Introduction

Maximal androgen blockade (MAB) versus castration alone in patients with metastatic prostate cancer has been extensively evaluated in randomized trials. The inconsistent results have led to the publication of multiple meta-analyses. The present review examines the evidence from meta-analytic reports to determine whether MAB using agents such as flutamide, nilutamide, and cyproterone acetate (CPA) is associated with a survival advantage.

Methods

We conducted a systematic review of the literature (MEDLINE, EMBASE, and the Cochrane Library through July 2004; CANCERLIT through October 2002) for meta-analyses that compared MAB with castration alone in previously untreated men with metastatic prostate cancer (D1 or D2, N+/M0 or M1). Two reviewers selected papers for eligibility; disagreement was resolved by all the authors through consensus.

Results

The literature search identified six meta-analyses that met the eligibility criteria of the review. Two of those reports were based on individual patient data (IPD), and four were based on data from the published literature. All six meta-analyses pooled data on overall survival.

The best evidence came from the largest meta-analysis, conducted by the Prostate Cancer Trialists Collaborative Group and based on IPD (8725 patients) from 27 trials. That analysis detected no difference in overall survival between MAB and castration alone at 2 or 5 years. However, a subgroup analysis showed that MAB with nonsteroidal anti-androgens (NSAA) was associated with a statistically significant improvement in 5-year survival over castration alone (27.6% vs. 24.7%; \( p = 0.005 \)). The combination of MAB with CPA, a steroidal anti-androgen, was associated with a statistically significant increased risk of death (15.4% vs. 18.1%; \( p = 0.04 \)). Compared with castration alone, MAB was associated with more side effects (that is, gastrointestinal, endocrine function) and reduced quality of life in domains related to treatment symptoms and emotional functioning.

Conclusions

The small survival benefit conferred by MAB with NSAA is of questionable clinical significance given the added toxicity and concomitant decline in quality of life observed in patients treated with MAB. Therefore, combined treatment with flutamide or nilutamide should not be routinely offered to patients with metastatic prostate cancer beyond the purpose of blocking testosterone flare. Monotherapy, consisting of orchietomy or the administration of a luteinizing hormone–releasing hormone agonist is recommended as standard treatment.

KEY WORDS

Prostatic neoplasms, androgen antagonists, hormonal anti-neoplastic agents
1. INTRODUCTION

Prostate cancer is currently the most prevalent form of male cancer in Canada. At diagnosis, 20%–30% of patients will present with advanced or metastatic disease. Of those men, approximately 25% will die from their disease within 2 years. Therapeutic interventions seek not only to increase survival in those patients, but also to improve quality of life (QOL).

The mainstay of treatment for advanced or metastatic prostate cancer is to inhibit the biosynthesis of androgens, the hormones responsible for prostate cancer cell growth. Androgen suppression can be achieved through surgical (bilateral orchiectomy) or medical castration. Medical castration involves the long-term use of luteinizing hormone–releasing hormone (LHRH) agonists. The two methods of castration appear equally effective in removing testicular androgens.

The testes are the major locale for testosterone production; however, the adrenal glands also produce a small but measurable quantity of androgens. It has been hypothesized that removing all circulating androgens—by blocking adrenal androgens in addition to inhibiting testicular androgen production—might be beneficial to patients. Combination treatment, in the form of surgical or medical castration plus administration of an anti-androgen [for example, flutamide, nilutamide, or cyproterone acetate (CPA)] is called “maximal androgen blockade” (MAB).

The use of MAB was first introduced in the early 1980s. Since then, a large number of randomized controlled trials have been conducted to evaluate the efficacy of MAB as compared with castration alone. The trials yielded inconsistent results. Most failed to provide convincing evidence of improved survival with MAB; however, a few of the larger trials detected survival benefits with combined treatment. Low statistical power, study immaturity, compliance to treatment, and imbalances in prognostic indicators between study arms of individual trials were implicated as potential sources of discrepancy.

Recent attempts to determine the treatment efficacy of MAB have involved meta-analyses of the trials. To determine whether MAB is associated with a survival advantage, the present review systematically examines the results of the meta-analyses comparing MAB with castration alone in patients with metastatic prostate cancer.

