Prostate cancer (metastatic)

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QUESTIONS

INTERVENTIONS

TREATMENT

Likely to be beneficial

Unknown effectiveness

Likely to be ineffective or harmful

ANDROGEN INDEPENDENT CANCER

Likely to be beneficial

Unknown effectiveness

Footnote

*Categorisation based on observational evidence; RCTs unlikely to be conducted.

Key points

- Prostate cancer is the sixth most common cancer in the world and 85% of cases are diagnosed in men over the age of 65 years.

  Prostate cancer metastasises predominantly to bone, which may cause pain, weakness, paralysis and death.

- Androgen deprivation may reduce mortality compared with no treatment in men with metastatic prostate cancer, but no one regimen has been shown to be more effective compared with the others.

  Immediate androgen deprivation therapy may slightly improve 10 year survival compared with deferred therapy in men with advanced, asymptomatic prostate cancer, and may reduce the risk of major complications.

  Combined androgen blockade (androgen deprivation plus non-steroidal antiandrogen) may improve 5 year survival compared with androgen deprivation alone.

  We don't know whether intermittent androgen deprivation improves survival, morbidity or quality of life.

- Chemotherapy plus corticosteroids may reduce pain and improve quality of life in men with symptomatic metastatic prostate cancer that has progressed despite androgen deprivation, compared with corticosteroids alone.

  Newer chemotherapy agents (mitoxantrone, suramin) may improve symptoms but have not been shown to increase overall survival. Older chemotherapy agents have not been shown to be beneficial.

  External beam radiation may completely relieve pain in about a quarter of men with bone metastases, but no one regimen has been shown to be more effective than the others.

  Radionuclide therapy with strontium-89 may reduce the number of new sites of pain compared with placebo in men given external beam radiation, but its effect on survival is unclear.

  We don't know whether bisphosphonates improve symptoms or survival in men with metastatic prostate cancer, as few studies have been found.

DEFINITION See prostate cancer (non-metastatic). Androgen independent metastatic disease is defined as disease that progresses despite androgen deprivation.

INCIDENCE/ PREVALENCE See prostate cancer (non-metastatic).

AETIOLOGY/ RISK FACTORS	See prostate cancer (non-metastatic).
PROGNOSIS	Prostate cancer metastasises predominantly to bone. Metastatic prostate cancer can result in pain, weakness, paralysis, and death.
AIMS OF INTERVENTION	To reduce mortality and disability; to control symptoms and maximise quality of life; and to minimise adverse effects of treatment.
OUTCOMES	Survival; response in terms of symptoms and signs; quality of life; adverse effects of treatment.
METHODS	*Clinical Evidence* search and appraisal September 2002.

QUESTION What are the effects of treatment for men with metastatic prostate cancer?

OPTION ANDROGEN DEPRIVATION

We found limited evidence from RCTs suggesting that androgen deprivation reduced mortality compared with no initial treatment. One systematic review and one subsequent RCT found no evidence of a difference in effectiveness between different methods of androgen deprivation (orchidectomy, diethylstilbestrol, and gonadorelin analogues).

Benefits:

Versus no initial treatment:
We found no systematic review or recent RCTs comparing androgen deprivation versus no initial treatment. Three RCTs (about 4000 men with all stages of prostate cancer) performed between 1959 and 1975 compared androgen deprivation (diethylstilbestrol [stilboestrol], orchidectomy [see glossary], or oestrogens) versus no initial treatment. They found no difference in overall survival. Reanalysis of updated data from these RCTs found a modest survival advantage with androgen deprivation. [1] The report did not provide statistical details.

