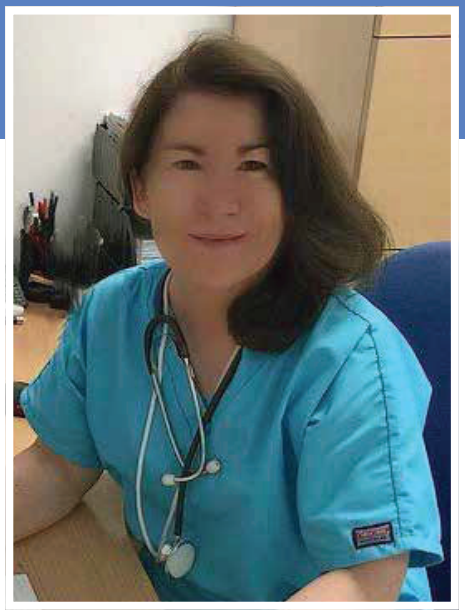
Pharmacy Management of Prostate Cancer



Interview with Theresa Lowry Lehnen (GPN, RNP, PhD)

Clinical Nurse Specialist and Associate Lecturer at Institute of Technology Carlow.

Member of the Irish General Practice Nurses Educational Association (IGPNEA)

About 3,890 men are diagnosed with prostate cancer each year in Ireland. This means that 1 in 7 men will be diagnosed with prostate cancer during their lifetime.

Prostate cancer can be treated with active surveillance, external beam radiotherapy, hormone therapy, brachytherapy, surgery, chemotherapy and watchful waiting. In 2018, 1,276,106 new cases of prostate cancer were registered worldwide, representing 7.1% of all cancers in men and 358,989 deaths representing 3.8% of all male cancer deaths.[1] 3,890 men are diagnosed with prostate cancer each year in Ireland indicating that 1 in 7 men in Ireland will be diagnosed with prostate cancer during their lifetime.[1, 2]

We recently spoke to Theresa Lowry Lehnen (GPN, RNP, PhD) Clinical Nurse Specialist and Associate Lecturer at Institute of Technology Carlow to find out more about current advances in this field.

The prostate is part of the male reproductive system, which includes the penis, prostate, seminal vesicles, and testicles. The prostate gland is located just below the bladder and in front of the rectum. It surrounds the urethra and produces fluid that makes up a part of semen.[5] The prostate gland is a conglomerate of tubular or saclike glands that secrete fluids into the urethra and ejaculatory ducts. The secretory ducts and glands are lined with a moist, folded mucous membrane. Beneath the mucous membrane lies connective tissue composed of a thick network of elastic fibres and blood vessels. The interstitial tissue surrounding the secretory ducts and glands contains muscle, elastic fibres, and collagen fibres that give the prostate gland support and firmness. The capsule enclosing the prostate is also composed of interstitial tissue.[1, 6]

Theresa, who is a member of the Irish General Practice Nurses Educational Association says, "Prostate cancer incidence rates are highly variable worldwide and the variations in incidence is likely to be attributed to PSA testing. In Europe, prostate cancer is the most frequently diagnosed cancer among men, accounting for 24% of all new cancers in 2018, with around 450,000 new prostate cancer cases detected in 2018.[3] Prostate cancer incidence increases with age."

Risk factors

So what are the most common risk factors for prostate cancer? Theresa reflects that increasing age is one of them.

She adds, "It usually affects men over the age of 50 and almost two in every three prostate cancers are diagnosed in men over the age of 65. In Ireland, the majority of cases are detected in men aged 65-to-84 years, with 37 per cent detected in men under 65 years of age. Genetic factors play a role. Family history is associated with an increased risk and men with a father or brother diagnosed with prostate cancer at age 50 years have an approximately two-fold increased risk of prostate cancer.[1]

"Risk is higher in males with a relative who developed prostate cancer at a younger age and in males who have more than one relative with the disease. Two genes, BRCA1 (breast cancer type 1) and *BRCA2* (breast cancer type 2), have been linked to prostate cancer. Like women, men can have mutations in the BRCA1 and BRCA2 genes."

The function of the BRCA genes is to repair cell damage and keep breast, ovarian, and other cells growing normally. "Men carrying mutations in BRCA2 gene have an increased risk of developing prostate cancer, and mutations in either gene can significantly reduce survival,[7] she adds.

"Studies have revealed an association between hereditary susceptibility to prostate cancer and sequence variations in the *RNASEL gene* (ribonuclease L), which plays a role in maintaining immunity against viral infections.

