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Survival in Men With Nonmetastatic Prostate Cancer Treated With Hormone Therapy: A Quantitative Systematic Review

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Abstract

Purpose—We aimed to describe disease-free survival (DFS) and overall survival (OS) in men with localized or locally advanced prostate cancer receiving immediate hormone therapy as adjunct to radiation therapy, adjunct to radical prostatectomy, or stand-alone therapy.

Materials and Methods—A systematic literature search of MEDLINE, EMBASE, CancerLit, the Cochrane Library, and Current Contents (from 1986 to September 2006) yielded 35 high-quality clinical trials (n = 11,105 patients) which formed the evidence base. Selected studies were required to address early hormone therapy in nonmetastatic prostate cancer only. Data on DFS and OS were extracted from individual trials, summarized statistically, and displayed in graphic form.

Results—Survival probabilities were extracted from 16 trials (n = 5,987 patients) addressing hormone therapy as an adjunct to radiation therapy, 11 trials (n = 1,885 patients) investigating hormone therapy as an adjunct to prostatectomy, and 10 trials (n = 3,233 patients) evaluating hormone therapy alone. In men receiving hormones and radiation, estimated 5-year DFS and OS were 52% and 82%, whereas median DFS and OS were 5.4 years and more than 7 years, respectively. In men receiving hormones and surgery, 5-year DFS and OS were 64% and 90%, whereas median DFS and OS were more than 6 years and more than 7 years, respectively. In men receiving hormones alone, 5-year DFS and OS were 57% and 70%, whereas median DFS and OS were 6.0 years and more than 7 years, respectively.

Conclusion—This systematic review provides a new baseline for expected DFS and OS in patients treated with hormone therapy for nonmetastatic prostate cancer. Survival in these men may be longer than estimated previously.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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INTRODUCTION

For more than 65 years, it has been known that androgens play a pivotal role in controlling growth and progression in prostate cancer.¹ At present, androgen-deprivation therapy is a key component in the management of metastatic prostate cancer, and is also being used increasingly for the treatment of locally advanced as well as high-risk localized disease. In patients with nonmetastatic prostate cancer, hormone therapy conventionally has been used for clinical or biochemical failure after local treatment. More recently, clinical trials have examined the efficacy of immediate androgen suppression used as adjunct therapy in men undergoing radiation therapy or radical prostatectomy for localized or locally advanced disease. Primary hormonal treatment has also been studied as stand-alone therapy in patients who are not candidates for radiation therapy or surgery, or in those who have declined these interventions.

Androgen deprivation therapy is available in many forms, and treatment regimens vary. The original method of androgen suppression by surgical orchiectomy has been replaced largely by pharmacologic agents, namely the luteinizing hormone–releasing hormone agonists, which include leuprolide and goserelin. The addition of an antiandrogen such as flutamide, bicalutamide, or cyproterone acetate may have additional theoretical benefits due to inhibition of adrenal androgens. However, clear clinical benefits of combined androgen blockade over monotherapy have not been shown.^{2–4} Also uncertain is the optimal duration of hormone therapy in men with nonmetastatic prostate cancer, as well as the timing of hormone therapy (adjuvant v neoadjuvant) when it is used as an adjunct to radiation therapy or surgery.

When considering a particular treatment for a particular cancer, patients and clinicians often ask the same question: for how long will the proposed treatment keep the cancer in remission, and what is the expected overall survival (OS) with this treatment? This study aimed to describe disease-free survival (DFS) and OS in men with localized or locally advanced prostate cancer treated with immediate hormone therapy by summarizing survival data collected in a systematic fashion from all available relevant clinical trials. Three separate categories were examined: hormone therapy used as an adjunct to radiation therapy, hormone therapy used as an adjunct to prostatectomy, and hormone therapy used alone as primary treatment. This study was designed to be descriptive, aiming to aid clinicians in counseling their patients on the effects of hormone therapy on survival, and does not attempt to compare directly the efficacy of different hormonal regimens.

MATERIALS AND METHODS

Literature Search and Study Selection

This systematic review was designed prospectively to define study objectives, literature search strategies, criteria for inclusion and exclusion of trials, data end points to be extracted, and quality assessment methods. On September 15, 2006, a comprehensive literature search was conducted using the databases MEDLINE, EMBASE, CancerLit, the Cochrane Library, and Current Contents on compact disk, to identify English-language studies published from 1986 to the present. Searches were performed using the Medical

Subject Heading term “prostatic neoplasms” combined with the keywords “hormone therapy,” “endocrine therapy,” “castration,” “androgen ablation,” “androgen suppression,” “androgen blockade,” “androgen deprivation,” “LHRH agonist,” “antiandrogen,” “leuprolide,” “goserelin,” “buserelin,” “triptorelin,” “deslorelin,” “flutamide,” “nilutamide,” “bicalutamide,” or “cyproterone acetate.” Additional studies were sought from the reference lists of retrieved articles and by a review of abstracts from meetings of professional organizations.

