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Machine Learning for Precision Medicine and Drug Development in Prostate Cancer

Part 1: Prostate Cancer and its Treatment

WHITE PAPER

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Background on Prostate Cancer

Ongoing research into novel treatments for prostate cancer is necessary based on several considerations:

1. Prostate cancer is a leading cause of cancer-related deaths in men (Haas et al, 2008; National Cancer Institute, 2012). Due to ageing populations, the incidence of prostate cancer has risen in recent years and is expected to continue rising.
2. Treatment for prostate cancer involves serious side effects. Prostatectomy involves a high risk of sexual dysfunction and incontinence. Radiotherapy involves additional side effects of gastrointestinal and immune problems, fatigue and lymphedema. Hormone therapy involves feminization and does not provide a cure, typically only delaying progression to 'castration-resistant prostate cancer' (CRPC). These side effects significantly reduce quality of life.

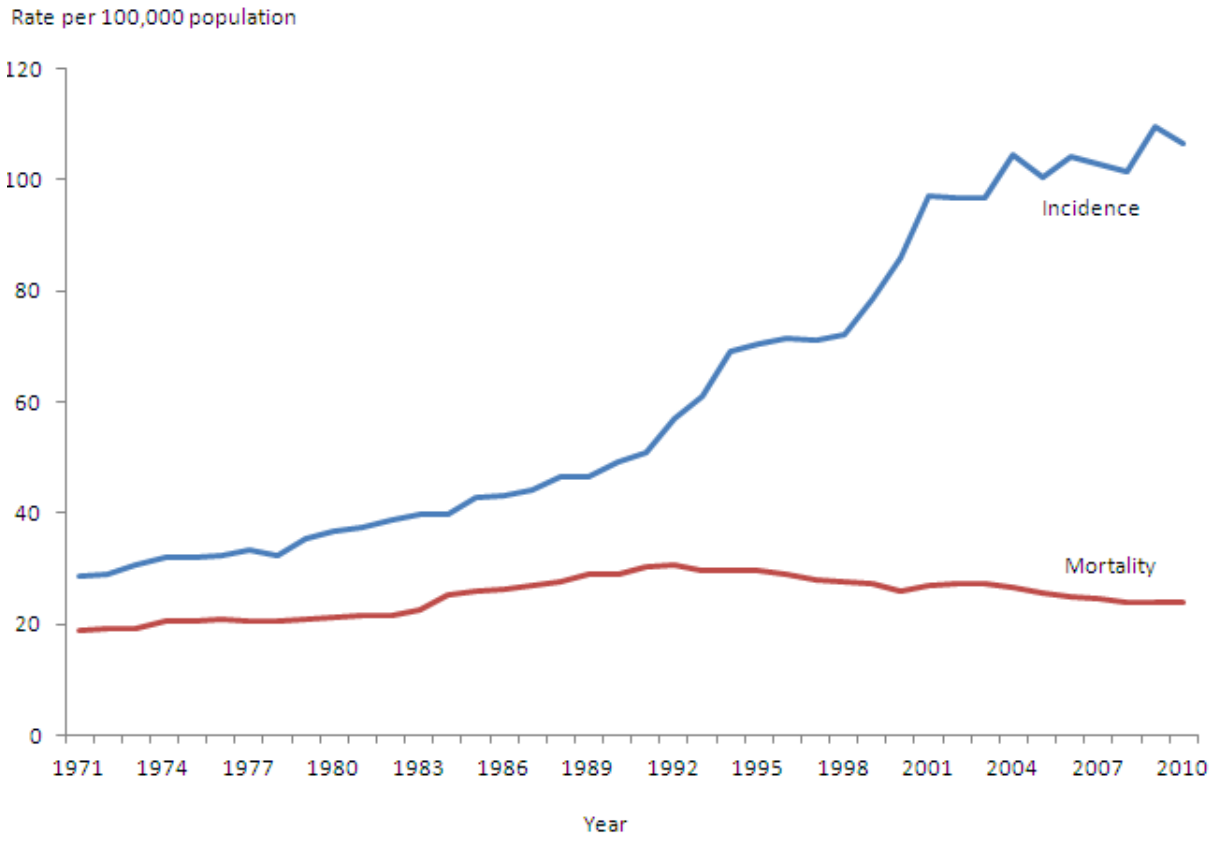


Figure 2: Prostate cancer incidence and mortality rates, England, 1971–2010 (Source: Office for National Statistics)

Signs and Symptoms of Prostate Cancer

The prostate is a gland below the bladder, found only in males, which produces and stores some constituents of semen.

Almost all prostate cancers are adenocarcinomas, i.e. originating in the glandular tissues, although other types of cancer can start in the prostate including transitional cell carcinomas (occurring in the urinary system) and sarcomas (occurring in connective tissue).

Most prostate cancers grow slowly and indeed autopsy studies show that many or most older men had prostate cancer but this was undiagnosed and had no impact on their lives.