2. MATERIALS AND METHODS

The present systematic review was originally completed in the context of developing a clinical practice guideline for Cancer Care Ontario’s Program in Evidence-Based Care (PEBC), using the methodology of the Practice Guidelines Development Cycle. The literature was searched by one member of PEBC’s Genitourinary Cancer Disease Site Group. Evidence was reviewed and selected by two members, and disagreements pertaining to eligibility were handled through consensus involving the five members of the writing group. Two reviewers assessed eligible reports for important aspects of methodologic quality as expressed in the Quorom statement.

2.1 Literature Search Strategy

We conducted a systematic search of MEDLINE (1980 through July 2004), EMBASE (1980 through 2004 wk 27), CANCERLIT (1980 through October 2002), and the Cochrane Library (2004, Issue 2) databases. In each database, subject headings were combined with disease-specific, treatment-specific, and design-specific search terms. The reference lists of all articles found, including reviews and articles held in personal files, were reviewed for additional citations. The search was restricted to reports published in the English language.

2.2 Eligibility Criteria

Published reports or abstracts of meta-analyses comparing MAB (orchiectomy or LHRH agonist plus administration of an anti-androgen) with castration alone (orchiectomy or LHRH agonist) in previously untreated men with metastatic prostate cancer (D1 or D2, N+ or M0 or M1) were eligible for inclusion. Papers were required to report overall mortality or disease progression-related outcomes, or both. Adverse effects and QOL were also outcomes of interest.

3. RESULTS

3.1 Literature Search Results

We identified eleven reports representing seven unique meta-analyses. One meta-analysis was excluded because it was based on language, leaving six analyses eligible for inclusion in the review. The meta-analyses pooled individual patient data (IPD) and four pooled summary data from published trial reports (literature-based).

3.1.2 IPD Meta-analyses

Bertagna et al. published the first IPD meta-analysis in 1994. That analysis was limited to seven double-blind, placebo-controlled trials of MAB with nilutamide (1056 patients). An update published in abstract form by Debruyne et al. provided extended follow-up data on survival and disease progression.

In 1995, the Prostate Cancer Trialists’ Collaborative Group (PCTCG) published an IPD meta-analysis that included 22 MAB trials (5710 patients). All randomized trials that compared castration alone to MAB, both published and unpublished, were sought for...
### TABLE 1  Meta-analyses identified by the literature search—descriptions