The selection criteria limited studies to randomized controlled trials or retrospective or prospective observational trials involving men with nonmetastatic prostate cancer treated with immediate hormone therapy either as adjunct to radiation therapy, adjunct to radical prostatectomy, or stand-alone therapy. All retrieved studies were evaluated critically using a predefined set of appraisal criteria that focused on research design, patient selection, outcome measures, results, and statistical analysis. Studies had to report DFS and/or OS, had to involve at least 50 participants, had to have a median follow-up of at least 2 years, and had to recruit patients from the post–prostate-specific antigen (PSA) era (after 1986). This cutoff was chosen because trials using PSA in diagnosis and follow-up are more representative of current clinical practice. Efficacy outcomes that were analyzed by duration of hormone therapy, timing of hormone therapy, intensity of hormone therapy, and patient risk groups were desirable but not necessary. In cases where multiple articles reported on different lengths of follow-up of the same patient cohort, only the most recent study was retrieved.

Data Extraction

The following data were sought from each study passing the appraisal process: years of patient recruitment, trial design, TNM cancer stage,⁵ patient prognostic risk group as described by Zelefsky et al⁶ (low risk: T1-2 tumor, PSA < 10 ng/mL, Gleason score <6; intermediate-risk: T3-4 tumor or PSA ≥ 10 ng/mL or Gleason score < 6; high-risk: two or more increased values), exact hormonal intervention used (agents and dosing, length of therapy, timing, and intensity), number of patients studied, median follow-up duration, DFS (including type of definition used: biochemical or clinical), and OS. Annual DFS and OS probabilities were extracted at every year of follow-up from either the text or tables of manuscripts, or they were extrapolated from survival curves. The number of patients at risk at each year of follow-up was also collected, if available.

Statistical Methods

Survival probabilities were combined statistically into summarized survival curves. Separate summary curves were generated for DFS and OS for each of the three categories examined: hormone therapy as adjunct to radiation, hormone therapy as adjunct to surgery, and hormone therapy used alone. Where there were adequate data, summarized survival curves were subdivided according to the type of DFS definition used (biochemical or clinical), the duration of hormone therapy (< 24 or ≥ 24 months), the timing of hormone therapy (adjuvant or neoadjuvant), the intensity of hormone therapy (combined androgen blockade or monotherapy), and by patient risk groups (low, intermediate, or high risk).

To generate these curves, we used the assumption of exponential decay. Under this assumption, the survival curve can be described simply by the hazard rate, λ , using the following relation between survival at time t [$S(t)$] and λ :

$$\lambda = \frac{-\log[S(t)]}{t} \quad (1)$$

The summary curves were then estimated using the following steps for each of DFS and OS.

First, for each study (or subgroup within a study), the hazard rate, λ_s , was estimated using the weighted average:

$$\lambda_s = \frac{\sum_t \frac{-\log[S(t)]}{t} \times S(t)}{\sum_t S(t)} \quad (2)$$

where $S(t)$ is the survival probability at year t for study S . $S(t)$ also corresponds to the weights because the number of individuals at risk was not available for all time points. Given the characteristics of survival analysis (there are more individuals at risk and that the survival probabilities are higher at earlier time points), the hazard rate estimates at earlier time points received higher weight. We tested the assumption of exponential decay using graphic displays of fitted versus observed estimates of DFS and OS. These comparisons showed a surprisingly good fit, suggesting that an exponential model was appropriate for generating summary statistics per study and for combining estimates across studies.

Second, a summary hazard rate across studies within the same treatment type was calculated for each outcome using a weighted average with the square root of the total sample size in each study as the weight:

$$\Lambda_k = \frac{\sum_s \lambda_s \sqrt{n_s}}{\sum_s \sqrt{n_s}}, k=1, 2, 3 \quad (3)$$

The index, k , corresponds to the three groups: hormone therapy used with radiation, hormone therapy used with prostatectomy, and hormone therapy used alone.

Third, a summary survival curve for each of the above described groups was calculated using a continuous set of time points and the summary hazard rates, Λ_k , in the equation $S(t) = e^{-\Lambda_k t}$. Curves were extrapolated out to the furthest time point at which more than 50% of the studies in the subgroup reported follow-up. The median and 5-year survival estimates were also calculated using this approach.

The empirically derived and the fitted survival curves are presented together in the figures.

All statistical analyses were completed using the programming freeware R.⁷

RESULTS

Evidence Base

The literature search yielded 2,198 articles, of which 84 passed the selection criteria and critical appraisal. Reasons for study exclusion were as follows: the studies were not human trials, the sample size was too small, the follow-up duration was too short, patients were recruited before 1986 (pre-PSA era), patients had metastatic prostate cancer, trials did not report DFS or OS, hormone therapy was used at disease progression and not immediately, patients received chemotherapy in addition to hormone therapy, or patients received primarily surgical and not medical castration.