"A common *RNASEL* variant involves a mutation resulting in decreased activity of the encoded ribonuclease L protein, reducing the immune defence against viruses. Men who inherit this mutation have a significant increased risk of developing prostate cancer.[7] It is estimated that about 20% of patients with prostate cancer report a family history, which may develop not only because of shared genes, but also for a similar pattern of exposure to certain environmental carcinogens and common lifestyle habits.[9]

"Afro-Caribbean men have the highest incidence of prostate cancer of any group (231.9 per 100,000) while Asian men have the lowest risk. Obesity and physical inactivity has been associated with higher-grade prostate cancers and studies have shown increased risk associated with various dietary intakes, including high levels of high-saturated fats and red meats and reduced intake of fish, fruit and vegetables.[1, 2, 9] Research is ongoing into the links between diet and prostate cancer and there is some evidence that a diet high in calcium is also linked to an increased risk of developing prostate cancer.[8]

"Although there are no studies that can sufficiently demonstrate the direct correlation between diet and nutrition with risk or prevention of prostate cancer development, many preclinical studies that look at links between certain eating behaviours and cancer suggest there may be a connection,"[9] says Theresa.

Unknown Factors

The aetiology of prostate cancer is the subject of numerous studies and remains largely unknown compared to other common cancers.

She continues, "While the exact causes of prostate cancer are not fully understood many cases do appear to be related to aberrant cell signalling that involves male androgen hormones, particularly testosterone and its metabolites.

"Within certain tissues, testosterone may be converted into one of two active compounds, oestradiol or dihydrotestosterone. Oestradiol promotes the growth of prostate cancer cells and dihydrotestosterone inhibits apoptosis of those cells. Testosterone plays a central role in maintaining prostate cells and stimulating apoptosis when abnormal cells arise. However, the mechanism by which testosterone and its active derivatives contribute to the development of prostate cancer is not entirely understood.[7]

"During the process of malignant transformation, cells gradually evolve from the benign to malignant phenotype. High-grade prostatic intraepithelial neoplasia (PIN) is the histological entity widely considered to be the most likely precursor of invasive prostatic cancer. It is characterised by cellular proliferation within pre-existing ducts and glands with cytological changes.[2]

"Although other prostate lesions may be associated with even higher rates of carcinoma, PIN has been identified as the most likely progenitor of the majority of prostatic adenocarcinomas."[9]

Symptoms and Diagnosis

When the prostate gland becomes cancerous, it can put pressure on the urethra, causing dysuria, a burning sensation and frequency of micturition. It can also cause hesitancy, a weak and intermittent flow, nocturia, haematuria and impotence or sexual dysfunction. Theresa continues, "Other symptoms include swollen lymph nodes in the groin and pain in the pelvis, hips, back, or ribs. More advanced stage of the disease may present with urinary retention and back pain, as the axis skeleton is the most common site of bony metastatic disease. Prostate cancer should not be confused with benign prostate hyperplasia, which has similar symptoms and often occurs in older men but is not a type of cancer."[7]

Prostate cancers usually grow very slowly, and symptoms may not occur for some time. She adds, "If the prostate is enlarged, a preliminary diagnosis can be made by rectal examination or transrectal ultrasound (TRUS). A PSA blood test for prostate-specific antigen is used to detect prostate tumours in their earliest stages in high-risk individuals.

"Although originally introduced as a tumour marker for the detection of cancer recurrence, PSA testing became widely adopted as a screening tool for prostate cancer. However, it is not prostate cancer-specific and other prostate conditions, such as benign prostatic hyperplasia (BPH) or prostatitis, can also affect PSA levels.[2] If prostate cancer is suspected a biopsy is done to confirm the diagnosis. When detected early, prostate cancer is treatable. A large majority of prostate cancers are diagnosed either before they have spread or when they have spread only locally. Survival rates in these cases are very high."[7]

Staging Systems

The TNM staging system refers to the size of the tumour **(T)**, if the cancer has spread to the lymph nodes **(N)** and if the cancer has spread to other parts of the body- metastasis **(M)**.[1]

Tumour (T) –Size of the tumour

T1 The tumour is within the prostate gland. It is too small to be felt during a rectal exam.

T2 The tumour is still within your prostate gland. It is large enough to be felt during a rectal exam.

T3 The tumour can be felt throughout the prostate, and may have broken through the outer layer of the prostate.

T4 The tumour has spread to organs outside the prostate gland.

Node (N) – Are the lymph nodes affected?

N Cancer is present in the lymph nodes.

N0 No cancer in the lymph nodes.

N1 Cancer has spread to 1 or more of the lymph nodes.

If diagnosed with early prostate cancer, **N0** signifies that the cancer has not spread outside the prostate.

Metastasis (M) – has it spread outside the prostate?

