

Medical management of metastatic prostate cancer

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SUMMARY

Androgen deprivation therapy has an important role in the medical treatment of advanced and metastatic prostate cancer.

The treatment of metastatic prostate cancer is influenced by whether the patient's disease has progressed on androgen deprivation therapy or not. It is considered to be castrate-resistant disease if the cancer has progressed despite adequate suppression of androgens.

Chemotherapy using docetaxel or cabazitaxel and anti-androgen drugs such as abiraterone and enzalutamide can be used to treat castrate-resistant disease. Radium-223 is an option for patients with bony metastases.

Metastatic castrate-resistant prostate cancer is now considered a chronic illness as the life expectancy of patients has almost doubled due to the new treatments. General practitioners are therefore more likely to encounter patients with disease- and treatment-related complications.

Introduction

Prostate cancer is the second most common cause of cancer death in Australian men. When localised, it can be cured with surgery or radiotherapy, but some patients will relapse with either overt metastases or an isolated rise in prostate specific antigen (PSA). A proportion of these patients are found to have a local relapse and can have salvage therapy (generally radiation), but the remainder of cases are considered to have incurable advanced disease. There is also a proportion of men who have metastases when the prostate cancer is first diagnosed.

The management of advanced disease is predominantly medical. While the cancer is incurable, it is not untreatable.

Androgen deprivation therapy

Androgen deprivation therapy underlies prostate cancer therapy at all stages of disease. It aims to reduce the growth of cancer cells in the prostate by reducing the testosterone concentration.

Surgical castration is effective but not commonly used mainly due to a perceived risk of psychological distress. Medical castration can be achieved with gonadotrophin-releasing hormone (GnRH) analogues such as goserelin or leuprorelin and GnRH antagonists such as degarelix. It works by suppressing luteinising hormone and therefore testicular testosterone production.

Androgen deprivation therapy is usually started when metastatic disease is diagnosed. However,

delaying treatment until the onset of symptoms does not decrease overall survival. Either approach can be used.¹

Intermittent versus continuous therapy

The common complications of androgen deprivation therapy include sexual dysfunction, mood disturbance, change in body composition and osteoporosis.^{2,3} In view of these adverse effects intermittent dosing has been considered. This is a period of androgen deprivation therapy followed by a break until disease progression, if a good response was attained. The optimal duration of androgen deprivation therapy is fairly arbitrary as the studies have looked into various periods ranging from three months to three years.

In patients with PSA relapse only (no overt metastases), intermittent therapy has been shown to be non-inferior to continuous dosing. There was also a better quality of life with intermittent dosing.⁴

In patients with objective metastases, intermittent androgen deprivation therapy had numerically worse outcomes than continuous treatment, but the study was statistically inconclusive. There was less sexual dysfunction and better mental health in the intermittent group, but this effect disappeared by 15 months when most people were back on continuous treatment.⁵ If short-term quality of life is important, even at the risk of possible worse survival, intermittent therapy is a reasonable approach.

Metastatic castration-resistant prostate cancer

Prostate cancer is termed 'castrate resistant' when the disease progresses despite continuous androgen deprivation therapy. After this, further treatment is needed to maintain disease control. Androgen deprivation therapy is continued as patients who continue it survive longer than those who stop.⁶

Micro-levels of peritumoural androgen have been shown to persist despite castration levels of serum testosterone.⁷ Anti-androgens are therefore added to androgen deprivation therapy.

'First-generation' anti-androgens

The early anti-androgens included non-steroidal drugs (such as bicalutamide, nilutamide and flutamide) and the steroidal drug cyproterone acetate. Even though these drugs have less benefit compared to the newer drugs, they are widely used in castrate-resistant disease as first-line drugs to achieve combined androgen blockade. This is for several reasons – current prescribing rules state that new anti-androgens are only subsidised in Australia for patients who are unfit for, or have already progressed after, chemotherapy and many men wish to delay having chemotherapy. In addition, because of the longitudinal nature of prostate cancer treatment, these anti-androgens allow additional time on oral treatments. Many men will respond and these drugs can delay the time to progression and the need for newer drugs which can then be used later in the disease course. Bicalutamide is most widely used due to its once-daily dosing and better tolerability.⁸

Common adverse effects of first-line anti-androgens are similar to those of androgen deprivation therapy (hot flushes, sexual dysfunction). Nilutamide causes changes in light accommodation (reversible on cessation). Cyproterone acetate increases cardiovascular risk and is not widely used.

