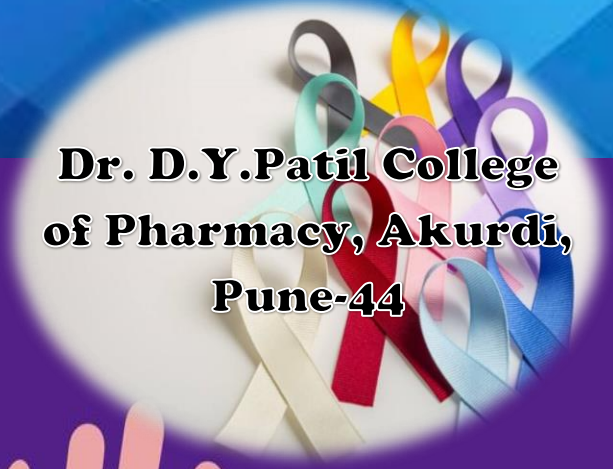
DR. D. Y. PATIL COLLEGE OF PHARMACY

Tech Pharma
Technical magazine 2024

Issue-12 (April) 2024



Dr. D.Y.Patil College of Pharmacy, Akurdi, Pune-44

VISION

To impart quality education to the Students and mould them into proactive multifaceted Pharmacists.

MISSION

To establish a centre of Academic excellence and research in Pharmacy Education and thereby produce professionally competent and ethically sound Pharmacist to cater to the needs of the global society.

PROGRAM EDUCATIONAL OBJECTIVES (PEOs)

After graduation students will

1. Reflect critical thinking and problem solving skills through their Pharmaceutical knowledge, expertise and competency in industry, higher studies and research.
2. Practice ethics and values in their profession.
3. Contribute effectively in various fields of social healthcare system.
4. Inculcate leadership and entrepreneurship capabilities through effective communications, appropriate time management and self-upgradation.

EDITORS DESK

Mr. Pavankumar Wankhade **Mrs. Kajal Bhagat**

The technological advancements, like media and internet, have surely helped the pharmacist patients as well as the clinicians. However, many traditional disease issues, remain the same. Yet the woes of treating the same continue and the pharmacist try to find and develop better ways to alleviate the sufferings of the patient. The advancements in science and technology continue, and different modes of new treatments and diagnostic modalities continue to emerge. Yet the common diseases, historically seen in the patients, are still the subject of medical research, books, journals and the medical industry as a whole. The current issue of the journal highlights on awareness of cancer. In the issue we published the papers about detail information about different types of cancer. Thus, this particular issue will be helpful, for all pharmacist to understand their role better.

Mr. Pavankumar Wankhade, Assistant Professor

The current issue focuses upon the topic of utmost priority that is “Health”, addressing the current need of an hour and spreading awareness about some common diseases, our students and faculty members have put forward some informative articles. world cancer day is an opportunity for people and communities to unite behind the theme “Close the Care Gap” to The campaign is all about understanding and recognizing the inequities in cancer care around the globe. This World Cancer Day, we recognize the power of working together. We know that every single one of us has the ability to make a difference, large or small, and that together we can make real progress in reducing the global impact of cancer.

Mrs. Kajal Bhagat, Assistant Professor

“We would like to express our gratitude and heartfelt thanks to our beloved Principal Dr. Niraj Vyawahare for constant support and motivation. We are also grateful to our Vice Principal Dr. (Mrs). Shilpa Chaudhari, all the teaching, non-teaching staff and our students.” Our organization feels special and privileged in presenting this issue.

THANK YOU ONCE AGAIN TO ALL.

TABLE OF CONTENTS

14	**A Review on Thyroid Cancer**	**Dr. Smeeta Sadar, Gauri Gawande, Ajay Lokhande**	
15	**Thyroid cancer**	**Mr. Siddharth Topale Mr. Mukesh Mohite**	
16	**Prostate Cancer**	**Mr. Sanket Palve, Dr. Prafulla Kadam**	
17	**Comprehensive review of ovarian cancer : pathophysiology , diagnosis and treatment strategies**	**Mr. Rushikesh Chaudhari, Ms Poonam Mulay, Ms. Tejashree Deokule**	
18	**Pancreatic Cancer**	**Ms. Rajashree Shinde, Mr. Omkar Shendge, Ms. Ankita Dudhal**	

Cancer is a large group of diseases that can start in almost any organ or tissue of the body when abnormal cells grow uncontrollably, go beyond their usual boundaries to invade adjoining parts of the body and/or spread to other organs. The latter process is called metastasizing and is a major cause of death from cancer.

A neoplasm and malignant tumour are other common names for cancer.

HEAD AND NECK CANCER

Mr. Sharayu Buchude, Mrs. Pranita Shankaratti
Department of PharmD: Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune

ABSTRACT

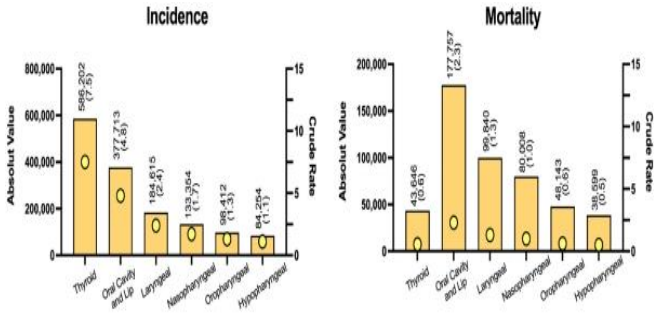
Head and neck cancer is the seventh most common type of cancer worldwide and comprise of a diverse group of tumours affecting the upper aero digestive tract. Although many different histology's exist, the most common is squamous cell carcinoma. Historical records as far back as 3000 BCE show that oral and head and neck cancer was a disease process well known to Egyptian physicians. During the 20th century, evidence-based medicine catalysed the development of rigorous science-based diagnostic and treatment protocols. Predominant risk factors include tobacco use, alcohol abuse, and oncogenic viruses, including human papillomavirus and Epstein-Barr virus. Head and neck malignancies remain challenging to treat, requiring a multidisciplinary approach, with surgery, radiotherapy, and systemic therapy serving as key components of the treatment of locally advanced disease. Although many treatment principles overlap, treatment is generally site-specific and histology specific. This Seminar outlines the current understanding of head and neck cancer and focuses on treatment principles, while also discussing future directions to improve the outcomes of patients with these malignancies.

INTRODUCTION

Head and neck cancer is the seventh most common type of cancer worldwide and comprise of a diverse group of tumours affecting the upper aero digestive tract. Head and neck cancer (HNC) is a group of epithelial malignancies involving the upper shared respiratory/digestive tract (lips, oral cavity, oropharynx, nasal cavity, nasopharynx, hypopharynx and larynx/upper trachea), the salivary glands and lymphadenopathy associated with these diseases. Cancers of the brain, the eye, the oesophagus, the thyroid gland, and the skin of the head and neck are not usually classified as head and neck cancers.[2] Although many different histology's exist, the most common is squamous cell carcinoma. Predominant risk factors include tobacco use, alcohol abuse, and oncogenic viruses, including human papillomavirus and Epstein-Barr virus. Lump or sore that does not heal, sore throat that does not go away, trouble swallowing, change in voice. The treatment can include surgery, radiation therapy, chemotherapy, targeted therapy, immunotherapy, or a combination of treatments. The treatment plan for an individual patient depends on a number of factors, including the location of the tumour, the stage of the cancer, and the person's age and general health. [3][1]

