

Review

Evaluating the use of early hormonal therapy in patients with localised or locally advanced prostate cancer

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This article evaluates the use of early hormonal therapy in patients with localised or locally advanced prostate cancer. In patients receiving radiotherapy, an overall survival benefit is proven for adjuvant goserelin ('Zoladex') in locally advanced disease. Adjuvant to radical prostatectomy, castration (goserelin or orchiectomy) has demonstrated an overall survival benefit in patients with lymph node metastases. Survival advantages have not yet been proven with nonsteroidal antiandrogens, but immediate or adjuvant bicalutamide ('Casodex') improves objective progression-free survival in patients with locally advanced disease, with certain quality-of-life advantages over castration.

Prostate Cancer and Prostatic Diseases (2005) 8, 140–151. doi:10.1038/sj.pcan.4500800
 Published online 26 April 2005

Keywords: prostate cancer; hormonal therapy; castration; luteinising hormone-releasing hormone agonist; nonsteroidal antiandrogen

Introduction

Since the onset and widespread use of prostate-specific antigen (PSA) testing, an increasing proportion of prostate cancer cases are being diagnosed at an earlier stage and in younger men.¹ In the USA in 2004, an estimated 86% of prostate cancer diagnoses were for localised or locally advanced disease.²

Men with localised or locally advanced prostate cancer and a life expectancy of ≥ 10 y are typically offered primary therapy of curative intent, that is, radical prostatectomy, external beam radiotherapy or brachytherapy. However, a significant proportion of patients undergoing these therapies experience disease progression (clinical and/or biochemical) and may ultimately die from their prostate cancer.^{3–6} Watchful waiting (where patients receive palliative therapy only) is an option for men who are not suitable for, or opt not to receive, primary therapy of curative intent. Around half

of those who undergo watchful waiting progress and require treatment initiation within 5 y,⁷ although among those with low-risk, localised disease (\leq cT2a, low Gleason score and low PSA level), this proportion may be reduced to around 20%.⁸

Prostate cancer progression can have a serious impact on patients' quality of life.^{9,10} Advancing disease may be associated with debilitating disease-related complications, such as painful bone metastases and urinary tract obstruction,^{11,12} and can cause considerable emotional distress.¹³ Moreover, disease progression poses a significant economic burden.^{14,15} A recent large retrospective cohort evaluation of US patients with prostate cancer showed that healthcare resource charges were more than 50% higher among those with metastatic progression compared with those with no evidence of progression ($P < 0.0001$).¹⁴

In patients with locally advanced disease (pT3, N0), external beam radiotherapy as adjuvant to radical prostatectomy has been shown to significantly improve clinical progression-free survival compared with radical prostatectomy alone (83 vs 75% at 5 y median follow-up; $P = 0.004$).¹⁶ However, both radical prostatectomy and radiotherapy target the prostatic area and neither single nor combined local therapies are able to eradicate distant disease. Many treatment failures after local therapies are likely to be due to the presence of distant micrometastases that were undetectable at the time of diagnosis.

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Received 10 March 2005; accepted 23 March 2005; published online 26 April 2005

The use of early hormonal therapy (ie given immediately rather than being deferred until clinical progression) has been evaluated with a view to improving the outcomes of primary therapy of curative intent and as an alternative to watchful waiting. As there are several different hormonal approaches that can be considered, physicians need to help patients weigh the potential benefits of treatment (in terms of reduced risk of disease progression and death from prostate cancer and increased overall survival) and the potential side effects. Only through this process can physicians be confident that their patients are able to select the approach most appropriate in their specific circumstances.

In this article, I review findings from randomised trials examining the use of early hormonal therapy (castration therapy and/or antiandrogens) as an alternative to watchful waiting, and as adjuvant or neoadjuvant therapy in patients receiving radical prostatectomy or radiotherapy.

Effects on clinical progression and overall survival

Hormonal therapy alone

On examining the evidence, I found that there are clear benefits associated with using early hormonal therapy as an alternative to watchful waiting in patients with locally advanced disease (Table 1). For this patient group, who have a high chance of progression, the results from trials of castration therapy¹⁷⁻¹⁹ or a nonsteroidal antiandrogen²⁰ indicate to me that a watchful waiting approach is not appropriate and that hormonal therapy is best started at, or soon after, diagnosis.

A significant clinical benefit in favour of early castration therapy was first demonstrated in a trial conducted by the Medical Research Council (MRC). This trial evaluated early orchiectomy or a luteinising hormone-releasing hormone agonist (LHRHa) *vs* the same treatment deferred until clinical progression in patients with either nonmetastatic (M0) disease considered too advanced for primary therapy of curative intent or asymptomatic metastatic (M1) disease. Among the subgroup of 500 patients with M0 disease, a first analysis (performed after 74% of the overall trial population had died; median follow-up time not reported) demonstrated significant advantages for early *vs* deferred castration therapy in reducing progression to M1 disease (38 *vs* 59%; $P < 0.001$) and improving overall survival (mortality 59 *vs* 70%; $P = 0.02$) (Table 1).¹⁷ A later analysis (performed after 86% of the overall trial population had died) found that the treatment difference in overall survival was no longer statistically significant (Table 1).¹⁸ The reduction in this treatment difference was explained by the emergence of a higher rate of nonprostate cancer deaths with early *vs* deferred castration therapy. More recently, a European Organisation for Research and Treatment of Cancer trial (EORTC 30846) also compared early *vs* deferred castration therapy (surgery or an LHRHa), in 234 patients with lymph node metastases.¹⁹ This trial is underpowered to show a statistically significant treatment difference in overall survival; however, at 8.7 y median follow-up, the hazard ratio

(HR) for overall survival (HR 1.23) indicated a non-significant 23% trend in favour of early castration therapy (Table 1).