| Meta-analysis | Flutamide | Trials included in meta-analysis: MAB with CPA |
|---------------|-----------|-----------------------------------------------|
| Individual patient data (IPD) meta-analyses | Bono (ILG), 1998 | Dijkman (IASS), 1997 |
| PCTCG 2000 18 | Eisenberger (NCI/SWOG), 1998 | Bertagna, 1994, 2000 |
| 31 RCTs included in review | Zalcberg (Australia), 1996 | Bélard (CASG), 1990 |
| 27 RCTs provided IPD for meta-analysis | Boccardo (PONCAP), 1993 | Namer, 1990 |
| 12 flutamide trials | Fourcade (France), 1993 | Knonagel, 1989 |
| 8 nilutamide trials | Iversen (DAPROCA), 1993 | Brisset, 1987 |
| 7 CPA trials | Tyrrell (IPCSG), 1991 | Navratil, 1987 |
| 88% of patients staged “metastatic”; 12% staged “locally advanced” | Ferrari (Italy), 1996 | None |
| Bertagna 1994 25, Debruyne 1996 26 | Namer, 1990 | None |
| Included 7 double-blind RCTs | Janknegt (IASS), 1993 | None |
| 7 nilutamide trials | Brisset, 1990 | None |
| % of patients staged D not reported | Namer, 1990 | None |
| Literature-based meta-analyses | Delaere, 1987 | None |
| Schmitt 2003 22 | Bono (ILG), 1998 | Dijkman (IASS), 1997 |
| 20 RCTs included in review | Eisenberger (NCI/SWOG/INT-1015), 1998 | Bertagna, 1994 |
| 14 RCTs provided data for meta-analysis | Zalcberg (Australia), 1996 | Bélard (CASG), 1990 |
| 9 flutamide trials | Boccardo (PONCAP), 1993 | Namer, 1990 |
| 5 nilutamide trials | Denis (EORTC), 1993 | Knonagel, 1989 |
| 96% of patients were stage D2 or M1 | Fourcade (France), 1990 | Brisset, 1987 |
| Aronson 1999 20 | Iversen (DAPROCA), 1990 | Bélard (CASG), 1988 |
| 27 RCTs included in review | Crawford (NCI), 1993 | None |
| 20 RCTs provided data for meta-analysis | Zalcberg (Australia), 1996 | Williams (U.K.), 1990 |
| 9 flutamide trials | Boccardo (PONCAP), 1993 | Klosterhalfen, 1987 |
| 5 nilutamide trials | Denis (EORTC), 1993 | 1999 |
| 6 CPA trials | Fourcade (France), 1993 | None |
| 93% of patients were stage D2 | Tyrrell (IPCSG), 1991 | Robinson (EORTC), 1995 |
| Bennet 1999 23 | Iversen (DAPROCA), 1990 | Jorgensen (SPCG), 1993 |
| 9 RCTs included in review | Crawford (NCI), 1993 | DiSilverio (Italy), 1990 |
| 9 RCTs provided data for meta-analysis | Zalcberg (Australia), 1996 | None |
| 9 flutamide trials | Boccardo (PONCAP), 1993 | None |
| 98% of patients were stage D | Denis (EORTC), 1993 | None |
| Caubet 1997 24 | Fourcade (France), 1993 | None |
| 13 RCTs included in review | Tyrrell (IPCSG), 1991 | None |
| 9 RCTs provided data for meta-analysis | Iversen (DAPROCA), 1990 | None |
| 6 flutamide trials | Crawford (NCI), 1989 | None |
| 3 nilutamide trials | Schulze (WPISG), 1988 | None |
| 57%–100% of patients staged D2 | Boccardo (PONCAP), 1993 | None |
| | Denis (EORTC), 1993 | None |
| | Fourcade (France), 1993 | None |
| | Tyrrell (IPCSG), 1993 | None |
| | Iversen (DAPROCA), 1990 | None |
| | Crawford (NCI), 1989 | None |
| | Schulze (WPISG), 1988 | None |

* The 14 trials listed in Table 1 contributed to the pooled analysis of 2-year survival data. Thirteen trials contributed to the pooled analysis of 1-year and 5-year survival data, respectively.  
MAB = maximal androgen blockade; CPA = cyproterone acetate; PCTCG = Prostate Cancer Trialists’ Collaborative Group; RCTs = randomized controlled trials; ILG = Italian Leuprorelin Group; EORTC = European Organization for Research and Treatment of Cancer; NCI = National Cancer Institute; SWOG = Southwest Oncology Group; PONCAP = Italian Prostatic Cancer Project; DAPROCA = Danish Prostatic Cancer Group; IPCSG = International Prostate Cancer Study Group; WPISG = Westfälische Prostatakarzinom Study Group; IASS = International Andronad Study Group; CASG = Canadian Andronad Study Group; SPCG = Scandinavian Prostatic Cancer Group.
3.2 Outcomes

3.2.1 Overall Survival

IPD Meta-analyses Results from the original PCTCG overview showed a small survival benefit with MAB that was not statistically significant (5-year survival: 22.8% vs. 26.2%; \( p > 0.1 \)) \(^{17} \). In the updated meta-analysis (2000), the PCTCG reported a nonsignificant overall hazard ratio (HR) of 0.96 [95% confidence interval (CI): 0.91–1.01; \( p = 0.11 \)], where ratios less than 1 favoured MAB \(^{18} \) (Table II). Further analyses at different follow-up periods also showed no difference in mortality and suggested an absolute 5-year survival difference of approximately 2% in favour of MAB. Subgroup analyses were performed by method of androgen suppression (orchiectomy vs. LHRH agonist), type of anti-androgen, patient age, stage of disease (metastases vs. no metastases), and non–prostate cancer mortality. With the exception of type of anti-androgen, no significant differences in treatment effect were observed within any of those subgroups. A small and statistically significant survival benefit was detected for MAB with flutamide (HR = 0.92; 95% CI: 0.86–0.98; \( p = 0.02 \)), and a similar but nonsignificant result was observed for nilutamide. MAB with CPA was associated with a significantly worse survival outcome than castration alone (HR = 1.13; 95% CI: 1.01–1.25; \( p = 0.04 \)). Treatment with MAB containing either of the NSAA increased 5-year survival over castration alone by 3% (27.6% vs. 24.7%, \( p = 0.005 \)).