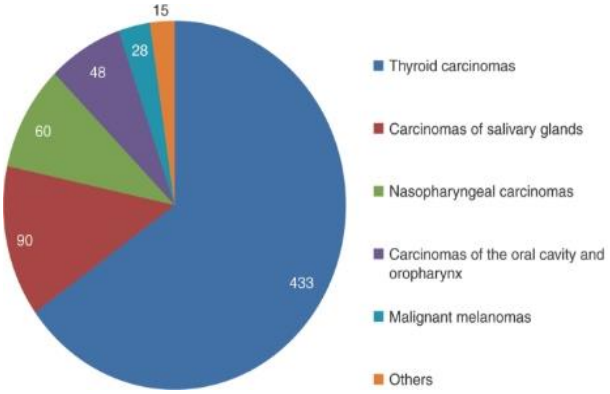
HISTORY

Historical records as far back as 3000 BCE show that oral and head and neck cancer was a disease process well known to Egyptian physicians. Luminaries such as Hippocrates, Galen, Pott, and Virchow were instrumental in shaping our understanding of the etiology and pathogenesis of cancer. During the 20th century, evidence-based medicine catalysed the development of rigorous science-based diagnostic and treatment protocols. [6] The use of surgery, therapeutic radiation, and chemotherapy as single-treatment agents or in combination with one another gradually emerged as the preferred approach to cancer therapy. The recognition of tobacco, alcohol, and human papillomavirus as etiological agents in oral and head and neck cancer prompted the development of new diagnostic aids and treatment strategies to mitigate cancer progression. More in-depth mechanistic insights into the multistep process of oral and head and neck cancer were made possible by the use of the hamster buccal pouch and mouse models. New technologies, such as the sequencing of the human genome, metabolomics, and proteomics, have provided the foundation for what we today call precision medicine. [5][2]



ETIOLOGY

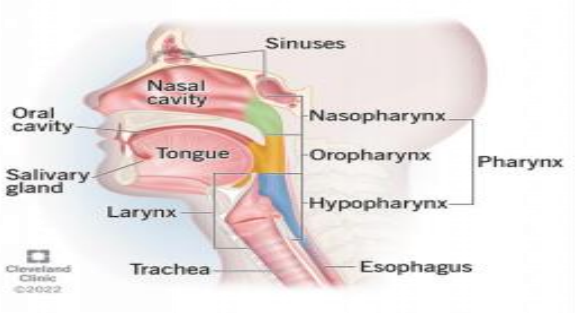
- **Using tobacco:** Tobacco use is the most common cause of head and neck cancers. Approximately 70% to 80% of these cancers are linked to tobacco use. Tobacco use includes smoking cigarettes, cigars or pipes or using chewing tobacco, snuff or dip. Exposure to second-hand smoke may also increase your risk.
- **Drinking too much alcohol:** Consuming too much alcohol can increase your risk. If you drink, the Centres for Disease Control and Prevention (CDC) recommends no more than two drinks daily for men and people AMAB and no more than one drink daily for women and people AFAB.
- **Human papillomavirus (HPV):** The occurrence of head and neck cancers associated with HPV infection is on the rise, especially among younger adults. Up to 75% of oropharyngeal cancers are associated with HPV infection. [5]
- **Epstein-Barr virus (EBV):** EBV is most commonly associated with mono, but it's related to cancer risk, too. Research suggests that an EBV infection can lead to nasopharyngeal cancer. [4]
- **Having a weak immune system:** A weakened immune system makes it harder for your body to fight cancer. HIV infection and recent major surgeries (like organ or bone marrow transplants) have both been associated with cancer resulting from weakened immune systems. [5]
- **Exposure to substances:** You may expose you to substances linked to head and neck cancers, including asbestos, pesticides, wood dust, paint fumes, etc.
- **Radiation exposure:** Radiation treatment for malignant or benign tumours has been linked to salivary gland cancer, but the risk is low.
- **Diet:** Eating too many salt-cured foods (like salt-cured meat and fish) can increase your risk of nasopharyngeal cancer.
- **Genes:** Your genes may increase your cancer risk. For example, people with Fanconi anaemia inherit genes from their biological parents that increase their risk of certain cancers, including head and neck cancers. Your genes may make you more likely to develop cancer if you use tobacco.
- **Poor dental hygiene:** Not taking care of your teeth and gums can increase your risk of periodontal disease and oral cancer.[7]



TYPES OF HEAD AND NECK CANCER

1. **Laryngeal and hypopharyngeal cancer:** the voice box is a short passageway
2. formed by cartilage just below the pharynx in the neck. The voice box contains the vocal cords and epiglottis.
3. **Nasal cavity and paranasal sinus cancer.** The nasal cavity is the space just behind the nose where air passes on its way to the throat. The paranasal sinuses are the air-filled areas that surround the nasal cavity.
4. **Nasopharyngeal cancer.** The nasopharynx is the air passageway at the upper part of the throat behind the nose.
5. **Oral and oropharyngeal cancer.** The oral cavity Includes the lips, the front two-thirds of the tongue, the gums, the lining inside the cheeks and lips, the floor under the tongue.
6. **Salivary gland cancer:** The major salivary glands are in the floor of the mouth and near the jawbone. The salivary glands produce saliva. Minor salivary glands are

located throughout the mucous membranes of the mouth and throat.



CLINICAL PRESENTATION

- A mouth sore that bleeds
- A red or white patch on the gums, tongue
- A swelling, thickness in the neck or face
- A persistent sore throat
- Chewing or swallowing difficulties
- Mouth or tongue numbness
- Persistent hoarseness or vocal changes
- Blood in the sputum Frequent nosebleeds
- Ear pain

DIAGNOSIS

- **A physical exam:** Include checking of oral and nasal cavities, neck, throat and tongue. The neck, lips, gum and cheeks may have lumps.
- **An endoscopy:** This procedure uses a thin, lighted tube called an endoscope that allows to see the nasal cavity, throat, voice box or other areas where patient experiencing symptoms. A nasal endoscopy helps to view nasal cavity. A laryngoscopy allows to view the voice box (larynx).
- **Imaging tests:** Head and neck X-rays, CT scans, MRIs and PET scans create pictures of areas inside the head and neck.
- **Lab tests:** Blood test, test for viruses like HPV or EBV, the biomarker testing (molecular testing) to check for proteins common in particular head and neck cancers.[7]
- **A biopsy**: A biopsy is the only way to diagnose cancer. Common biopsy methods used to diagnose head and neck cancers include fine needle aspiration and core needle biopsy.

TREATMENT

- **Surgery:** Surgeons may remove the tumor and a margin of surrounding healthy tissue. The surgeon may also remove the lymph nodes in your neck if they suspect the cancer's spread there.
- **Radiation therapy:** The most common form of radiation for head and neck cancers uses a machine that directs high-energy X-rays toward your tumor (EBRT). You may receive radiation as a standalone treatment or alongside other treatments like surgery and chemotherapy. Radiation therapy can help relieve symptoms, too.[6]
- **Chemotherapy:** Chemotherapy uses a single drug or a combination of drugs to kill cancer cells. It's more commonly used for advanced-stage head and neck cancers.
- **Targeted therapy:** These drugs target specific types of cancer. They're most often used in combination with other treatments to treat advanced head and neck cancers. Cetuximab is a drug that targets a tumor protein called epidermal growth factor (EGFR) and is U.S. Food and Drug Administration (FDA)-approved to treat particular head and neck cancers. There are treatments approved by the FDA specific to genetic changes, such as Larotrectinib, which is used to treat people with mutations in their NTRK gene.[8][5]
- **Immunotherapy:** Immunotherapy drugs activate (or boost) your immune system to identify and destroy cancer cells more effectively. Pembrolizumab and nivolumab are two FDA-approved immunotherapy drugs used to treat certain head and neck cancers that've spread or returned following treatment.

REFRENCES

1. Cancer Research UK. Head and neck cancers statistics. Available at https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/head-and-neck-cancers#heading-Zero (accessed June 2022).

2. Powell J, Cooles F A H, Carrie S, Paleri V. Is undergraduate medical education working for ENT surgery? A survey of UK medical school graduates. *J Laryngol Otol* 2011; **125:** 896-905. [PubMed]

3. British Association of Head and Neck Oncologists. Publications: BAHNO standards 2020. 2020. Available at

https://bahno.org.uk/clinicians_area/publications.aspx (accessed June 2022)

4. Jain K S, Sikora A G, Baxi S S, Morris L G T. Synchronous cancers in patients with head and neck cancer: risks in the era of human papillomavirus-associated oropharyngeal cancer. *Cancer* 2013; **119:** 1832-1837. [PubMed]

5. Waridel F, Estreicher A, Bron L *et al.* Field cancerisation and polyclonal p53 mutation in the upper aero-digestive tract. *Oncogene* 1997 **14:** 163-169. [PubMed]

6. Olivero C, Lanfredini S, Borgogna C, Gariglio M, Patel G K. HPV-Induced Field Cancerisation: Transformation of Adult Tissue Stem Cell Into Cancer Stem Cell. *Front Microbiol* 2018; **9:** 546. [PMC free article]

7. National Institute for Health and Care Excellence. Improving outcomes in head and neck cancers. 2004. Available at https://www.nice.org.uk/guidance/csg6 (accessed October 2022).