After additional exclusion of studies reporting on the same trial population, 35 studies involving 11,105 patients were used for evidence synthesis: 16 trials involving patients receiving hormone therapy with radiation therapy (Table 1), 11 trials involving men receiving hormone therapy with surgery (Table 2), and 10 trials involving men receiving hormone therapy only (Table 3). One article¹⁷ reported two different trials within the same manuscript; these were considered separately. Two studies^{9,23} included one patient population that received hormone therapy as an adjunct to radiation or surgery, and another population that received hormones alone. These cohorts were also considered separately.

Trial Characteristics

Of the 16 trials addressing hormone therapy as an adjunct to radiation therapy (n = 5,987 patients), 10 were randomized controlled studies and six were observational trials (Table 1). Only 11 studies reported the exact hormonal agents used. Patient recruitment dates ranged from 1987 to 2003, tumor stage was from T1b to T4 (five trials included patients with nodal metastases), the number of patients ranged from 57 to 1,514, and the median follow-up duration was from 2.6 to 7.8 years.

Of the 11 trials investigating hormone therapy as an adjunct to prostatectomy (n = 1,885 patients), eight studies were randomized and three were observational (Table 2). Nine studies reported on the details of the hormone therapy used. Patients were recruited between 1986 and 2002, tumor stage ranged from T1b to T4 (two trials included patients with nodal disease), the number of patients ranged from 47 to 520, and median follow-up duration ranged from 2.8 to 10.4 years.

Of the 10 trials evaluating hormones as stand-alone therapy (n=3,233 patients), seven were randomized and three were observational (Table 3). All but one study described the exact hormone therapy used. Patient recruitment was from 1986 to 2003, tumor stage was from T1a to T4 (three trials included patients with nodal involvement), sample size ranged from 52 to 993, and median follow-up was between 3.9 and 10.4 years.

DFS

Figure 1A shows observed DFS curves for men treated with hormone therapy as an adjunct to radiation therapy (data from 14 trials; n=5,852 patients). In six studies (n=4,064), DFS was determined by clinical criteria; in eight studies (n = 1,788), this was determined by

biochemical criteria (serum PSA elevations). A summary curve of DFS is depicted in the same figure. When this curve is used, the estimated median DFS in these patients is 5.4 years, and the 5-year DFS is 52%.

Figure 1B depicts observed DFS curves for men receiving hormone therapy as an adjunct to radical prostatectomy (data from 10 trials; n = 1,733 patients). DFS was determined clinically in four studies (n=526), and PSA level was used in six studies (n=1,207). A summary curve of DFS is also shown. From this curve, the median DFS in this group is not reached (ie, is >6 years), and the 5-year DFS is 64%.

Figure 1C shows observed DFS curves for men treated with primary hormone therapy only (data from four trials; n = 781 patients). In three studies (n = 729), DFS was determined clinically; in one study (n=52), DFS was determined biochemically. A summary curve is depicted. Using this curve, the median DFS in this cohort is 6.0 years, and the 5-year DFS is 57%.

Because the definition of DFS in these trials is so heterogeneous, an attempt was made to stratify data according to the two broad definitions of DFS used: biochemical and clinical. To this end, Figure 2 shows summated DFS across the three treatment groups, stratified by these two broad definitions. From these curves, the median DFS (biochemical v clinical) across treatment groups is more than 6 versus 4.3 years, more than 6 versus more than 6 years, and more than 7 versus 5.8 years, respectively. The 5-year DFS (biochemical v clinical) across treatment groups is 64 v 45%, 64 v 65%, and 68 v 55%, respectively.

OS

Figure 3A depicts observed OS curves as well as a summary curve of OS for men receiving hormone therapy and radiation. Data were available from 11 trials (n = 4,688 patients). From the summarized curve, the median OS in this cohort was not reached (ie, > 7 years), and the 5-year OS was 82%.

Figure 3B shows observed OS curves and a summary curve of OS for men receiving hormone therapy and prostatectomy. Data were available from six trials (n = 607 patients). Using the summarized curve, the median OS in these men was not reached (ie, > 7 years), and the 5-year OS was 90%.

Figure 3C depicts observed OS curves and a summary curve of OS for men treated with hormone therapy only. Data were available from all 10 trials (n = 3,233 patients). From the summarized curve, the median OS in this group was also not reached (ie, > 7 years), and the 5-year OS was 70%.

Subset Analysis

Observed and summary curves of DFS and OS stratified according to duration of hormone therapy (< 24 or ≥ 24 months), timing of hormone therapy (adjuvant or neoadjuvant), intensity of hormone therapy (combined androgen blockade or monotherapy), and patient risk groups (low, intermediate, or high risk) are included in Appendix Figures A1 to A8 (online only).