Turning to the nonsteroidal antiandrogens, the ongoing bicalutamide Early Prostate Cancer (EPC) programme recently demonstrated that bicalutamide ('Casodex') monotherapy significantly reduces the risk of disease progression in patients with locally advanced disease.²⁰ The EPC programme is the world's largest prostate cancer treatment programme, consisting of three randomised, placebo-controlled trials conducted in different geographical areas and involving 8113 patients. The programme is evaluating bicalutamide given in addition to standard care (watchful waiting, radical prostatectomy or radiotherapy) in patients with localised or locally advanced disease. A subgroup of 2285 patients in the programme are undergoing watchful waiting as standard care; among these patients, analysis at 5.4 y median follow-up revealed that the relative effect of bicalutamide was dependent on disease stage (Table 1).²⁰

In the watchful waiting patients with locally advanced disease, bicalutamide significantly reduced the risk of objective progression by 47% compared with watchful waiting alone (HR 0.53; $P < 0.0001$; Figure 1).²⁰ This does appear to be translating into a survival benefit as there was a trend toward improved overall survival with bicalutamide (HR 0.81; $P = 0.097$; Figure 2).

In the watchful waiting patients with localised disease, the effect of bicalutamide on progression was smaller (HR 0.81; $P = 0.018$; Figure 1) and there was a trend towards reduced overall survival with bicalutamide (HR 1.23; $P = 0.05$; Figure 2).²⁰ These data suggest that, for patients with localised disease not suitable for primary therapy of curative intent because of age or comorbidities, watchful waiting with hormonal therapy deferred until signs of progression may be the best option.

This strategy would be consistent with a recent report on the use of active surveillance for patients with low-risk localised disease, with selective delayed intervention being initiated depending on specific disease progression criteria (eg rapid PSA progression).⁸ The active surveillance approach offers a practical compromise between therapy of curative intent for all, which results in overtreatment in those with indolent disease, and watchful waiting with palliative therapy only, which results in undertreatment in those with aggressive disease. Klotz⁸ conducted the first feasibility study of the active surveillance approach in 299 patients with low-risk, localised disease (mostly \leq cT2a disease, PSA level < 10 ng/ml and Gleason score ≤ 6), and concluded that a PSA doubling time of < 3 y is the optimal threshold for radical intervention, and that this included around 20% of patients in his series. Klotz did not consider the use of hormonal therapy in their study design, but in light of the recent data from the EPC programme, one wonders whether it is possible that a similar approach might also be relevant in deciding when hormonal therapy may become appropriate in patients with localised disease.

Radical prostatectomy setting

Adjuvant hormonal therapy In the radical prostatectomy setting, the use of adjuvant hormonal therapy in

Table 1 Randomised, controlled trials evaluating the use of early hormonal therapy as an alternative to watchful waiting

Study group	Type of patients ^a	No. of patients	Treatment arms		Median follow-up (y)	Treatment difference: early hormonal therapy <i>vs</i> control			
			Early hormonal therapy	Control		Clinical progression		Overall survival	
						Progression rate (%)	HR ^b (P-value)	Mortality rate (%)	HR ^b (P-value)
MRC trial, M0 subgroup ¹⁷	cT2–4, any N	500	Orchiectomy or LHRHa	Same treatment deferred	Follow-up at 74% deaths ^c	38 <i>vs</i> 59	HR not reported (P < 0.001)	59 <i>vs</i> 70	HR not reported (P = 0.02)
MRC trial, M0 subgroup ¹⁸	cT2–4, any N	500	Orchiectomy or LHRHa	Same treatment deferred	Follow-up at 86% deaths ^c	Not reported	Not reported	Not reported	HR not reported (NS)
EORTC 30846 ¹⁹	pN1–3	234	Surgical castration or LHRHa	Same treatment deferred	8.7	Not reported	Not reported	61 <i>vs</i> 62	1.23 ^d (NS)
Early Prostate Cancer programme, watchful waiting subgroup ^{20,e}	Locally advanced: cT3–4, any N or any T, N+	657	Bicalutamide (150 mg/day)	Placebo	5.4 ^f	44 <i>vs</i> 61	0.53 (P < 0.0001)	34 <i>vs</i> 41	0.81 (P = 0.097)
	Localised: cT1–2, N0 or Nx	1627	Bicalutamide (150 mg/day)	Placebo	5.4 ^f	29 <i>vs</i> 32	0.81 (P = 0.018)	25 <i>vs</i> 21	1.23 (P = 0.050)

HR, hazard ratio; LHRHa, luteinising hormone-releasing hormone agonist; NS, not significant.

^aAll M0.

^bHR for early hormonal therapy *vs* control, unless otherwise stated.

^cFollow-up in the overall MRC trial population (M0 and M1 patients).

^dHR for control *vs* early hormonal therapy.

^ePatients in the Early Prostate Cancer programme received standard care of radiotherapy, radical prostatectomy or watchful waiting, for locally advanced or localized disease (total *n* = 8113); these data are from the watchful waiting subgroup, by disease stage.

^fFollow-up in the overall Early Prostate Cancer programme.