Different types of androgen deprivation:
We found one systematic review [2] and one subsequent RCT. [3] The systematic review (search date 1998, 24 RCTs, > 6600 men with metastatic prostate cancer) found no significant differences between treatment groups in overall progression free survival, time to progression, or overall survival in the most of the trials. [2] It found no significant differences in 2 year survival between orchidectomy and the gonadorelin analogues leuprolide or goserelin acetate (HR 1.26, 95% CI 0.91 to 1.39), diethylstilbestrol (HR 0.98, 95% CI 0.76 to 1.27), or non-steroidal antiandrogen monotherapy (HR 1.22, 95% CI 0.99 to 1.50). One large subsequent RCT (915 men with advanced prostate cancer stage T0–4, M1; see table 1 in prostate cancer non-metastatic) compared parenteral oestrogen versus total androgen ablation (orchidectomy or triptorelin). [3] It found no significant difference in mortality at follow up (mortality at 18 months' median follow up 266/458 [58%] with oestrogen *v* 269/457 [59%] with total androgen ablation; RR 0.99, 95% 0.89 to 1.10).

Harms:

All forms of androgen deprivation are known to be associated with vasomotor flushing, loss of libido, gynaecomastia, weight gain, osteoporosis, and loss of muscle mass; we found insufficient prospective frequency data for these adverse effects. One RCT (915 men with metastatic prostate cancer) found that androgen deprivation by orchidectomy, or by combination of gonadotrophin releasing hormone analogue with an antiandrogen, induces significantly more hot flushes than polyestradiol phosphate (1 or more flushes, 336/452 [74.3%] *v* 135/449 [30.1%]; RR 2.5, 95% CI 2.1 to 2.9; NNH 3, 95% CI 2 to 3). [4] Diethylstilbestrol is associated with an increased risk of cardiovascular events, gastric irritation, and allergic reactions, and for these reasons is not used routinely. [1] Orchidectomy has cosmetic and potential psychological consequences. Gonadorelin analogues may cause an initial clinical flare owing to transient increases in androgen levels.

Comment:

Androgen deprivation therapy has been used as the standard of care for men with metastatic disease because of the frequency and duration of effect; therefore, there are no contemporary randomised trials with a no treatment arm. The lack of apparent benefit in earlier trials [1] was probably because of the high cardiovascular event rate associated with high dose diethylstilbestrol.

OPTION IMMEDIATE VERSUS DEFERRED ANDROGEN DEPRIVATION

One systematic review found limited evidence of a small survival advantage at 10 years for immediate androgen deprivation therapy in men with advanced, asymptomatic prostate cancer. There was no significant change in overall survival at 1, 2, or 5 years. The risk of major complications is increased in men whose treatment is deferred until disease progression.

Benefits: We found one systematic review (search date 2001, 4 RCTs, 2167 men with locally advanced prostate cancer or asymptomatic metastases), which compared immediate versus deferred androgen deprivation therapy. [5] Outcome measures were overall survival, progression free survival, and complications due to prostate cancer at 1, 2, 5, and 10 years. The review found a significant improvement in overall survival only at 10 years, favouring the immediate therapy group (at 1 year: OR 1.16, 95% CI 0.90 to 1.49; at 2 years: OR 1.08, 95% CI 0.89 to 1.33; at 5 years: 1.19, 95% CI 0.95 to 1.50; and at 10 years: 1.50, 95% CI 1.04 to 2.16). Progression free survival was consistently better in all studies in the immediate therapy group, but disease specific survival was not significantly different at any point. One large RCT included in the review reported complications due to disease progression. It found an approximate halving of the risk of major complications, including spinal cord compression (9/469 [1.9%] with immediate treatment *v* 23/465 [4.9%] with deferred treatment; P < 0.025), ureteric obstruction (33/469 [7%] with immediate treatment *v* 55/465 [12%] with deferred treatment: P < 0.025), extraskeletal metastases (37/469 [7.9%] with immediate treatment *v* 55/465 [12%] with deferred treatment; P < 0.05), and a non-significant reduction in pathological fractures (11/469 [2.3%] with immediate treatment *v* 21/465 [4.5%] with deferred treatment; P > 0.05). [6] The trial did not make clear the time interval over which outcomes were recorded, although this seemed to be at least 10 years.