DISCUSSION

This quantitative systematic review is the first to report summated data on DFS and OS in men with nonmetastatic prostate cancer treated with androgen deprivation therapy. Our results estimate that men receiving hormone therapy as an adjunct to external-beam radiation have a 5-year DFS of 52% and a 5-year OS of 82%; men receiving hormone therapy as an adjunct to radical prostatectomy have a 5-year DFS of 64% and a 5-year OS of 90%; and men receiving hormone therapy as stand-alone treatment have a 5-year DFS of 57% and a 5-year OS of 70%. These pooled data can serve to guide clinicians advising patients with localized or locally advanced disease on the effects of androgen suppression therapy on survival. They may also serve as a new baseline of DFS and OS in this patient population, aiding in the design of future clinical trials.

To date, there are no meta-analyses or systematic reviews reporting summarized survival estimates in patients receiving hormone therapy as adjunct to definitive local treatment. Although this study falls short of a formal meta-analysis, it represents a first attempt at achieving this. Previous studies in this area have focused mainly on the use of primary hormone therapy in men with metastatic prostate cancer. In a meta-analysis by the Prostate Cancer Trialists' Collaborative Group² summarizing data from 27 trials and 8,275 patients, the median OS was 2.6 years, the 5-year OS was 25%, and the 10-year OS was 6%. In that study, 88% of men had distant metastases and 12% had locally advanced disease. In a separate meta-analysis⁴² pooling data from 14 trials involving 4,819 patients, the median OS was reported to be mostly between 1.7 and 3.3 years. The majority of men in that study also had metastatic disease. Our study suggests that OS in patients treated with hormone therapy alone may be higher than previously believed, especially when considering only patients with nonmetastatic prostate cancer. However, it is also possible that this effect, at least in part, may be attributed to stage migration shifts and lead-time bias created by using PSA in diagnosis.

A significant limitation of this study was its attempt to pool together data from trials involving patients with different disease stages as well as different hormonal regimens. It may be argued, for instance, that patients with nodal involvement should have been considered separately, or that men with localized disease should not have been analyzed jointly with men demonstrating locally advanced disease. Some may have also preferred to exclude trials using the steroidal antiandrogen cyproterone acetate, given that this agent may be slightly inferior to nonsteroidal antiandrogens.^{2,43} Others may have suggested exclusion of trials using bicalutamide as monotherapy for similar reasons.⁴⁴ In addition, the observational nature of some of the studies included in the analysis could bias the results, given that patients with higher-risk disease may have been treated with more aggressive therapies. However, the main limitation of this study related to the significant heterogeneity in the definition of DFS, and combining data on clinical and biochemical DFS may have been too simplistic. To try to address some of these issues, summary survival curves were generated after stratification by broad DFS definition, type of hormone therapy, duration of hormone therapy, timing of hormone therapy, and patient risk groups.

Although this overview brings together all of the available high-quality evidence on DFS and OS, it does not assess other clinical end points, treatment-related adverse events, quality-of-life issues, or cost-effectiveness. Importantly, the survival benefits of androgen deprivation therapy should be weighed against the many serious complications of long-term treatment including osteoporosis and the risk of fractures, as well as development of the metabolic syndrome with its associated cardiovascular risks. Furthermore, this study was not designed to answer questions about superiority or inferiority of one hormone therapy over another. The chief aim was simply to assess the effects of hormone therapy, as a general modality, on DFS and OS as comprehensively and accurately as possible. To this end, decisions regarding which hormonal regimen to choose, or whether to combine androgen suppression with definitive local therapy, should be based on clinical and tumor characteristics and on patient wishes. Large randomized controlled trials and comparative meta-analyses will also guide decisions about preferential treatments.

In summary, we present a descriptive report of DFS and OS in patients treated with immediate androgen deprivation therapy for localized and locally advanced prostate cancer. We propose a new baseline for expected survival in men receiving hormone therapy for nonmetastatic disease, and hope to convey that this may be much longer than previously estimated. Future meta-analyses may aim to compare early hormone therapy versus a delayed approach, or continuous hormone therapy versus intermittent therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1. Observed and summarized disease-free survival in men receiving hormone therapy as (A) adjunct to radiation therapy, (B) adjunct to prostatectomy, or (C) stand-alone therapy.

Fig. 2. Disease-free survival (DFS) stratified according to broad DFS definition (biochemically determined, or clinically determined). Observed and summarized DFS in men receiving hormone therapy as (A,D) adjunct to radiation therapy, (B,E) adjunct to prostatectomy, or (C,F) stand-alone therapy.

Fig. 3. Observed and summarized overall survival in men receiving hormone therapy as (A) adjunct to radiation therapy, (B) adjunct to prostatectomy, or (C) stand-alone therapy.