Early prostate cancer usually causes no symptoms. More advanced prostate cancers can cause difficulty urinating, blood in the urine or semen or erectile dysfunction. Metastatic prostate cancer most often spreads to the bones and this can cause pain in the hips, spine, ribs, or other bones.

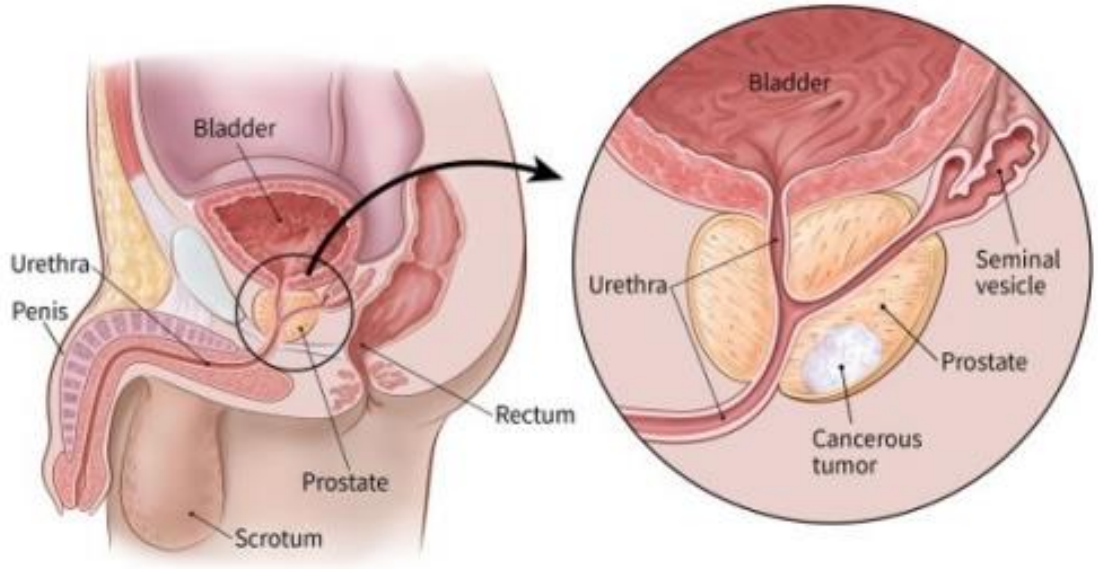


Figure 3: Location of the Prostate

Diagnosis of Prostate Cancer

Early-stage prostate cancers are often symptomless and most are initially detected by routine screening with a prostate-specific antigen (PSA) blood test or a digital rectal exam (DRE).

Prostate-specific antigen (PSA) Test

PSA is a protein found mostly in semen and made by cells in the prostate gland. Blood PSA levels are strongly correlated with tumor diagnosis, tumor aggressiveness, and bone metastasis (Lojanapiwat et al 2014). The American Cancer Society recommends that PSA levels above 4 ng/mL should lead to further testing. A PSA level of above 10 ng/mL indicates a chance of prostate cancer of over 50%. PSA levels are used to help stage a cancer (which can affect treatment options), measure disease progression, treatment effectiveness and detect possible recurrence.

Digital Rectal Exam (DRE)

A DRE checks for bumps or hard areas on the prostate and can determine the rough location of a tumour and whether it has spread to neighboring regions.

Prostate biopsy

If PSA and/or DRE results are a concern, a prostate biopsy is conducted and this is the basis of a formal diagnosis of prostate cancer. In a biopsy, around 12 core samples are taken from different parts of the prostate with a core needle, either transrectally or through the perineum. The samples are examined under a microscope and classified as either positive for cancer (cancer cells observed), negative for cancer (no cancer cells observed) or suspicious (some abnormalities whose interpretation is unclear). However, false-negatives are possible if the biopsy needles happened to miss cancerous tissue. If this is suspected, other tests may be performed (such as the Prostate Health Index, 4Kscore test, PCA3 tests and a biopsy may be repeated, sampling from other parts of the prostate.

Gleason score

Prostate cancer found on a biopsy will be graded, often by its Gleason score. The more abnormal the tissue appears under the microscope, the higher the grade and the more likely the tumour is to spread. With grade 1, the cancer tissue looks similar to normal prostate tissue. However, grades 1 and 2 are rarely used. Grade 5 means that the cancer tissue looks highly abnormal.

Prostate cancers usually have different areas with different grades, so grades are assigned to the 2 areas that make up most of the cancer and these two grades are added to give the Gleason score. Thus, the Gleason score can be between 2 and 10, but scores below 6 are rare. A Gleason score of 6 or less is considered 'low-grade'. A Gleason score of 7 is considered 'intermediate-grade'. A Gleason score of 8+ is considered 'high-grade'.