Harms: We found no systematic review or RCTs with prospective data on adverse effects of immediate compared with deferred androgen deprivation in men with metastatic prostate cancer. Adverse effects of immediate therapy were not analysed in the systematic review. However, adverse events reported in one trial were much more common in the immediate treatment arm (OR 5.66, 95% CI 2.76 to 11.62). [5]

Comment: The systematic review included two RCTs published in the 1970s, and the remaining two in 1997 and 1999. Treatments received and indications varied between RCTs. [5] Androgen deprivation therapy may be offered at an earlier stage of disease than that considered for participants in the systematic review.

OPTION COMBINED ANDROGEN BLOCKADE (ANDROGEN DEPRIVATION AND ANTIANDROGEN)

Systematic reviews found limited evidence of a 2–5% improvement in 5 year survival associated with combined androgen blockade (androgen deprivation plus a non-steroidal antiandrogen) compared with androgen deprivation alone.

Benefits: We found two systematic reviews. [7] [8] The first and largest systematic review (search date not stated, 27 RCTs, 8275 men, most of whom had stage D2 disease [see table 1 in non-metastatic prostate cancer]) compared different methods of androgen deprivation (orchidectomy, flutamide, gonadorelin analogue, or a combination of these [see glossary] versus androgen deprivation alone. [7] It found no clearly significant difference in mortality (72.4% with androgen deprivation alone *v* 70.4% with combined blockage; RR 0.96, 95% CI 0.94 to 1.00). Exclusion of seven trials (1784 men) of cyproterone acetate found a small reduction in mortality from combined androgen blockade (20 RCTs, 6491 men: 75.3% with androgen deprivation alone *v* 72.4% combined with non-steroidal antiandrogens; ARR 2.9%; P = 0.005). The second systematic review (search date 1998, 21 RCTs, 6871 men) compared androgen deprivation alone (orchidectomy or gonadorelin analogues) versus androgen deprivation combined with steroidal or non-steroidal antiandrogens (cyproterone, nilutamide, and flutamide). [8] Overall, the review found a significant improvement in 5 year survival in men receiving combined androgen blockade (HR 0.871, 95% CI 0.805 to 0.942). No significant differences were seen at 1 or 2 years' follow up. Five years' follow up was only provided in 10 of the 21 RCTs.

Harms: The most recent review did not report on adverse events. [8] An overlapping, earlier systematic review of 6320 men in 20 RCTs found that, compared with monotherapy (androgen deprivation alone), combined androgen blockade using non-steroidal antiandrogens increased the risk of diarrhoea (10% with combined antiandrogen blockade *v* 2% with monotherapy), gastrointestinal pain (7% with combined antiandrogen blockade *v* 2% with monotherapy), and non-specific ophthalmologic events (29% with combined antiandrogen blockade *v* 5% with monotherapy). [9] Flutamide is also associated with a higher rate of anaemia (8% *v* 5%). [4]

Comment: The authors of the most recent overview note the need for quality of life data, given the modest survival benefit and the potential for toxicity. [8]

OPTION INTERMITTENT VERSUS CONTINUOUS ANDROGEN DEPRIVATION

We found insufficient evidence on the effects of intermittent androgen deprivation in men with metastatic prostate cancer.

Benefits: We found no systematic review and no RCTs assessing the long term effects of intermittent androgen deprivation on mortality, morbidity, or quality of life.

Harms: We found insufficient evidence to assess harms.

Comment: None.

QUESTION What are the effects of treatments for men with symptomatic androgen independent metastatic disease?

OPTION CHEMOTHERAPY

RCTs found limited evidence that chemotherapy with some new agents (mitoxantrone or suramin) plus corticosteroids reduced pain, lengthened palliation, and improved quality of life, but found no improvement in overall survival compared with corticosteroids alone. Earlier RCTs failed to demonstrate any benefit of chemotherapy in men with metastatic prostate cancer.