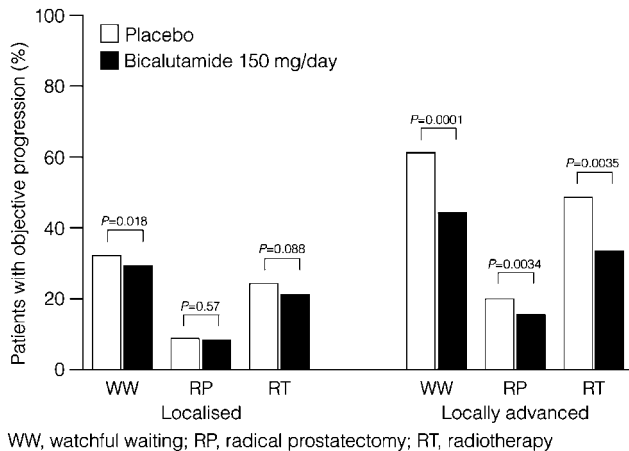


Figure 1 Rates of objective progression with bicalutamide 150 mg/day or placebo, each added to standard care, in patients with localised (T1–2, N0 or Nx) or locally advanced (T3–4, any N or any T, N+) disease, by primary therapy. Data are from the Early Prostate Cancer programme, at 5.4 y median follow-up, and are reproduced with permission from the Journal of Urology.²⁰

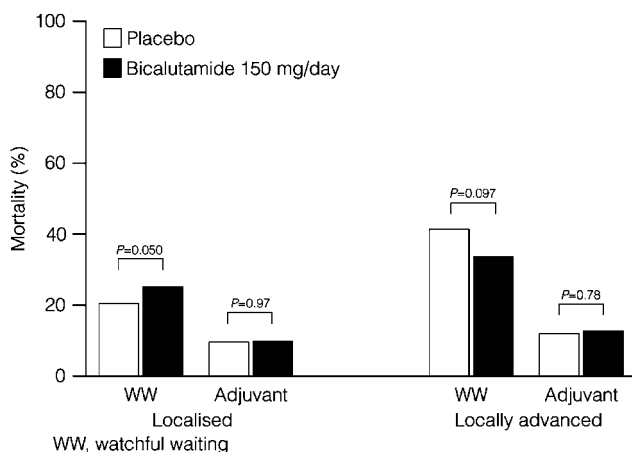


Figure 2 Rates of overall mortality with bicalutamide 150 mg/day or placebo, each added to standard care, in patients with localised (T1–2, N0 or Nx) or locally advanced (T3–4, any N or any T, N+) disease, by primary therapy. Data are from the Early Prostate Cancer programme, at 5.4 y median follow-up, and are reproduced with permission from the Journal of Urology.²⁰ Note: Data for the radiotherapy and radical prostatectomy subgroups are considered together, as adjuvant therapy, as data for the individual subgroups are immature.

patients with locally advanced disease is supported by a number of randomised trials evaluating the clinical benefits of castration therapy^{21–23} or a nonsteroidal antiandrogen,^{20,24} (Table 2).

Evidence that adjuvant castration therapy significantly improves overall survival in patients with lymph node metastases is provided by an Eastern Cooperative Oncology Group trial (ECOG 7787), with long-term follow-up (Table 2).^{21,22} The trial was conducted in 98 patients who underwent radical prostatectomy and pelvic lymphadenectomy for cT1–2 disease, and whose excised lymph nodes were found to contain nodal metastases. It compared castration therapy (the LHRHa goserelin ('Zoladex'), or orchiectomy) commenced immediately vs the same therapy deferred until distant

metastases were identified. At 7.1 y median follow-up, patients who received early adjuvant castration therapy experienced significant improvements in both recurrence-free survival (HR 12.2; $P < 0.001$) and overall survival (HR 3.0; $P = 0.02$) compared with deferred treatment.²² These findings were corroborated at 10 y median follow-up, where overall survival rates were 72 and 49% in the early and deferred adjuvant castration therapy arms, respectively (treatment difference $P = 0.025$).²¹ An additional trial in 201 patients with Stage C disease further demonstrated a clinical benefit for adjuvant castration therapy. Patients receiving adjuvant goserelin achieved a statistically significant 25% PSA progression-free survival advantage compared with radical prostatectomy alone at 5 y median follow-up (P -value not reported); overall survival data were not reported (Table 2).²³

According to my research, one additional study has been conducted to assess the benefits of castration therapy adjuvant to radical prostatectomy.²⁵ This study involved the retrospective analysis of a large case series from the Mayo Clinic database. In total, 707 patients with pT3b, seminal vesicle-positive disease treated with radical prostatectomy were followed. Of these, 157 patients received adjuvant hormonal therapy (the type of hormonal therapy was not reported). At a mean 10 y follow-up, the patients receiving adjuvant hormonal therapy had significantly better PSA progression-free survival (67 vs 23%; $P < 0.001$) and prostate cancer-specific survival (95 vs 87%; $P = 0.046$) than those who received radical prostatectomy alone; overall survival data were not reported.

With respect to the potential role of nonsteroidal antiandrogen therapy in this setting, a subgroup of 4454 patients in the bicalutamide EPC programme received radical prostatectomy as standard care (Table 2). At 5.4 y median follow-up, adjuvant bicalutamide significantly reduced the risk of objective progression by 29% compared with radical prostatectomy alone in patients with locally advanced disease (HR 0.71; $P = 0.0034$; Figure 1), indicating a clinical benefit in these patients.²⁰ There was no significant treatment difference in objective progression-free survival in those with localised disease (Figure 1). The survival data for patients in the EPC programme who underwent adjuvant therapy are considered immature currently, and survival data for the radical prostatectomy subgroup have not been published (Figure 2).