Debruyne \(^{26} \) reported a reduction in the odds of death in patients treated with nilutamide-containing MAB; MAB was associated with a 16% reduction in mortality as compared with castration alone [odds ratio (OR) = 0.84; 95% CI: 0.71–0.99; \( p = 0.038 \)].

Literature-based Meta-analyses Table III summarizes the results for overall mortality from the four literature-based meta-analyses. Aronson \(^{20} \) detected no significant difference in overall mortality at 2 years, although at 5 years, overall mortality was significantly improved with MAB (HR = 0.87; 95% CI: 0.81–0.94). However, the 5-year estimate was based on half the trials (10 trials, 66% of patients) that contributed to the 2-year estimate. No differences in treatment effect were detected in any of the subgroup analyses performed (method of androgen suppression, stage of disease, type of anti-androgen, or trial quality).

Schmitt \(^{22} \) reported no difference in mortality at 1 or 2 years between NSAA MAB and castration-only arms, but 5-year mortality was better with MAB (OR = 1.29; 95% CI: 1.11–1.50; \( p = 0.0009 \)). The two other literature-based reports examining NSAA MAB detected significant reductions in the risk for mortality with MAB that ranged between 10% and 22% \(^{23,24} \).

3.2.2 Disease Progression

Pooled analyses of disease progression data were available from three of the six meta-analyses \(^{22,24,26} \), however, those analyses are limited by the inclusion of a small proportion of MAB trials. Each of those reports combined data from trials of MAB using NSAA. Debruyne \(^{26} \) reported that, among seven trials, the odds of progression were reduced by 17% by MAB with nilutamide (OR = 0.83; 95% CI: 0.70–0.98; \( p = 0.031 \)). Schmitt \(^{22} \) pooled published DFS data at 1 (seven trials), 2 (five trials), and 5 years (two trials); the odds of progression were significantly
reduced with MAB at 1 year (OR = 1.38; 95% CI: 1.15–1.67; p = 0.0006), but not at 2 or 5 years. Caubet et al. reported a 23%–26% reduction in the risk for progression with MAB depending on the type of meta-analytic method used [relative risk (RR) = 0.74, p < 0.001 among seven trials; RR = 0.77, p < 0.001 among seven trials].

A more representative presentation of disease progression data was provided by Aronson et al. They summarized twenty-three trials reporting no significant difference between MAB and castration alone on those measures reporting those data. Nineteen of the trials reported no significant difference between MAB and castration alone on those measures reporting those data. Among six trials reporting...
Six meta-analyses form the evidence base of the present review. Evidence from those analyses suggests that patient outcomes depend on the type of anti-androgen used with MAB. The PCTCG meta-analysis showed that MAB was not associated with a statistically significant improvement in overall survival. However, when outcomes were analyzed by type of anti-androgen, varying treatment efficacies among the agents were evident. Small but statistically significant survival benefits in the range of 3% at 5 years were detected among trials that used MAB with an NSAA (as compared with castration alone). Compared with castration alone, MAB with CPA (a steroidal anti-androgen) was associated with an approximate 3% increased risk of death.

