Modern treatment of metastatic prostate cancer

The treatment of prostate cancer with remote metastases has advanced greatly in recent years. Treatment options are dependent on the extent of the metastases, the patient's general condition and wishes, and the treatment response. We present an overview of the latest options for systemic treatment of patients with metastatic prostate cancer, based on availability in Norway.

Henriette Veiby Holm
holm.henriette@gmail.com
Department of Surgery
Bærum Hospital

Alv A. Dahl
National Advisory Unit on Late Effects After Cancer Treatment
Oslo University Hospital, Norwegian Radium Hospital

Olbjørn Harald Klepp
Department of Oncology
Helse Møre og Romsdal

Sophie D. Fosså
National Advisory Unit on Late Effects After Cancer Treatment
Oslo University Hospital, Norwegian Radium Hospital

MAIN POINTS

The aim of treatment in both the castration-sensitive and castration-resistant phases is to maintain disease control and an acceptable quality of life for as long as possible

In the castration-sensitive phase, early use of chemotherapy should be considered in addition to castration therapy

In the castration-resistant phase, the options are chemotherapy and newer hormone therapy, but the order and initiation of treatment should be tailored to the individual

As the incidence of localised prostate cancer has increased, the proportion of patients with remote metastases at the time of diagnosis has fallen from 25 % to 7 %, while the total number of patients with remote metastases has remained stable (~ 400/year) since the 1980s in Norway (1). Five-year relative survival for patients with remote metastases at the time of diagnosis has increased from 19 % (in the period 1981–85) to 34 % (2011–15) (1). Prostate cancer spreads primarily to regional lymph nodes and to the skeleton, but spreading to the liver, lungs, peritoneum, adrenal glands and brain may also occur.

The standard treatment for non-metastatic prostate cancer is radical prostatectomy or radiation therapy. Any increase in the level of prostate specific antigen (PSA) following radical prostatectomy is evidence of renewed tumour activity. Recurrence after radical radiation therapy is suspected if the PSA level has increased by at least 2 nmol/l above the nadir associated with radiation therapy (2, 3). Upon suspicion of renewed tumour activity, the general practitioner should refer the patient to the specialist health care service (2, 3).

The clinical course of metastatic prostate cancer begins in the majority of patients with a *castration-sensitive phase*, which lasts on average three years (4). During this phase disease development can be inhibited by eliminating the growth-stimulatory effect of testosterone by surgical or medical castration. Sooner or later cancer cells will be stimulated by minimal androgen levels in the blood (e.g. from the adrenal glands) or grow independently of androgen stimulation. The disease will then have entered the *castration-resistant phase*. The first sign of this is often an increase in PSA level, or possibly radiological detection of increasing remote metastases, prior to the patient experiencing any symptoms.

In contrast to 10–15 years ago, there are now several life-extending treatments for patients with castration-resistant metastatic prostate cancer: new hormone therapies, chemotherapy, radioisotopes and immunotherapy (3).

The *Norwegian national action programme with guidelines for diagnosis, treatment and follow-up of prostate cancer* has yet to be updated with the newest treatment options for metastatic prostate cancer (2). We therefore wish to provide an overview of the latest options for systemic treatment of this patient group based on international guidelines and recent key studies (3, 5, 6). Local treatment of metastases is discussed briefly.

Treatment of patients with remote metastases

The aim of treatment is to extend life and to relieve symptoms while ensuring the best possible quality of life. Prognosis is dependent on the metastatic burden (number/location, PSA level), general condition and response to treatment beyond castration.

We present two algorithms for the systemic treatment of metastatic prostate cancer: one for the castration-sensitive phase (Fig. 1) and another for the castration-resistant phase (Fig. 2).