The use of a nonsteroidal antiandrogen as adjuvant to radical prostatectomy in patients with locally advanced disease is further supported by findings from an open-label trial comparing flutamide as adjuvant to radical prostatectomy with radical prostatectomy alone in 309 patients with pT3, N0 disease. At 6.1 y median follow-up, adjuvant flutamide significantly improved PSA progression-free survival (HR 0.51 vs radical prostatectomy alone; $P = 0.0041$) (Table 2).²⁴ The overall survival rate was ~80% with adjuvant flutamide and ~45% with radical prostatectomy alone, but the treatment difference was not statistically significant.

Neoadjuvant hormonal therapy Regarding the use of neoadjuvant hormonal therapy prior to radical prostatectomy, clinical progression and overall survival data

Table 2 Randomised trials evaluating the use of early hormonal therapy as adjuvant to radical prostatectomy

Study group	Type of patients ^a	No. of patients	Treatment arms		Median follow-up (y)	Treatment difference: early hormonal therapy <i>vs</i> control			
			Early hormonal therapy	Control		Clinical progression		Overall survival	
						Progression rate (%)	HR ^b (<i>P</i> -value)	Mortality rate (%)	HR ^b (<i>P</i> -value)
ECOG 7887 ^{21,22}	cT1–2, pN+	98	Goserelin (3.6 mg/4 weeks) or orchiectomy	Same treatment deferred	7.1 10	15 <i>vs</i> 82 ^c Not reported	12.2 ^{c,d} (<i>P</i> < 0.001) Not reported	15 <i>vs</i> 35 28 <i>vs</i> 51	3.0 ^d (<i>P</i> = 0.02) HR not reported (<i>P</i> = 0.025)
Prayer-Galetti <i>et al</i> ²³	Stage C	201	Goserelin (3.6 mg/4 weeks)	No adjuvant treatment	5	Not reported	Significant ^{c,e} (<i>P</i> -value not reported)	Not reported	Not reported
Early Prostate Cancer programme, radical prostatectomy subgroup ^{20,f}	Locally advanced: pT3–4, any N or any T, N+	1719	Bicalutamide (150 mg/day)	Placebo	5.4 ^g	16 <i>vs</i> 20	0.71 (<i>P</i> = 0.0034)	Data immature	Data immature
	Localised: pT1–2, N0 or Nx	2734	Bicalutamide (150 mg/day)	Placebo	5.4 ^g	8 <i>vs</i> 9	0.93 (<i>P</i> = 0.57)	Data immature	Data immature
Wirth <i>et al</i> ²⁴	pT3, N0	309	Flutamide (250 mg, three times daily)	No adjuvant treatment	6.1	Not reported	0.51 ^c (<i>P</i> = 0.0041)	Not reported	1.04 (<i>P</i> = 0.92)

HR, hazard ratio; NS, not significant.

^aAll M0.^bHR for early hormonal therapy *vs* control, unless otherwise stated.^cData include patients with PSA progression: clinical progression only was not reported for these studies.^dHR for control *vs* early hormonal therapy.^eA 25% PSA progression-free survival advantage for goserelin over no adjuvant treatment.^fPatients in the Early Prostate Cancer programme received standard care of radiotherapy, radical prostatectomy or watchful waiting, for locally advanced or localised disease (total *n* = 8113); these data are from the radical prostatectomy subgroup, by disease stage.^gFollow-up in the overall Early Prostate Cancer programme.

are lacking. Trials in this setting mostly studied combination therapy with an LHRHa (leuprorelin or goserelin) plus an antiandrogen (flutamide or the steroidal antiandrogen cyproterone acetate), and in general they have shown positive effects on short-term end points such as tumour volume and surgical margin status.^{26–31}

PSA progression was also evaluated in some trials with longer follow-up (longest follow-up median 6.8 y), but none found a significant benefit of neoadjuvant hormonal therapy on this endpoint.^{27–30} Reported PSA progression-free survival rates were 63–74% with neoadjuvant hormonal therapy *vs* 66–68% with radical prostatectomy alone.

According to data from a small subgroup analysis, some patients with higher risk localised disease may gain a clinically significant benefit from hormonal therapy neoadjuvant to radical prostatectomy. This subgroup analysis, which used data from a trial in patients with cT1–2 disease, demonstrated a significant PSA progression-free survival benefit favouring neoadjuvant therapy with the steroidal antiandrogen cyproterone acetate over radical prostatectomy alone in patients with baseline PSA levels >20 ng/ml ($P=0.015$).²⁷ The subgroup was small ($n=33$) and the analysis can, therefore, only be considered exploratory; nevertheless, this finding does suggest that further research is warranted evaluating the use of neoadjuvant hormonal therapy to radical prostatectomy in patients with high-risk localised disease. However, I envisage that the strategy will unlikely provide a long-term clinical benefit in most patients with localised disease.

Radiotherapy setting

Adjuvant hormonal therapy In my view, in the radiotherapy setting, there is now categorical randomised trial evidence that adjuvant hormonal therapy provides clinical benefits in patients with locally advanced disease (Table 3).^{20,32–36}

Goserelin leads the way, with two large trials proving an overall survival benefit, as well as a clinical progression-free survival advantage, for adjuvant goserelin to radiotherapy in patients with locally advanced disease.^{32–34} The EORTC 22863 trial compared adjuvant goserelin (given for 3 y after radiotherapy) with radiotherapy alone in 415 patients with World Health Organization grade 3 or cT3–4 disease.³² At 5.5 y median follow-up, 5-y overall survival rates were 78% with adjuvant goserelin *vs* 62% with radiotherapy alone (treatment difference $P=0.0002$). A Radiation Therapy Oncology Group trial (RTOG 85-31) compared adjuvant goserelin (given until signs of progression) with goserelin given upon relapse in 977 patients undergoing radiotherapy for cT3 disease or lymph node metastases.^{33,34} At the most recent analysis performed at 7.3 y median follow-up, estimated 10-y overall survival rates were 47 *vs* 38% with adjuvant *vs* delayed goserelin (treatment difference $P=0.0043$).³⁴