Variability in the magnitude of outcome among meta-analyses may arise from a number of factors, including the number and size of the trials contributing to the pooled estimate, the type of anti-androgens being evaluated, and the use of published summary data or IPD for the analyses. The four literature-based meta-analyses included fewer trials (and fewer patients) than did the PCTCG meta-analysis, but the resulting pooled estimates were of greater magnitude (in favour of MAB) than those generated using IPD. In meta-analyses based on published data, publication bias is more likely to exaggerate treatment effects. Only one of the four literature-based meta-analyses assessed the influence of publication status on the overall pooled result. With IPD, many of the problems associated with published data that introduce bias are eliminated by the ability to incorporate all trial data (published and unpublished), to check the integrity of patient randomization, and to perform proper time-to-event analyses (as compared with fixed time point) by intent-to-treat. Further, because of greater patient numbers, IPD often provides greater statistical power to properly perform subgroup analyses. The methodologic weaknesses of the PCTCG have been identified, but the advantages of using IPD currently make the PCTCG meta-analysis the most reliable evidence comparing MAB with castration alone.

To decide whether MAB should be the preferred treatment for patients, the small survival benefit and the additional adverse effects of combined treatment must be balanced. The clinical significance of a statistically significant 3% improvement in survival with NSAA MAB is questionable, especially when the toxicity of MAB is considered. Data on adverse effects and QOL are limited, but they suggest increased toxicity and a concomitant decline in QOL in MAB-treated patients. In addition, data on disease progression provide further evidence that MAB does not provide superior treatment efficacy over castration alone.

Based on the evidence reviewed, MAB should not be routinely offered to patients with metastatic prostate cancer. Monotherapy, consisting of orchectomy or the administration of an LHRH agonist, should be recommended as standard treatment.

It is important to distinguish between MAB as long-term treatment and short-term use of MAB in the prevention of testosterone flare. In patients treated with...
medical castration, initial treatment with an LHRH agonist is accompanied by a surge in serum testosterone during the first week or weeks of therapy, followed by a decline. That surge may exacerbate existing metastatic disease, therefore short-term use of an anti-androgen is indicated to prevent or block the flare phenomenon. Administration of an anti-androgen is reasonable for a period of 2–4 weeks when treatment with an LHRH agonist is initiated.

Because of the small survival improvement observed with MAB, some clinicians may still choose MAB over monotherapy for individual patients. If MAB is administered with this intent, MAB containing a NSAA is suggested. Given its higher mortality, MAB with CPA should be avoided as compared with castration alone.

The present review did not identify any meta-analyses that included trials evaluating MAB with the newer anti-androgen bicalutamide.

| Table IV: Adverse effects by category, combined results |
|-----------------------------------------------|
| **Adverse effect** | **Castration only** | **MAB: Castration + NSAA** | **MAB: Castration + CPA** | **Any MAB** |
| | **Patients [n (%)]** | **Studies (n)** | **Patients [n (%)]** | **Studies (n)** | **Patients [n (%)]** | **Studies (n)** |
| Cardiovascular | | | | | | |
| Cardiovascular, not specified | 570 (4) | 4 | 387 (4.9) | 3 | 175 (1.7) | 1 | 562 (3.9) | 4 |
| Edema | 569 (3.2) | 3 | 293 (2) | 1 | 277 (6.5) | 2 | 570 (4.2) | 3 |
| Endocrine | | | | | | |
| Hot flashes | 2954 (40.1) | 16 | 2789 (40) | 12 | 488 (52.7) | 4 | 3277 (41.9) | 16 |
| Gynecomastia | 1441 (9.4) | 10 | 1987 (7) | 9 | 257 (17.5) | 2 | 2244 (8.2) | 11 |
| Breast tenderness or pain | 649 (7.7) | 5 | 1206 (5.1) | 5 | 257 (6.6) | 2 | 1463 (5.4) | 7 |
| Impotence | 515 (71.1) | 5 | 362 (66) | 4 | 156 (82.1) | 1 | 518 (70.8) | 5 |
| Decreased libido | 519 (70.1) | 5 | 367 (65.4) | 4 | 156 (78.8) | 1 | 523 (69.4) | 5 |
| Gastrointestinal (GI) | | | | | | |
| GI, not specified | 959 (2.3) | 7 | 768 (10.3) | 6 | 175 (0.6) | 1 | 943 (8.5) | 7 |
| Nausea or vomiting | 1872 (3.2–7.1) | 8 | 1851 (5.6–9.2) | 8 | 0 (0) | 0 | 1851 (5.6–9.2) | 8 |
| Diarrhea | 1464 (2.2) | 6 | 1458 (8.2) | 6 | 0 (0) | 0 | 1458 (8.2) | 6 |
| GI pain | 124 (1.6) | 2 | 122 (7.4) | 2 | 0 (0) | 0 | 122 (7.4) | 2 |
| Hepatic | | | | | | |
| Hepatic, not specified | 1197 (1.3) | 4 | 2004 (5) | 6 | 0 (0) | 0 | | |
| Increased liver enzymes | 483 (2.7) | 3 | 474 (6.8) | 3 | 0 (0) | 0 | | |
| Ophthalmologic | | | | | | |
| Ophthalmologic, not specified | 407 (5.4) | 3 | 396 (29) | 3 | NR | NR | |