Castration-sensitive phase

The principle behind treatment in the castration-sensitive phase is to abolish the stimulation of cancer cells by inhibiting testicular testosterone production and thereby reducing androgen levels in the blood: so-called androgen deprivation therapy (ADT). Surgical or medical castration are suitable forms of androgen deprivation therapy (Fig. 1). Anti-androgen therapy, which blocks androgen receptors, is generally not recommended as monotherapy for metastatic prostate cancer, but may be considered by a specialist in the event of pronounced side effects of castration therapy (2, 3). Treatment in this phase is initiated in the specialist health care service and can be continued in the primary health care service.

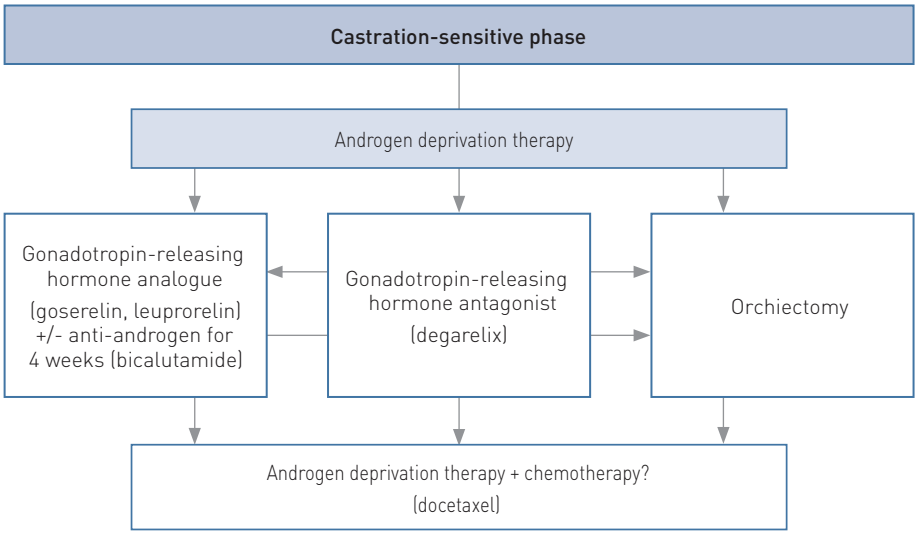

Figure 1 *Our proposed treatment algorithm for castration-sensitive metastatic prostate cancer. In the castration-sensitive phase, treatment consists of medical or surgical castration plus early chemotherapy in patients with widespread metastases and good general condition*

Surgical castration, orchiectomy, should be used if a very rapid reduction in testosterone levels is required (2, 3). A therapeutic decrease in testosterone levels is achieved from day one. However, orchiectomy has become less relevant following the introduction of medical castration.

Medical castration with analogues of gonadotropin-releasing hormone (luteinising hormone-releasing hormone, LHRH) – goserelin and leuprorelin (Zoladex, Eligard, Enanton, Procren) – is the most widely used systemic first line treatment of metastatic prostate cancer (2). The drugs are injected monthly or every 3–6 months.

Gonadotropin-releasing hormone analogues initially increase testosterone levels, which may cause an acute exacerbation of the clinical condition known as a flare reaction (3). This is seen particularly in cases of widespread bone metastases or urinary tract obstruction. A fall in serum testosterone to castrate level (< 0.7–1.7 nmol/l) is first achieved after 2–4 weeks. During this period, anti-androgen therapy with bicalutamide tablets (Casodex) should be used to counteract flare.

An alternative option is the gonadotropin-releasing hormone antagonist degarelix (Firmagon), which yields castrate levels of serum testosterone after three days *without* a flare reaction (3). The gonadotropin-releasing hormone antagonist is administered as monthly injections and may cause irritation at the injection site.

During androgen deprivation therapy, the PSA level should be checked by a general practitioner every 3–6 months, and the patient referred back to a specialist if levels increase. If testosterone is not at the castrate level, it may be appropriate to switch to another gonadotropin-releasing hormone analogue or to perform orchiectomy. Discontinuing anti-androgens during androgen deprivation therapy may trigger a withdrawal response in which the PSA level falls (seen in 15–20 % of patients) (7).