These drugs can also be used sequentially as second-line therapy after progression on another anti-androgen as there may be a brief response in a selected cohort of patients. For example, flutamide could be tried after a patient progresses despite taking bicalutamide.⁹ However, in the current era, the older anti-androgens are rarely used in second- or third-line settings.

New anti-androgens

The new anti-androgens target various steps of the androgen production pathway which is crucial in tumour growth. They are added to androgen deprivation therapy. These anti-androgens are used in men not fit for chemotherapy, and in those whose disease has progressed on previous chemotherapy.

In men who are fit for chemotherapy the drugs are usually reserved until after the disease progresses on first-line docetaxel chemotherapy. This is due to the current prescribing restrictions and also due to the ability to give the drugs later when these men may no longer be well enough for further chemotherapy.

Abiraterone acetate

The cytochrome P450 17 alpha-hydroxylase and C17,20-lyase are enzymes involved in testosterone synthesis. They mediate conversion of pregnenolone-like steroids into androgens. Abiraterone is an oral inhibitor of these enzymes so it halts both extragonadal and testicular androgen synthesis.¹⁰

Abiraterone improves the survival of patients with metastatic castrate-resistant prostate cancer whether they are chemotherapy (docetaxel) naïve or have cancer that has progressed post chemotherapy.^{11,12} Co-administration of prednisone is important to minimise the abiraterone-induced reduction of serum cortisol and increase of mineralocorticoid. Patients need to be monitored for hypertension, hypokalaemia and peripheral oedema as well as the elevation of hepatic aminotransferases which may require a temporary suspension of treatment.

Enzalutamide

Enzalutamide is an androgen-receptor signalling inhibitor.¹³ It improves survival in metastatic castrate-resistant prostate cancer, and is significantly more effective than the older drug, bicalutamide.^{14,15} Enzalutamide has activity both before and after chemotherapy.^{15,16} Adverse effects include hypertension, fatigue, memory impairment, falls and, less commonly, seizures.

Chemotherapy

Anthracyclines and taxanes have been used to treat metastatic castrate-resistant prostate cancer.

Mitoxantrone

Mitoxantrone is an anthracycline compound. It was the first approved cytotoxic drug for the treatment of metastatic castrate-resistant prostate cancer and was widely used before docetaxel was available. Mitoxantrone significantly improved cancer symptoms and quality of life, but did not improve survival.¹⁷ A small number of patients may benefit from mitoxantrone and other older cytotoxic drugs such as cyclophosphamide and etoposide in third- and fourth-line settings.

Docetaxel

Docetaxel is a taxane that has been studied in a variety of cancers. It was the first cytotoxic drug to show a survival benefit for patients with prostate cancer.

It became the standard of care for metastatic castrate-resistant disease after a phase III trial reported a median survival benefit of 2.4 months over mitoxantrone (18.9 vs 16.5 months). Although adverse events were more common with docetaxel, some patients had a better quality of life.¹⁸ Adverse effects include neutropenia, fatigue, diarrhoea, hair loss, nail changes and sensory neuropathy.

Cabazitaxel

Cabazitaxel is a newer taxane. In patients with cancer that has progressed following or during docetaxel chemotherapy it improved survival by 2.4 months compared with mitoxantrone (15.1 vs 12.7 months).¹⁹

Cabazitaxel is generally better tolerated than docetaxel with the common adverse effects of myelosuppression, diarrhoea, nausea and fatigue. A recent study evaluating a lower dose of cabazitaxel (20 mg/m² every three weeks) reported non-inferiority in overall survival compared to the standard dose (25 mg/m² every three weeks). There was less myelosuppression and infection which may benefit frail older patients.²⁰

Metastatic hormone-sensitive prostate cancer

Studies of the optimal sequence of treatment have found that early introduction of the drugs previously reserved for castrate-resistant disease can improve overall survival in other patients with metastases. This has been proven for both abiraterone and docetaxel. The studies introduced these drugs shortly after the diagnosis of metastatic disease, at the time androgen deprivation therapy was commenced. The survival benefit for both drugs was highly significant, with an additional survival of more than one year.²¹⁻²⁴ At present, only the prescribing of docetaxel is not restricted for this condition. Abiraterone is not reimbursed. A study into upfront enzalutamide is ongoing.