Alternatively, Gleason scores may be grouped in the following way:

Grade Group 1 = Gleason 6 (or less)
Grade Group 2 = Gleason 3+4=7
Grade Group 3 = Gleason 4+3=7
Grade Group 4 = Gleason 8
Grade Group 5 = Gleason 9-10

Recently 'liquid biopsies' have been developed which may increase diagnostic accuracy on the basis of blood samples. These new approaches include measurements of

- Circulating tumor cells (CTCs) which allows the assessment of gene mutations and gene expression levels (Pantel et al, 2019).
- Circulating tumor DNA (ctDNA) which allows for the assessment of gene mutations and amplifications (repeats; Ignatiadis et al, 2015)
- Customized ctDNA which allows for the assessment of genetic polymorphisms, methylation, and genetic aberrations such as insertions and deletions.

If prostate cancer is diagnosed, imaging tests (usually MRI or CT) may be conducted to check for cancer spread, if this is considered to be a significant risk (e.g. based on PSA levels or Gleason score).

Clinical Staging of Prostate Cancer

There are 4 main stages which are used to grade prostate cancer size: T1 to T4.

T1 Grades

T1 is the smallest grade and this means the cancer is too small to be detected by a scan or digital prostate examination. T1 is subdivided into T1a, T1b and T1c.

- T1a is where a surgery is performed for other reasons and cancer tissue is present in less than 5% of tissue removed.

- T1b is where a surgery is performed for other reasons and cancer tissue is present in 5% or more of tissue removed.
- T1c is where a biopsy has been performed, for example after raised PSA levels have caused a concern.

T2 Grades

T2 means the cancer is completely contained within the prostate. T2 grades are subdivided into T2a, T2b and T2c.

- T2a means that cancerous tissue is only present in half of one side of the prostate.
- T2b is where cancerous tissue is present in more than a half of one side of the prostate, but not both sides.
- T2c is where the cancer is in both sides but still completely contained within the prostate.

T3 Grades

T3 is where the cancer has breached the capsule of the prostate. T2 grades are subdivided into T3a and T3b.

- T3a is where the cancer has not spread into the seminal vesicles.
- T3b means the cancer has spread into the seminal vesicles.

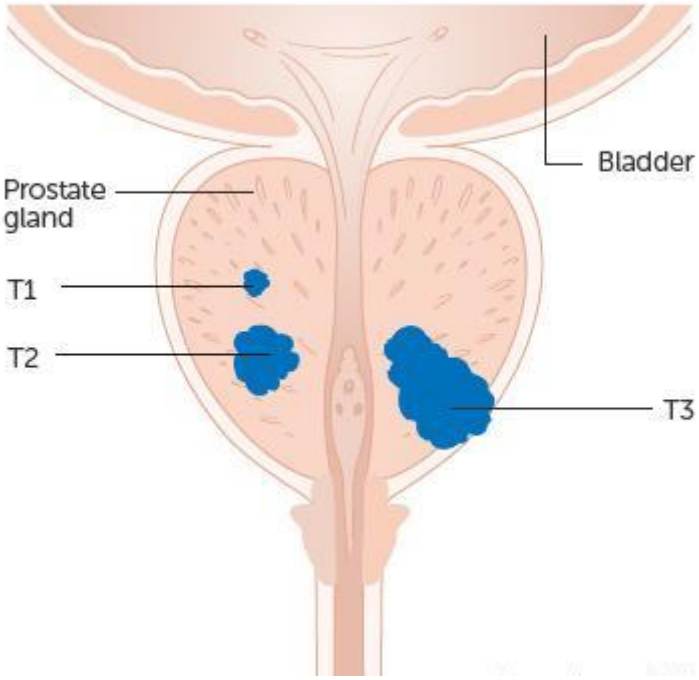
Note, the term 'localized advanced prostate cancer' (LAPC) overlaps with T3 grades in that LAPC refers to the situation where the cancer has spread to organs neighboring the prostate, but not to more distant sites.

T4

T4 means the cancer has spread into other parts of the body. Localized stage 4 prostate cancer may occur in any of the organs in the pelvic area. However, it is typically found in the nearby lymph nodes. Distant metastatic prostate cancer is where the cancer has spread to areas outside the pelvic region, most commonly bones, lymph nodes, lungs and the liver.

The staging of prostate cancer is illustrated in Figure 4 (Credit: Cancer Research UK).

