

End of life care for Advanced Prostate Cancer

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Introduction:

Prostate cancer is the second most common cancer in men worldwide. The treatment of prostate cancer includes surgery, radiation therapy, hormone therapy, chemotherapy, and immunotherapy. Metastatic prostate cancer is incurable and causes significant morbidity. Modern medicine can only control the metastatic disease but cannot offer a cure at this stage.



Fig.1: Whole body bone scan image of a Patient with metastatic prostate Cancer

The focus of treatment of metastatic prostate cancer should be on bringing an adequate control of the disease, thereby reducing the complication of side effects of the drugs. This principle of management will be achieving a longer progression free survival and improving quality of life through appropriate oncological treatment and palliative care.

However, in advanced stages of the disease, when the disease is not responding to any form of treatment, the focus shifts to palliative care. The aims and objectives of palliative care is to improve the quality

of life of patients by managing their symptoms along with the patients and the family providing emotional and spiritual support.

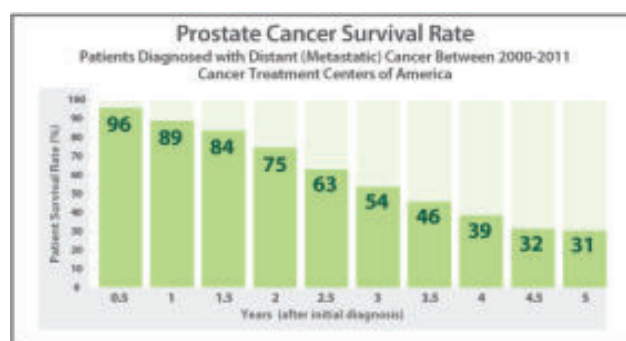


Fig.2: Survival of patients with metastatic Prostate cancer

This article will discuss the palliative care of prostate cancer. Palliative care is an essential component of the management of advanced prostate cancer. It involves a multidisciplinary approach. The following are the key aspects of palliative care for prostate cancer:

Local and locally invasive disease

There are only two curative option for patient with localized prostate cancer, one is Radical surgery and the other is Radical radiation therapy. Other treatment options for localized prostate cancer, including watchful waiting, brachytherapy, high-intensity focused ultrasound and cryotherapy. The treatments available for the disease at this potentially curative stage are associated with a variable degree of morbidity with both type of radical treatment option.¹

Metastatic Disease

Despite an increase in early detection, a large number of patients will have advanced disease at presentation. Average survival at this point is approximately 3 years,

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but may be considerably longer. Patients should be reviewed by an appropriate specialist and may be offered androgen manipulation, chemotherapy, radiotherapy and/or radioisotopes, but any treatment at this stage is palliative in nature^{2,3}. Prostate cancer is far more common in older men, with 80% of cases being diagnosed in the over 65s. Although incidence is increasing, this apparent increase is probably secondary to the introduction of prostatic specific antigen testing. There is an increased risk of developing prostate cancer if one or more first degree relatives have it. If it is just one then the risk is doubled. However, if two or more are affected then the risk is increased by five to 11 times.²

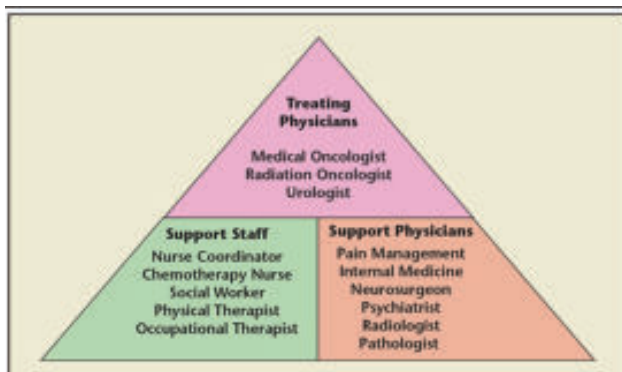


Figure 3 Multidisciplinary approach to the management of Advanced Prostate cancer

Unfortunately, mortality remains fairly stable and country specific mortalities are also similar despite incidence variation. There is variance in incidence among different ethnic groups, with African Americans having the highest risk. There is a relatively low risk among the Asian population, but this disappears in migration.^{1,2}

Palliative care

Palliative care is a multi-professional, holistic approach to managing advanced disease with a limited prognosis. It encompasses controlling symptoms that are physical, psychological, spiritual and social and involves those close to the patient.

The modern hospice movement was founded by Dame Cicely Saunders in 1967. Cicely Saunders founded the first modern hospice and, more than anybody else, was responsible for establishing the discipline and the culture of palliative care. She introduced effective pain management and insisted that dying people needed dignity, compassion, and respect, as well as rigorous

scientific methodology in the testing of treatments. She abolished the prevailing ethic that patients should be cured, that those who could not be cured were a sign of failure, and that it was acceptable and even desirable to lie to them about their prognosis.³

It is now recognized that palliative care should be extended to all patients with life-limiting illness, regardless of the diagnosis. Traditionally, palliative care has been concentrated in the last few weeks and months of life, taking over when active treatment has failed. Palliative care team should integrate in a seamless way with all cancer treatment services to provide the best possible quality of life for the patient and their family.

1. Symptom management: The symptoms of advanced prostate cancer can be debilitating and affect the patient's quality of life. Palliative care aims to manage these symptoms, which may include pain, fatigue, nausea, vomiting, urinary and bowel problems, and sexual dysfunction. Medications, such as opioids, antiemetics, laxatives, and hormone therapy, are used to manage these symptoms.

2. Emotional and spiritual support: Palliative care also provides emotional and spiritual support to patients and their families. This includes counseling, support groups, and religious services. The emotional and spiritual needs of patients are often overlooked but are critical in improving their quality of life.

3. Advance care planning: Advance care planning involves discussions between patients, their families, and healthcare providers about the patient's end-of-life care preferences. This includes decisions about resuscitation, life-sustaining treatments, and hospice care. Advance care planning ensures that the patient's wishes are respected and followed.