The overall survival benefit for goserelin appears to be greatest in patients with higher Gleason scores, as evidenced by data from two RTOG trials: RTOG 85-31 and RTOG 92-02. Analysis of the RTOG 85-31 trial data by pretreatment Gleason score found a significant overall

survival advantage in favour of adjuvant goserelin in patients with Gleason score 7 ($P=0.042$) or 8–10 ($P=0.0061$).³⁴ Also, there was a trend toward improved overall survival in those with Gleason score 2–6, the smallest of the Gleason score subgroups and the subgroup with the lowest number of mortality events.³⁴ The RTOG 92-02 trial evaluated adjuvant goserelin (given for 24 months) *vs* no adjuvant treatment in 1554 patients with cT2c–4 disease who had already received neoadjuvant hormonal therapy (goserelin plus flutamide for 2 months before and 2 months during radiotherapy) (Table 3).³⁵ At 5.8 y median follow-up, adjuvant goserelin significantly improved clinical progression-free survival compared with no adjuvant treatment ($P<0.0001$). There was no statistically significant treatment difference in overall survival in the overall trial population. However, in the subgroup of patients with Gleason score 8–10, adjuvant goserelin did show a significant overall survival advantage ($P=0.044$): estimated 5-y overall survival rates in this subgroup were 81% with adjuvant goserelin *vs* 71% with no adjuvant treatment. There was no statistically significant treatment difference in overall survival in patients with lower Gleason scores.

Orchiectomy has demonstrated overall survival and clinical progression-free survival benefits as adjuvant to radiotherapy only in patients with lymph node metastases. In a trial in 91 men with cT1–4, pN0–3 disease, at 9.3 y median follow-up, there were significant clinical progression-free survival and overall survival treatment differences in favour of adjuvant orchiectomy compared with radiotherapy alone (Table 3).³⁶ However, analyses by nodal status showed that these benefits of adjuvant orchiectomy were significant only for patients with lymph node metastases ($P=0.01$ for clinical progression-free survival; $P=0.007$ for overall survival); the treatment differences were not statistically significant in those with pN0 disease.

Findings from a subgroup of patients in the bicalutamide EPC programme (1370 patients who received radiotherapy as standard care) demonstrate that castration therapy adjuvant to radiotherapy is not the only hormonal therapy to provide significant benefit to patients with locally advanced disease (Table 3).²⁰ At 5.4 y median follow-up, in those radiotherapy patients with locally advanced disease, adjuvant bicalutamide significantly reduced the risk of objective progression by 42% *vs* radiotherapy alone (HR 0.58; $P=0.0035$; Figure 1). In those with localised disease, adjuvant bicalutamide produced a small decrease in the risk of objective progression *vs* radiotherapy alone; however, the reduction was not statistically significant (HR 0.80; $P=0.088$; Figure 1). The survival data for the EPC programme patients who underwent adjuvant therapy are considered immature currently, and survival data for the radiotherapy subgroup have not been published (Figure 2).

Recently, the first evidence of clinical benefits of giving hormonal therapy in addition to radiotherapy in patients with high-risk localised disease were reported.³⁷ In a randomised trial, combination hormonal therapy with an LHRHa (either goserelin or leuprolide) plus flutamide added to radiotherapy for 6 months (2 months each of neoadjuvant, concurrent and adjuvant treatment) was compared with radiotherapy alone in 206 patients with cT1b–2b disease and PSA level ≥ 10 ng/ml, Gleason

Table 3 Randomised trials evaluating the use of early hormonal therapy as adjuvant to radiotherapy

Study group	Type of patients ^a	No. of patients	Treatment arms		Median follow-up (y)	Treatment difference: early hormonal therapy <i>vs</i> control			
			Early hormonal therapy	Control		Clinical progression		Overall survival	
						Progression rate (%)	HR ^b (<i>P</i> -value)	Mortality rate (%)	HR ^b (<i>P</i> -value)
EORTC 22863 ³²	cT1–2, WHO grade 3, N0–1 or cT3–4, N0–1	415	Goserelin (3.6 mg/4 weeks)	No adjuvant treatment	5.5	26 <i>vs</i> 60 (5-y rate)	0.34 (<i>P</i> < 0.0001)	22 <i>vs</i> 38 (5-y rate)	0.51 (<i>P</i> = 0.0002)
RTOG 85-31 ^{33,34}	cT1–2, N+ or cT3, any N	977	Goserelin (3.6 mg/4 weeks)	Same treatment deferred	5.6	64 <i>vs</i> 75 (estimated 8-y rate)	HR not reported (<i>P</i> < 0.0001)	51 <i>vs</i> 53 (estimated 8-y rate)	HR not reported (<i>P</i> = 0.36)
					7.3	64 <i>vs</i> 78 (estimated 10-y rate)	HR not reported (<i>P</i> < 0.0001)	53 <i>vs</i> 62 (estimated 10-y rate)	HR not reported (<i>P</i> = 0.0043)
RTOG 92-02 ³⁵	CT2c–4, N0–1	1554	Neoadjuvant goserelin plus flutamide then adjuvant goserelin (3.6 mg/4 weeks)	Neoadjuvant goserelin plus flutamide alone	5.8	54 <i>vs</i> 72 (estimated 5-y rate)	HR not reported (<i>P</i> < 0.0001)	20 <i>vs</i> 22 (estimated 5-y rate)	HR not reported (<i>P</i> = 0.73)
Granfors <i>et al</i> ³⁶	CT1–4, pN0–3	91	Orchiectomy	No adjuvant treatment	9.3	31 <i>vs</i> 61	Not reported (<i>P</i> = 0.005)	38 <i>vs</i> 61	HR not reported (<i>P</i> = 0.02)
Early Prostate Cancer programme, radiotherapy subgroup ^{2b,c}	Locally advanced: cT3–4, any N or any T, N+	305	Bicalutamide (150 mg/day)	Placebo	5.4 ^d	34 <i>vs</i> 49	0.58 (<i>P</i> = 0.0035)	Data immature	Data immature
	Localised: cT1–2, N0 or Nx	1065	Bicalutamide (150 mg/day)	Placebo	5.4 ^d	21 <i>vs</i> 24	0.80 (<i>P</i> = 0.088)	Data immature	Data immature