M The cancer has spread to lymph nodes and/or other organs, commonly bones

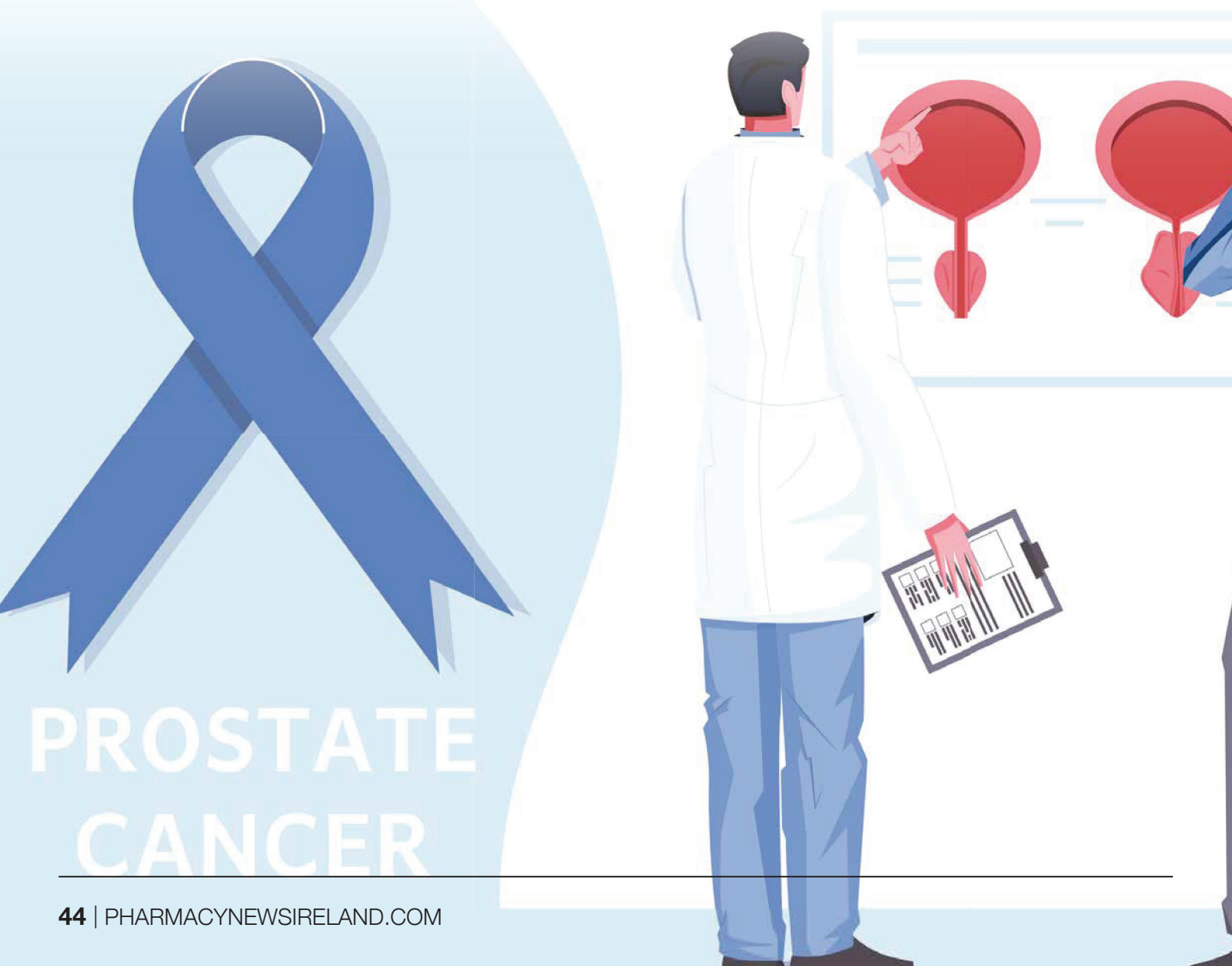
M0 The cancer has not spread.

If diagnosed with early prostate cancer **M0** signifies that the cancer has not spread outside the prostate.

The Gleason Score

The Gleason Score is a grading system used to determine the aggressiveness of prostate cancer and can be used to choose appropriate treatment options. "The Gleason Score ranges from 1-5 and describes how much the cancer looks like healthy or abnormal tissue," she notes.