Table 1
Summary of Trials Evaluating a Combination of Radiation and Hormone Therapy for Nonmetastatic Prostate Cancer

Trial	Recruitment Period	Design	AJCC Stage	Hormonal Intervention*	No. of Patients	Median Follow-Up (years)	DFS	OS
D'Amico et al ⁸ (2006)	1989–2002	Prospective observational clinical trial	T1c-3, N0, M0	(Leuprolide 7.5 mg IM every month or goserelin 3.6 mg SC every month) + flutamide 250 mg PO tid; 2 months before, 2 months during, 2 months after XRT	91	4.6	1 year, 98% [†] 2 years, 91% 3 years, 82% 4 years, 74% 5 years, 66% 6 years, 58% 7 years, 52% 8 years, 52%	1 year, 98% 2 years, 98% 3 years, 96% 4 years, 92% 5 years, 88% 6 years, 83% 7 years, 83% 8 years, 83%
Saito et al ⁹ (2006)	1992–2003	Retrospective observational clinical trial	T3, N0, M0	(Leuprolide or goserelin) ± (flutamide or bicalutamide); 4–12 months before XRT, indefinitely after	78	4.6		1 year, 100% 2 years, 99% 3 years, 97% 4 years, 97% 5 years, 95% 6 years, 90% 7 years, 90% 8 years, 90% 9 years, 79% 10 years, 70%
Higgins et al ¹⁰ (2006)	1996–2001	Retrospective observational clinical trial	T1-3, N0, M0	LHRH agonist + antiandrogen; before and during XRT, for 3 months	300	4.8	1 year, 93% [†] 2 years, 72% 3 years, 58% 4 years, 48% 5 years, 43%	5 years, 77%

Trial	Recruitment Period	Design	AJCC Stage	Hormonal Intervention *	No. of Patients	Median Follow-Up (years)	DFS	OS
Denham et al ¹¹ (2005)	1996–2000	Phase III randomized controlled trial	T2b–4, N0, M0,	Goserelin 3.6 mg SC every month + flutamide 250 mg PO tid; before and during XRT, for 3 or 6 months	532	5.9	1 year, 92% [†] 2 years, 81% 3 years, 69% 4 years, 62% 5 years, 54% 6 years, 51%	
Hashine et al ¹² (2005)	1992–1998	Prospective observational clinical trial	T1b–3b, N0, M0	LHRH agonist + antiandrogen; after XRT, indefinitely	57	7.8	1 year, 96% 2 years, 89% 3 years, 82% 4 years, 75% 5 years, 68% 6 years, 60% 7 years, 51% 8 years, 44% 9 years, 44% 10 years, 33%	
Zapatero et al ¹³ (2005)	1999–2001	Prospective observational clinical trial	T2a–3b, N0, M0	(Leuprolide 7.5 mg IM every month or goserelin 3.6 mg SC every month) + (flutamide 250 mg PO tid or bicalutamide 150 mg PO once a day); before and during XRT for 4–6 months, and after for 24 months	65	3.0	1 year, 92% [†] 2 years, 83% 3 years, 74% 4 years, 71% 5 years, 63%	
Pilepich et al ¹⁴ (2005)	1987–1992	Phase III randomized controlled trial	T3, N0–1, M0	Goserelin 3.6 mg SC every month; after XRT, indefinitely	477	7.6		1 year, 97% 2 years, 94%

Trial	Recruitment Period	Design	AJCC Stage	Hormonal Intervention *	No. of Patients	Median Follow-Up (years)	DFS	OS
							3 years, 88% 4 years, 82% 5 years, 62% [‡] 6 years, 70% 7 years, 65% 8 years, 58% 9 years, 54% 10 years, 37% 10 years, 49%	
Crook et al ¹⁵ (2004)	1995–2001	Phase III randomized controlled trial	T1c–3b, N0, M0	Goserelin 3.6 mg SC every 4 weeks + flutamide 250 mg PO tid; before XRT, for 3 or 8 months	361	3.7	1 year, 91% [‡] 2 years, 80% 3 years, 67% 4 years, 64% 5 years, 62% 5 years, 87%	
D'Amico et al ¹⁶ (2004)	1996–2001	Phase III randomized controlled trial	T1b–2b, N0, M0,	(Leuprolide 7.5 mg IM every month or goserelin 3.6 mg SC every month) + flutamide 250 mg PO tid; 2 months before, 2 months during, 2 months after XRT	98	4.5	1 year, 98% [‡] 2 years, 94% 3 years, 87% 4 years, 84% 5 years, 82% 6 years, 72% 6 years, 84%	1 year, 98% 2 years, 95% 3 years, 91% 4 years, 90% 5 years, 88% 6 years, 84%
Lavertière et al ¹⁷ (2004)	1990–1999	Phase III randomized controlled trial	T2–3, N0, M0	LHRH agonist + antiandrogen; before XRT for 3 months, or during and after for 10 months	118	5.0	1 year, 97% [‡] 2 years, 95% 3 years, 86% 4 years, 81% 5 years, 75% 6 years, 72%	