8. National Institute for Health and Care Excellence. Cancer of the upper aerodigestive tract: assessment and management in people aged 16 and over. 2016. Available at https://www.nice.org.uk/guidance/ng36 (accessed October 2022). [PubMed]

BLADDER CANCER: ADVANCE TREATMENTS

Mrs. Kajal Bhagat
Department of Pharmacognosy, Dr. D.Y Patil College of Pharmacy. Akurdi, Pune

INTRODUCTION

Bladder cancer is a common type of cancer that begins in the cells of the bladder. The bladder is a hollow muscular organ in your lower abdomen that stores urine.

Bladder cancer most often begins in the cells (urothelial cells) that line the inside of your bladder. Urothelial cells are also found in your kidneys and the tubes (ureters) that connect the kidneys to the bladder. Urothelial cancer can happen in the kidneys and ureters, too, but it's much more common in the bladder.

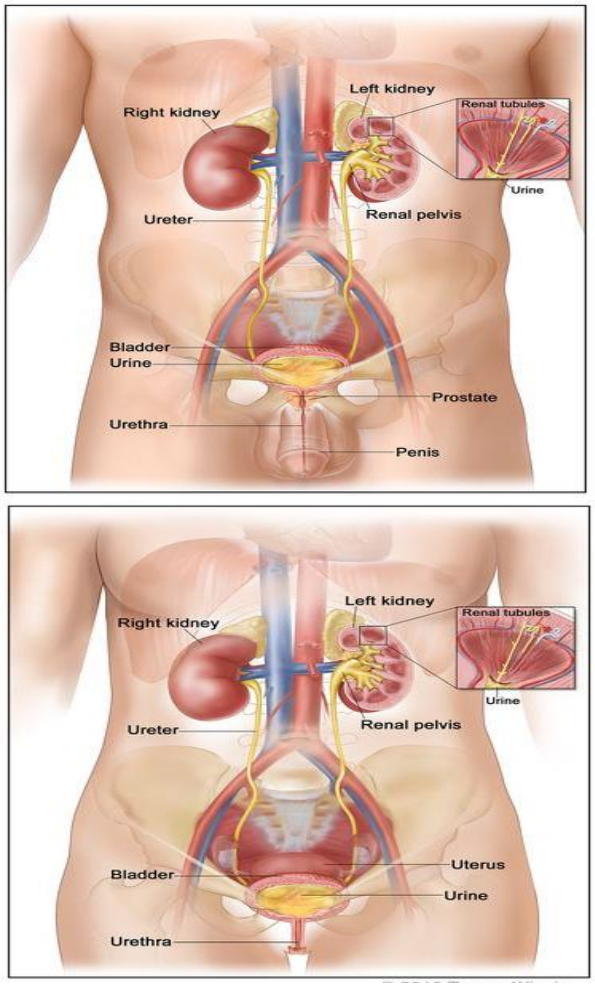
Most bladder cancers are diagnosed at an early stage, when the cancer is highly treatable. But even early-stage bladder cancers can come back after successful treatment. For this reason, people with bladder cancer typically need follow-up tests for years after treatment to look for bladder cancer that recurs.

Bladder cancer occurs when cells in the bladder start to grow without control. The bladder is a hollow, balloon-shaped organ in the lower part of the abdomen that stores urine.

The bladder has a muscular wall that allows it to get larger to store urine made by the kidneys and to shrink to squeeze urine out of the body. There are two kidneys, one on each side of the backbone, above the waist. The bladder and kidneys work together to remove toxins and wastes from body through urine:

- Tiny tubules in the kidneys filter and clean the blood.
- These tubules take out waste products and make urine.
- The urine passes from each kidney through a long tube called a ureter into the bladder.
- The bladder holds the urine until it passes through a tube called the urethra and leaves the body.

ANATOMY OF FEMALE AND MALE BLADDER



Anatomy of the male urinary system (left panel) and female urinary system (right panel) showing the kidneys, ureters, bladder, and urethra. The inside of the left kidney shows the renal pelvis. An inset shows the renal tubules and urine. Also shown are the prostate and penis (left panel) and the uterus (right panel). Urine is made in the renal tubules and collects in the renal pelvis of each kidney. The urine flows from the kidneys through the ureters to the bladder. The urine is stored in the bladder until it leaves the body through the urethra.

TYPES OF BLADDER CANCER

Urothelial carcinoma (also called transitional cell carcinoma) is cancer that begins in the urothelial cells, which line the urethra, bladder, ureters, renal

pelvis, and some other organs. Almost all bladder cancers are urothelial carcinomas. Urothelial cells are also called transitional cells because they change shape. These cells are able to stretch when the bladder is full of urine and shrink when it is emptied.

Other types of bladder cancer are rare:

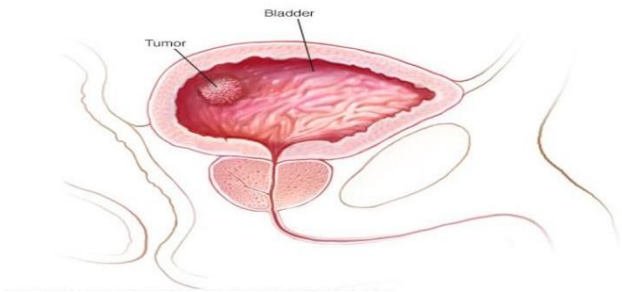
- **Squamous cell carcinoma** is cancer that begins in squamous cells (thin, flat cells lining the inside of the bladder). This type of cancer may form after long-term irritation or infection with a tropical parasite called schistosomiasis, which is common in Africa and the Middle East but rare in the United States. When chronic irritation occurs, transitional cells that line the bladder can gradually change to squamous cells.
- **Adenocarcinoma:** is cancer that begins in glandular cells that are found in the lining of the bladder. Glandular cells in the bladder make mucus and other substances.
- **Small cell carcinoma of the bladder:** Is cancer that begins in neuroendocrine cells (nerve-like cells that release hormones into the blood in response to a signal from the nervous system).

SYMPTOMS

Bladder cancer signs and symptoms may include:

- Blood in urine (hematuria), which may cause urine to appear bright red or cola colored, though sometimes the urine appears normal, and blood is detected on a lab test
- Frequent urination
- Painful urination
- Back pain

CAUSES



Bladder cancer begins when cells in the bladder develop changes (mutations) in their DNA. A cell's DNA contains instructions that tell the cell what to do. The changes tell the cell to multiply rapidly and to go on living when healthy cells would die. The abnormal cells form a tumor that can invade and destroy normal body tissue. In time, the abnormal cells can break away and spread (metastasize) through the body.

BLADDER CANCER DIAGNOSIS

If patient have symptoms or lab test results that suggest bladder cancer, doctor will need to find out if they are due to cancer or another condition. Doctor may

- Ask about personal and family medical history to learn more about symptoms and possible risk factors for bladder cancer.
- Ask for a sample of urine so it can be checked in the lab for blood, abnormal cells, or infection.
- Do a physical exam, which for women, may include a pelvic exam, to check for signs of cancer

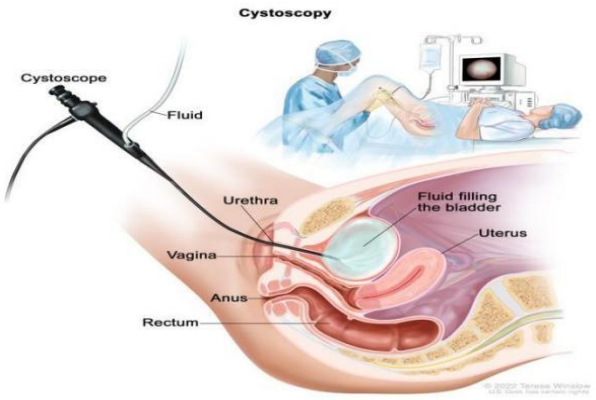
TESTS TO DIAGNOSE BLADDER CANCER

1. Cystoscopy:

A cystoscope (a thin, tube-like instrument with a light and a lens for viewing) is inserted through the urethra into the bladder. Fluid is used to fill the bladder. The doctor looks at an image of the inner wall of the bladder on a computer monitor to check for abnormal areas.