Radiopharmaceuticals

Radiopharmaceuticals, such as radium-223, mimic calcium and are incorporated into bone growth around bony metastases. Radium-223 emits alpha particles. These emit more energy, yet have a much shorter range than beta or gamma particles and therefore provide more targeted radiation without causing significant collateral damage to surrounding bone marrow.

Radium-223 is a well-tolerated treatment when added to standard androgen deprivation therapy. It resulted in a 30% improvement in overall survival and the delay of the onset of first skeletal-related events when compared to placebo in patients with bony metastases.²⁵ Lutetium-177-prostate-

specific membrane antigen therapy has also been shown to be active in metastatic castrate-resistant prostate cancer.²⁶

Supportive care

Modern therapies have prolonged survival (see Table) so now advanced prostate cancer is akin to a chronic disease. The median survival in metastatic disease can be more than five years with best available treatment.^{23,24} In biochemical relapse (raised PSA), median survival in the modern era is around nine years.⁴ As more treatments become accessible, it is likely that the duration of survival will continue to extend. As a result, men with prostate cancer have more time to accumulate physical and psychological adverse effects.

Bone health

Long-term androgen deprivation therapy increases the risk of osteoporosis. Indirect evidence suggests that there is a role for smoking cessation and weight-bearing exercise in reducing the risk of osteoporosis and fractures.²⁷ Bisphosphonates and denosumab can reduce the risk of fracture in men on long-term androgen deprivation therapy.^{28,29} It is important for these men to have regular measurements of bone mineral density to assess their risk of fractures.

Bisphosphonates and denosumab prevent skeletal events (e.g. fracture, need for radiotherapy or surgery) in patients with bony metastases. Denosumab is more effective than bisphosphonates.³⁰ Both therapies are associated with hypocalcaemia and a very small risk of osteonecrosis of the jaw. It is therefore recommended that patients should take calcium supplements and have dental reviews before starting these drugs.

Vitamin D supplementation is recommended in patients with vitamin D deficiency and in all patients taking denosumab or bisphosphonates.

Mental health

Common treatments for prostate cancer including prostatectomy and androgen deprivation therapy have significant risks of sexual, urinary and bowel dysfunction which impair health-related quality of life.³¹ There is an increased risk of depression in men on androgen deprivation therapy.³² Using intermittent androgen deprivation therapy improves short-term, but not long-term, mental health outcomes.^{4,5}

Physical function

Loss of lean muscle mass is a known adverse effect of androgen deprivation therapy. A randomised trial of an aerobic and resistance exercise program showed a benefit in muscle mass, strength, physical function and balance in men on androgen deprivation therapy.³³

Table Summary of survival data for metastatic prostate cancer treatments

Intervention	Comparator	Study design	Survival benefit	Median survival duration	Comment
Hormone-sensitive disease					
Docetaxel (at start of androgen deprivation therapy)	Androgen deprivation therapy alone (standard of care)	CHAARTED Phase III RCT 792 men, unblinded, dual arm ²³	13.6 months (metastatic only)	57.6 months (docetaxel) vs 44 months	Study included patients with local recurrence as well as metastatic disease
Abiraterone (at start of androgen deprivation therapy) ²¹	Androgen deprivation therapy alone (standard of care)	STAMPEDE Phase III RCT 2962 men, unblinded, multiarm ²⁴	10 months (metastatic and non-metastatic)	81 months (docetaxel) vs 71 months	Median overall survival not reached in study follow-up Not PBS-funded in Australia
Castrate-resistant disease					
Docetaxel chemotherapy ¹⁸	Mitoxantrone	Unblinded phase III RCT 1006 men, 3 arms (2 docetaxel arms - weekly or 3-weekly)	2.4 months	18.9 months (3-weekly docetaxel) vs 16.5 months (mitoxantrone)	Weekly docetaxel was less effective than 3-weekly
Cabazitaxel chemotherapy ¹⁹	Mitoxantrone	Unblinded phase III RCT 755 men	2.4 months	15.1 months (cabazitaxel) vs 12.7 months (mitoxantrone)	The men in this study had already progressed after docetaxel, hence the shorter overall survival than in the other docetaxel study
Abiraterone after chemotherapy ¹¹	Prednisone	Blinded phase III RCT 1195 men	3.9 months	14.8 months (abiraterone) vs 10.9 months (placebo/ prednisone)	
Abiraterone before chemotherapy ¹²	Prednisone	Blinded phase III RCT 1088 men	4.4 months	34.7 (abiraterone) vs 30.3 months (prednisone alone)	
Enzalutamide after chemotherapy ¹⁵	Placebo	Blinded phase III RCT 1199 men	4.8 months	18.4 months (enzalutamide) vs 13.6 months (placebo)	
Enzalutamide before chemotherapy ¹⁶	Placebo	Blinded phase III RCT 1717 men	65% vs 14% had not progressed at 1 year, 29% risk reduction for death at close of study (medians not reached)		Need more mature data for accurate survival benefit
Enzalutamide before chemotherapy ¹⁴	Bicalutamide	Unblinded RCT 396 men	Median time to progression 19.4 months with enzalutamide vs 5.7 months with bicalutamide		Data is for progression of disease, not survival - follow-up not long enough for survival yet
Radium-223 ²⁵	Placebo	Blinded RCT 921 men	3.6 months	14.9 (radium-223) vs 11.3 months (placebo)	Not PBS-funded in Australia