MAB = maximal androgen blockade; NSAA = nonsteroidal anti-androgen; CPA = cyproterone acetate; NR = not reported. Adapted, with permission, from Aronson et al. 20, Appendix II, Tables II-6 to II-10.

| Table V: Adverse effects leading to withdrawal from treatment, combined results |
|-----------------------------------------------|
| **Treatment** | **Studies (n)** | **Treatment group (n)** | **Withdrawals from treatment [n (%)]** |
| | | | | |
| Leuprolide (1 daily) | 1 | 268 | 0 (0) |
| Goserelin (3.6, 1-month) | 11 | 1679 | 33 (2) |
| Goserelin (10.8, 3-month) | 2 | 77 | 1 (1.3) |
| Busarelin (0.4) | 1 | 72 | 3 (4.2) |
| Orchiectomy + nilutamide (150) | 2 | 271 | 38 (14) |
| Orchiectomy + nilutamide (300) | 3 | 209 | 24 (11.5) |
| Orchiectomy + CPA (150) | 1 | 102 | 3 (2.9) |
| Orchiectomy + CPA (300) | 1 | 20 | 2 (10) |
| Orchiectomy or LHRH agonist or both | 28 | 4275 | 82 (1.9) |
| Goserelin (3.6, 1-month) + flutamide (750) | 5 | 846 | 94 (11.1) |
| Orchiectomy or LHRH agonist + flutamide (750) or both | 9 | 2804 | 233 (8.3) |
| Orchiectomy or LHRH agonist + bicalutamide (50) or both | 1 | 401 | 41 (10.2) |
| Orchiectomy or LHRH agonist + nilutamide (150 or 300) or both | 5 | 480 | 62 (12.9) |
| Orchiectomy or LHRH agonist + CPA (150 or 300) or both | 2 | 122 | 5 (4.1) |

CPA = cyproterone acetate; LHRH = luteinizing hormone–releasing hormone. From Aronson et al. 20, Appendix II, Table II-11. Used with permission.
based MAB has been compared in a randomized trial only with combination flutamide. A castration-only control arm was deemed unethical at the time the bicalutamide trial was designed because MAB was considered standard care (over monotherapy). The trial compared bicalutamide plus an LHRH agonist with flutamide plus an LHRH agonist and detected a survival improvement with bicalutamide that was not statistically significant (median survival: 180 weeks vs. 148 weeks; HR = 0.87; 95% CI: 0.72–1.05; p = 0.15). With the exception of a higher incidence of hematuria, bicalutamide appeared less toxic than flutamide. Klotz et al. recently re-analyzed the data from the bicalutamide trial and the PTCTCG meta-analysis (subgroup of trials comparing MAB with flutamide versus castration alone) to calculate an estimate of the likely benefit of MAB with bicalutamide relative to castration alone. They reported an estimated HR of 0.80 (95% CI: 0.66–0.98) for bicalutamide-based MAB versus castration alone, which equates to a 20% relative reduction in the risk of death with bicalutamide. On the basis of those data, use of bicalutamide in patients who are offered MAB would also be reasonable. A randomized trial comparing MAB with bicalutamide to castration alone is ongoing, but that trial is assessing bicalutamide at a dose of 80 mg.