4. Hospice care: Hospice care is provided to patients with advanced cancer who have a life expectancy of six months or less. It focuses on managing the patient's symptoms and providing emotional and spiritual support to the patient and their family. Hospice care can be provided in the patient's home, a hospice facility, or a hospital. Hospice care is a specialized type of palliative care that is provided to patients with advanced cancer who have a life expectancy of six months or less. The focus of hospice care is on managing the patient's symptoms and providing emotional and spiritual support to the patient and their family during the end-of-life stage. Hospice care for

advanced prostate cancer may include the following services:

1. **Pain management:** Pain is a common symptom in advanced prostate cancer. Hospice care providers focus on managing pain effectively to ensure that the patient is as comfortable as possible. This may involve the use of medications such as opioids, which are powerful pain relievers.

2. **Symptom management:** In addition to pain, advanced prostate cancer may cause other symptoms such as fatigue, nausea, vomiting, urinary and bowel problems, and sexual dysfunction. Hospice care providers work with the patient's healthcare team to manage these symptoms effectively.

3. **Emotional and spiritual support:** Hospice care providers offer emotional and spiritual support to patients and their families. This includes counseling, support groups, and chaplaincy services. Emotional and spiritual support is essential in helping patients and their families cope with the emotional turmoil that comes with facing the end-of-life stage.⁴

4. **Assistance with activities of daily living:** As the disease progresses, patients may find it difficult to perform activities of daily living such as bathing, dressing, and eating. Hospice care providers may assist with these activities to ensure that patients are comfortable and have the best possible quality of life.

5. **Medical equipment and supplies:** Hospice care providers may provide medical equipment and supplies such as hospital beds, wheelchairs, and oxygen to manage the patient's symptoms effectively.

6. **Respite care:** Caregivers play a critical role in the care of patients with advanced prostate cancer. However, caregiving can be physically and emotionally exhausting. Hospice care providers may offer respite care to give caregivers a break from their responsibilities.

In conclusion, hospice care is a specialized type of palliative care that focuses on managing the symptoms of advanced prostate cancer and providing emotional and spiritual support to patients and their families during the end-of-life stage. Hospice care providers offer a range of services, including pain and symptom management, emotional and spiritual support, assistance with activities of daily living, medical equipment and supplies, and respite care for caregivers. By providing comprehensive care, hospice

care can improve the quality of life of patients with advanced prostate cancer and their families during a difficult time.

Pain Control:

Pain is an extremely common symptom in advanced cancer, present in approximately 70–90% of patients. This can significantly impact on quality of life, interfering with eating, sleeping and interaction with others.⁵ Treatment of pain in cancer can be difficult and complex and the term 'Total Pain' was used by Dame Cicely Saunders to describe intense suffering physically, psychologically, spiritually and socially.⁶ Not all patients will experience all of these problems, but where they are present treating one without the other will inevitably be unsuccessful. For example, attempting to treat physical pain when there is psychological pain will be suboptimal. Equally, attempting to treat psychological symptoms without addressing physical suffering will be fraught with difficulty. Somatic and psychological management should take place simultaneously via multidisciplinary approach to control pain in the terminally ill patients.⁷

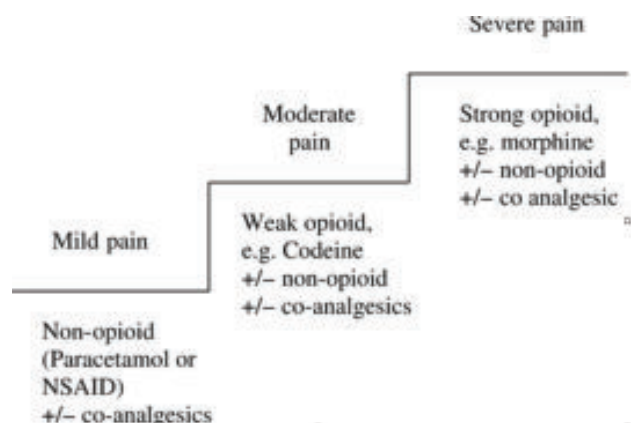


Fig.4. Algorithm of Pain management

- **Over-the-counter pain relievers.** For mild and moderate levels of pain, pain relievers that don't require a prescription may help. Examples include aspirin, Paracetamol/acetaminophen and ibuprofen.
- **Medications derived from opium (opioids).** Opioids are prescription medications used to treat moderate to severe pain. Examples of opioids include morphine (Kadian, Ms Contin, others) and oxycodone (Oxycontin, Roxicodone, others).

Some opioids are short-acting medicines, so pain relief comes quickly but you may need to take them

more often. Other opioid drugs are long-acting medicines, so pain relief takes longer but the medicine doesn't need to be taken as often. Sometimes short-acting and long-acting opioids are used together.

- **Other prescription medicines.** Other types of medicine can help relieve pain, including antidepressants, anti-seizure drugs and steroids.
- **Nerve Blocks.** A nerve block procedure can be used to stop pain signals from being sent to the brain. In this procedure, a numbing medicine is injected around or into a nerve.
- **Integrative therapies.** Some people find some pain relief through acupuncture, massage, physical therapy, relaxation exercises, meditation and hypnosis.
- **Music Therapy:** Music Therapy Many National Cancer Institute-designated cancer centers that offer music therapy as an integrative treatment for cancer. There have been a surprising number of studies done to examine potential benefits of music for cancer patients. It would seem we're guessing intuitively that music has a role.⁸ A decrease in pain was noted in some of the studies mentioned, but the effect of music on pain was studied specifically among people who were undergoing interventions.⁹

Acupuncture:

Acupuncture may represent a potentially valuable adjunct to existing strategies for pain relief and is known to be relatively free of harmful side-effects¹⁰⁻¹²; however, although acupuncture is widely used in palliative care settings¹³ for all types of cancer pain the evidence-base is sparse and inconclusive.¹⁴ Furthermore, safety guidelines for the use of acupuncture treatment in cancer patients exist¹⁵, yet there have been no studies specifically looking at adverse events in patients with bony metastases and no high-quality randomized controlled trials have been conducted to investigate the effects of acupuncture on advanced PC.