2. Biopsy:

A biopsy is usually done during a cystoscopy procedure. Biopsy is a procedure in which a sample of cells or tissue is removed from the bladder so that a pathologist can view it under a microscope to check for signs of cancer. It may be possible to remove the entire tumor at the time of the biopsy.



Talk with your doctor to learn what to expect during and after your cystoscopy and biopsy. Some people have blood in the urine or discomfort and a burning sensation while urinating for a day or two.

To learn about the type of information that can be found in a pathologist's report about the cells or tissue removed during a biopsy, see Pathology Reports.

3. Computed tomography (CT) urogram or intravenous pyelogram (IVP):

CT urogram is a test that takes a CT scan of the urinary tract using a contrast dye injected into a vein. To begin the procedure, a CT machine takes a series of detailed pictures of the kidneys. The contrast dye is then injected, and another CT scan of the kidneys, bladder, and ureters is done. About 10 minutes later, a final scan is taken as the contrast dye drains from the kidneys into the bladder. CT urogram also captures detailed pictures of nearby bones, soft tissues, and blood vessels. This allows the doctor to see how well your urinary tract is working and to check for signs of disease.

IVP is an x-ray imaging test of your urinary tract. After a contrast dye is injected into a vein, a series of x-ray pictures of the kidneys, ureters, and bladder are taken to find out if cancer is present in these organs. As the contrast dye moves through the kidneys, ureters, and bladder, more x-ray pictures are taken at specific times. This allows your doctor to see how well your urinary tract is working and to check for signs of disease.

4. Urine tumor marker test:

Urinary tumor markers are substances found in the urine that are either made by bladder cancer cells or that the body makes in response to bladder cancer. For this test, a sample of urine is checked in the lab to detect the presence of these substances. Urine tumor marker tests may be used to help diagnose some types of bladder cancer.

TESTS TO STAGE BLADDER CANCER

If you're diagnosed with bladder cancer, you will be referred to a urologic oncologist. This is a doctor who specializes in diagnosing and treating cancers of the male and female urinary tract and the male reproductive organs. They will recommend tests to determine the extent of cancer. Sometimes the cancer is only in the bladder. Or, it may have spread from the bladder to other parts of the body. The process of learning the extent of cancer in the body is called staging. It is important to know the stage of the bladder cancer to plan treatment.

1. Computed tomography (CT) scan:

A CT scan uses a computer linked to an x-ray machine to make a series of detailed x-ray pictures of areas inside the body from different angles. A dye may be injected into a vein or swallowed to help the organs or tissues show up more clearly.

2. Magnetic resonance imaging (MRI):

MRI uses a magnet, radio waves, and a computer to make a series of detailed pictures of areas inside the body, such as the bladder. This procedure is also called nuclear magnetic resonance imaging. Images may be taken at three different times after the dye is injected, to get the best picture of abnormal areas in the bladder. This is called triple-phase MRI.

3. Chest x-ray:

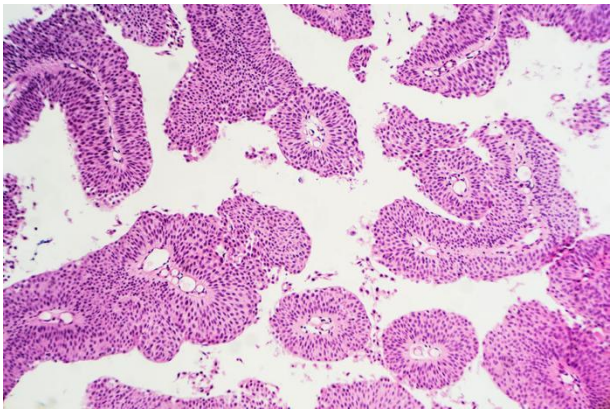
A chest x-ray is an x-ray of the organs and bones inside the chest. An x-ray is a type of high-energy radiation that can go through the body and onto film, making a picture of areas inside the chest.

4. Bone scan:

A bone scan is a procedure that checks to see if there are rapidly dividing cells, such as cancer cells, in the bone. A very small amount of radioactive material is injected into a vein and travels through the bloodstream. The radioactive material collects in the bones with cancer and is detected by a scanner.

5. Advances in Bladder Cancer Research:

NCI-funded researchers are working to improve our understanding of how to treat bladder cancer. With recent advances in immunotherapy and targeted therapy, treatment has the potential to become more effective and less toxic.



Microscopic view of a papillary urothelial (transitional cell) carcinoma.

NEW BLADDER CANCER TREATMENTS

Bladder cancer treatments are based on the type of bladder cancer and the stage of the disease. The most common type of bladder cancer is transitional cell carcinoma, also called urothelial carcinoma, which begins in cells in the innermost tissue layer of the bladder. There are other types of bladder cancers such as squamous cell carcinoma, small cell carcinoma, and adenocarcinoma, among others.

The mainstays of bladder cancer treatment are surgery, radiation therapy, chemotherapy, and immunotherapy, depending on the stage. Scientists continue to study novel treatments and drugs, along with new combinations of existing treatments.

1. Chemotherapy Combo Effective for Common Bladder Cancer:

Gemcitabine and docetaxel combo proves a good alternative to BCG for high-risk non-muscle-invasive bladder cancer.

Non-muscle-invasive bladder cancer is cancer that has grown through the lining of the bladder but hasn't yet invaded the muscle layer of the bladder. Treatment for this cancer is usually to remove the tumor by scraping it from the bladder wall. Some patients may receive additional treatment after surgery with an immune-based therapy called bacillus Calmette-Guérin (BCG), or with chemotherapy drugs such as mitomycin C (Jelmyto) or gemcitabine put directly into the bladder to reduce the risk that the cancer will recur.

2. Immunotherapy:

Immunotherapy is treatment that helps the body's immune system fight cancer more effectively. Certain immunotherapy drugs, called immune checkpoint inhibitors, are approved to treat some patients with locally advanced or metastatic bladder cancer.

Patients whose bladder cancers respond to immune checkpoint inhibitors tend to maintain those responses for long periods. Ongoing clinical trials will help researchers learn whether these extended responses help patients live longer.

However, only a small number of patients respond to immune checkpoint inhibitors. Scientists are trying to develop biomarkers that could help doctors identify which patients with bladder cancer are likely to respond to these drugs. For example, a checkpoint protein called PD-L1 has been studied as a biomarker for response to treatment with immune checkpoint inhibitors.

Scientists have now begun to test immune checkpoint inhibitors in earlier stages of bladder cancer and in combination with other treatments, such as chemotherapy:

- The NCI-sponsored AMBASSADOR trial is comparing the immune checkpoint inhibitor pembrolizumab (Keytruda) with observation. This is being done in patients with bladder cancer that invades the muscle layer of the bladder wall (localized muscle-invasive disease) or that has spread to nearby lymph nodes (locally advanced disease) and has been surgically removed. The trial will see if pembrolizumab improves overall survival or disease-free survival.
- In 2021, the Food and Drug Administration (FDA) approved the immune checkpoint inhibitor nivolumab (Opdivo) as an additional (adjuvant) treatment of patients with urothelial carcinoma who are at high risk of recurrence after undergoing surgery for the disease. This was the first FDA approval for the adjuvant treatment of patients with this type of cancer. In 2023, updated trial results showed that people who received nivolumab had a median disease-free survival of 22 months, compared with about 11 months for those who received a placebo.
- In 2020, the FDA approved the immune checkpoint inhibitor avelumab (Bavencio) for people with advanced bladder cancer that has shrunk or stopped growing after receiving platinum-based chemotherapy. The approval is for the use of avelumab as maintenance therapy for advanced disease that has not spread (locally advanced) or disease that has spread beyond the bladder (metastatic).