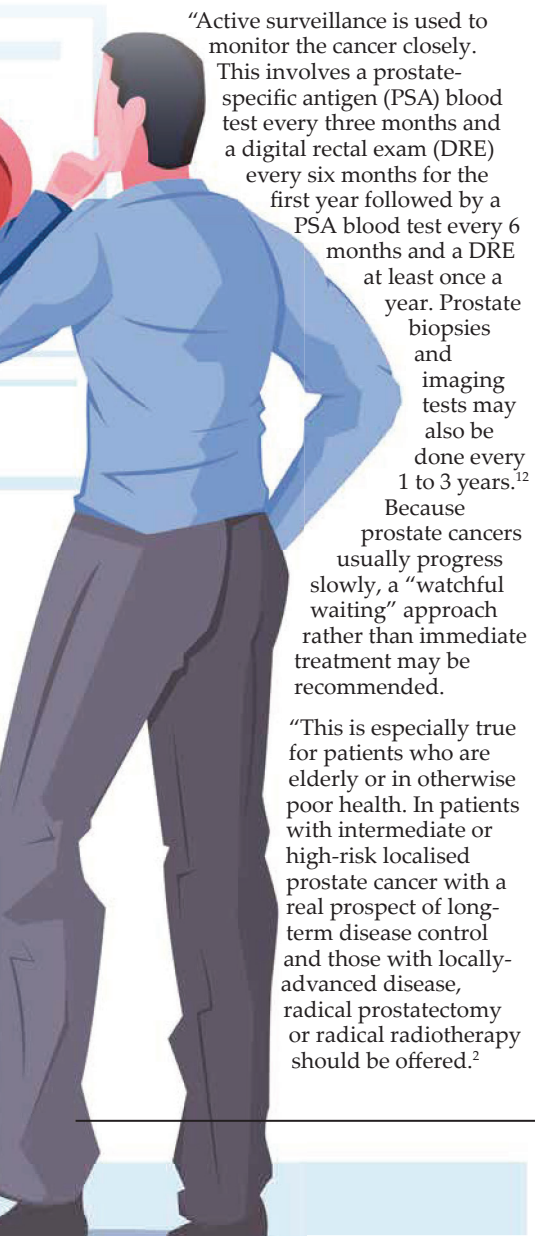
"Most cancers score a grade 3 or higher. Since prostate tumours are often made up of cancerous cells that have different grades, two grades are assigned for each patient. A primary grade is given to describe the



cells that make up the largest area of the tumour and a secondary grade is given to describe the cells of the next largest area. If the Gleason Score is written as 3+4=7, it means most of the tumour is grade 3 and the next largest section of the tumour is grade 4. If the cancer is almost entirely made up of cells with the same score, the grade for that area is counted twice to calculate the total Gleason Score. Typical Gleason Scores range from 6-10. The higher the Gleason Score, the more likely that the cancer will grow and spread quickly. Scores of 6 or less describe cancer cells that look similar to normal cells and suggest that the cancer is likely to grow slowly. A score of 7 suggests an intermediate risk for aggressive cancer. Scoring a 7 means that the largest section of the tumour (primary score) scored a 3 or 4. Tumours with a primary score of 3 and a secondary score of 4 have a reasonably good outlook, whereas cancers with a primary Gleason Score of 4 and a secondary score of 3, are more likely to grow and spread. Scores of 8 or higher describe cancers that are likely to spread more rapidly and these cancers are often referred to as high grade or poorly differentiated."[10]

Treatment Options

Treatment options for patients with prostate cancer depend on the stage and grade of the cancer and include active surveillance, watchful waiting, hormone therapy, radical prostatectomy, external beam radiotherapy, and brachytherapy.[1]



"Active surveillance is used to monitor the cancer closely. This involves a prostate-specific antigen (PSA) blood test every three months and a digital rectal exam (DRE) every six months for the first year followed by a PSA blood test every 6 months and a DRE at least once a year. Prostate biopsies and imaging tests may also be done every 1 to 3 years.[12] Because prostate cancers usually progress slowly, a "watchful waiting" approach rather than immediate treatment may be recommended.

"This is especially true for patients who are elderly or in otherwise poor health. In patients with intermediate or high-risk localised prostate cancer with a real prospect of long-term disease control and those with locally-advanced disease, radical prostatectomy or radical radiotherapy should be offered.[2]

"Hormone therapy is the primary treatment for metastatic prostate cancer, but is also used for patients with locally-advanced, non-metastatic disease. In patients with localised prostate cancer, the choice of treatment depends on whether the disease is low, intermediate, or high risk.[2] Hormone therapy also called androgen suppression or androgen deprivation therapy (ADT) attacks androgens that stimulate the growth of prostate cancer. A form of hormone therapy involves drugs called LHRH analogs, or LHRH agonists such as buserelin, goserelin, leuprorelin acetate or triptorelin that chemically block the production of androgens. Side effects of hormone therapy include reduced libido, sexual dysfunction, osteoporosis, gynaecomastia and hot flushes.[2, 7]