Cord compression:

Spinal cord compression affects 1–12% of patients with metastatic prostate cancer and is an oncological emergency.¹⁶ Prevention of cord compression is important and clinicians should have a high index of suspicion. Disability arising from delay is associated

with decreased survival.¹⁷ and any function lost before treatment is rarely regained. For this reason, speed is of the essence and investigation and management should not wait for classical signs to develop. Treatment should initially be with high dose steroids followed by early radiotherapy or surgery depending on performance status and prognosis.¹⁸

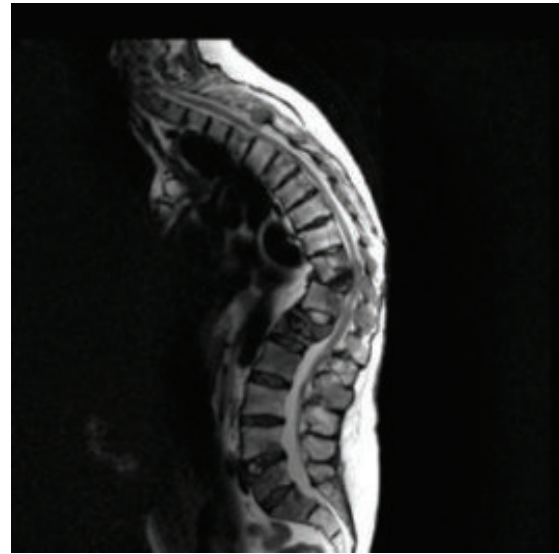


Fig.5 Metastatic lesion in spine can cause cord compression

Decompressive surgery plus postoperative radiotherapy has been shown to be more effective than radiotherapy alone.¹⁹ Although, many patients will not be suitable for this treatment.

Adverse Effects of Androgen Deprivation Therapy for Prostate Cancer: Prevention and Management

The prostate is an androgen-dependent organ. The increase, growth, homeostasis, and function of the prostate largely depend upon the intraprostatic and serum concentrations of androgens. Therefore, androgens are essential for the physiologic growth of prostatic epithelium. Prostate cancer, the second leading cause of death for men, is also androgen dependent, and androgen suppression is the mainstay of treatment for advanced and metastatic disease. In the state of metastatic disease, androgen suppression is a palliative treatment leading to a median progression-free survival of 18–20 months and an overall survival of 24–36 months. Theoretically, the majority of patients will develop hormone-refractory disease provided that they will not die from other causes. Although androgen suppression therapy may be associated with significant and sometimes durable

responses, it is not considered a cure, and its potential efficacy is further limited by an array of significant and bothersome adverse effects caused by the suppression of androgens. These effects have potentially significant consequences on a variety of parameters of everyday living and may further decrease health-related quality of life. This review focuses on the aetiology of these adverse effects and provides information on their prevention and management.

Hot Flashes;

LHRH agonists are well known to cause a surge in serum testosterone levels during the first week of therapy due to the initial stimulation of LHRH receptors, the so-called “flare” phenomenon. The flare phenomenon was considered to be the cause of significant sequela if LHRH agonists are administered to men with high-volume metastatic disease.

However, there are wide discrepancies regarding the frequency and severity of acute clinical progression that might result from the testosterone surge. The clinical consequences of the flare phenomenon are considered to be prevented by the concomitant administration of antiandrogens. Antiandrogens inhibit the stimulatory effect of the testosterone surge at the level of the androgen receptor, although there is not a clear consensus as to whether antiandrogens should be routinely given to all patients during the first month of LHRH therapy to prevent flare responses

The symptom of hot flashes is among the most common and early described side effects of ADT as it was reported by Huggins and Hodges in 1941 in 9 of the first 21 prostate cancer patients ever to undergo ADT. Hot flashes are caused by inappropriate stimulation of thermoregulatory centers in the hypothalamus, resulting in peripheral vasodilatation.³⁰ Hot flashes are described by patients as the perception of intense warmth and subsequent cooling, flushing of the skin, perspiration, and chills in the upper part of the body, usually the neck and face. Associated symptoms may include anxiety and palpitations. Hot flashes usually last from a few seconds to several minutes but can persist for up to 20 min. Many patients only report mild consequences from their symptoms and only experience these sporadically. However, some patients experience multiple hot flashes each day and report significant effect on daily functioning and quality of life.³¹

Treatment options for hot flashes include a variety of options ranging from estrogens to antidepressants,

anticonvulsant agents, and even acupuncture. According to a recent review, diethylstilbestrol, megestrol acetate, and cyproterone acetate provide the greatest efficacy, up to a greater than 75% decrease of the number of hot flashes, although this improvement comes with the risk of bothersome side effects.³¹ However, since cyproterone is a drug approved for the treatment of prostate cancer, its use could interfere with hormonal therapy, and medroxyprogesterone could be considered the standard treatment for hot flashes in men undergoing androgen suppression for prostate cancer.

Estrogens, in particular DES (0.5–1 mg/day), has been effective in alleviating hot flashes in 75–90% of men, although concerns about the safety of these agents were raised given the high incidence of painful gynecomastia.

Megestrol acetate, a progesterone derivative, achieved an 85% reduction in hot flashes, compared to a significant reduction in patients under placebo. A 2–3 week course of therapy is required to obtain maximal symptomatic reduction, with symptomatic relief lasting for several weeks after therapy. Initial enthusiasm for megestrol acetate has been somewhat tempered by reports of elevations in serum PSA levels with subsequent decline in PSA levels upon its withdrawal.³² PSA levels should be closely followed while on treatment.

Newer antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs-paroxetine 10 mg/day) and serotonin-norepinephrine reuptake inhibitors (SNRIs-venlafaxine 37.5 mg/day), are thought to alleviate hot flashes by increasing serotonin levels and by altering the neurotransmitter milieu within the thermoregulatory center [31,32]. Therefore, there is a reason to believe that they might also reduce the frequency and severity of flushing in men with prostate cancer under ADT. A moderate effect of both SSRIs/SNRIs on hot flashes is to be anticipated, however, no results from RCTs are available.³³

Sexual Dysfunction

ADT induces changes in serum testosterone that can result in changes in both sexual desire and function. The overwhelming majority of men under ADT will develop variable degrees of erectile dysfunction due to the lack of androgens. The two most important predictive factors for ED following ADT were age >70 and presence of diabetes mellitus.³⁵ Undoubtedly, ED

can significantly affect the self-esteem, self-perception, and quality of life of younger, sexually active men, especially when coupled with the side effects of ADT on muscle and fat distribution.²⁶

Depending on the severity of erectile dysfunction the patients with significant Erectile Dysfunction might have various treatment options. All treatment options may have risks and benefits of each treatment and will consider the patients preferences.