PBS Pharmaceutical Benefits Scheme RCT randomised controlled trial

Note: Survival duration in each trial is measured from when the trial intervention started. In some cases this is from diagnosis of prostate cancer and in other cases this is after all standard therapies have failed. Care should be taken in interpretation of absolute survival duration as it is highly context specific.

Body composition changes

Androgen deprivation therapy results in increased fat deposition and loss of lean body mass. As a result, the incidence of type 2 diabetes increases.³⁴ There have also been concerns about an increase in cardiovascular risk, but this has not been consistently shown. It appears that men with recent cardiovascular events are at an increased risk of further events during androgen deprivation therapy,³⁵ whereas in other men with prostate cancer the risk does not seem to increase.³⁴

Stopping treatment

Eventually, prostate cancer evolves to the point that it is no longer sensitive to the treatment currently available. This is usually when androgen deprivation therapy, new anti-androgens and chemotherapy have all been tried but the disease continues to progress. At this point, if the patient is well enough and wishes to persist with treatment, they could be referred for a clinical trial. Alternatively, different combinations

of older anti-androgens or less effective but broad-spectrum cytotoxic drugs can be tried. Ultimately, the success rate of these approaches is low and palliative care should be instigated in parallel. Equally, it is appropriate to stop active treatment when the major drugs with proven survival benefit have been exhausted. In practice it is usually a combination of patient preference and patient fitness that are the deciding factors.

Conclusion

Advanced prostate cancer is a complex disease with an often prolonged course. There are many treatment options which are used sequentially and should be tailored for each patient. There is a significant need for GPs to provide high-quality supportive care alongside the specialist care in what is now a chronic disease. ◀

Conflict of interest: none declared



SELF-TEST QUESTIONS

True or false?