A: T1, T2 and T3 stages of prostate cancer



A: T4 stage of prostate cancer

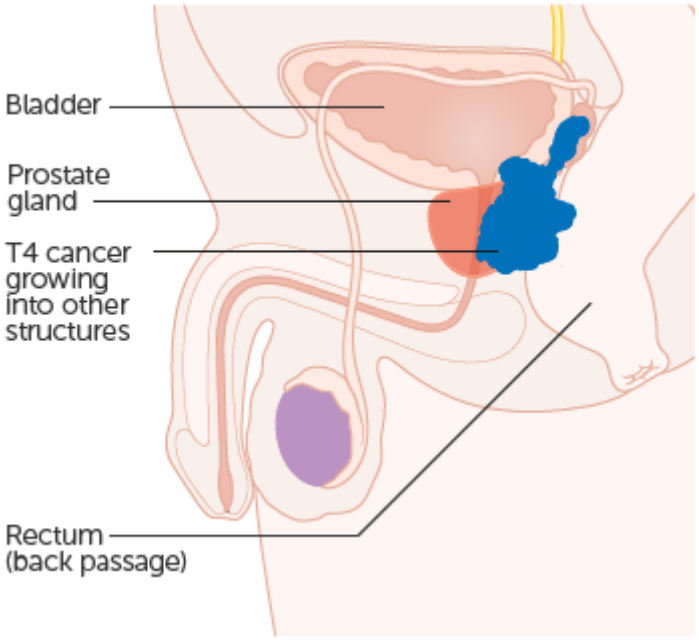


Figure 4: Staging of Prostate Cancer

Risk factors for Prostate Cancer

Established risk factors for prostate cancer include:

Age
The chance of having prostate cancer rises rapidly after 50 years.

Race
In the US African-American men are at higher risk than men of other races.

Region of the world
Prostate cancer is most common in North America, Europe, and Australia and is less common in Asia, Africa, and Central and South America. This may however, reflect more intensive screening for prostate cancer in more developed countries but may reflect lifestyle differences (diet, etc.).

Family history
Prostate cancer tends to runs in families: having a father or brother affected more than doubles a man's risk.

Genetics
Several genetic mutations appear to be associated with increased risk but these associations are relatively weak. In particular, mutations of the BRCA1 or BRCA2 genes (which are also linked to breast and ovarian cancers) can increase prostate cancer risk.

Other factors which may increase risk include high dietary intake of calcium, inflammation of the prostate (prostatitis), sexually transmitted infections and vasectomy. Finally, obesity does not appear to increase overall risk of getting prostate cancer, but may increase risk of developing a more aggressive form, and therefore of dying from prostate cancer.

Mechanisms of Prostate Cancer

Mechanisms of Prostate Cancer Genesis

Epidemiological studies have demonstrated familial clustering of prostate cancer, suggesting that genetic factors influence risk. Twin studies suggest that around 40% of risk for prostate cancer could be explained by heritable factors (Lichtenstein et al, 2000).

It has been known since the 1940s that the development of prostate cancer is dependent on androgens. Androgens include testosterone (95% of which is synthesized by the Leydig cells of the testes), dehydroepiandrosterone (DHEA, which is made by the adrenal glands) and dihydrotestosterone (DHT, which is converted from testosterone within the prostate).

Testosterone circulating in the bloodstream is mostly bound to globulin and albumin and these cannot enter prostate cells. However, testosterone in its free form can enter prostate cells. Inside the cell, testosterone is converted to DHT by the enzyme 5-alpha-reductase. Both testosterone and DHT can bind to the AR in the cytoplasm. However, DHT forms a more stable receptor–ligand complex and therefore is up to 10 times more potent in its activation of ARs (El-Alfy et al, 1999).

Once androgens bind to the AR in the cytoplasm of target cells, they are released from an inactive protein complex and can move into the cell nucleus. Inside the nucleus the ARs bind to androgen response elements in the promoter regions of target genes such as the prostate-specific antigen (PSA) gene and the transmembrane protease serine 2 (TMPRSS2) gene (Tan et al, 2015). These activated genes then promote cell proliferation and survival and induce the development of both primary male sex characteristics (growth of cells constituting the penis, testes, epididymis, vas deferens etc.) including the prostate, as well as secondary male sex characteristics, such as facial hair and muscle mass. Aberrant activation of AR signaling has been implicated in the development of prostate cancer (Culig and Santer 2014).

That androgens play a role in the genesis of prostate cancer is apparent from the effectiveness of ADT. It is also evident from epidemiological studies, which have related racial differences in androgen levels to differences in risk for prostate cancer. For example, 5-alpha-reductase activity is reduced in Asian men compared to white Europeans, reducing DHT levels (e.g. de Jong et al, 1991). This may be related to a lower risk for prostate cancer in Asian men.

Given the clear role of androgens in prostate cancer, the most widely studied genetic mutations are to the androgen receptor (AR) gene, located on the X chromosome (region q11-q12). In a healthy prostate, the ratio of cell proliferation to cell death is balanced. This ratio is regulated by levels of androgens and ARs. The emergence of prostate cancer is related to an increase in this ratio, resulting in continuous cell growth. Over a hundred AR gene mutations have been linked to prostate cancer (e.g. Gottlieb et al, 2012), therefore the mechanisms relating AR metabolism and prostate cancer are likely to be complex and heterogeneous. Several other genetic mutations have been linked to prostate cancer (e.g. GSTP1, PTEN, TP53 BRCA2, CHECK2), but it remains that the AR pathway is considered to be the major pathway involved in the genesis of prostate cancer.