Level 1 treatment: Oral medications

Oral medications are a successful erectile dysfunction treatment for many men. They include:

- Sildenafil (Viagra)
- Tadalafil (Adcirca, Cialis)
- Vardenafil (Levitra, Staxyn)
- Avanafil (Stendra)

All four medications enhance the effects of nitric oxide — a natural chemical body produces that relaxes muscles in the penis. This increases blood flow and allows to get an erection in response to sexual stimulation.

Taking one of these tablets will not automatically produce an erection. Sexual stimulation is needed first to cause the release of nitric oxide from the penile nerves. These medications amplify that signal, allowing normal penile function in some people.

The medications vary in dosage, how long they work and side effects. Possible side effects include flushing, nasal congestion, headache, visual changes, backache and stomach upset.

Care should be taken to use the drug:

- Take nitrate drugs — commonly prescribed for chest pain (angina) — such as nitroglycerin (Nitro-Dur, Nitrostat, others), isosorbide mononitrate (Monoket) and isosorbide dinitrate (Isordil, Bidil)
- Have heart disease or heart failure
- Have very low blood pressure (hypotension)

Penis pumps, surgery and implants

Battery-powered penis pump for erectile dysfunction

If medications aren't effective or appropriate in such case, the medication may be combined with a

professionally designed penile pump may be recommend .

- **Penile pumps.** A penis pump (vacuum erection device) is a hollow tube with a hand-powered or battery-powered pump. The tube is placed over the penis, and then the pump is activated to suck out the air inside the tube. This creates a vacuum that pulls blood into your penis.



Fig. 6. Penile pump for erectile dysfunction may be used for sexual rehabilitation

Once the erection is achieved a tension ring is slipped around the base of the penis to hold in the blood and keep it firm. Then remove the vacuum device.

The tension ring is removed after intercourse. Bruising of the penis is a possible side effect, and ejaculation will be restricted by the band. A specific model may be more suitable for function and comfort.

Level ii Treatment: Alprostadil self-injection.

With this method, a fine needle to inject alprostadil (Caverject, Edex) into the base or side of the penis. In some cases, medications generally used for other conditions are used for penile injections on their own or in combination. Examples include alprostadil and phentolamine. Often these combination medications are known as Bimix (if two medications are included) or Trimix (if three are included).

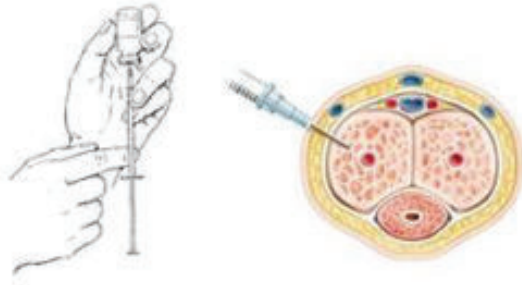


Fig. 7. Principle of *Alprostadil self-injection*.

Each injection is dosed to create an erection lasting no longer than an hour. Because the needle used is very fine, pain from the injection site is usually minor.

Side effects can include mild bleeding from the injection, prolonged erection (priapism) and, rarely, formation of fibrous tissue at the injection site. If a priapism is seen after an hour of injection a hospital service in the emergency department. A simple urological procedure to remove the aspirate the accumulated blood and to irrigate the corpora with phenylephrine or ephedrine

Alprostadil urethral suppository. Alprostadil (Muse) intraurethral therapy involves placing a tiny alprostadil suppository inside the penile urethra. Use of a special applicator to insert the suppository into urethra is helpful.



Fig. 8. *Alprostadil (Muse) intraurethral therapy*

The erection usually starts within 10 minutes and, when effective, lasts between 30 and 60 minutes. Side effects can include a burning feeling in the penis, minor bleeding in the urethra and formation of fibrous tissue inside your penis.

Testosterone replacement. Some people have erectile dysfunction that might be complicated by low levels of the hormone testosterone. In this case, testosterone replacement therapy might be recommended as the first step or given in combination with other therapies.

Level iii Treatment :

Penile implants. This treatment involves surgically placing devices into both corpora of the penis. These implants consist of either inflatable or malleable (bendable) rods. Inflatable devices allow freedom to control the time and duration of erection. The malleable rods keep your penis firm but bendable.

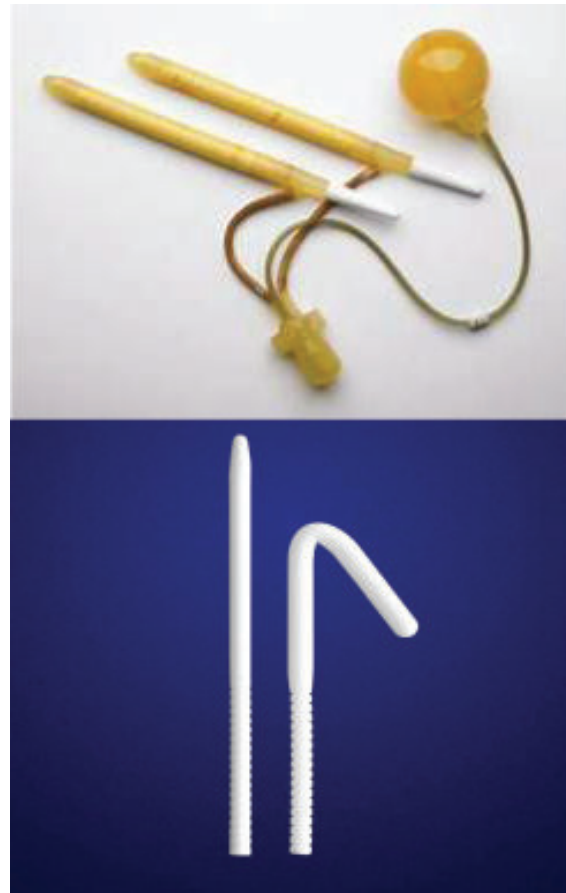


Fig.9. *Inflatable and malleable Penile prosthesis*

Penile implants are usually not recommended until other methods have been tried first. Implants have a high degree of satisfaction among those who have tried and failed more-conservative therapies. As with any surgery, there's a risk of complications, such as infection. Penile implant surgery is not recommended if you currently have a urinary tract infection.