3. Targeted Therapy:

Targeted therapy treats cancer by targeting proteins that control how cancer cells grow, divide, and spread. In 2019, erdafitinib (Balversa) became the first targeted therapy to be approved by FDA to treat patients with locally advanced or metastatic urothelial carcinoma. This drug can be used to treat some patients whose cancers have certain alterations in the FGFR2 gene or FGFR3 gene. Only about 20% of bladder cancers harbor an FGFR gene alteration.

An ongoing phase 3 study is comparing erdafitinib with standard chemotherapy and with pembrolizumab in patients with advanced bladder cancer whose tumors have an FGFR gene alteration. This study could help researchers learn whether patients with FGFR-altered bladder cancer benefit more from erdafitinib or an immune checkpoint inhibitor versus chemotherapy.

4. Combination Therapy:

Researchers are testing many combinations of therapies for bladder cancer, either by combining several immunotherapy drugs or by combining an immunotherapy drug with another type of treatment.

- An early-phase clinical trial for patients with muscle-invasive bladder cancer is studying the combination of durvalumab (Imfinzi) with tremelimumab before surgery. Giving these drugs together before surgery may make the tumor smaller and reduce the amount of normal tissue that needs to be removed.
- A phase 3 trial is testing chemotherapy and radiation therapy with or without the immune checkpoint inhibitor atezolizumab in patients with localized muscle-invasive bladder cancer. Combining chemotherapy with radiation therapy may kill more tumor cells than chemotherapy alone. Adding atezolizumab (Tecentriq) to radiation therapy and chemotherapy may further improve outcomes in patients with localized muscle-invasive bladder cancer.
- A study is testing the safety and efficacy of the combination of the immune checkpoint inhibitor durvalumab and the drug oportuzumab monatox (Vicinium) for treating bladder cancer that has not spread to the muscle in the bladder. Non-muscle-invasive bladder cancer is early-stage cancer, but it usually comes back after treatment. The two drugs may act together to help the immune system find and destroy cancer cells.
- One study is testing the experimental drug enfortumab vedotin alone and with different combinations of treatments, including pembrolizumab, for treating bladder cancer. Some parts of the study will focus on patients with locally advanced and metastatic urothelial cancer, whereas other parts will focus on patients with muscle-invasive bladder cancer.

5. Antibody Drug Conjugates:

A monoclonal antibody is a type of protein made in the lab that can bind to certain targets in the body, such as those on cancer cells. An antibody drug conjugate is a substance made up of a monoclonal antibody that is chemically linked to a drug. It has the ability to kill cancer cells without harming other cells.

The antibody drug conjugate enfortumab vedotin-ejfv (Padcev) has been approved to treat advanced/metastatic bladder cancer. It showed positive results in patients who had previously been treated with chemotherapy and an immune checkpoint inhibitor. Researchers continue to study this drug to see whether it can be used to treat bladder cancer earlier in the disease process and to evaluate it in combination with immunotherapy and/or chemotherapy.

The combination of enfortumab vedotin-ejfv and pembrolizumab is also being evaluated as a treatment for patients with previously untreated advanced bladder cancer.

6. Gene Therapy:

In 2022, the FDA approved a type of gene therapy called nadofaragene firadenovec-vncg (Adstiladrin) for some adults with a certain type of high-risk, non-muscle-invasive bladder cancer. By helping the immune system recognize and kill cancer cells, this treatment can benefit patients whose tumors don't respond to the commonly used BCG therapy.

7. Clinical Trials for Bladder Cancer:

NCI funds and oversees both early- and late-phase clinical trials to develop new treatments and improve patient care. Trials are available for bladder cancer treatment.

8. NCI-Supported Research Programs:

Many NCI-funded researchers working at the NIH campus and across the United States and the world are seeking ways to address bladder cancer more effectively. Some research is basic, exploring questions as diverse as the biological underpinnings of cancer. And some is more clinical, seeking to translate this basic information into improving patient outcomes.

The Bladder Specialized Program of Research Excellence, or SPORE, is a cornerstone of the NCI's efforts to promote collaborative, interdisciplinary translational research on bladder cancer. It is currently located at Memorial Sloan Kettering Cancer Center. NCI's Division of Cancer Epidemiology and Genetics (DCEG) conducts studies on bladder cancer to learn about risk factors for the disease. Investigators in the Genitourinary Malignancies Branch of NCI's Center for Cancer Research conduct basic, translational, and clinical studies on bladder cancer. In addition, NCI has funding opportunities for researchers aimed at encouraging investigations of the biology and underlying mechanisms of bladder cancer.

RISK FACTORS

Factors that may increase bladder cancer risk include:

1. **Smoking.** Smoking cigarettes, cigars or pipes may increase the risk of bladder cancer by causing harmful chemicals to accumulate in the urine. When you smoke, your body processes the chemicals in the smoke and excretes some of them in your urine. These harmful chemicals may damage the lining of your bladder, which can increase your risk of cancer.
2. **Increasing age:** Bladder cancer risk increases as you age. Though it can occur at any age, most people diagnosed with bladder cancer are older than 55.
3. **Being male:** Men are more likely to develop bladder cancer than women are.

4. **Exposure to certain chemicals:** Kidneys play a key role in filtering harmful chemicals from your bloodstream and moving them into your bladder. Because of this, it's thought that being around certain chemicals may increase the risk of bladder cancer. Chemicals linked to bladder cancer risk include arsenic and chemicals used in the manufacture of dyes, rubber, leather, textiles and paint products.

5. **Previous cancer treatment.** Treatment with the anti-cancer drug cyclophosphamide increases the risk of bladder cancer. People who received radiation treatments aimed at the pelvis for a previous cancer have a higher risk of developing bladder cancer.

6. **Chronic bladder inflammation.** Chronic or repeated urinary infections or inflammations (cystitis), such as might happen with long-term use of a urinary catheter, may increase the risk of a squamous cell bladder cancer. In some areas of the world, squamous cell carcinoma is linked to chronic bladder inflammation caused by the parasitic infection known as schistosomiasis.

7. **Personal or family history of cancer.** If you've had bladder cancer, you're more likely to get it again. If one of your blood relatives — a parent, sibling or child — has a history of bladder cancer, you may have an increased risk of the disease, although it's rare for bladder cancer to run in families. A family history of Lynch syndrome, also known as hereditary nonpolyposis colorectal cancer (HNPCC), can increase the risk of cancer in the urinary system, as well as in the colon, uterus, ovaries and other organs.

CONCLUSION

- **Don't smoke.** If you don't smoke, don't start. If you smoke, talk to your doctor about a plan to help you stop. Support groups, medications and other methods may help you quit.
- **Take caution around chemicals.** If you work with chemicals, follow all safety instructions to avoid exposure.
- **Choose a variety of fruits and vegetables.** Choose a diet rich in a variety of colorful fruits and vegetables. The antioxidants in fruits and vegetables may help reduce your risk of cancer.

RESEARCH RESULTS

The following are some of our latest news articles on bladder cancer research.

- Groundbreaking Trial Results Expand Treatment Options for Some People with Bladder Cancer
- Loss of Y Chromosome in Men Makes Bladder Cancer More Aggressive
- Immunotherapy after Surgery Shows Long-Term Benefits for High-Risk Bladder Cancer
- For Common Form of Bladder Cancer, Chemo Combo Effective Alternative to BCG
- Study Clarifies Timing of Immunotherapy for Advanced Bladder Cancer
- Enfortumab Vedotin Approved for Recurrent Bladder Cancer

REFERENCES:

1. Vaibhav G. Patel MD, William K. Oh MD, Matthew D. Galsky MD"Treatment of muscle-invasive and advanced bladder cancer"First published: 07 August 2020 https://doi.org/10.3322/caac.21631
2. Shana Spindler "Groundbreaking Trial Results Expand Treatment Options for Some People with Bladder Cancer" National cancer institute November 30, 2023.
3. Simon J. Crabb†, * and James Douglas "The latest treatment options for bladder cancer" British Medical Bulletin, 2018, 128:85–95 doi: 10.1093/bmb/ldy034 Advance Access Publication Date: 29 October 2018
4. F M Torti and B L Lum The biology and treatment of superficial bladder cancer. Journal of Clinical Oncology Volume 2, Number 5.
5. Andrew T. Lenis, MD, MS1; Patrick M. Lec, MD1; Karim Chamie; et al "Bladder Cancer A Review" JAMA. 2020;324(19):1980-1991.