Benefits: We found no systematic review. Multiple earlier RCTs found no benefit in men with metastatic prostate cancer of various chemotherapy drugs, including mitomycin C, cyclophosphamide, doxorubicin, methotrexate, 5-fluorouracil, or estramustine phosphate (EMP). [10] [11] [12] [13] [14] In the largest of these studies, 419 men with untreated metastatic or locally advanced prostate cancer were randomised to orchiectomy alone versus orchiectomy plus EMP. [12] There was no difference between groups in overall survival or time to progression. Subgroup analyses demonstrated no benefit in the group of men with metastatic disease, but did demonstrate significant delay in time to progression in younger patients (aged < 73 years). An earlier study randomised 319 men to androgen deprivation therapy, combination of androgen deprivation therapy and chemotherapy (cyclophosphamide plus 5-fluorouracil), or EMP alone. [10] It found no significant differences between the groups in progression free or overall survival. However, we found three more recent RCTs demonstrating benefit of newer chemotherapy agents in men with advanced prostate cancer. [15] [16] [17] The first of these (161 men with symptomatic androgen independent metastatic prostate cancer) compared mitoxantrone plus prednisone versus prednisone alone. [15] Men taking placebo were crossed over to mitoxantrone at disease progression or if not responding at 6 weeks. It found that men receiving chemotherapy were significantly more likely to experience pain reduction (29% with chemotherapy plus prednisone *v* 12% with prednisone alone; P = 0.01), enjoy longer pain relief (43 *v* 18 weeks; P < 0.0001), and show improvements in quality of life. It found no significant difference in overall survival. The comparison was done before crossover. The second unblinded RCT (242 men) compared mitoxantrone plus hydrocortisone versus hydrocortisone alone. [16] Men were allowed alternative chemotherapy after disease progression. It found no significant difference in survival (median duration 12.3 months with mitoxantrone plus hydrocortisone *v* 12.6 months with hydrocortisone; P = 0.77). However, pain and analgesic use were significantly reduced after chemotherapy. The third RCT (458 men with prostate cancer and painful bone metastases) compared suramin plus hydrocortisone versus placebo plus hydrocortisone. [17] Men on placebo were allowed to cross over to suramin at disease progression. It found that chemotherapy reduced pain (pain response 43% *v* 28%; P = 0.01). It found no significant effect on survival (median survival 286 days with suramin *v* 279 days with placebo; reported as non-significant, statistics not reported).

Harms: The RCTs reported no treatment related deaths. There were nine episodes of febrile neutropenia (World Health Organization grade 3 or 4) among 130 men treated with 796 courses of mitoxantrone. [17] Five men experienced cardiac arrhythmias or decreased left ventricular ejection fraction, including two who developed congestive heart failure. A higher incidence of nausea and cardiovascular events was observed in men receiving EMP plus orchiectomy compared with orchiectomy alone. [12]

Comment: The crossover design in the recent chemotherapy trials reduced the contrast between treatment arms and increased the study size in order to find small survival benefits, as most people allocated to placebo eventually received chemotherapy. Early, unpublished clinical trials have suggested high response rates for taxane based chemotherapy, and an intergroup RCT comparing it with established regimens is ongoing.

OPTION EXTERNAL BEAM RADIATION THERAPY

We found no RCTs comparing external beam radiation versus palliative treatments other than radionuclides. Observational evidence suggests complete pain relief in about a quarter of people, and placebo controlled RCTs would probably be considered unethical. A systematic review of one RCT in men with symptomatic bone metastases found no difference in survival between external beam radiation and strontium-89; however, strontium-89 was associated with significantly fewer new sites of pain and reduced need for additional ra-

diotherapy. One systematic review found no significant differences in pain relief between different radiation treatment fraction schedules and doses.

Benefits:

Versus no treatment or placebo:
We found one systematic review (search date 1996, no RCTs), which found no RCTs comparing external beam radiation versus no treatment or placebo. [18] We found no additional RCTs (see comment below). Eleven observational studies of 1486 people found complete pain relief in 368/1373 (27%) of people and at least 50% pain relief in 628/1486 (42%) of people treated with external beam radiotherapy (see comment below).

External beam versus radionuclides:
We found one systematic review (search date 1996, 1 RCT, 284 men). [18] The RCT (305 men) compared external beam radiation versus strontium-89. [19] It found that strontium-89 was associated with significantly fewer new sites of pain ($P < 0.05$), and significantly reduced the need for additional radiotherapy ($P < 0.04$). However, it found no significant difference in survival (median survival 33 weeks with strontium-89 *v* 28 weeks with radiotherapy; $P = 0.10$). [19]

Different schedules and doses:
We found one systematic review (search date 1996, 9 RCTs, 1486 men with symptomatic bone metastases from a variety of malignancies). [18] The RCTs compared different radiation treatment fractionation schedules and doses of external beam radiation. It found minimal differences in pain relief between different fractionation schedules and doses.