Exercise

Recent studies have found that exercise, especially moderate to vigorous aerobic activity, can improve erectile dysfunction. Even less strenuous, regular exercise might reduce the risk of erectile dysfunction. Increasing your level of activity might also further reduce your risk.

Psychological counseling

Psychological counseling may be important if the erectile dysfunction is caused by stress, anxiety or depression or the condition is creating stress and relationship tension. Couple counselling with both the partner and the psychologist or counselor may be of help.

Although these pharmacologic and mechanical approaches may restore the ability to achieve an erection, the additional loss of libido as a result of treatment often limits patients' motivation for pursuing treatment to restore erections. Lately, the cautious use of estrogens has also been proposed for the improvement of both sexual interest and ED in these men.³⁶

Treatment to Reduce Bone Loss and Skeletal-Related Events

In any case a fracture is a landmark event in the life of men with prostate cancer under ADT. Hip fractures in men over the age of 75 for any cause carry a mortality rate of 30%, while bone fractures in patients with prostate cancer have been associated with adverse overall survival outcomes.³⁶

Therefore, androgen ablation is a cause of skeletal-related events associated with significant morbidity and mortality even for patients with nonmetastatic prostate cancer. Risk factors for osteoporotic fracture include the duration of ADT (>3 years), age (mainly through decreased testosterone levels), ethnicity (Caucasian patients are at greater risk), smoking, lower BMI, and medications (e.g., glucocorticoids).

Lifestyle modifications that apply to all men under ADT irrespective of their bone status include regular light weight lifting or resistance exercises, cessation of smoking, limiting alcohol and caffeine consumption, and vitamin D and calcium supplementation.

The management of ADT-induced osteopenia and osteoporosis has been a field of significant evolution during the last years, as bone-targeted therapies have recently been the focus of considerable research and drug development. The osteoclast has been recognized as a validated therapeutic target in the management of prostate cancer. Osteoclast inhibition with bisphosphonates reduces the risk for skeletal events in men with castration-resistant prostate cancer metastatic to bone. Osteoclast activity inhibition improves bone mineral density, a surrogate for osteoporotic fracture risk.

Late generation bisphosphonates such as zoledronic acid (Zometa, Novartis Technology) seem to markedly reduce bone resorption and increase BMD in prostate cancer patients under ADT. Zoledronic acid has also shown efficacy in preventing bone metastases and skeletal-related events in patients under ADT reducing by 7-fold the risk of pathological fractures after 20 months of treatment. Certain precautions should be taken with the use of zoledronic acid; the risk of osteonecrosis of the jaw is further limited if patients are asked to refrain from dental procedures while on therapy, while the dose and administration of the drug (3 mL intravenous infusion in no less than 15 minutes) should be adjusted for patients on CKD.³⁷

Psychological and Cognitive Effects mPC patients and how to deal it:

Hormonal therapy has also been shown to cause neurologic impairment, manifested by decreased cognitive function, mood, and self-esteem while also negatively affecting memory and attention. Low levels of testosterone are significantly associated with depression in elderly men and testosterone replacement appears to reduce depressive symptoms in such patients. Consequently, depression seems to be common in men with prostate cancer.³⁸

Estrogens can also be used to reduce the cognitive effects of androgen ablation, but the benefits of this should be balanced against the well-recognized risk of cardiovascular events.

There is evidence of an increased occurrence of depression, anxiety, low self-body image perception, sleep disturbances, and diminished quality of life in prostate cancer patients undergoing adjuvant androgen deprivation therapy (ADT). A combined resistance/aerobic exercise programme may lead to significant improvement in fatigue and cognitive function.³⁹

Although depression has been reported after a diagnosis of PC, whether ADT leads to or worsens depression is not clear. A study on 257 patients with nonmetastatic CaP receiving ADT for 1 year showed no association between worsening of depressive symptoms among nondepressed or depressed patients with nonmetastatic prostate cancer. Although depression associated with ADT typically does not respond to antidepressants, these are commonly prescribed to prostate cancer patients.⁴⁰

Metabolic Syndrome and Cardiovascular Morbidity

Metabolic alterations caused by testosterone suppression may mediate the mechanisms underlying the high frequency of cardiovascular disease that has been observed in some men under ADT. Concerns have been raised about the well-being of, particularly older, men on AST as there is evidence that ADT can lead to a symptom complex consistent with the metabolic syndrome. This syndrome is associated with an increased risk of death as a result of myocardial infarction, even in the absence of known cardiovascular disease or diabetes.

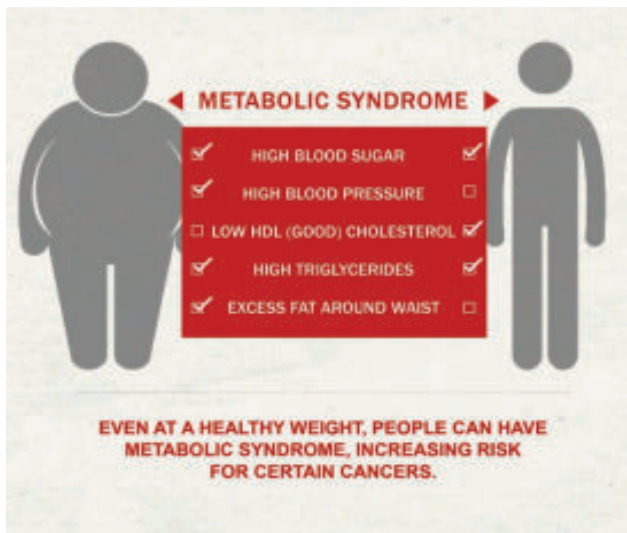


Figure 9. Features of metabolic syndrome

Some of these androgen deprivation therapy-related metabolic changes (obesity, insulin resistance, and increased triglycerides) overlap with features of the metabolic syndrome. However, in contrast to the

metabolic syndrome, androgen deprivation therapy increases subcutaneous fat and high density lipoprotein cholesterol. Toremifene has been shown to improve the lipid profile, while metformin coupled with lifestyle interventions is a safe treatment option for adverse metabolic changes.⁴¹

Clinical evidence from two studies lend support to this association between ADT and cardiovascular morbidity. The increased cardiovascular toxicity was hypothesized to be mediated through changes in lipoproteins, arterial stiffness, and QT interval prolongation.