Trial	Recruitment Period	Design	AJCC Stage	Hormonal Intervention *	No. of Patients	Median Follow-Up (years)	DFS	OS
Lavertière et al ¹⁷ (2004)	1990–1999	Phase III randomized controlled trial	T2-3, N0, M0	LHRH agonist + antiandrogen; before, during and after XRT; for 5–10 months	295	3.7	7 years, 68% 4 years, 70% [‡]	
Roach et al ¹⁸ (2003)	1995–1999	Phase III randomized controlled trial	T1b-4, N0-1, M0	(Leuprolide 7.5 mg IM every month or goserelin 3.6 mg SC every month) + flutamide 250 mg PO tid: before and during XRT for 4 months, or after for 4 months	1,279	5.0	1 year, 83% [‡] 2 years, 64% 3 years, 56% 4 years, 50% 5 years, 47%	4 years, 86%
Hanks et al ¹⁹ (2003)	1992–1995	Phase III randomized controlled trial	T2c-4, N0-1, M0	Goserelin 3.6 mg SC every month + flutamide 250 mg PO tid; before and during XRT for 4 months, or the same plus 24 months after	1,514	5.8	1 year, 78% [‡] 2 years, 64% 3 years, 54% 4 years, 44% 5 years, 38% 6 years, 36% 7 years, 30%	1 year, 97% 2 years, 95% 3 years, 91% 4 years, 85% 5 years, 79% 6 years, 76% 7 years, 70%
Bolla et al ²⁰ (2002)	1987–1995	Phase III randomized controlled trial	T2-4, N0-1, M0	Goserelin 3.6 mg SC every 4 weeks during and after XRT; for 3 years; + cyproterone 50 mg PO tid during XRT, for 1 month	207	5.5	1 year, 97% [‡] 2 years, 92% 3 years, 87% 4 years, 83% 5 years, 74% 6 years, 65% 7 years, 57% 8 years, 50%	1 year, 97% 2 year, 93% 3 year, 89% 4 year, 86% 5 years, 78% 6 years, 75% 7 years, 71% 8 years, 70%

Trial	Recruitment Period	Design	AJCC Stage	Hormonal Intervention *	No. of Patients	Median Follow-Up (years)	DFS	OS
Pilepich et al ²¹ (2001)	1987–1991	Phase III randomized controlled trial	T2b–4, N0–1, M0	Goserelin 3.6 mg SC every 4 weeks; + flutamide 250 mg PO tid; 2 months before, 2 months during XRT	226	6.7	1 year, 93% [‡]	1 year, 97%
							2 years, 78%	2 years, 93%
							3 years, 64%	3 years, 88%
							4 years, 55%	4 years, 77%
							5 years, 49%	5 years, 72%
							6 years, 43%	6 years, 65%
							7 years, 35%	7 years, 57%
							8 years, 33%	8 years, 53%
							9 years, 28%	9 years, 48%
Ludgate et al ²² (2000)	1992–1997	Retrospective observational clinical trial	T1c–3, N0, M0	LHRH agonist ± antiandrogen; before XRT, for 3–8 months	289	2.6	1 year, 92% [‡]	
							2 years, 85%	
							3 years, 81%	
							4 years, 72%	
							5 years, 64%	

Abbreviations: AJCC, American Joint Commission on Cancer5; DFS, disease-free survival; OS, overall survival; IM, intramuscularly; SC, subcutaneously; PO, orally; XRT, radiation therapy; LHRH, luteinizing hormone–releasing hormone.

* All patients also received external-beam radiation therapy (total, 60–72 Gy) to the prostate.

[‡] Defined as no biochemical evidence of disease (based on prostate-specific antigen levels).

[‡] Defined as no clinical evidence of disease (based on local failure or distant metastases).

Table 2
Summary of Trials Evaluating a Combination of Surgery and Hormone Therapy for Nonmetastatic Prostate Cancer

Trial	Recruitment Period	Design	AJCC Stage	Hormonal Intervention *	No. of Patients	Median Follow-up (years)	DFS	OS
Akaza et al ²³ (2006)	1993–1995	Phase III randomized controlled trial	T1b-3, N0, M0	Leuprolide 3.75 mg IM every 4 weeks after RRP, for > 24 months; + chlormadinone 100 mg every day; after RRP, for 3 months	176	10.4	1 year, 96% [†]	1 year, 98%
							2 years, 92%	2 years, 97%
							3 years, 86%	3 years, 96%
							4 years, 84%	4 years, 91%
							5 years, 81%	5 years, 86%
							6 years, 80%	6 years, 82%
							7 years, 74%	7 years, 78%
							8 years, 76%	8 years, 76%
							9 years, 75%	9 years, 75%
							10 years, 73%	10 years, 73%
Kroepfl et al ²⁴ (2006)	1993–2002	Prospective observational clinical trial	T1–4, N1, M0	LHRH agonist + antiandrogen [‡] ; after RRP, indefinitely	57	4.6	1 year, 90% [§]	1 year, 100%
							2 years, 75%	2 years, 96%
							3 years, 71%	3 years, 93%
							4 years, 68%	4 years, 91%
							5 years, 67%	5 years, 91%
							6 years, 62%	6 years, 88%
							7 years, 62%	7 years, 88%
							8 years, 62%	8 years, 80%
							9 years, 62%	9 years, 80%
							10 years, 62%	10 years, 80%
Wirth et al ²⁵ (2004)	1989–1996	Phase III randomized controlled trial	T3, N0, M0	Flutamide 250 mg PO tid; after RRP, indefinitely	152	6.1		1 year, 99%
								2 years, 97%
								3 years, 95%

