:37–46.
15 Bolla M, Collette L, Blank L, Warde P, Dubois JB, Mirimanoff R-O, *et al.* Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomised trial. *Lancet* 2002; **360**:103–108.
16 Pilepich MV, Winter K, Lawton CA, Krisch RE, Wolkov HB, Movsas B, *et al.* Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma – long-term results of phase III RTOG 85-31. *Int J Radiat Oncol Biol Phys* 2005; **61**:1285–1290.
17 Hanks GE, Pajak TF, Porter A, Grignon D, Brereton H, Venkatesan V, *et al.* Phase III trial of long-term adjuvant androgen deprivation after neoadjuvant hormonal cytoreduction and radiotherapy in locally advanced carcinoma of the prostate: the Radiation Therapy Oncology Group Protocol 92-02. *J Clin Oncol* 2003; **21**:3972–3978.
18 Wirth MP, See WA, McLeod D, Iversen P, Morris T, Carroll K. Bicalutamide 150 mg in addition to standard care in patients with localized or locally advanced prostate cancer: results from the second analysis of the early prostate cancer program at median followup of 5.4 years. *J Urol* 2004; **172**:1865–1870.
19 Kirby R. Treatment options for early prostate cancer. *Urology* 1998; **52**:948–962.
20 Daniell HW, Dunn SR, Ferguson DW, Lomas G, Niazi Z, Stratte PT. Progressive osteoporosis during androgen deprivation therapy for prostate cancer. *J Urol* 2000; **163**:181–186.
21 Sieber PR, Keiller DL, Kahnoski RJ, Gallo J, McFadden S. Bicalutamide 150 mg maintains bone mineral density during monotherapy for localized or locally advanced prostate cancer. *J Urol* 2004; **171**:2272–2276.
22 Smith MR, Goode M, Zietman AL, McGovern FJ, Lee H, Finkelstein JS. Bicalutamide monotherapy versus leuprolide monotherapy for prostate cancer: effects on bone mineral density and body composition. *J Clin Oncol* 2004; **22**:2546–2553.
23 Fourcade R-O, McLeod D. Tolerability of antiandrogens in the treatment of prostate cancer. *UroOncology* 2004; **4**:5–13.
24 Tyrrell CJ, Payne H, Tammela TL, Bakke A, Lodding P, Goedhals L, *et al.* Prophylactic breast irradiation with a single dose of electron beam radiotherapy (10 Gy) significantly reduces the incidence of bicalutamide-induced gynecomastia. *Int J Radiat Oncol Biol Phys* 2004; **60**: 476–483.
25 Boccardo F, Rubagotti A, Garofalo L, Di Tonno P, Conti G, Bertaccini A, *et al.* Tamoxifen (T) is more effective than anastrozole (A) in preventing gynecomastia induced by bicalutamide (B) monotherapy in prostate cancer (pca) patients (pts). *Proc Am Soc Clin Oncol* 2003; **22**:400.