doi:10.1001/jama.2020.17598November 17, 2020

6. M Gaber, R Abd El-aal Bakheet, F Ibrahim Mahmoud "RISK FACTORS OF CANCER AND HOW TO PREVENT" 10.21608/SMJ.2017.41298
7. https://doi.org/10.1200/JCO.1984.2.5.505
8. https://www.cancer.gov/types/bladder/diagnosis
9. https://www.cancer.gov/types/bladder
10. https://www.mayoclinic.org/diseases-conditions/bladder-cancer/symptoms-causes/syc-20356104

ENDOMETRIAL CANCER

Ms. Gayatri Patil, Mr Pavankumar Wankhade
Department of Pharmacology, Dr. D.Y Patil College of Pharmacy. Akurdi, Pune

INTRODUCTION

Endometrial carcinoma is a malignant epithelial tumour, arising in the endometrium with glandular differentiation, but it may have variable morphology. It mainly arises from the uterine endometrium is currently the fourth most common cancer in women with ever increasing incidence, particularly in the last decade. It is the cancer that affects the female genital tract with its increasing incidence due to risk factors, such as aging and obesity, tends to become a public health issue. The risk of developing recurrence is associated with stage, grading, tumour size, lymphovascular-space invasion (LVSI), depth of myometrial invasion, and histo type. Survival rates are dependent on stage at diagnosis, ranging from 95% for stage I cancers to 15% for stage IV, therefore early diagnosis is essential for good outcomes. Early diagnosis may also enable conservative treatment for women of reproductive age or for those for whom surgery carries considerable risks, such as the elderly or morbidly obese.

EPIDEMIOLOGY OF EC

Endometrial cancer is commonly grouped into 2 different profiles with distinct risk factors. As stated by the FIGO platform Global Library of Women's Medicine, endometrial cancer is a common gynecologic malignancy affecting hundreds of thousands of women globally [1. In 2018 more than 382,000 new cases were diagnosed, and nearly 90,000 women died worldwide from the disease.[1]

The National Cancer Institute Surveillance, Epidemiology, and End Results program data documents that 11% of women with endometrial cancer are younger than 50 years old and others have documented that 75% are postmenopausal at the time of diagnosis. Plaxe reports that the increased proportion of high-risk endometrial cancers in African Americans is secondary to a reduction in low-risk disease, not an increase in high-risk disease.

RISK FACTORS

As with most cancers, older age is the main risk factor for EC. The most significant risk factor is exposure to endogenous and exogenous unopposed oestrogens, which cause proliferative changes in the endometrium. Women with Lynch Syndrome (LS), previously referred to as Hereditary Nonpolyposis Colorectal Cancer (HNPCC), are at markedly increased risk of EC compared with women in the general population. Other risk factors not involving unopposed estrogen include family history of endometrial cancer, age older than 50 years, hypertension, diabetes mellitus, obesity, thyroid disease, and Lynch syndrome.[2–6] Although they are less common overall, type II tumors are found predominantly in black women older than 50 years.[2]

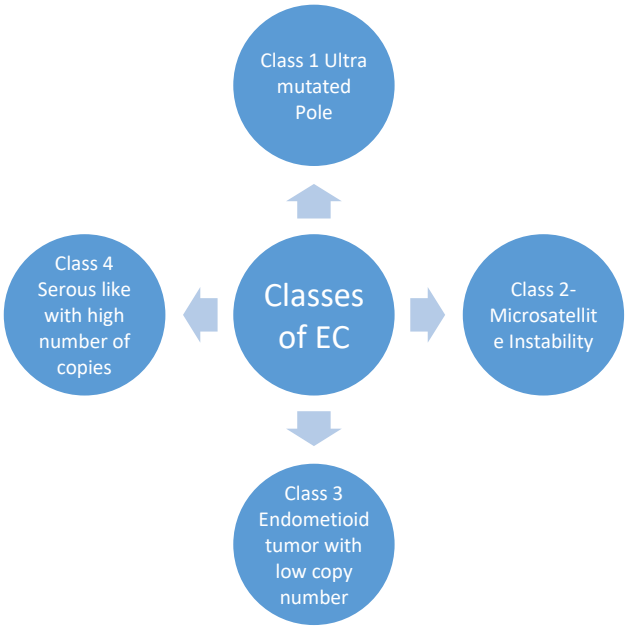
TYPES OF EC

ECs have traditionally been categorized into two broad classifications: type I and type II.

1. Type 1 endometrial cancer, which is more common (80% of all cases), consists of tumours of endometrioid histology. Type I is believed to be hormone-related and to be significantly associated with both unopposed estrogen therapy and obesity. Type I is the most common form, representing more than 70% of cases. Type I tumors are associated with unopposed estrogen stimulation and are known as endometrioid adenocarcinoma.[3] These tumors are generally low grade.

2. Type 2 endometrial cancer, which is less common (20% of all cases), consists of less common histological subtypes such as papillary serous, clear cell. Type II tumors are more likely to be high grade and of papillary serous or clear cell histologic type. They carry a poor prognosis and have a high risk of relapse and metastasis. Type II accounts for only 10% of endometrial cancers, but it is associated with 40% of related deaths.[3]

As per new classification, it is divided into 4 classes-



1. **Class 1:** These tumors are characterized by a high percentage of mutations and hot spots mutations in esonucleasic POLE domain (DNA subunit polymerase that has role in DNA replication).
   In these cancers, there are few aberrations about copies number; there is an increased frequency of C-A transversions, PTEN, PIK3R1, PIK3CA, KRAS, and FBXW7 gene mutations. The prognosis is favorable.

2. **Class 2:** This group is characterized by MSI caused by MLH1 promoter methylation. There are a large number of mutations, such as few aberrations in copy numbers, and RPL22 frameshift mutations; KRAS and PTEN mutations are frequent.

3. **Class 3:** In this class, there are endometrioid tumors of grade 1 and 2 with microsatellite stability. They have a low frequency of mutations. In particular, alteration of β catenin gene (CTNNB1) is characteristic in this class.

4. **Class 4:** These neoplasms are characterized by a high number of aberrations in copy numbers and a low frequency of mutations. P53, FBXW7, and PPP2R1A gene mutations are frequent. PTEN and KRAS mutations, instead, are rare. The prognosis is unfavorable. This genomic class includes the majority of serous carcinomas, some of mixed carcinomas and ¼ of endometrioid G3 carcinomas.[4]

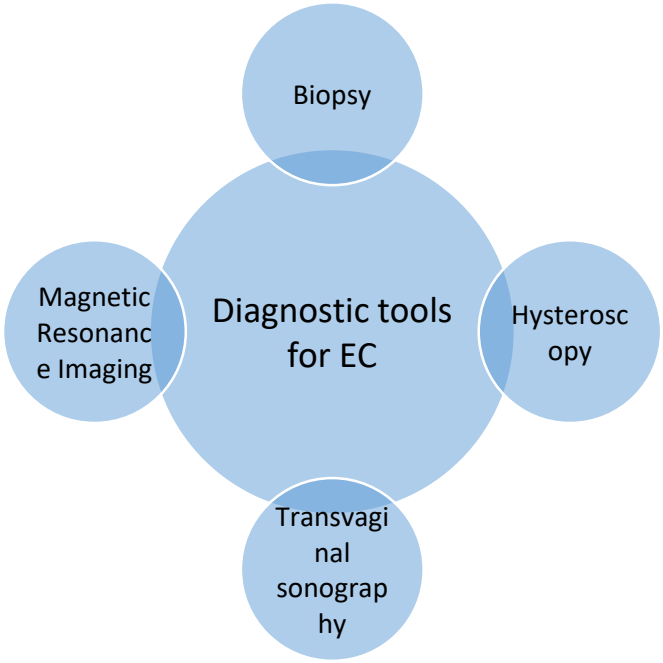
PATHOGENESIS OF EC

Endometrioid carcinoma is generally characterized by frequent derangements of the PI3KPTEN-AKT-mTOR, RAS-MEK-ERK, and canonical WNT-β-catenin pathways. Endometrial cancer presents more mutations than any other tumor type studied thus far in the PI3K/AKT pathway by TCGA. The PI3K-PTENAKT-mTOR signal transduction pathway regulates cell growth and survival, synthesis of specific proteins, and metabolism. The RAS-RAF-MEK-ERK pathway plays a central role in regulation of cell proliferation, cell survival, and differentiation, is activated by KRAS mutations in endometrioid carcinoma, and can co-occur with alterations in PTEN, PIK3CA, and/or PIK3R1.