Harms:

The systematic review reported that adverse event reporting was poor. [18]

Comment:

In men with painful bone metastases, it would be considered unethical to compare external beam radiation versus placebo or no treatment. It is reasonable to consider the effectiveness of no treatment to be zero, as spontaneous remission has not been described in bone metastases from prostate cancer.

OPTION RADIONUCLIDE THERAPY

One systematic review found one small RCT in men with symptomatic bone metastases, which found no difference in survival between external beam radiation plus placebo and external beam radiation plus strontium-89. However, strontium-89 significantly reduced the number of new sites of pain. One small subsequent RCT in men with painful bone metastases found that samarium-153 significantly reduced pain scores compared with placebo. A second small subsequent RCT in a selected population found an improvement in survival with strontium-89 compared with placebo, but the results are difficult to generalise.

Benefits:

Versus other palliative treatments:
We found one systematic review (search date 1996, 1 RCT, 126 men) [18] and two subsequent RCTs. [20] [21] The RCT in the systematic review (126 men) compared external beam radiation plus strontium-89 versus external beam radiation plus placebo. [22] Although the RCT found no significant difference in overall survival or symptom relief, strontium-89 significantly reduced the number of new sites of pain ($P < 0.02$) and significantly reduced analgesic requirement (17% stopped taking analgesics with radionuclide *v* 2% on placebo; $P < 0.05$). The first subsequent RCT (118 people with painful bone metastases from multiple primaries) compared samarium-153 lexidronam 0.5 mCi/kg versus samarium-153 lexidronam 1 mCi/kg versus placebo over 4 weeks. [21] It found that samarium-153 1 mCi/kg significantly reduced pain scores compared with placebo at weeks 1–4 ($P < 0.034$). Samarium-153 0.5 mCi/kg reduced pain scores significantly more than placebo at week 1 ($P = 0.044$) but not at other weeks ($P > 0.078$). The second subsequent RCT (72 men with androgen independent, metastatic prostate cancer who had initially responded to "induction" chemotherapy with ketoconazole and doxorubicin alternating with estramustine and vinblastine) compared maintenance chemotherapy (doxorubicin) with and without strontium-89. [20] From follow up of 67 people to death, it was estimated that strontium-89 significantly increased median overall survival (27.7 months with chemotherapy plus strontium-89 *v* 16.8 months with chemotherapy alone; $P < 0.002$) and significantly increased time to progression (13.9 months with chemotherapy plus strontium-89 *v* 7.0 months with chemotherapy alone; $P < 0.0001$) (see comment below).

Versus external beam radiation:
See external beam versus radionuclides under benefits of external beam radiation therapy, p 4
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Harms:

Strontium-89 was associated with thrombocytopenia (World Health Organization grade 3 or 4) in 7–33% of men and leukopenia (World Health Organization grade 3 or 4) in 3–12% of men. [18] [23] Other radionuclides with selective bone localisation have similar rates of haematological toxicity.

There was no significant difference between treatment schedules and doses of external beam radiation in rates of nausea, vomiting, or diarrhoea. [24]

Comment: One RCT [23] included in previous versions of *Clinical Evidence* was removed because of its small size and weak methods. The results of the second subsequent RCT are difficult to generalise because a selected population was used, and participants reacted favourably to a particular chemotherapy regimen. [20]

OPTION BISPHOSPHONATES

One systematic review of two RCTs found insufficient evidence about the effects of bisphosphonates compared with no treatment.