Mechanisms of Progression to Castration-Resistant Prostate Cancer (CRPC)

Androgen deprivation therapy (ADT) is the standard second line treatment of metastatic prostate cancer; however, almost all such patients relapse after 2–3 years; this is known as castration resistant prostate cancer (CRPC; Rini and Small, 2002). CRPC is defined by growth in tumor cells despite castrate levels of androgens, i.e. hormone therapy has become ineffective. When prostate cancer initially appears, its cells are almost all 'androgen-sensitive', that is their growth is stimulated by the presence of androgens. Accordingly, the reduction in androgen levels involved in ADT leads to the arrest or even a reversal in tumour growth. Androgen-insensitive tumor cells may be present initially but only in small numbers. However, in the low androgen environment these androgen-insensitive tumor cells are selected for. Thus, over time the population of cancer cell shifts in its composition to predominantly of the androgen-insensitive type. This is the same principle that underlies the development of drug-resistance in several types of cancer.

Several mechanisms may underlie the development of CRPC, including

1. *Point mutations in the AR gene:* these have been found in 15% to 30% of CRPC patients (e.g. Waltering et al, 2012).
2. *AR amplification*: this has been found in 30% to 50% of CRPC patients, resulting in the overexpression of AR (Montgomery et al, 2008). Prostate cancer cells with AR amplification can survive under ADT.
3. *Changes in androgen synthesis*: in CRPC there can be an overexpression of the enzymes (CYP11A1 and CYP17A1) that convert weak adrenal androgens (DHEA and androstenedione) into strong androgens (testosterone and DHT). Abiraterone, a CYP17A1 inhibitor, is designed to stop this route of androgen supply from the adrenal glands.

4. *Changes in AR cofactor:* AR coactivators are proteins which interact with ARs enhancing their activation. AR coactivators implicated in prostate cancer include SRC-1, SRC-2, SRC-3. The expression of these coactivators may be increased in metastatic prostate cancer or CRPC.
5. *AR splicing variants*: AR has variants, a regulated process in which a gene can produce different proteins. These AR variants can be active even under forms of ADT such as enzalutamide and abiraterone (Mostaghel et al, 2011). There are changes in some of variants in circulating prostate tumor cells and the expression of some of these AD variants is associated with poor survival. It is possible, therefore, that the association between differences in AR variants and CRPC is causative.

Mechanisms of Progression to Metastatic Disease

CRPC generally leads to metastatic disease and this is the leading cause of death from prostate cancer. Lymph nodes adjacent to the primary tumors are the main site of metastases (Datta et al. 2010), but metastases can also affect the liver, lungs and bones.

One proposed mechanism in various cancer metastasis, including prostate cancer, is Epithelial–mesenchymal transition (EMT). This is the concept that epithelial cells (which line the surfaces of organs and blood vessels) can (either fully or partially) acquire the characteristics of mesenchymal stem cells, which are able to differentiate into various cell types. This points to an inherent plasticity of epithelial cells. EMT is important to processes such as wound healing, fibrosis and embryonic development.

After undergoing EMT cancer cells enter the bloodstream as circulating tumor cells (CTCs). They can then recruit platelets to protect themselves from immune cells and adhere to endothelial cells lining the blood vessels. Following this adhesion, the cancer cells can then exit the bloodstream at a new site. The cancer cells are able to overcome several barriers and migrate, even, for example to bone marrow cavities. In the new site the cancer cells can begin the formation of a new tumor.

Once prostate cancer cells have invaded the bone marrow, the cancer cells cause a “vicious cycle” of bone formation and destruction—an environment in which the tumor can grow stimulated by various growth factors secreted by the cancer cells (Body et al. 2015).

Treatments for Prostate Cancer

Routine screening for prostate cancer is common, using serum prostate-specific antigen (PSA) levels and rectal examination. Screening programs have led to the detection of most prostate cancers at an early stage: while they are organ confined and potentially curable. Also, prostate cancer tends to progress slowly, and thus the incidence of lethal metastatic disease has declined (Buzzoni et al, 2015).

First Line Treatments

Surgery

Surgery is a common first choice if the cancer is thought not to have spread. The main type of surgery for prostate cancer is a radical prostatectomy, in which the entire prostate gland and some of the surrounding tissue, including the seminal vesicles, are removed. Radical prostatectomy can be conducted using open surgery or laparoscopically (using several incisions and sometimes using robotic arms). Laparoscopic prostatectomy is usually preferred as it is less invasive and gives similar results.

Radiation Therapy

Radiation therapy uses high-energy gamma rays to kill cancer cells. It is a first line treatment for prostate cancers which are low grade and have not spread. Radiation therapy may also be used as a follow up treatment if the tumour was not completely removed by surgery or if it has regrown after surgery. Radiation therapy is also used in advanced cases, to keep the tumour under control for as long as possible and to relieve symptoms. Efficacy is about the same as for radical prostatectomy.

There are two main types of radiation therapy for prostate cancer: External beam radiation and Brachytherapy.