HR, hazard ratio; NS, not significant.

^aAll M0.^bHR for early hormonal therapy *vs* control.^cPatients in the Early Prostate Cancer programme received standard care of radiotherapy, radical prostatectomy or watchful waiting, for locally advanced or localised disease (total *n* = 8113)—these data are from the radiotherapy subgroup, by disease stage.^dFollow-up in the overall Early Prostate Cancer programme.

score ≥ 7 or radiographic evidence of extraprostatic disease. At 4.5 y median follow-up, adding hormonal therapy significantly improved PSA progression-free survival (HR 2.9; $P < 0.001$) and overall survival (HR 2.1; $P = 0.04$) compared with radiotherapy alone. Estimated 5-y overall survival rates were 88% with hormonal therapy *vs* 78% with radiotherapy alone. These data indicate that adding hormonal therapy to radiotherapy may be beneficial in patients with high-risk localised disease. However, in my opinion, further randomised trials are needed to ascertain the optimal timing of androgen suppression therapy (neoadjuvant, adjuvant or both) and also the type of hormonal therapy required (combination therapy or monotherapy).

Neoadjuvant hormonal therapy Considering neoadjuvant hormonal therapy alone prior to radiotherapy, the RTOG 86-10 trial provided evidence that combination therapy may improve overall survival in patients with cT2-4, Gleason score 2-6 disease, though not in patients with higher Gleason scores.³⁸ This randomised trial compared neoadjuvant combination therapy (goserelin and flutamide given for 2 months before and 2 months during radiotherapy) with radiotherapy alone in 471 patients with cT2-4 disease. At 6.7 y median follow-up, neoadjuvant combination therapy significantly improved clinical progression-free survival compared with radiotherapy alone ($P = 0.004$; estimated 8-y survival rates 33 *vs* 21%), and there was a trend toward improved prostate cancer-specific survival ($P = 0.05$; estimated 8-y survival rates 77 *vs* 69%). There was no statistically significant treatment difference in overall survival in the overall trial population. However, an overall survival benefit in favour of neoadjuvant combination therapy was found in the subgroup of patients with Gleason score 2-6 ($P = 0.015$ *vs* radiotherapy alone): estimated 8-y overall survival rates in this subgroup were 70% with neoadjuvant combination therapy *vs* 52% with radiotherapy alone. In patients with higher Gleason scores, no statistically significant treatment differences in clinical progression or overall survival were detected.

No other survival data are available in the neoadjuvant hormonal therapy to radiotherapy setting. However, further randomised trials have demonstrated a significant clinical progression-free survival benefit for neoadjuvant cyproterone acetate in patients with stage B2-C disease³⁹ and a PSA progression-free survival benefit for neoadjuvant combination therapy (an LHRHa plus an antiandrogen) in patients with cT2-3 disease.⁴⁰

Efficacy of second-line hormonal therapy

A concern in the use of early hormonal therapy is that there may be a reduced response to subsequent hormonal manipulation upon disease progression. Data are lacking on the use of second-line hormonal therapy after castration therapy in patients with localised or locally advanced disease. However, studies of second-line hormonal therapy in patients with advanced disease demonstrate that a proportion (20-80%) of those who progress upon castration-based therapy will respond to

second-line hormonal therapy, with PSA level decreases of $\geq 50\%$.⁴¹

The efficacy of second-line hormonal therapy in patients with localised or locally advanced disease who received prior antiandrogen therapy was evaluated in 67 patients from the EPC programme who received bicalutamide, had evidence of disease progression (PSA and/or objective) and went on to receive second-line hormonal therapy ($>90\%$ received castration-based therapy).⁴² The overall response rate to second-line hormonal therapy, defined as a reduction in PSA level of $\geq 20\%$ after ≥ 3 months, was 55%. This small exploratory analysis indicates that there is a reasonable expectation that many patients undergoing early bicalutamide therapy will respond to subsequent castration therapy upon disease progression.

Quality-of-life considerations

In my view, decisions on the use of early hormonal therapy in men with localised or locally advanced disease need to be made on an individual patient basis, in an informed discussion between the clinician, the patient and the patient's family. Decisions need to be made first on whether to administer early hormonal therapy (or whether to defer hormonal therapy until there are signs of progression), and then on the type of hormonal therapy to administer. When making these decisions, the expected benefit of early hormonal therapy in improving clinical progression-free survival and overall survival should be discussed alongside quality-of-life considerations, including the expected benefit in reducing disease-related complications, the patient's emotional state and the risks of treatment side effects. For many patients, weighing the pros (eg, efficacy benefits) and cons (eg, risk of side effects) of the various treatment options is a difficult balancing act.