When selecting treatments, quality of life must be balanced against side effects. Typical side effects of castration therapy include decreased libido, erectile dysfunction, hot flushes, loss of vitality, depression, and cognitive impairment as well as metabolic changes (osteoporosis, metabolic syndrome). In our experience, patients that have been well informed in advance accept these side effects, but in a few individuals they may be serious and troublesome.

The general practitioner has an important role to play in detecting and preventing some of these side effects. Blood pressure, blood glucose levels and serum lipids should be checked annually. Bone density measurements and pharmaceutical prophylaxis of osteoporosis should be considered if androgen deprivation therapy is used over several years (3). Patients must be encouraged to follow the Norwegian Directorate of Health's recommendations regarding diet and physical activity (8).

There are alternatives to conventional androgen deprivation therapy that should be considered within the specialist health care service and discussed with certain patients: total androgen blockade (androgen deprivation therapy combined with anti-androgens) and intermittent androgen deprivation. The use of these options is dependent on the disease course and symptoms (3).

Two studies have shown that early use of docetaxel (Taxotere) in combination with androgen deprivation therapy in the castration-sensitive phase increases survival in patients with metastatic prostate cancer compared to androgen deprivation therapy alone (5, 6). These studies revealed an average survival benefit of 14 and 15 months respectively in the groups that received docetaxel in addition to androgen deprivation therapy. In both studies, the largest effect was seen in those with the most advanced disease.

Induction therapy with docetaxel should be considered within three months of initiation of castration therapy in most patients

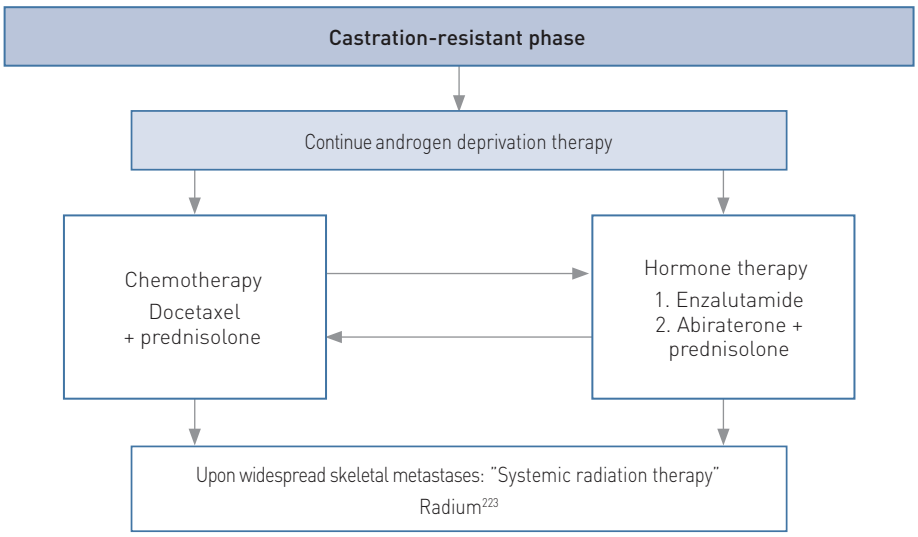

Figure 2 *Our proposed treatment algorithm for castration-resistant metastatic prostate cancer. When the patient becomes castration-resistant, the choice is between chemotherapy or second-generation hormone therapy, and possibly radioisotope therapy upon further progression*

with newly diagnosed metastatic prostate cancer (3). Chemotherapy should be administered at an outpatient oncology clinic under the direction of an oncologist.

Castration-resistant phase

An increase in PSA level or progression of metastases while serum testosterone is at the castrate level (< 0.7–1.7 nmol/l) implies castration resistance. These patients should be referred to an oncologist. Treatment in this phase was previously supplemented with prednisolone, which provided pain relief and a PSA response but did not increase survival. In the course of the past 15 years, several new life-extending drugs have been developed (3). When to initiate treatment and which drug to use must be decided on the basis of the patient's general condition and wishes, as well as the efficacy and side effects of the drugs in that individual.