Before beginning MAB, selected patients should be advised of the magnitude of the survival benefit and on possible adverse effects and their potential impact on QOL.

Progressive prostate cancer is usually detected through a rise in prostate-specific antigen (PSA), which usually predates clinical or radiologic evidence of metastases. Most patients included in MAB trials had documented metastases (stage D2), and whether results from those trials are generalizable to patients with a rising PSA without evidence of metastatic disease is unknown. Only a handful of trials have analyzed outcomes by extent of metastatic involvement. Most of those have not shown a benefit of MAB in patients with minimal disease, although the subgroup analyses included small numbers of patients. Only 12% of patients (approximately 1000) in the PTCTCG meta-analysis had documented non-metastatic prostate cancer. An analysis of those patients showed slightly worse survival with MAB, although the difference did not reach statistical significance. Prospective randomized trials to investigate the efficacy of MAB in that subgroup of patients are warranted.

5. CONCLUSIONS

The small survival benefit conferred by MAB with NSAA is of questionable clinical significance given the added toxicity and concomitant decline in QOL observed in patients treated with MAB. Therefore, combined treatment with flutamide or nilutamide should not be routinely offered to patients with metastatic prostate cancer (beyond the purpose of blocking testosterone flare). Monotherapy consisting of orchiectomy or the administration of an LHRH agonist is recommended as standard treatment.

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# Jack Barkin, Glenn Bauman, Julie Bowen, Michael Brundage, Joseph Chin, Richard Choo, Juanita Crook, Libni Eapen, Neil Fleshner, Barbara Markman, William Orovan, Kathleen Pritchard, Thomas Short, and John Srigley also contributed to the development of this systematic review through input in the discussion of the evidence. Please see the Cancer Care Ontario Program in Evidence-based Care Practice Guidelines Initiative Web site (www.cancercare.on.ca/access_PEBC) for a complete list of current Genitourinary Cancer Disease Site Members.
**APPENDIX A** Meta-analysis quality, as evaluated using the quality of reporting of meta-analyses (Quorom) statement; closed circles denote fully described items, open circles denote partially described items, and dashes denote items not described.

| Quorum checklist item                              | **IPD Literature-based** | Meta-analyses |
|----------------------------------------------------|--------------------------|---------------|
|                                                    | PCTCG 2000               | PCTCG 1995    |
|                                                    | Bertagna 1994 (25)       | Debruyne 1996 (26) |
|                                                    | Schmitt 2003 (22)        | Bennett 1999 (23) |
|                                                    | Caubet 1997 (24)        |               |

**INTRODUCTION**
- Clinical problem
- Biologic rationale for treatment
- Rationale for review

**METHODS**
- Searching
  - Information sources (e.g., databases, registers)
  - Restrictions (e.g., years, publication status, language)
- Selection
  - Inclusion/exclusion criteria (e.g., defining population, intervention, outcomes, and study design)
- Validity assessment
  - Criteria and process used (e.g., masked conditions, quality assessment, and their findings)
- Data abstraction
  - Process used (e.g., completed independently or in duplicate)
- Study characteristics
  - Type of study design
  - Participants’ characteristics
  - Details of intervention
  - Outcome definitions
  - How clinical heterogeneity assessed
- Quantitative data synthesis
  - Measures of effect (e.g., relative risk, hazard ratio)
  - Method of combining results (e.g., statistical testing, CIs)
  - Handling of missing data
  - How statistical heterogeneity was assessed
  - Rationale for any *a priori* sub-group and sensitivity analyses
  - Assessment of publication bias

**RESULTS**
- Trial flow
- Study characteristics
- Quantitative data synthesis
- Present summary results (for each treatment group in trial and each outcome)
- Present data needed to calculate effect sizes and CIs in ITT analyses (e.g., 2×2 tables of counts, means, proportions, SDs)

**DISCUSSION**
- Summarize key findings
- Discuss clinical inferences based on internal and external validity
- Interpret results in light of the totality of evidence
- Describe potential biases in the review process (e.g., publication bias)
- Suggest future research agenda