As I discussed earlier, hormonal therapy has a proven overall survival benefit in a number of settings. However, some trials do not currently show a significant overall survival benefit. These trials include the RTOG 92-02 trial evaluating adjuvant goserelin given in addition to neoadjuvant combination hormonal therapy, and the EPC programme and Wirth *et al* trial investigating the use of nonsteroidal antiandrogens.^{20,24,35} It is important to remember that the various trials of hormonal therapy employed differing patient inclusion criteria and were analysed at differing follow-up times, and that some trials, including the EPC programme, are still ongoing.

Disease-related complications An important quality-of-life consideration is that patients experiencing disease progression are at risk of developing debilitating disease-related complications. Pain is the most common symptom of advancing disease; further complications include bone fracture, urinary tract obstruction, spinal cord compression and ineffective haematopoiesis.^{11,12} Palliative treatments, such as radiotherapy, bisphosphonates, steroids, chemotherapy or analgesia, can provide relief

from some disease-related complications, but adequate palliation is not always achieved. Treatments that delay clinical progression would be expected to also reduce the risk of disease-related complications.

To date, only one trial has directly evaluated the merits of early hormonal therapy in reducing the risk of disease-related complications: the MRC trial of early *vs* deferred castration therapy (orchiectomy or an LHRHa) in patients with M0 or M1 disease.^{17,18} The trial considered complications of pathological fractures, spinal cord compression, ureteric obstruction and extraskelatal metastases. At the analysis performed after 74% of patients had died, the incidence of serious disease-related complications was approximately two-fold lower with early *vs* deferred castration therapy, and there were significant treatment differences in the risks of developing spinal cord compression (2 *vs* 5%; $P < 0.025$) and ureteric obstruction (7 *vs* 12%; $P < 0.025$).¹⁷ The later analysis, performed after 86% of patients had died, also showed a lower incidence of spinal cord compression (2 *vs* 5%) and ureteric obstruction (9 *vs* 13%) with early *vs* deferred castration therapy.¹⁸ As expected, these benefits of early hormonal therapy were more apparent in patients with M1 disease (who, given their advanced disease, are more likely to experience disease-related complications) than in patients with M0 disease.

Many cases of disease-related complications are caused by metastases, and there is now extensive randomised trial evidence showing that early hormonal therapy reduces the risk of metastases in patients with locally advanced disease. At the earlier analysis of the MRC trial, for patients with M0 disease, early castration therapy significantly reduced the risk of progression to M1 disease by around one-third compared with deferred hormonal therapy (38 *vs* 59%; $P < 0.001$).¹⁷ Early castration therapy also considerably reduced the risk of developing pain from metastatic disease (14 *vs* 34% with deferred hormonal therapy; P -value not reported).

In the radiotherapy setting, adjuvant goserelin was shown to significantly reduce the risk of distant metastases in the EORTC 22863 trial (5-y rate 10 *vs* 29% with radiotherapy alone; $P < 0.0001$),³² RTOG 85-31 trial (estimated 10-y rate 25 *vs* 39% with delayed goserelin; $P < 0.0001$)³⁴ and RTOG 92-02 trial (estimated 5-y rate 12 *vs* 17% with only neoadjuvant hormonal therapy; $P = 0.0035$).³⁵ In the RTOG 86-10 trial, neoadjuvant combination therapy (goserelin plus flutamide) to radiotherapy also significantly reduced the risk of distant metastases (estimated 8-y rate 34 *vs* 45% with radiotherapy alone; $P = 0.04$).³⁸

The benefit of hormonal therapy on disease-related complications is not restricted to management approaches that contain an LHRHa. Analysis of data from the EPC programme at 5.4 y median follow-up showed that adding bicalutamide significantly reduced the risk of bone metastases by 35% compared with standard care alone in patients with locally advanced disease (HR 0.65; $P < 0.0001$). This benefit occurred irrespective of whether bicalutamide was given as adjuvant therapy (HR 0.73; $P = 0.0054$) or in watchful waiting patients (HR 0.57; $P < 0.0001$) (See WA, personal communication).

Patients' emotional state In my opinion, the patient's emotional state is a further important consideration

when deciding whether to administer early hormonal therapy. With uncertainty regarding the expected course of their disease and an array of competing treatment options, many patients diagnosed with prostate cancer experience depressive symptoms (8–46%) and/or anxiety (13–45%) within the first few months.⁴³ Signs of disease progression, in particular, development of disease-related complications and a rising PSA level, can also adversely affect patients' emotional state.^{13,44,45} A survey in 270 patients who had undergone radical prostatectomy found that more severe urinary tract symptoms were associated with increased cancer fear (measured using the American Urological Association symptom index; $P < 0.05$) and increased mood disturbance (measured using the Profile of Mood States; $P < 0.05$).¹³ Among the patients with severe urinary tract symptoms, those with PSA recurrence had significantly greater cancer fear and mood disturbance than those with no PSA recurrence (each $P < 0.01$). To my knowledge, only one published trial has evaluated the effects of early hormonal therapy on emotional symptoms in patients with prostate cancer. This was a randomised trial in 62 patients with nonlocalised prostate cancer for whom hormonal therapy was considered optional, and compared four treatment arms: goserelin, leuprolide, cyproterone acetate and watchful waiting.⁴⁶ Over 1 y, patients in the watchful waiting and cyproterone acetate groups experienced significant worsening over time in emotional distress (measured using the Depression/Anxiety Stress Scales; $P = 0.002$ and 0.041 , respectively). By contrast, in the two LHRHa groups, emotional distress did not significantly change over time. Although this trial is relatively small, the data suggest that LHRHa therapy may provide benefit over watchful waiting in terms of patients' emotional state. No data are available on the effects of nonsteroidal antiandrogen therapy on emotional symptoms.