Castration therapy should be continued in the castration-resistant phase (Fig. 2) (2, 3). Two types of chemotherapy (docetaxel, cabazitaxel) and two different second-generation hormone therapies (enzalutamide, abiraterone) have proven to be effective as additional treatments in this phase (2, 3, 9, 10).

Cabazitaxel (Jevtana) has yet to be approved for use in the public health care system in Norway, following a central cost-benefit analysis. The national cancer plan lists docetaxel as the first line treatment for castration-resistant metastatic prostate cancer. The drug is usually administered as an intravenous infusion at 1–3 week intervals for 12 weeks, together with prednisolone. Those with a good response continue for another 2–3 months, and may benefit from additional courses of docetaxel upon further progression. With skilled management of sequencing these options, such treatment can increase survival and improve quality of life, even in elderly patients.

The two new hormone therapies represent equally valid second line treatments. Both are taken daily in tablet form. On the basis of health economic assessments, enzalutamide (Xtandi), a «super anti-androgen», is the recommended first choice in Norway (2). The second choice, Abiraterone (Zytiga) inhibits adrenal androgen production and is used in combination with prednisolone. These hormone therapies are administered in the castration-resistant phase if the patient is asymptomatic, or if the patient does not want or is unsuitable for chemotherapy. The developments that have occurred in this area of clinical practice in recent years are not yet reflected in the national guidelines in Norway (2, 3).

Docetaxel was previously the only drug with a demonstrable survival benefit in castration-resistant metastatic prostate cancer, and its use was often delayed in patients with slow asymptomatic progression owing to its side effects. Now, tumour control can be achieved in the asymptomatic phase using drugs with no or few side effects (9, 10). Advantages include increased survival, delayed onset of functional impairment and the need for opiate analgesia, and delayed initiation of chemotherapy. A poor response to primary castration therapy, however, argues in favour of early chemotherapy. The sequencing of the different medications should always be tailored to the individual patient under the direction of an experienced oncologist.

In patients with multiple skeletal metastases, radioisotope therapy with radium^{223} (Xofigo) may be appropriate. This is a form of systemic «radiation therapy» that can yield survival benefits and symptom relief – with moderate side effects (11, 12). Radioisotope therapy is administered intravenously every four weeks, up to six times. The treatment may be repeated if bone marrow function is monitored. Radiation hygiene measures are required because the patient's bodily fluids will be radioactive the week after the infusion.

In Norway, immunotherapy is currently only available in clinical trials. Sipuleucel-T (Provenge) has been approved in the United States as the first therapeutic cancer vaccine for metastatic prostate cancer, but it is not available in Europe (3).

Treatment of local events

Both the disease and its treatment can give rise to troublesome and serious consequences; it is important to take these into account and to inform the patient about them early on.

Skeletal pain can be treated with palliative radiation therapy, steroids and opiates. An MRI examination should be performed promptly upon suspicion of impending spinal cord injury. If confirmed, treatment consists of immediate administration of high dose steroids combined with surgery and/or radiation therapy (2, 3).

Skeletal-related events (pathological fractures, spinal cord injury, skeletal surgery or radiation therapy) may be prevented with zoledronic acid (Zometa, intravenous infusion, first choice in the Norwegian public health care system) or denosumab (Xgeva, subcutaneous injection) (2, 3, 12). Dosing intervals and when to initiate treatment are poorly defined, but common practice is to administer treatment every three months, beginning when symptomatic skeletal metastases are present. The patient should be examined by a dentist prior to use of zoledronic acid or denosumab, as there is a risk of osteonecrosis in the jaw bone (1–11 %) (3, 13, 14). Calcium and vitamin D supplements should be taken during treatment (3).

Obstruction of the urinary tract or bowel may be relieved by palliative surgery, drainage (nephrostomy, JJ stents, bladder catheters) or radiation therapy. Surgery, radiation therapy or embolisation may be appropriate in the event of haemorrhage.