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**IPD** = individual patient data; **PCTCG** = Prostate Cancer Trialists’ Collaborative Group; **CIs** = confidence intervals; **ITT** = intent-to-treat; **SDs** = standard deviations.
### Literature search strategy

**MEDLINE**

1. practice guidelines/
2. practice guideline.pt.
3. practice guideline?.ti, tw.
4. meta-analysis/
5. metaanal:.ti, tw.
6. meta-anal:.ti, tw.
7. metanal:.ti, tw.
8. systematic review?.ti, tw.
9. systematic overview?.ti, tw.
10. quantitative overview?.ti, tw.
11. quantitative synthesis?.s, ti, tw.
12. randomized controlled trials/
13. randomized controlled trial, phase iii, pt.
14. random allocation/
15. double-blind method/
16. single-blind method/
17. random:.ti, tw.
18. controlled clinical trial, pt.
19. clinical trial, phase iii, pt.
20. or/1–19
21. leuprolide, ti, tw.
22. lupon, ti, tw.
23. goserelin, ti, tw.
24. zoladex, ti, tw.
25. buserelin, ti, tw.
26. suprefact, ti, tw.
27. flutamide, ti, tw.
28. eulexin, ti, tw.
29. nilutamide, ti, tw.
30. anandron, ti, tw.
31. nilandron, ti, tw.
32. bicalutamide, ti, tw.
33. casodex, ti, tw.
34. cyproterone acetate, ti, tw.
35. androcur, ti, tw.
36. diethylstilbestrol, ti, tw.
37. des, ti, tw.
38. total androgen blockade, ti, tw.
39. maximal androgen blockade, ti, tw.
40. combined androgen blockade, ti, tw.
41. androgen ablation, ti, tw.
42. exp gonadorelin/
43. exp androgen antagonists/
44. exp diethylstilbestrol/
45. or/21–44
46. exp castration/
47. castration, ti, tw.
48. orchidectomy, ti, tw.
49. orchitectomy, ti, tw.
50. monotherapy, ti, tw.
51. or/46–50
52. prostatic neoplasms/
53. prostat: cancer, ti, tw.
54. *prostatic neoplasms/dt
55. or/52–54
56. 45 and 51 and 55
57. 56 and 20

**EMBASE**

1. exp randomized controlled trial/
2. exp controlled study/
3. Major Clinical Study/
4. Clinical trial/
5. or/1–4
6. random:.ti, tw.
7. 5 and 6
8. exp meta-analysis/
9. meta-analysis, ti, tw.
10. (meta-anal: or meta anal:).ti, tw.
11. (quantitative overview: or quantitative synth:).ti, tw.
12. (systematic review: or systematic overview:).ti, tw.
13. exp practice guideline/
14. practice guideline, ti, tw.
15. or/8–14
16. 7 or 15
17. exp prostate tumor/
18. exp prostate cancer/
19. (prostat: cancer or prostat: carcinoma: or prostat: tumor: or prostat: malignan:).ti, tw.
20. *prostate tumor/dt
21. *prostate cancer/dt
22. or/17–21
23. total androgen blockade, ti, tw.
24. maximal androgen blockade, ti, tw.
25. androgen ablation, ti, tw.
26. flutamide, ti, tw.
27. eulexin, ti, tw.
28. nilutamide, ti, tw.
29. anandron, ti, tw.
30. nilandron, ti, tw.
31. bicalutamide, ti, tw.
32. casodex, ti, tw.
33. cyproterone acetate, ti, tw.
34. androcur, ti, tw.
35. diethylstilbestrol, ti, tw.
36. des, ti, tw.
37. exp gonadorelin/
38. exp androgen antagonists/
39. exp diethylstilbestrol/
40. or/23–39
41. exp castration/
42. castration, ti, tw.
43. orchidectomy, ti, tw.
44. orchitectomy, ti, tw.
45. monotherapy, ti, tw.
46. leuprolide, ti, tw.
47. lupon, ti, tw.
48. goserelin, ti, tw.
49. zoladex, ti, tw.
50. buserelin, ti, tw.
51. suprefact, ti, tw.
52. or/41–51
53. 22 and 40 and 52
54. 53 and 16