External beam radiation therapy (EBRT)

In EBRT, beams of radiation are focused on the prostate gland from several directions using a targeting machine. The most common type of EBRT for prostate cancer is Intensity Modulated Radiation Therapy (IMRT), in which a beam generator moves around the patient delivering the gamma ray beam. Treatment is usually 5 days a week for several weeks.

Brachytherapy ('seed implantation')

Brachytherapy uses needles to implant rice grain-sized radioactive pellets (or 'seeds') directly into the prostate. Imaging using ultrasound, CT, or MRI is used to guide the placement of the seeds. Radiation from the seeds travels only a very short distance, so the treatment can be highly focused, limiting the damage to nearby healthy tissues. Usually, around 100 seeds are used, depending on the size of the tumour. The radioactivity decays to safe levels after a few weeks or months and the seeds are left in place.

Brachytherapy is sometimes combined with external radiation in men with a high risk of metastases.

Side Effects of Radiation Therapy

The side effects of radiation therapy are related to the exposure to gamma rays and damage to healthy neighboring tissue. These side effects include bowel problems (e.g. diarrhea, blood in the stool), urinary problems, erectile dysfunction, fatigue and lymphedema (poor lymph drainage due to damage of the lymph nodes around the prostate). Brachytherapy involves a small additional risk that some of the seeds can enter the bloodstream and migrate to other parts of the body.

Second Line Treatments

Hormone Therapy / Androgen Deprivation Therapy

The two main androgens are testosterone and dihydrotestosterone, which is a more potent androgen derived from testosterone. Both androgens are mostly produced by the testes, but also by the adrenal glands and prostate. Androgens regulate the development and maintenance of male characteristics and are required for normal growth and function of the prostate. Androgens promote the growth of both normal and cancerous prostate cells by binding to, and activating, their androgen receptors.

Given that androgens stimulate prostate cancer cell growth, the proliferation of cancer cells can be prevented by androgen deprivation therapy (ADT), which reduces androgen levels to the levels associated with surgical castration ('castrate levels'). ADT is effective in slowing or even reversing the

growth of prostate tumours and, on average, ADT adds two to three years to life expectancy. ADT does not, however, provide a cure. Over time, prostate cancer cells develop resistance to ADT, for example via changes such as increased expression in androgen receptors, and eventually the tumour grows back.

Several observational studies suggest a link between ADT and increased risk of CV events. In 2010, the American Heart Association released a statement acknowledging the possible association between ADT and adverse CV events. More recently, the Prostate Cancer Survivorship Care Guidelines by American Society of Clinical Oncology (ASCO) endorsed evaluation and screening of CV risk factors in men receiving ADT6. Given the growing population of prostate cancer patients and survivors receiving ADT, it is crucial for practicing physicians to better understand ADT and the possible association with CVD.

ADT is the main second line treatment for prostate cancer and as many as 50% of prostate cancer patients receive ADT at some point (Conteduca et al, 2013). In general, it is used:

- if surgery or radiation treatment are not viable or have already failed
- if a patient is at high risk of the cancer recurring (e.g., based on high PSA levels, and/or the presence of metastases)
- to shrink the cancer to improve the chances for radiation treatment.

All forms of ADT can cause similar side effects related demasculinization/feminization, including: reduced or absent sexual desire, erectile dysfunction, shrinkage of testes and penis, hot flushes, breast tenderness, osteoporosis, weight gain and loss of muscle mass. These side effects are directly related to the therapeutic mechanism, i.e., reduction in androgen levels. In addition, some forms of ADT may increase the risk of high blood pressure, diabetes, stroke, and heart disease (e.g., Levine et al, 2010). These side effects explain why hormone therapy is used as a second line but not a first line treatment.

Types of Hormone Therapy

Orchiectomy/Surgical Castration

Orchiectomy is the removal of one or both testes. This is an inexpensive and simple form of ADT, but is permanent, and is unacceptable to most men. Thus, pharmacological equivalents are more common. Pharmacological treatments typically lower testosterone levels as much as orchiectomy and are thus sometimes known as 'chemical castration'.

Luteinizing hormone-releasing hormone (LHRH) Agonists and Antagonists

Luteinizing hormone-releasing hormone (LHRH) is a hormone which is produced by the hypothalamus. LHRH stimulates the production of luteinizing hormone (LH), which stimulates the testes to produce testosterone.

LHRH agonists (also known as gonadotropin-releasing hormone agonists) are synthetic proteins, structurally similar to LHRH but much more powerful. LHRH agonists initially stimulates production of testosterone, known as a testosterone 'flare', lasting for one or two weeks. After this, testosterone levels fall to castrate levels, thus arresting the growth and spread of prostate cancer cells.

Degarelix is an LHRH antagonist, which works in a similar way to LHRH agonists. Degarelix binds to LHRH receptors in the pituitary gland and blocks their interaction with LHRH. This reduces LH levels and in turn, levels of testosterone (Princivalle et al, 2007).