A recent study has corroborated previous findings suggesting that the use of ADT is associated with earlier onset of fatal MIs in men aged 65 years or older who are treated for 6 months compared with men who are not treated with ADT.

ADT has also been found to be the cause of decreased muscle strength due to its catabolic effect. Muscle weakness and impaired cognitive function are associated with an earlier decrease in functional capacity of the individual, compromising independent living and consequently decreasing quality of life. Daily physical exercise is considered the key lifestyle modification in avoidance of these consequences of ADT as has been shown in relevant studies.⁴¹

Minimizing Androgen Deprivation Side Effects

There is growing evidence that ADT negatively affects men's psychosocial well-being (e.g., causing sexual dysfunction, bodily feminization) and physical health (e.g., increasing the risk of osteoporosis and metabolic syndrome). Although strategies for managing the majority of side effects exist, it is not clear that patients are benefiting from this knowledge.⁴²

A recent study showed that more than 70% of 79 newly prescribed ADT patients did not know that anemia, memory problems, loss of body hair, and depression can occur following treatment. Moreover, over 50% were unaware of significant potential side effects such as reduced muscle mass, osteoporosis, increased fracture risk, weight gain, genital shrinkage, and gynecomastia. The lack of awareness of ADT side effects may partially explain why ADT currently results in significant decreases in the quality of life of patients and their partners.

Increased recognition of the side effects has resulted in strategies to minimize complications associated with ADT. Improved efforts to educate patients about treatment side effects and coping strategies may result

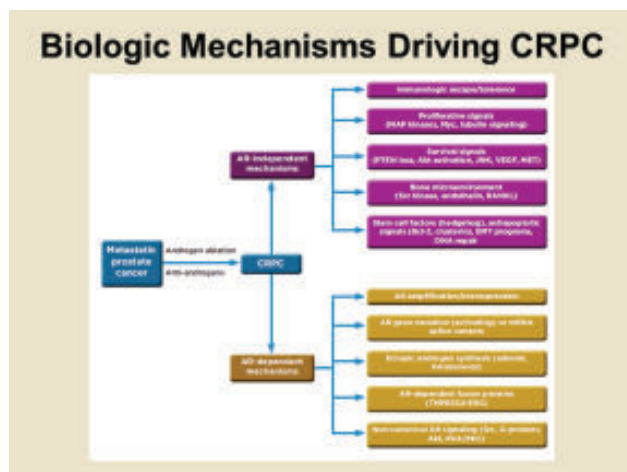


Fig.10 Biologic Mechanism driving the development of Castrate Resistant Prostate Cancer

in improved psychosocial and physical health for CaP patients undergoing ADT. Attempts to reduce ADT adverse effects include intermittent hormonal therapy and methods to reduce amount of intracellular androgens without reducing the circulating testosterone levels.⁴³

Due to the adverse events associated with ADT, the option of intermittent ADT therapy has been evaluated as a measure to reduce morbidity of treatment. It is reasonable to assume that both the acute and chronic complications of LHRH agonists would be ameliorated by delivering therapy in an intermittent mode. Prostate cancer is amenable to control by intermittent androgen suppression, affording these patients improved quality of life during time of therapy, with reduced toxicity and costs. In a recent study, return of potency and resolution of anemia have been achieved with intermittent ADT. Still, the unresolved issue is whether prostate cancer survival is negatively impacted by intermittent therapy. Currently, there are ongoing trials directly comparing continuous with intermittent hormonal therapy regimens. One of these trials is comparing intermittent ADT with continuous ADT in men with newly diagnosed metastatic prostate cancer. With regard to side effects, there is evidence that intermittent ADT improves early side effects such as hot flashes, sexual activity, and fatigue, although its effect on long-term side effects remains inconclusive.⁴⁴

Gastrointestinal symptoms:

Anorexia and weight loss are commonly seen in advanced cancer and contribute not only to tiredness and lethargy, but also family concern. Drugs are often prescribed to treat these symptoms and include megestrol acetate and corticosteroids. Megestrol acetate is usually effective after 1–2 weeks and can increase food intake and improve well-being. Corticosteroids, when used can also have antiemetic and analgesic properties, but are short lived as appetite stimulants and have unpleasant medium-to-long-term side effects.

Nausea is a very common problem in advanced cancer and the cause is multifactorial, including autonomic failure, gastroparesis, constipation and the use of strong opioids. It is important to treat the underlying cause as much as possible and use an antiemetic that is appropriate to the most likely cause.

Constipation affects a large majority of patients with advanced prostate cancer and can exacerbate other symptoms such as nausea, urinary retention, lethargy, abdominal pain and anorexia.⁴⁵

Lymphoedema:

Lymphedema is an accumulation of lymphatic fluids that produces an abnormal swelling in the body. This condition can appear in some people who have been through advanced Prostate Cancer. When lymphatic drainage is blocked, protein-rich fluid gradually builds up and stagnates in the soft tissues where bacterial growth can develop, possibly leading to infection. Some people with cancer have a higher risk of developing lymphedema than others. Those who are obese, advancing in age or who have complications after surgery are at a higher risk. Lymphoedema can be painful, prone to infection and can affect relationships with family and friends and cause feelings of isolation and exclusion.⁴⁶ Penile and scrotal oedema can be particularly distressing, characterized by extreme discomfort for patients, with limitation of ambulation and voiding in the standing position. Sexual intercourse is often impossible, and with impairment of proper hygiene of the perineal region, the patient's quality of life and self-esteem are often severely affected.⁴⁷ Lower limb lymphoedema can be caused by lymph node enlargement, inferior vena caval (IVC) obstruction or large tumor load in the pelvis and management is difficult. Treatment can include bandaging, manual lymphatic drainage, skin care, prompt treatment of cellulitis, IVC stenting if appropriate, scrotal support and emotional support.