Benefits: One systematic review (search date not stated, 2 RCTs, 156 men with prostate cancer and symptomatic bone metastases) found no reduction in bone pain with bisphosphonates compared with no bisphosphonates. [25]

Harms: The systematic review identified 18 RCTs of bisphosphonates in men with bone metastases from a variety of cancers. [25] No RCT reported major toxicity. Treatment with pamidronate was associated with increased frequency of anterior uveitis and episcleritis. [25]

Drug safety alert:

Since the last update of this review, a drug safety alert has been issued by the FDA on severe musculoskeletal pain associated with bisphosphonates (http://www.fda.gov/cder/drug/infopage/bisphosphonates/default.htm).

Comment: Both RCTs in the systematic review [25] had weak methods; one did not use a pain scale, whereas the other assessed etidronate, a bisphosphonate that is pharmacologically unsuitable for treating bone metastases. One RCT found potential benefit of pamidronate in preventing bone loss in men receiving androgen deprivation therapy, but it was not designed to assess effect on disease progression.

GLOSSARY

Androgen deprivation Orchiectomy, gonadorelin analogue (leuprolide or goserelin), or estrogenic treatment.
Antiandrogen Androgen receptor blockers such as flutamide, nilutamide or bicalutamide.
Orchidectomy Also known as orchiectomy, meaning surgical removal of the testicles.