ECs resemble proliferative rather than secretory endometrium. Specific tumor suppressor gene, *PTEN* that is expressed most highly in an estrogen-rich environment, could be responsible for the disease development. Progestogens affect *PTEN* expression and promote involution of *PTEN*-mutated endometrial cells in various histopathological settings. This hypothesis can explain therapeutic effect of progestogens in EC cases.[5]

Chronic inflammation related to obesity can be an important mechanism of endometrial oncogenesis. The plasma concentrations of the proinflammatory cytokines TNF-α and IL-6 positively correlate with BMI, and, in turn, have been directly associated with endometrial cancer promotion and progression. Indeed, IL-6 has been found to be overexpressed in the stroma of endometrial cancer. Thus, inflammation can contribute to the development of endometrial cancer, in conjunction with estrogen exposure.[6]

DIAGNOSIS AND EVALUATION OF EC



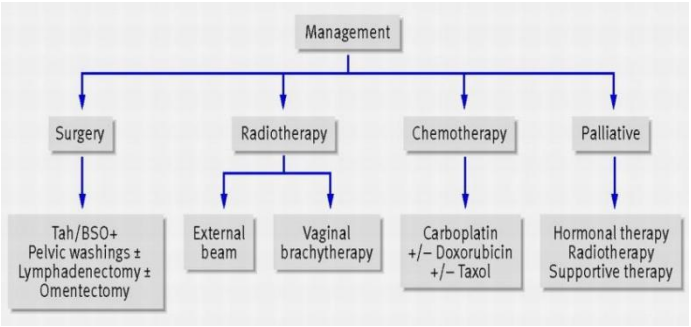
Hysteroscopy is direct visualisation of the uterine cavity via a fine bore scope to identify pathology, take directed biopsies and carry out therapeutic procedures, such as polypectomy.

TVS provides a non-invasive assessment of double-layered endometrial thickness, which can be used to triage women for further investigations. The diagnostic accuracy of TVS for EC detection depends on the endometrial thickness cut-off used.

MRI is usually reserved for the preoperative staging of EC. On rare occasions, it might be required for more detailed assessment of a thickened endometrium on TVS where hysteroscopy fails or is contraindicated. An endometrial biopsy is indicated if a woman presenting with Post Mmenopausal bleeding has a thickened endometrium on TVS.[7]

MANAGEMENT OF EC

Endometrial cancer can be managed by various factors including surgery, radiotherapy, chemotherapy and supportive therapy. Management of risk factors such as obesity, diabetes, and hypertension could play a role in the prevention of endometrial cancer. For women on hormone therapy, the addition of progesterone has been shown to decrease the risk of endometrial cancer.[8]



CONCLUSION

Endometrial Cancer is a type of cancer that affects the inner lining of the uterus. It involves the growth of cells in the uterus. It is a hormone-dependent cancer typically treated with surgery and/or chemo/radiation therapy. There are various risk factors involved that are associated with its pathogenesis. Early diagnosis is key to improving outcomes and there is much interest in the development of minimally invasive detection tools for the rapid triage of symptomatic women. New advances in treatment and diagnosis are being discovered. The therapies target the different mechanism by cellular and molecular ways to treat the symptoms and ease the pain experienced by the patients. Finally, the observation of the immunosuppressive nature of the EC environment is leading to promote studies to assess therapies aimed to boost immune response, which might represent a significant potential in the treatment of EC.

REFERENCES

1 Mahdy H, Casey MJ, Crotzer D. Endometrial cancer.

2. Gambini D, Ferrero S, Kuhn E. Lynch Syndrome: From Carcinogenesis to Prevention Interventions. Cancers (Basel). 2022 Aug 24;14(17):4102. doi: 10.3390/cancers14174102. PMID: 36077639; PMCID: PMC9454739.

3. Makker V, MacKay H, Ray-Coquard I, Levine DA, Westin SN, Aoki D, Oaknin A. Endometrial cancer. Nat Rev Dis Primers. 2021 Dec 9;7(1):88. doi: 10.1038/s41572-021-00324-8. PMID: 34887451; PMCID: PMC9421940.

4. Paleari L, Pesce S, Rutigliani M, Greppi M, Obino V, Gorlero F, Vellone VG, Marcenaro E.

New insights into endometrial cancer. Cancers. 2021 Mar 24;13(7):1496.

5. Terzic M, Aimagambetova G, Kunz J, Bapayeva G, Aitbayeva B, Terzic S, Laganà AS. Molecular Basis of Endometriosis and Endometrial Cancer: Current Knowledge and Future Perspectives. Int J Mol Sci. 2021 Aug 27;22(17):9274. doi: 10.3390/ijms22179274. PMID: 34502183; PMCID: PMC8431548.

6. Artemniak-Wojtowicz D, Kucharska AM, Pyrżak B. Obesity and chronic inflammation crosslinking. Cent Eur J Immunol. 2020;45(4):461-468. doi: 10.5114/ceji.2020.103418. Epub 2021 Jan 30. PMID: 33658893; PMCID: PMC7882402.

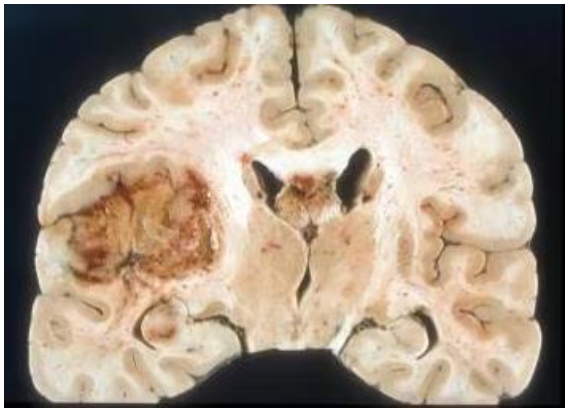
7. Jones ER, O'Flynn H, Njoku K, Crosbie EJ. Detecting endometrial cancer. The Obstetrician & Gynaecologist. 2021 Apr;23(2):103-12.

8. Braun MM, Overbeek-Wager EA, Grumbo RJ. Diagnosis and management of endometrial cancer. American family physician. 2016 Mar 15;93(6):468-74.

GLIOBLASTOMA

Dr Ashish Kulkarni
Department of Pharmacology, Dr. D.Y Patil College of Pharmacy. Akurdi, Pune

Glioblastoma is a highly aggressive form of brain cancer that arises from glial cells in the brain, particularly astrocytes. It is the most common and deadliest primary malignant brain tumor in adults[1]



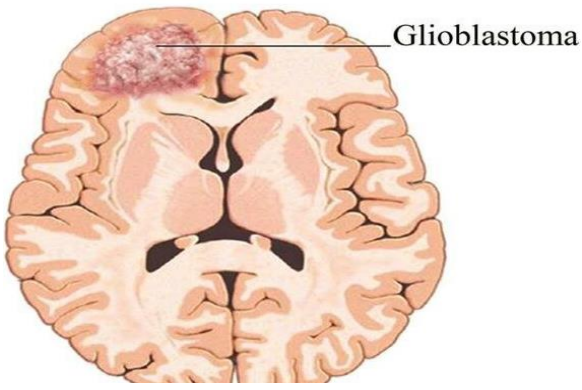
INCIDENCE AND PREVALENCE:

Glioblastoma typically affects adults aged 45-70 years, although it can occur at any age. It comprises about 15% of all primary brain tumors and has an annual incidence of about 3 cases per 100,000 people [2].

SYMPTOMS [3]

Symptoms of glioblastoma depend on its location but commonly include

- Headache
- Nausea
- Vomiting
- Seizures
- Cognitive impairment
- Focal neurological deficits such as weakness or sensory disturbance



PATHOPHYSIOLOGY [1,3]

Pathophysiology of glioblastoma involves outlining the various molecular and cellular events involved in its development and progression.