CYP17 inhibitors

CYP17 inhibitors are so called because they block CYP17, an enzyme involved in the production of androgens. CYP17 inhibitors reduce androgen production in the adrenal and prostate glands, but not the testes.

Anti-androgens

Antiandrogens are variously known as 'androgen antagonists', 'testosterone blockers' and 'androgen receptor antagonists'. They do not reduce androgen levels. Rather, they compete with endogenous androgens for binding to androgen receptors in cancer cells, keeping the androgens from stimulating tumor growth. They are functional opposites of androgen receptor agonists, like anabolic steroids, testosterone, DHT, and nandrolone.

Anti-androgens are sometimes combined with LHRH agonists or antagonists. This is known as 'combined androgen blockade' (CAB). However, the added value of CAB over conventional forms of ADT appears to be marginal (Yang et al, 2019).

Estrogens

Estrogens reduce androgen production by the testes and were one of the first treatments for prostate cancer in the 1940s. Since then, estrogens have been largely replaced by other forms of hormone therapy but are still sometimes used if other treatments have been ineffective.

Chemotherapy

Chemotherapy targets rapidly dividing cells, including cancer cells, but also healthy fast-growing cells, such skin cells and hair cells. This non-specific action causes various side effects and why chemotherapy is a second line treatment, used only if prostate cancer has spread and first line treatments (like surgery) have failed. Also, chemotherapy may slow the spread of prostate and reduce symptoms, but is not curative. Recent research indicates that chemotherapy may be effective in combination with hormone therapy.

Chemotherapy is usually given in two- or three-week long cycles, with treatments being followed by a rest period, to help the patient recover from the side effects.

Third Line Treatments

Immunotherapy

Immunotherapy works by stimulating a person’s immune system to recognize and destroy cancer cells. There are currently two FDA-approved immunotherapy options for prostate cancer, which can be used for advanced cases where hormone therapy has been ineffective.

Sipuleucel-T Vaccine (brand name Provenge)

In 2010, sipuleucel-T became the first anticancer vaccine approved by the FDA, indicating that there is a significant immunological component to prostate cancer. The vaccine is made specifically for each patient: a sample of white blood cells is removed and mixed with prostatic acid phosphatase (PAP), a protein from prostate cancer cells. The modified white blood cells are given to the patient in three infusions. The concept is that the activated white blood cells will induce an immune response against the tumor antigen and thus stimulate the immune system to recognize and attack prostate cancer cells.

The phase III trial which led to its approval by the FDA in 2010, reported a 4.1-month improvement in median survival and an improved rate of 3-year survival (31% c.f. 23%; Kantoff et al, 2010). Research is ongoing to explore its efficacy at different stages of disease and with different combinations with conventional treatments.

Immune Checkpoint Inhibitors (ICIs)

Immune checkpoints are molecules expressed on the surfaces of various lymphocytes: T cells, B cells, Natural Killer cells (NKs), and Myeloid-Derived Suppressor Cells (MDSCs). The checkpoints are activated when they bind to ligands expressed by other cells. When stimulatory checkpoints (such as CD28, ICOS, and CD137) are activated the lymphocyte mounts an immune response, i.e. it attacks the cell. Conversely, when inhibitory checkpoints (such as PD1, CTLA-4, and VISTA) are activated the lymphocyte does not mount an immune response. Thus, immune checkpoints help the immune system selectively attack pathogens, rather than indiscriminately attacking all cells, including healthy cells. This is known as 'self-tolerance'.

In a well-functioning immune system, cancer cells are attacked and destroyed by immune cells. However, cancer cells sometimes express ligands which stimulate inhibitory checkpoints in lymphocyte, effectively 'hiding' the cancer cells from the immune system. An example of this is cancer cells which produce the PD-1 ligands PD-L1 and PD-L2. These ligands activate the Programmed cell death protein 1 (the PD-1 receptor) of. PD-1 is an inhibitory checkpoint and its activation inhibits proliferation of T cells and production of cytokines (signalling molecules which regulate the balance of immune responses). This PD-1 activation is therefore one mechanism by which cancer cells hide themselves from the immune system.

PD-1 is the target for 6 of the 7 currently FDA-approved ICIs. There is currently one available PD-1 inhibitor: pembrolizumab, which was approved by the FDA in 2020 for prostate cancer patients whose tumors exhibit high levels of microsatellite instability. However, this group may represent only around 3% of patients (Abida et al, 2019).

The concept behind PD-1 inhibitors is that this molecule binds to the PD-1 receptor on T cells thereby blocking its interaction with the PD-L1 and PD-L2 ligands on the surface of cancer cells. The removal of this interaction leads to the cancer cell being 'unmasked' and the T cell attacking the cancer cell. Similarly, the concept behind PD-L1 inhibitors is that the molecule binds to the PD-L1 ligands on the surface of the cancer cell, blocking its interaction with the PD-1 receptors on T cells. Again, this leads to the T cell attacking the cancer cell. PD-L1 is expressed not only on the surface of many tumor cells but multiple tissue types. PD-L2 is more restricted to hematopoietic stem cells, which produce other blood cells in bone marrow.