Trial	Recruitment Period	Design	AJCC Stage	Hormonal Intervention*	No. of Patients	Median Follow-up (years)	DFS	OS
Klotz et al ²⁶ (2003)	1993–1994	Phase III randomized controlled trial	T1b-2c, N0, M0	Cyproterone 100 mg PO tid; before RRP, for 3 months	112	5.8	1 year, 83% [†]	4 years, 94%
							2 years, 75%	5 years, 92%
							3 years, 70%	6 years, 91%
							4 years, 67%	7 years, 91%
							5 years, 67%	8 years, 91%
							6 years, 64%	9 years, 81%
							7 years, 63%	10 years, 66%
Aus et al ²⁷ (2002)	1992–1994	Phase III randomized controlled trial	T1b-3a, N0, M0	Triptorelin 3.75 mg IM every month, before RRP, for 3 months; + cyproterone 50 mg PO tid, before RRP, for 1 months	63	6.8	1 year, 80% [§]	1 year, 97%
							2 years, 75%	2 years, 94%
							3 years, 69%	3 years, 91%
							4 years, 62%	4 years, 87%
							5 years, 57%	5 years, 87%
							6 years, 54%	6 years, 85%
							7 years, 49%	7 years, 81%
Soloway et al ²⁸ (2002)	1992–1994	Phase III randomized controlled trial	T2b, N0, M0	Leuprolide 7.5 mg IM every month + flutamide 250 mg PO tid; before RRP, for 3 months	138	5.0	1 year, 86% [§]	
							2 years, 81%	
							3 years, 74%	
							4 years, 68%	

Trial	Recruitment Period	Design	AJCC Stage	Hormonal Intervention*	No. of Patients	Median Follow-up (years)	DFS	OS
Schulman et al ²⁹ (2000)	1991–1995	Phase III randomized controlled trial	T2-3, N0, M0	Goserelin 3.6 mg SC every month + flutamide 250 mg PO tid; before RRP, for 3 months	191	4.0	1 year, 82% [†] 2 years, 76% 3 years, 70% 4 years, 63%	5 years, 65%
Fair et al ³⁰ (2000)	1986–1999	Prospective observational clinical trial	T1c-3, N0, M0	Goserelin 3.6 mg SC every month + flutamide 250 mg PO tid; before RRP, for 3–11 months	520	2.8	1 year, 94% [§] 2 years, 86% 3 years, 81% 4 years, 76% 5 years, 72% 6 years, 67% 7 years, 56% 8 years, 50% 9 years, 45% 10 years, 45%	
Messing et al ³¹ (1999)	1988–1993	Phase III randomized controlled trial	T1b-2, N1, M0	Goserelin 3.6 mg SC every 4 weeks [‡] ; after RRP, indefinitely	47	7.1	1 year, 100% [†] 2 years, 98% 3 years, 96% 4 years, 90% 5 years, 85% 6 years, 85%	1 year, 100% 2 years, 100% 3 years, 98% 4 years, 92% 5 years, 90% 6 years, 87%
Fair et al ³² (1999)	1993–1996	Phase III randomized controlled trial	T1b-3, N0, M0	Goserelin 3.6 mg SC every month + flutamide 250 mg PO tid; before RRP, for 3 months	137	2.9	1 year, 93% [§] 2 years, 87% 3 years, 81% 4 years, 73%	

Trial	Recruitment Period	Design	AJCC Stage	Hormonal Intervention*	No. of Patients	Median Follow-up (years)	DFS	OS
Meyer et al ³³ (1999)	1988–1997	Prospective observational clinical trial	T1–3, N0, M0	LHRH agonist + antiandrogen; before RRP, for 3 months	292	3.2	5 years, 73% 1 year, 92% [§] 2 years, 82% 3 years, 75% 4 years, 70% 5 years, 67% 6 years, 63%	

Abbreviations: AJCC, American Joint Commission on Cancer⁵; DFS, disease-free survival; OS, overall survival; IM, intramuscularly; RRP, radical retropubic prostatectomy; LHRH, luteinizing hormone–releasing hormone; PO, orally.

* All patients also underwent RRP.

[†] Defined as no clinical evidence of disease (based on local failure or distant metastases).

[‡] A small minority of patients in these trials were treated with bilateral orchiectomy instead of hormone therapy.

[§] Defined as no biochemical evidence of disease (based on prostate-specific antigen levels).