Fig. 11 *Compressing bandaging of Lymphedema affecting Lower limb*



Fig.12 Principles of or suprapubic catheterization

Drug therapy is unfortunately largely ineffective and diuretics do little to reduce swelling [48]. One should always be aware of the possibility of co-existent deep vein thrombosis (DVT), especially if unilateral, unequal or painful. If this is suspected, it should be investigated using ultrasound Doppler and is usually treated with regular low molecular weight heparin at treatment dose in this group of patients, rather than warfarin.

Urinary obstruction from advanced prostate cancer

In patients with advanced prostate cancer (PCa), urinary obstruction (UO) can lead to urinary retention requiring indwelling or suprapubic catheterization, which negatively impacts quality of life.

Palliative options for UO from advanced PCa include surgical and medical treatment. Surgical intervention, including prostatectomy, pelvic exenteration and TURP, may confer undue risk to patients with advanced disease.

Medical palliation may require months to take effect. Stereotactic Body Radiotherapy (SBRT) is a non-invasive technique that delivers high-dose and highly

conformal radiation in d"5 fractions, often used to treat PCa and metastatic disease.

SBRT is an effective treatment to palliate UO from locally advanced PCa, leading to removal of urinary catheters and presumed improved in quality of life. Further investigation is required to establish the optimal dose and fractionation of palliative SBRT for UO from Pca.⁴⁹

Side effects associated with Hormonal Therapy

Hormonal manipulation is widely used for controlling advanced prostate cancer. With expanding indications for androgen deprivation therapy for the treatment of prostate cancer, it is imperative that health care providers be cognizant of the possible adverse effects of therapy, as well as their prevention and treatment.⁵⁰⁻⁵²

Neurologic and psychiatric effects include depression and declines in cognitive function. Musculoskeletal effects of hormonal therapy include osteoporosis, decrease in muscle mass, and fatigue. Gynecomastia, weight gain, and erectile dysfunction are also seen, as are hematologic effects. Further research is needed to evaluate alternative forms of therapy, such as intermittent hormonal deprivation and antiandrogen monotherapy.⁴³

Androgen deprivation therapy - to suppress male hormones - may be prescribed to slow the growth of prostate cancer cells, and it has been shown to extend the lives of men with advanced prostate cancer. The oral and injectable medications are likely to produce the same side effects: hot flashes, fatigue, mood swings and others. Goldberg tells his patients it's similar to menopause.⁵⁴⁻⁵⁵

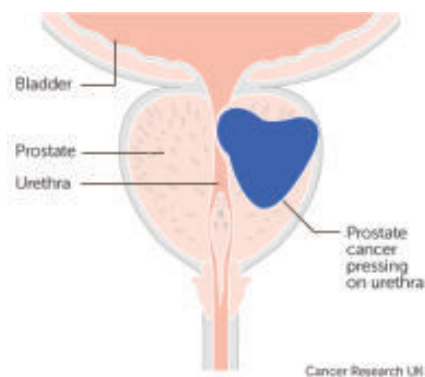


Fig. 13 Prostate Cancer Compressing the Urethra causing retention

Hormone therapy can affect interest in sex or libido, and also ability to get and keep an erection. There are medications, injections and vacuum devices to help with sexual problems. Hot flushes and sweating happen because the lack of testosterone affects the part of the brain that regulates heat. Patients might put on weight, and lose some of muscle tone and strength. Taking some exercise and eating well may help you to avoid putting on too much weight. Suitable exercise and diet may help in this situation. Fatigue is extreme tiredness. The patients might find that taking regular exercise may be helpful.

Osteoporosis is a skeletal disorder characterized by compromised bone strength, resulting in increased fracture risk. Patients with prostate cancer may have multiple risk factors contributing to bone fragility: advanced age, hypogonadism, and long-term use of androgen-deprivation therapy. Despite absence of metastatic disease, patients with nonmetastatic castrate-resistant prostate cancer receiving newer androgen receptor inhibitors can experience decreased bone mineral density. A systematic approach to bone health care has been hampered by a simplistic view that does not account for heterogeneity among prostate cancer patients or treatments they receive. Bone loss is a possible side effect of ADT and can lead to osteoporosis or broken bones. Prolia (denosumab) is the only FDA-approved medication for preventing ADT-related bone loss.⁴⁶

Music Therapy

Music therapy has been used successfully for over 30 years as part of palliative care programs for severely

ill patients.⁵⁷⁻⁵⁹ There is nonetheless a lack of high-quality studies that would enable an evidence-based evaluation of its psychological and physiological effects.

Music therapy is the “systematic use of music within a therapeutic relationship which aims at restoring, maintaining and furthering emotional, physical and mental health” [60]. Music therapy is offered in an extensive range of settings in psychiatric, psychosomatic, neurological, geriatric, pediatric, intensive, and palliative care.⁶¹

A distinction is drawn between active techniques, in which the patient takes part in producing music using his or her voice or an instrument, and receptive techniques, which involve only listening attentively to music and sounds.