Risks of treatment side effects Given the trend for diagnosis of prostate cancer at an earlier stage and in younger men, in my experience the risks of treatment side effects are becoming increasingly important to patients when deciding which type of hormonal therapy to choose. In a recent preferences survey, patients with nonmetastatic prostate cancer indicated that they were willing to trade off some life expectancy to be relieved of the burden of troublesome side effects.⁴⁷

The side-effect profile of castration therapy is well established. Data from long-term trials (≥ 1 y) found that castration is associated with side effects including fatigue, decreased libido, sexual dysfunction, hot flushes, loss of bone mineral density, osteoporotic fractures and anaemia.^{46,48–53}

Use of a nonsteroidal antiandrogen is associated with a lower risk of side effects compared with castration therapy. Randomised trials investigating bicalutamide monotherapy compared with castration therapy in patients with nonmetastatic disease demonstrated treatment differences in favour of bicalutamide in terms of maintaining sexual interest and physical capacity⁵² and avoiding loss of bone mineral density.⁴⁸ A further trial specifically evaluated the impact of bicalutamide on sexual interest and function (measured using a shortened version of the Golombok Rust Inventory of Sexual

Satisfaction), and, after 1 y, found little differences from placebo on these parameters.⁵⁴

Mild-to-moderate gynaecomastia and breast pain are the most frequent side effects of non-steroidal antiandrogen therapy.⁵⁵ The reported incidence of gynaecomastia is similar for the three available agents: 37–68% with bicalutamide; 21–80% with flutamide; and 50% with nilutamide.^{20,55} Data from the EPC programme suggest that patients who perceive a clinical benefit of early hormonal therapy may be more likely to tolerate the side effects.²⁰ In many trials to date, including the EPC programme, patients were not offered any management for gynaecomastia or breast pain. However, various strategies are available for the prophylaxis and treatment of these adverse events, including breast irradiation^{56–58} and antiestrogen tamoxifen therapy.^{59–61}

Some nonpharmacological side effects differ in frequency between individual nonsteroidal antiandrogens.⁵⁵ In particular, flutamide is associated with gastrointestinal effects and hepatotoxicity,^{24,62} and nilutamide is associated with delayed adaptation to darkness, alcohol intolerance and interstitial pneumonitis.⁵⁵ No specific nonpharmacological complications have been linked to bicalutamide.⁵⁵ The steroidal antiandrogen cyproterone acetate is associated with side effects of loss of sexual interest and erectile dysfunction, adverse changes in serum lipids, cardiovascular events and hepatotoxicity.^{55,62}

Conclusions

As an alternative to watchful waiting in patients with locally advanced disease, castration therapy alone (orchiectomy or an LHRHa) was shown in a large randomised trial to reduce the risk of progression to metastatic disease and also the risk of developing pain from metastatic disease.¹⁷ However, effects on overall survival were unclear, with an observed benefit of castration therapy¹⁷ reducing over time.¹⁸

In the radical prostatectomy setting, adjuvant castration therapy (orchiectomy or goserelin) has demonstrated recurrence-free and overall survival advantages in a randomised trial in patients with lymph node metastases.²¹ There is little evidence to support the use of neoadjuvant hormonal therapy to radical prostatectomy.

In the radiotherapy setting, there is clear evidence from large, randomised trials that the LHRHa goserelin as adjuvant to radiotherapy confers significant clinical benefits in terms of delaying disease progression and improving overall survival in patients with locally advanced disease.^{32,34,35} Adding a 6-month course of combination hormonal therapy (with an LHRHa plus flutamide, started 2 months prior to radiotherapy) to radiotherapy has also demonstrated an overall survival benefit in patients with high-risk localised disease.³⁷ Subgroup analysis data suggest that neoadjuvant combination therapy to radiotherapy (with goserelin plus flutamide, for 2 months prior to and 2 months during radiotherapy) may improve overall survival in patients with cT2–4, Gleason score 2–6 disease.³⁸

Data from the EPC programme demonstrate that adding the nonsteroidal antiandrogen bicalutamide to standard care significantly improves objective progres-

sion-free survival in patients with locally advanced disease, when given either in addition to watchful waiting or as adjuvant therapy (to radiotherapy or radical prostatectomy).²⁰ Data are emerging to suggest that active surveillance or a watchful waiting alone approach may be the preferred option for patients with localised disease.

Quality-of-life considerations, including the expected benefit of treatment in reducing disease-related complications, the patient's emotional state and the risks of treatment side effects, are important in the decisions on whether to administer early hormonal therapy and the type of hormonal therapy to administer. There are multiple hormonal therapy options, and patients and their families need to evaluate the benefits and risks of these options to enable them to make an informed decision. Clinical aspects, such as whether the disease is indolent or not, need to be considered alongside patient aspects, ie the weight they place on the expected improvement in overall survival *vs* lifestyle considerations. For a patient whose primary concern is improved overall survival, hormonal therapy using an LHRHa may be most appropriate. In contrast, a patient for whom maintaining lifestyle is important may prefer to receive a nonsteroidal antiandrogen.

Acknowledgements

Editorial support was provided by Cath Carsberg, PhD and financial assistance for this support was provided by AstraZeneca.

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