Henriette Veiby Holm (born 1977)
PhD, specialty registrar in surgery and urology at Bærum Hospital.
The author has completed the ICMJE form and reports no conflicts of interest.

Alv A. Dahl (born 1944)
research advisor and professor emeritus at the University of Oslo.
The author has completed the ICMJE form and reports no conflicts of interest.

Olbjørn Harald Klepp (born 1944)
specialist in oncology and professor emeritus at the Norwegian University of Science and Technology. He has previously served as head of the oncology departments in Trondheim and in Ålesund. He is a co-author of previous national guidelines, textbook chapters and other publications on prostate cancer.
The author has completed the ICMJE form and reports no conflicts of interest.

Sophie D. Fosså (born 1941)
specialist in oncology, professor emerita at the University of Oslo, and retired senior consultant. She is a senior researcher at Oslo University Hospital, the Norwegian Radium Hospital, and the Cancer Registry of Norway.
The author has completed the ICMJE form and reports no conflicts of interest.

References

1. Cancer Registry of Norway. Cancer in Norway 2015 – Cancer incidence, mortality, survival and prevalence in Norway. Oslo: Kreftregisteret, 2016. www.kreftregisteret.no/globalassets/cancer-in-norway/2015/cin-2015-special-issue.pdf (4.1.2017).
2. Solberg A, Angelsen A, Berge V et al. Nasjonalt handlingsprogram med retningslinjer for diagnostikk, behandling og oppfølging av prostatakreft. Oslo: Helsedirektoratet, 2015. www.helsebiblioteket.no/retningslinjer/prostatakreft/forord (4.1.2017).
3. Cornford P, Bellmunt J, Bolla M et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part II: Treatment of Relapsing, Metastatic, and Castration-Resistant Prostate Cancer. Eur Urol 2017; 71: 630–42.
4. Omlin A, Pezaro C, Mukherji D et al. Improved survival in a cohort of trial participants with metastatic castration-resistant prostate cancer demonstrates the need for updated prognostic nomograms. Eur Urol 2013; 64: 300–6.
5. Sweeney CJ, Chen YH, Carducci M et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med 2015; 373: 737–46.

>>>

6. James ND, Sydes MR, Clarke NW et al. 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.
7. Small EJ, Srinivas S. The antiandrogen withdrawal syndrome. Experience in a large cohort of unselected patients with advanced prostate cancer. Cancer 1995; 76: 1428–34.
8. Østergren PB, Kistorp C, Bennedbæk FN et al. The use of exercise interventions to overcome adverse effects of androgen deprivation therapy. Nat Rev Urol 2016; 13: 353–64.
9. Rathkopf DE, Smith MR, de Bono JS et al. Updated interim efficacy analysis and long-term safety of abiraterone acetate in metastatic castration-resistant prostate cancer patients without prior chemotherapy (COU-AA-302). Eur Urol 2014; 66: 815–25.
10. Beer TM, Armstrong AJ, Rathkopf DE et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 2014; 371: 424–33.
11. Parker C, Nilsson S, Heinrich D et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med 2013; 369: 213–23.
12. Vignani F, Bertaglia V, Buttigliero C et al. Skeletal metastases and impact of anticancer and bone-targeted agents in patients with castration-resistant prostate cancer. Cancer Treat Rev 2016; 44: 61–73.
13. Vehmanen L, Suojanen J, Kontio R et al. High frequency of osteonecrosis of the jaw among denosumab-treated prostate cancer patients. Acta Oncol 2017; 56: 104–6.
14. Aapro M, Abrahamsson PA, Body JJ et al. Guidance on the use of bisphosphonates in solid tumours: recommendations of an international expert panel. Ann Oncol 2008; 19: 420–32.

Received 22 March 2016, first revision submitted 11 October 2016, accepted 13 March 2017. Editor: Inge Rasmus Groote.