Music therapy may be an effective nonpharmacological approach to managing distressing symptoms in palliative care patients. The findings also suggest that group music therapy may be a cost-efficient and effective way to support staff caring for palliative care patients. We encourage others to continue developing the evidence base in order to expand our understanding of how music therapy works, with the aim of informing and improving the provision of music therapy for palliative care patients.⁶²

The challenges of the palliative care of advanced prostate cancer in country like India and Bangladesh:

South Asia is one of the fastest-growing regions in the world, with average gross domestic product (GDP) growth projected to be 7 percent in 2015 and well above

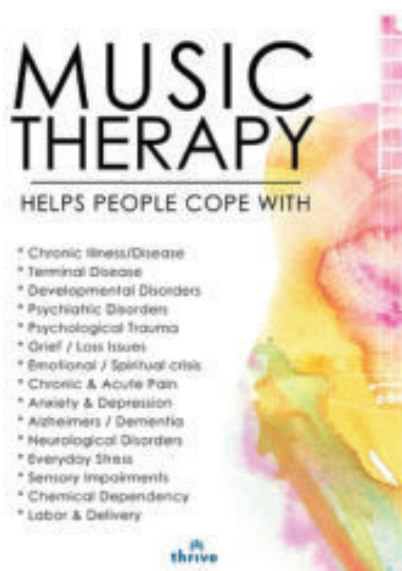


Fig. 14 Music therapy sessions

8 percent by 2020. India is the bright spot in the region, with 8 percent GDP growth projected by 2018, spurred by 12 percent growth in investment as the country continues to shift from consumption to investment-led economic development.⁶⁶

Globally, people live longer and the proportion of older people is growing, especially those in low-income and middle-income countries.⁶⁷ Southeastern Asia is where the rate of an aging population is overgrowing, with a growing rate of people aged 60 or above increasing from 9.8%, 13.7%, and 20.3% in 2017, 2030, and 2050, respectively.⁶⁸ Although life expectancy at birth in Southeast Asia has increased, older persons spend up to 10 years with impairments.⁶⁹ Various health problems that older people are facing include non-communicable diseases (NCDs), mental health, dementia, injuries, and disabilities due to declining functional ability.⁶⁸

Significant positive predictors of active aging among the ASEAN population include perceived high level of age-friendly environments, healthy lifestyles, higher educational level, and living with a partner. Among age-friendly environment predictors, the positive significant age-friendly predictors are neighborhoods with⁶⁷ respect and social inclusion,⁶⁸ job support,⁶⁹ enough elderly parking lots, and more accessible bus stations.⁷⁰

Research from Hong Kong also confirmed that among the domains of perceived neighborhood environment, "transportation" and "respect and social inclusion" were the physical and the social-environmental factors most strongly associated with self-rated health mediated by a sense of community.⁷¹

India, being home to one -sixth of the world's population has a huge burden of suffering from life limiting diseases. It is estimated that in India the total no. of people who need palliative care (PC) is likely to be 5.4 million people a year. Though PC was introduced nearly 30 years ago, it is still in its infancy with less than 1% of patients having access to PC. India ranks at the bottom of the Quality Of Death Index in overall score. Obstacles are too many and not only include factors like population density, poverty, geographical density, restrictive policies regarding opioid prescription, workforce development at base level but also limited national PC policy and lack of institutional interest in palliative care. However there has been a steady progress in the past few years through community owned PC services. South Indian

state of Kerala which has 3% of Indian population, stands out in terms of achieving coverage of palliative care. On the national level recent years saw several palpable changes including the creation of a National Programme for Palliative care and also the Parliament amended India's cumbersome Narcotic Drugs and Psychotropic Substances Act (NDPS) thus overcoming many of the legal barriers to opioid access. Initially WHO and now the IAPC has taken over the responsibility of spreading the message of palliative care in India, but we still have a long way to go. Education of the professionals and sensitization of the public through awareness campaigns are vitals for improving access to PC in India. Process of implementing PC plan into action requires strong Advocacy, political support and integration across all levels of care.⁷²

Despite the significant benefits of palliative care (PC) services for cancer patients, multiple challenges hinder the provision of PC services for these patients. Low- and middle-income countries (LMICs) are witnessing a sharp growth in the burden of non-communicable diseases. There is a significant gap between demand and supply of PC in LMICs in current health services. This review aims to synthesise evidence from previous reviews and deliver a more comprehensive mapping of the existing literature about personal, system, policy, and organisational challenges and possible facilitators on the provision of PC services for cancer patients in LMICs.

Understanding challenges to the provision of PC for people with cancer could help in the development of a PC pathway in LMICs. This knowledge could be used as a guide to develop an intervention programme to improve PC. Political influence and support are also required to ensure the sustainability and the provision of high-quality PC. Although PC for patients with cancer is gaining gradual recognition worldwide.⁷³

In low-income countries like Bangladesh and India. The following are some of the key challenges:

1. **Limited access to healthcare:** Access to healthcare is a significant challenge in low-income countries. Many patients with advanced prostate cancer in these countries do not have access to appropriate medical care, including palliative care. This is due to a lack of healthcare infrastructure, limited resources, and inadequate healthcare policies.
2. **Limited access to pain management:** Pain management is a critical component of palliative care for advanced prostate cancer. However, in

low-income countries like Bangladesh and India, there is limited access to pain management medications such as opioids. This is due to strict regulations and limited availability of these medications.

3. **Limited availability of trained healthcare professionals:** Palliative care for advanced prostate cancer requires a multidisciplinary team, including physicians, nurses, social workers, and chaplains. However, in low-income countries, there is a shortage of trained healthcare professionals, particularly in rural areas.
4. **Cultural and religious beliefs: Cultural and religious beliefs :**
Cultural and religious beliefs: Cultural and religious beliefs can create barriers to palliative care in low-income countries like Bangladesh and India. Some patients and their families may refuse palliative care due to cultural or religious beliefs, which may limit their access to appropriate medical care.
5. **Stigma and lack of awareness:** Stigma associated with cancer and palliative care can create a barrier to accessing appropriate medical care. Many patients and their families may not be aware of the benefits of palliative care, and may not seek it out due to stigma and lack of awareness.
6. **Cost of care:** The cost of palliative care can be a significant barrier to accessing appropriate medical care in low-income countries. Many patients and their families cannot afford the cost of medical treatment and palliative care, which limits their access to appropriate medical care. In conclusion, palliative care for advanced prostate cancer faces several challenges in low-income countries like Bangladesh and India. These challenges include limited access to healthcare, limited access to pain management, limited availability of trained healthcare professionals, cultural and religious beliefs, stigma, lack of awareness, and the cost of care. Addressing these challenges requires a comprehensive approach that involves improving healthcare infrastructure, increasing access to pain management medications, increasing the number of trained healthcare professionals, raising awareness, and developing appropriate healthcare policies.

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