REFERENCES

1. Byar DP, Corle DK. Hormone therapy for prostate cancer: results of the Veterans Administration Cooperative Urologic Research Group studies. *NCI Monogr* 1988;7:165–170.[PubMed]
2. Seidenfeld J, Samson DJ, Hasselblad V, et al. Single-therapy androgen suppression in men with advanced prostate cancer: a systematic review and meta-analysis. *Ann Intern Med* 2000;132:566–577. Search date 1998; primary sources Medline, Cancerlit, Embase, The Cochrane Library, and Current Contents.[PubMed]
3. Hedlund PO, Henriksson P. Parenteral estrogen versus total androgen ablation in the treatment of advanced prostate carcinoma: effects on overall survival and cardiovascular mortality. *Urology* 2000;55:328–332.[PubMed]
4. Spetz A, Hammar M, Lindberg B, et al. Prospective evaluation of hot flashes during treatment with parenteral estrogen or complete androgen ablation for metastatic carcinoma of the prostate. *J Urol* 2001;166:517–520.[PubMed]
5. Nair B, Wilt T, MacDonald R, et al. Early versus deferred androgen suppression in the treatment of advnaced prostatic cancer. In: The Cochrane Library, Issue 3, 2002. Oxford: Update Software. Search date 2001; primary sources Medline, Cancerlit, Embase, Cochrane Controlled Trials Register, VA Cochrane Prostate Disease and Urologic Cancer Register, and Current Contents.
6. Medical Research Council Prostate Cancer Working Party Investigators Group. Immediate versus deferred treatment for advanced prostatic cancer: initial results of the Medical Research Council trial. *Br J Urol* 1997;79:235–246.[PubMed]
7. Prostate Cancer Clinical Trialists' Collaborative Group. Maximum androgen blockade in advanced prostate cancer: an overview of the randomized trials. *Lancet* 2000;355:1491–1498. Search date not stated; primary sources computerised literature search, proceedings of congresses, contacts with authors, trial groups, and pharmaceutical industry.[PubMed]
8. Samson DJ, Seidenfeld J, Schmitt B, et al. Systematic review and meta-analysis of monotherapy compared with combined androgen blockade for patients with advanced prostate carcinoma. *Cancer* 2002;95:361. Search date 1998; primary sources Medline, Embase, Cancerlit, Cochrane databases, and Current Contents.[PubMed]
9. Schmitt B, Wilt TJ, Schellhammer PF, et al. Combined androgen blockade with non-steroidal antiandrogens for advanced prostate cancer: a systematic review. *Urology* 2001;57:727–732. Search date not stated; primary sources Blue Cross and Blue Shield Association's Technology Evaluation Center data set, Cochrane Controlled Trials Register, Cochrane Central Register, and the Veterans Administration Cochrane Prostate Disease and Urologic Malignancy Register.[PubMed]
10. Murphy GP, Huben RP, Priore R. Results of another trial of chemotherapy with and without hormones in patients with newly diagnosed metastatic prostate cancer. *Urology* 1986;28:36.[PubMed]
11. Saxman S, Ansari R, Drasga R, et al. Phase III trial of cyclophosphamide versus cyclophosphamide, doxorubicin, and methotrexate in hormone-refractory prostatic cancer: A Hoosier Oncology Group study. *Cancer* 1992;70:2488.[PubMed]
12. Janknegt RA, Boon TA, Van De Beek C, et al Combined hormono/chemotherapy as primary treatment for metastatic prostate cancer: A randomized, multicenter study of orchiectomy alone versus orchiectomy plus estramustine phosphate. *Urology* 1997;49:411.[PubMed]
13. Fontana D, Bertetto O, Fasolis G, et al. Randomized comparison of goserelin acetate versus mitomycin C plus goserelin acetate in previously untreated prostate cancer patients with bone metastases. *Tumori* 1998;84:39.[PubMed]
14. De Reijke TM, Keuppens, FI, Whelan P, et al. Orchiectomy and orchiectomy plus mitomycin C for metastatic prostate cancer in patients with poor prognosis: the final results of a European Organization for Research in Cancer Therapy Genitourinary Group Trila. *J Urol* 1999;162:1658.[PubMed]
15. Tannock IF, Osoba D, Stockler MR, et al. Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points. *J Clin Oncol* 1996;14:1756–1764.[PubMed]
16. Kantoff PW, Halabi S, Conaway M, et al. Hydrocortisone with or without mitoxantrone in men with hormone-refractory prostate cancer: results of the Cancer and Leukemia Group B 9182 Study. *J Clin Oncol* 1999;17:2506–2513.[PubMed]
17. Small EJ, Marshall E, Reyno L, et al. Suramin therapy for patients with symptomatic hormone-refractory prostate cancer: results of a randomised phase III trial comparing suramin plus hydrocortisone to placebo plus hydrocortisone. *J Clin Oncol* 2000;18:1440–1450.[PubMed]
18. McQuay HJ, Carroll D, Moore RA. Radiotherapy for painful bone metastases: a systematic review. *Clin Oncol* 1997;9:150–154. Search date 1996; primary sources Medline, the Oxford Pain Relief database, Embase, Cochrane Library, and reference lists.
19. Quilty PM, Kirk D, Bolger JJ, et al. A comparison of the palliative effects of strontium-89 and external beam radiotherapy in metastatic prostate cancer. *Radiother Oncol* 1994;31:33–40.[PubMed]
20. Tu S, Millikan RE, Mengistu B, et al. Bone-targeted therapy for advanced androgen-independent carcinoma of the prostate: a randomized Phase II trial. *Lancet* 2001;357:336–341.[PubMed]
21. Serafini AN, Houston SJ, Resche I, et al. Palliation of pain associated with metastatic bone cancer using samarium-153 lexidronam: a double-blind placebo-controlled clinical trial. *J Clin Oncol* 1998;16:1574–1581.[PubMed]
22. Porter AT, McEwan AJ, Powe JE, et al. Results of a randomized Phase-III trial to evaluate the efficacy of strontium-89 adjuvant to local field external beam irra-

diation in the management of endocrine resistant metastatic prostate cancer. *Int J Radiat Oncol Biol Phys* 1993;25:805–813.[PubMed]

23. Maxon HR, Schroder LE, Hertzberg VS, et al. Rhenium-186(Sn)HEDP for treatment of painful osseous metastases: results of a double-blind crossover comparison with placebo. *J Nucl Med* 1991;32:1877–1881.[PubMed]

24. Robinson RG, Preston DF, Schiefelbein M, et al. Strontium 89 therapy for the palliation of pain due to osseous metastases. *JAMA* 1995;274:420–424. Search date 1994; primary source Medline.[PubMed]

25. Bloomfield DJ. Should bisphosphonates be part of the standard therapy of patients with multiple myeloma or bone metastases from other cancers? An evidence-based review. *J Clin Oncol* 1998;16:1218–1225. Search date not stated; primary sources Medline, hand search of major cancer journals, reference lists, and contact with experts.[PubMed]

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