3. Androgen deprivation therapy is ceased once prostate cancer metastasises.

4. Docetaxel improves survival in hormone-sensitive metastatic prostate cancer.

Answers on page 173

REFERENCES

- Loblaw DA, Virgo KS, Nam R, Somerfield MR, Ben-Josef E, Mendelson DS, et al.; American Society of Clinical Oncology. Initial hormonal management of androgen-sensitive metastatic, recurrent, or progressive prostate cancer: 2006 update of an American Society of Clinical Oncology practice guideline. *J Clin Oncol* 2007;25:1596-605. <https://doi.org/10.1200/JCO.2006.10.1949>
- Gay HA, Sanda MG, Liu J, Wu N, Hamstra DA, Wei JT, et al.; Prostate Cancer Outcomes and Satisfaction with Treatment Quality Assessment Consortium. External beam radiation therapy or brachytherapy with or without short-course neoadjuvant androgen deprivation therapy: results of a multicenter, prospective study of quality of life. *Int J Radiat Oncol Biol Phys* 2017;98:304-17. <https://doi.org/10.1016/j.ijrobp.2017.02.019>
- Nguyen PL, Alibhai SM, Basaria S, D'Amico AV, Kantoff PW, Keating NL, et al. Adverse effects of androgen deprivation therapy and strategies to mitigate them. *Eur Urol* 2015;67:825-36. <https://doi.org/10.1016/j.eururo.2014.07.010>
- Crook JM, O'Callaghan CJ, Duncan G, Dearnaley DP, Higano CS, Horwitz EM, et al. Intermittent androgen suppression for rising PSA level after radiotherapy. *N Engl J Med* 2012;367:895-903. <https://doi.org/10.1056/NEJMoal201546>
- Hussain M, Tangen CM, Berry DL, Higano CS, Crawford ED, Liu G, et al. Intermittent versus continuous androgen deprivation in prostate cancer. *N Engl J Med* 2013;368:1314-25. <https://doi.org/10.1056/NEJMoal212299>
- Taylor CD, Elson P, Trump DL. Importance of continued testicular suppression in hormone-refractory prostate cancer. *J Clin Oncol* 1993;11:2167-72. <https://doi.org/10.1200/JCO.1993.11.11.2167>
- Montgomery RB, Mostaghel EA, Vessella R, Hess DL, Kalhorn TF, Higano CS, et al. Maintenance of intratumoral androgens in metastatic prostate cancer: a mechanism for castration-resistant tumor growth. *Cancer Res* 2008;68:4447-54. <https://doi.org/10.1158/0008-5472.CAN-08-0249>
- Kucuk O, Fisher E, Moinpour CM, Coleman D, Hussain MH, Sartor AO, et al. Phase II trial of bicalutamide in patients with advanced prostate cancer in whom conventional hormonal therapy failed: a Southwest Oncology Group study (SWOG 9235). *Urology* 2001;58:53-8. [https://doi.org/10.1016/S0090-4295\(01\)01010-X](https://doi.org/10.1016/S0090-4295(01)01010-X)
- Miyake H, Hara I, Eto H. Clinical outcome of maximum androgen blockade using flutamide as second-line hormonal therapy for hormone-refractory prostate cancer. *BJU Int* 2005;96:791-5. <https://doi.org/10.1111/j.1464-410X.2005.05766.x>
- Attard G, Reid AH, Yap TA, Raynaud F, Dowsett M, Settatree S, et al. Phase I clinical trial of a selective inhibitor of CYP17, abiraterone acetate, confirms that castration-resistant prostate cancer commonly remains hormone driven. *J Clin Oncol* 2008;26:4563-71. <https://doi.org/10.1200/JCO.2007.15.9749>
- de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, et al.; COU-AA-301 Investigators. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med* 2011;364:1995-2005. <https://doi.org/10.1056/NEJMoal014618>
- Ryan CJ, Smith MR, Fizazi K, Saad F, Mulders PF, Sternberg CN, et al.; COU-AA-302 Investigators. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naïve men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol* 2015;16:152-60. [https://doi.org/10.1016/S1470-2045\(14\)71205-7](https://doi.org/10.1016/S1470-2045(14)71205-7)
- Tran C, Ouk S, Clegg NJ, Chen Y, Watson PA, Arora V, et al. Development of a second-generation antiandrogen for treatment of advanced prostate cancer. *Science* 2009;324:787-90. <https://doi.org/10.1126/science.1168175>
- Penson DF, Armstrong AJ, Concepcion R, Agarwal N, Olsson C, Karsh L, et al. Enzalutamide versus bicalutamide in castration-resistant prostate cancer: The STRIVE Trial. *J Clin Oncol* 2016;34:2098-106. <https://doi.org/10.1200/JCO.2015.64.9285>
- Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, et al.; AFFIRM Investigators. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med* 2012;367:1187-97. <https://doi.org/10.1056/NEJMoal207506>
- Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, et al.; PREVAIL Investigators. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med* 2014;371:424-33. <https://doi.org/10.1056/NEJMoal405095>
- Tannock IF, Osoba D, Stockler MR, Ernst DS, Neville AJ, Moore MJ, 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;14:1756-64. <https://doi.org/10.1200/JCO.1996.14.6.1756>

18. Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, et al.; TAX 327 Investigators. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 2004;351:1502-12. <https://doi.org/10.1056/NEJMoa040720>
19. de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I, et al.; TROPIC Investigators. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet* 2010;376:1147-54. [https://doi.org/10.1016/S0140-6736\(10\)61389-X](https://doi.org/10.1016/S0140-6736(10)61389-X)
20. Eisenberger M, Hardy-Bessard AC, Kim CS, Géczi L, Ford D, Mourey L, et al. Phase III study comparing a reduced dose of cabazitaxel (20 mg/m²) and the currently approved dose (25 mg/m²) in postdocetaxel patients with metastatic castration-resistant prostate cancer-PROSELICA. *J Clin Oncol* 2017;35:3198-206. <https://doi.org/10.1200/JCO.2016.72.1076>
21. James ND, de Bono JS, Spears MR, Clarke NW, Mason MD, Dearnaley DP, et al.; STAMPEDE Investigators. Abiraterone for prostate cancer not previously treated with hormone therapy. *N Engl J Med* 2017;377:338-51. <https://doi.org/10.1056/NEJMoa1702900>
22. Fizazi K, Tran N, Fein L, Matsubara N, Rodriguez-Antolin A, Alekseev BY, et al.; LATITUDE Investigators. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. *N Engl J Med* 2017;377:352-60. <https://doi.org/10.1056/NEJMoa1704174>
23. Sweeney CJ, Chen YH, Carducci M, Liu G, Jarrard DF, Eisenberger M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *N Engl J Med* 2015;373:737-46. <https://doi.org/10.1056/NEJMoa1503747>
24. James ND, Sydes MR, Clarke NW, Mason MD, Dearnaley DP, Spears MR, et al.; STAMPEDE investigators. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. *Lancet* 2016;387:1163-77. [https://doi.org/10.1016/S0140-6736\(15\)01037-5](https://doi.org/10.1016/S0140-6736(15)01037-5)
25. Parker C, Nilsson S, Heinrich D, Helle SI, O'Sullivan JM, Fosså SD, et al.; ALSYMPCA Investigators. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med* 2013;369:213-23. <https://doi.org/10.1056/NEJMoa1213755>
26. Emmett L, Willows K, Violet J, Shin J, Blanksby A, Lee J. Lutetium 177 PSMA radionuclide therapy for men with prostate cancer: a review of the current literature and discussion of practical aspects of therapy. *J Med Radiat Sci* 2017;64:52-60. <https://doi.org/10.1002/jmrs.227>
27. Lee CE, Leslie WD, Czaykowski P, Gingerich J, Geirnaert M, Lau YK. A comprehensive bone-health management approach for men with prostate cancer receiving androgen deprivation therapy. *Curr Oncol* 2011;18:e163-72. <https://doi.org/10.3747/co.v18i4.746>
28. Smith MR, Egerdie B, Hernández Toriz N, Feldman R, Tammela TL, Saad F, et al.; Denosumab HALT Prostate Cancer Study Group. Denosumab in men receiving androgen-deprivation therapy for prostate cancer. *N Engl J Med* 2009;361:745-55. <https://doi.org/10.1056/NEJMoa0809003>
29. Serpa Neto A, Tobias-Machado M, Esteves MA, Senra MD, Wroclawski ML, Fonseca FL, et al. Bisphosphonate therapy in patients under androgen deprivation therapy for prostate cancer: a systematic review and meta-analysis. *Prostate Cancer Prostatic Dis* 2012;15:36-44. <https://doi.org/10.1038/pcan.2011.4>
30. Fizazi K, Carducci M, Smith M, Damião R, Brown J, Karsh L, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *Lancet* 2011;377:813-22. [https://doi.org/10.1016/S0140-6736\(10\)62344-6](https://doi.org/10.1016/S0140-6736(10)62344-6)
31. Litwin MS, Lubeck DP, Henning JM, Carroll PR. Differences in urologist and patient assessments of health related quality of life in men with prostate cancer: results of the CaPSURE database. *J Urol* 1998;159:1988-92. [https://doi.org/10.1016/S0022-5347\(01\)63222-1](https://doi.org/10.1016/S0022-5347(01)63222-1)
32. Nead KT, Sinha S, Yang DD, Nguyen PL. Association of androgen deprivation therapy and depression in the treatment of prostate cancer: a systematic review and meta-analysis. *Urol Oncol* 2017;35:664.e1-664.e9. <https://doi.org/10.1016/j.urolonc.2017.07.016>
33. Galvão DA, Taaffe DR, Spry N, Joseph D, Newton RU. Combined resistance and aerobic exercise program reverses muscle loss in men undergoing androgen suppression therapy for prostate cancer without bone metastases: a randomized controlled trial. *J Clin Oncol* 2010;28:340-7. <https://doi.org/10.1200/JCO.2009.23.2488>
34. Alibhai SM, Duong-Hua M, Sutradhar R, Fleshner NE, Warde P, Cheung AM, et al. Impact of androgen deprivation therapy on cardiovascular disease and diabetes. *J Clin Oncol* 2009;27:3452-8. <https://doi.org/10.1200/JCO.2008.20.0923>
35. O'Farrell S, Garmo H, Holmberg L, Adolphsson J, Stattin P, Van Hemelrijck M. Risk and timing of cardiovascular disease after androgen-deprivation therapy in men with prostate cancer. *J Clin Oncol* 2015;33:1243-51. <https://doi.org/10.1200/JCO.2014.59.1792>