Pembrolizumab is currently the only ICI approved by the FDA and is indicated for CRPC patients whose tumours have certain genetic anomalies (mismatch repair deficiency or microsatellite instability). To date the success of pembrolizumab has been limited, with only a subset of patients having been demonstrated to have a significant benefit (Hansen et al 2018).

A second potential immune treatment for prostate cancer is Ipilimumab. This is an inhibitor of CTLA-4, a protein receptor that downregulates the immune response of cytotoxic T lymphocytes (CTLs) which detect and destroy cancer cells. By blocking the activity of CTLA-4, it is hoped that Ipilimumab can promote the effect of CTLs against cancer cells. Ipilimumab is FDA approved for the treatment of melanoma, and is currently undergoing clinical trials for the treatment of lung cancer, bladder cancer and metastatic prostate cancer (Clinical trial number NCT00323882 at ClinicalTrials.gov).

Immune checkpoint inhibitors may involve immunological side effects (Buque et al 2015) and further research is required to properly assess their efficacy and safety profile.

Poly-ADP-ribose polymerase (PARP) Inhibitors

Defective DNA repair is a risk for carcinogenesis in general and has been observed in around 20% of patients with mCRPC (Robinson et al 2015). Accordingly, some new anti-cancer drugs modulate the pathways for DNA repair. Best known of these are Poly-ADP-ribose polymerase (PARP) inhibitors. These have proven effective for treating ovarian and breast cancers, particularly in patients with hereditary BRCA1 and BRCA2 mutations. These mutations are normally associated with risk of breast cancer but are also associated with increased risk for prostate cancer.

BRCA proteins and PARP proteins are both involved in DNA repair: BRCA proteins help repair double-strand DNA breaks, and PARP proteins repair single stranded DNA breaks. Tumors with BRCA1 and BRCA2 mutations are highly sensitive to PARP inhibition because inhibiting PARP proteins means removing the backup system for DNA repair within the tumour cells, and excessive level of DNA damage triggers cell death ('apoptosis') in the tumour. In 2020 the FDA approved olaparib (brand name 'Lynparza') and Rucaparib (brand name 'Rubraca'), specifically for people with hereditary BRCA1 or BRCA2 mutations, due to the interaction between BRCA and PARP metabolism.

PARP Inhibitors are considered to be one of the most promising directions for new research in cancer treatment.

Cryotherapy

Cryotherapy uses very cold gases (either nitrous oxide or carbon dioxide), administered through needles, to freeze and kill prostate cancer cells. Cryotherapy is sometimes used if the cancer has recurred after first line treatment, or to treat men with low risk, early-stage prostate cancer who cannot have surgery or radiation therapy. Cryotherapy is less invasive than surgery, but less is known about its long-term effectiveness.

Table 2: Summary of treatments of prostate cancer

First line treatments		
	Primary examples	Common side effects
Surgery	Radical prostatectomy, i.e. removal of prostate	Urinary incontinence, erectile dysfunction, which can last for several months or more.
Radiation Therapy	1. External beam radiation therapy 2. Brachytherapy ('seed implantation')	Bowel problems, urinary problems, erectile dysfunction, fatigue, lymphedema (poor lymph drainage)
Second line treatments		
	Primary examples	Common side effects
Hormone Therapies	*ALL hormone therapies*	*All* hormone therapies involve demasculinization/feminization: loss of muscle mass, increased body fat, loss of sex drive, erectile dysfunction, osteoporosis, genital shrinkage and growth of breast tissue. Below are given side effects *in addition* to these.
	Orchiectomy/Surgical castration	Post-operative swelling and pain.
	LHRH agonists and antagonists	Sweating, nausea and vomiting.
	CYP17 inhibitors	Joint and muscle pain, high blood pressure, fluid buildup in the body, diarrhea.
	Steroidal anti-androgens	Nausea, hepatotoxicity and fatigue. Sexual side effects may be less than for LHRH agonists. Diarrhea is common with combinations of anti-androgens and LHRH agonists.
	Non-steroidal anti-androgens	
	Estrogen patch	Dermatological problems (eczema, erythema)
Chemotherapy	Docetaxel (Taxotere), Cabazitaxel (Jevtana), Mitoxantrone (Novantrone),Estramustine (Emcyt)	Hair loss, mouth sores, loss of appetite, vomiting, diarrhea, general infections, fatigue.
Third line treatments		
	Primary examples	Common side effects
Cryotherapy	Not applicable	As for surgery, but with a shorter recovery period
Immunotherapy	Sipuleucel-T (Provenge) Vaccine	Fever, fatigue, joint pain, nausea, and headache.
	Immune checkpoint inhibitors	Fever, fatigue, joint pain, headache and nausea (only for a few days).

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