Table 3
Summary of Trials Evaluating Primary Hormone Therapy Used Alone for Nonmetastatic Prostate Cancer

Trial	Recruitment Period	Design	AJCC Stage	Hormonal Intervention	No. of Patients	Median Follow-up (years)	DFS	OS
Akaza et al ²³ (2006)	1993–1995	Phase III randomized controlled trial	T1b–3, N0, M0	Leuprolide 3.75 mg IM every 4 weeks ± chlormadinone 100 mg every day; for 24 months	151	10.4	1 years, 91% [*]	1 years, 97% 2 years, 90% 3 years, 81% 4 years, 76% 5 years, 69% 6 years, 64% 7 years, 60% 8 years, 52% 9 years, 48% 10 years, 41%
Saito et al ⁹ (2006)	1992–2003	Retrospective observational clinical trial	T3, N0, M0	(Leuprolide or goserelin) ± (flutamide or bicalutamide); indefinitely	101	4.6		1 years, 95% 2 years, 90% 3 years, 85% 4 years, 76% 5 years, 66% 6 years, 60% 7 years, 50% 8 years, 43% 9 years, 27% 10 years, 17%
Studer et al ³⁴ (2006)	1990–1999	Phase III randomized controlled trial	T1–4, N0–1, M0	Buserelin 6.3 mg SC every 8 weeks, [†] indefinitely; + cyproterone 50 mg PO tid, first 2 weeks	492	7.8		1 years, 96% 2 years, 88% 3 years, 83% 4 years, 76%

Trial	Recruitment Period	Design	AJCC Stage	Hormonal Intervention	No. of Patients	Median Follow-up (years)	DFS	OS
Kawakami et al ³⁵ (2006)	1989–2002	Retrospective observational clinical trial	T1-3, N0, M0	LHRH agonist ± antiandrogen; indefinitely	993	5.0		5 years, 68% 6 years, 61% 7 years, 52% 8 years, 47% 9 years, 41% 10 years, 36%
Iversen et al ³⁶ (2004)	1995–1998	Phase III randomized controlled trial	T1-4, N0-1, M0	Bicalutamide 150 mg PO every day; indefinitely	486	5.3		1 years, 97% 2 years, 93% 3 years, 89% 4 years, 82% 5 years, 73% 5 years, 65%* 6 years, 67%
Schroder et al ³⁷ (2004)	1986–1998	Phase III randomized controlled trial	T1-4, N1-3, M0	Goserelin 3.6 mg SC every month, [†] indefinitely; + cyproterone 50 mg PO tid, first 4 weeks	119	8.7		1 years, 97% 2 years, 94% 3 years, 86% 4 years, 79% 5 years, 72% 6 years, 61% 7 years, 56% 8 years, 47%

Trial	Recruitment Period	Design	AJCC Stage	Hormonal Intervention	No. of Patients	Median Follow-up (years)	DFS	OS
Labrie et al ³⁸ (2002)	1988–1997	Prospective observational clinical trial	T2-3, N0, M0	(Leuprolide 7.5 mg IM every month or goserelin 3.6 mg SC every month or deslorelin 250 µg SC every day) + flutamide 250 mg PO tid; indefinitely	52	7.7	1 years, 94% [‡]	9 years, 40% 10 years, 33% 1 years, 98% 2 years, 96% 3 years, 88% 4 years, 85% 5 years, 85% 6 years, 79% 7 years, 79%
Boccardo et al ³⁹ (2002)	1993–1996	Phase III randomized controlled trial	T3-4, N0, M0	(Goserelin 3.6 mg SC every 4 weeks + flutamide 250 mg PO tid) or bicalutamide 150 mg PO every day; indefinitely	92	4.5	1 years, 85% [*]	1 years, 96% 2 years, 88% 3 years, 80% 4 years, 67% 5 years, 58% 6 years, 49% 7 years, 40%
Tyrrell et al ⁴⁰ (2000)	1986–1987	Phase III randomized controlled trial	T3-4, N0, M0	Goserelin 3.6 mg SC every 4 weeks ± flutamide 250 mg PO tid; indefinitely	267	4.9		1 years, 91% 2 years, 79% 3 years, 67% 4 years, 57% 5 years, 48% 6 years, 41% 7 years, 38% 8 years, 33% 9 years, 25%

Trial	Recruitment Period	Design	AJCC Stage	Hormonal Intervention	No. of Patients	Median Follow-up (years)	DFS	OS
Iversen et al ⁴¹ (1998)	1992–1993	Phase III randomized controlled trial	T3–4, N0, M0	Goserelin 3.6 mg SC every 4 weeks or bicalutamide 150 mg PO every day; indefinitely	480	3.9		10 years, 20% 1 years, 93% 2 years, 84% 3 years, 76% 4 years, 66%

Abbreviations: AJCC, American Joint Commission on Cancer⁵; DFS, disease-free survival; OS, overall survival; IM, intramuscularly; SC, subcutaneously; PO, orally; LHRH, luteinizing hormone–releasing hormone.

* Defined as no clinical evidence of disease (based on local failure or distant metastases).

[†] A small minority of patients in these trials were treated with bilateral orchiectomy instead of hormone therapy.

[‡] Defined as no biochemical evidence of disease (based on prostate-specific antigen levels).