"Brachytherapy is a form of radiation therapy used to treat prostate cancer. Prostate brachytherapy involves placing radioactive seeds in the prostate gland which destroys the cancer cells while causing less damage to healthy tissue nearby. Prostate brachytherapy procedures vary based on the type. High dose rate (HDR) brachytherapy is a temporary type of prostate brachytherapy that involves placing radioactive sources in the prostate gland and delivering a high dose of radiation over a few minutes before the sources are removed. Treatment may involve several sessions. Low dose rate (LDR) brachytherapy is permanent and involves placing radioactive seeds in the prostate gland permanently, where they slowly release radiation over several months. Brachytherapy may be the only treatment used for early-stage prostate cancer that is less likely to spread beyond the prostate. For larger prostate cancers or those that have a greater chance of spreading beyond the prostate, brachytherapy may be used along with other treatments, such as external beam radiation therapy (EBRT) or hormone therapy.[1, 11]

"In external beam radiation therapy, beams of radiation are focused on the prostate gland from a machine outside the body. This type of radiation can be used to try to cure earlier stage cancers, or to help relieve symptoms such as bone pain if the cancer has spread to a specific area of bone."[1]

Surgery is usually only carried out if the cancer has not spread from the prostate, Theresa explains. "A radical prostatectomy may be considered if examination of the pelvic lymph nodes reveals that they are not cancerous. Surgical risks can include impotence and urinary incontinence.[7] Transurethral resection of the prostate (TURP) can be used to relieve symptoms but does not remove all of the cancer. TURP is often used in men who cannot have a radical prostatectomy because of advanced age or illness or in men who have a noncancerous enlargement of the prostate.

"In men who are unable to have traditional surgery, cryosurgery may also be used. In this procedure, a metal probe is inserted into the cancerous regions of the prostate; liquid nitrogen is then used to freeze the probe, killing the surrounding cells. If the cancer has spread from the prostate, radiation therapy may be used. Bi lateral orchidectomy should be offered to all patients with metastatic prostate cancer as an alternative to continuous LHRH agonist treatment. Removal of the testicles cuts off the supply of testosterone to the tumour, which the prostate cancer needs in order to continue growing. It can delay or stop the tumour growth and eliminates the need for other hormone therapy. If surgery or hormone therapy fails, chemotherapy may be used. While chemotherapy can slow the growth of the tumour, it is not very effective in treating prostate cancer."[7]

Prognosis and Outlook

The outlook for prostate cancer is generally good because, unlike many other types of cancer, it usually progresses very slowly. If treated early, prostate cancer can often be cured. She concludes, "The survival rate is over 90% and many men die with prostate cancer, rather than as a result of having it. Prostate cancer has one of the highest survival rates of any type of cancer. 92% of all prostate cancers are found when they are in the early stage, and almost 100% of men who have local or regional prostate cancer will survive more than five years after diagnosis. For most with local or regional prostate cancer, the relative 10-year survival rate is 98% and the relative 15-year survival rate is 96%. Once prostate cancer has spread beyond the prostate, however, survival rates fall and about 7% have more advanced prostate cancer at the time of diagnosis. For men with prostate cancer that has spread to other parts of the body, the 5-year survival rate is 30%.[13, 14]

"Prostate cancer presents a number of challenges for primary care clinicians. Many men with prostate cancer are asymptomatic until the tumour has progressed, and common symptoms have significant crossover with benign conditions affecting the prostate. PSA-based testing of prostate cancer is very common but remains controversial. The value of screening remains uncertain because the PSA test does not distinguish between benign and malignant disease, and there has been no proof that early treatment leads to increased cure rates. Digital rectal examination alone is insufficient for screening as its positive predictive value is only 11%–26%. Current diagnostic tests have limitations in terms of significant false positive and false negative rates however research is ongoing into improved methods for diagnosing prostate cancer. Nanotechnology has shown initial success in prostate cancer disease diagnosis, imaging and treatment. A number of new tests and testing strategies are being trialled to improve the diagnosis of clinically significant prostate cancer and blood-based biomarkers for prostate cancer are also being extensively investigated.[15, 16] Because the value of PSA-based testing of prostate cancer remains unclear, more genetic testing–based detection strategies are needed to identify individuals at high risk of prostate cancer and novel drugs need to be evaluated to substantially improve the clinical care of patients with prostate cancer. Continued clinical and translational research in prostate cancer is important and could be key to the treatment and management of prostate cancer through leading improvements in prostate cancer imaging and diagnosis.[16]

References available upon request