1. **Genetic predisposition or environmental factors**:

Glioblastoma can arise sporadically or in individuals with certain genetic predispositions (e.g., Li-Fraumeni syndrome neurofibromatosis, etc.) or exposure to ionizing radiation.

2. **Genetic alterations:**

- **Primary mutations**: Commonly involve genes like TP53, PTEN, EGFR, and IDH1/2
- **Secondary mutations**: Amplifications, deletions, and mutations in genes like EGFR, PDGFRA, and CDKN2A/B

3. **Tumour initiation and growth:**

- **Tumour suppressor loss**: Inactivation of tumor suppressor genes like TP53 and PTEN
- **Oncogene activation**: Activation of growth-promoting genes like EGFR and PDGFRA
- **Genomic instability**: Chromosomal alterations and DNA repair deficiencies contribute to genomic instability

4. **Angiogenesis and microenvironment changes:**

- **Hypoxia-induced angiogenesis:** Tumour cells release pro-angiogenic factors (e.g., VEGF) leading to the formation of abnormal blood vessels
- **Immune suppression**: Tumor cells evade immune surveillance through various mechanisms, including expression of immune checkpoint molecules
- **Tumor microenvironment**: Infiltration of immune cells, fibroblasts, and other stromal components contribute to tumour growth and invasion

5. **Invasion and Metastasis**

- **Extracellular matrix remodeling** Tumor cells secrete enzymes (e.g., MMPs) to degrade the extracellular matrix, facilitating invasion.
- **Cellular migration**: Tumor cells migrate along white matter tracts, infiltrating surrounding brain tissue
- **Metastasis**: Glioblastoma rarely metastasizes outside the central nervous system, but it can spread locally within the brain

6. **Resistance to therapy:**

- **Chemoresistance**: Tumor cells develop mechanisms to evade the effects of chemotherapy drugs (e.g., upregulation of drug efflux pumps).
- **Radioresistance**: Ability of tumor cells to survive and proliferate after exposure to radiation therapy
- **Heterogeneity**: Presence of diverse tumor cell populations with varying sensitivities to treatment

DIAGNOSIS [5]

Diagnosis often involves a combination of imaging studies like MRI or CT scans and a biopsy to confirm the presence of tumor cells. Molecular profiling may also be done to identify specific genetic mutations or biomarkers that can guide treatment decisions

PALLIATIVE CARE:

TREATMENT AND MANAGEMENT OF GLIOBLASTOMA [5]

Initial Treatment Options:

- **Surgery:** Maximal safe resection to remove tumour mass
- **Radiation Therapy:** External beam of radiation to target tumour cells
- **Chemotherapy:** Temozolomide (Teodora) often used as first-line chemotherapy.

Temozolomide is an oral alkylating agent. It is a prodrug that, following oral absorption, is easily absorbed into the small intestine. Due to its tiny molecular size (194 Da), it exhibits good blood-brain barrier penetration. It then spontaneously hydrolyzes inside cells to become MTIC, a strong methylating agent → MTIC methylates several nucleobases, the most significant of which is the guanine base. Cellular repair processes cannot adapt to the methylated base, which causes nicks in the DNA to develop and apoptosis to occur

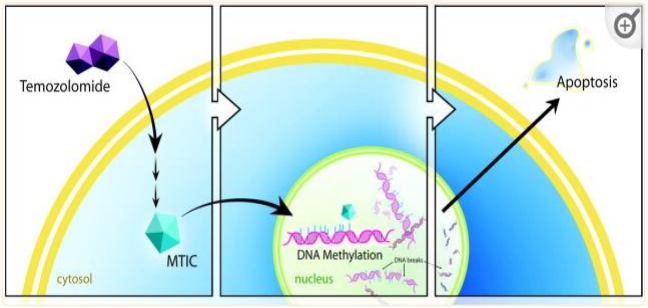


Fig.1: Schematic representation of Temozolomide mechanism of action **[4]**

MONITORING AND SURVEILLANCE:

- Regular clinical evaluations
- Imaging studies (MRI, CT scan)
- Neurological assessments

MANAGEMENT OF SYMPTOMS AND COMPLICATIONS

- Corticosteroids for edema management
- Antiepileptics drugs for seizure control
- Symptomatic treatment for pain, nausea, and other symptom

Supportive care to improve quality of life

Management of end-of-life symptoms

Emotional and psychological support for patients and caregivers

CHALLENGES [6]

Glioblastoma poses several challenges to treatment, including its invasive nature, resistance to conventional therapies, and the presence of the blood brain barrier, which limits the delivery of drugs to the tumour site. Additionally, the heterogeneity of the tumour makes it difficult to develop effective targeted therapies. In summary, glioblastoma is a formidable challenge in oncology due to its aggressive nature, limited treatment options, and poor prognosis. Continued research efforts are crucial to develop more effective therapies and improve the outlook for patients facing this devastating diagnosis.

REFERENCES

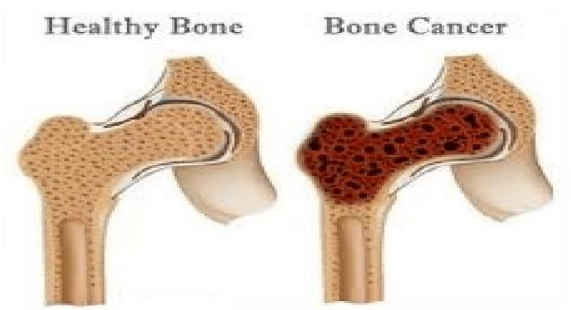
1. Kanderi T, Munakomi S, Gupta V. Glioblastoma Multiforme. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK558954/
2. Hanif F, Muzaffar K, Perveen K, Malhi S, Simjee S. Glioblastoma Multiforme: A Review of its Epidemiology and Pathogenesis through Clinical Presentation and Treatment. Asian Pacific Journal of Cancer Prevention. 2017; 18: 3-9
3. Bruce JN. Glioblastoma. 2023. https://emedicine.medscape.com/article/283252-overview?form=fpf
4. Wesolowsk JR, Rajdev P, Mukherji SK. Temozolomide (Temodar). American Journal of Neuroradiology. 2010; 31 (8): 1383-1384
5. Gilard V, Tebani A, Dabaj I, Laquerrière A, Fontanilles M, Derrey S, Marret S, Bekri S. Diagnosis and Management of Glioblastoma: A Comprehensive Perspective. J. Pers. Med. 2021; 11: 258.
6. Pineda E, Domenech M, Hemandez A, Comas S, Balana C. Recurrent Glioblastom: Ongoing Clinical Challenges and Future Prospects. Onco Targets Ther. 2023; 16: 71-86

BONE CANCER: A REVIEW

Mr. Akash Chaurasiya, Mr. Yashwant Chavan, Ms. Amruta Sapate
Department of Pharmaceutics, Dr. D.Y Patil College of Pharmacy. Akurdi, Pune

ABSTRACT

Primary bone cancers are osteosarcoma, Ewing's sarcoma and chondrosarcoma. They account for less than 1% of diagnosed cancers each year and are associated with significant morbidity and mortality. Timely diagnosis is difficult due to late patient presentation, non-specific symptoms mimicking



common musculoskeletal injuries and low suspicion of physicians. A plain X-ray is the recommended diagnostic test. X-ray suspicion of bone malignancy requires rapid referral to a cancer center for multidisciplinary therapy. Osteosarcoma, the most common bone cancer, occurs most often in children and teenagers. It usually develops in the metaphyses of long bones, especially the distal femur, proximal tibia, and proximal humerus. Pulmonary metastases are common. The use of neoadjuvant and adjuvant chemotherapy combined with surgery has improved survival for patients with localized disease to almost 80%, and 90-95% of patients do not require limb amputation. Ewing's sarcoma is the second most common bone cancer and is similar to osteosarcoma in symptoms, age of onset and treatment. The prognosis for osteosarcoma and Ewing's sarcoma depends on the presence of metastases, which reduce the five-year survival rate by 20-30%. Chondrosarcoma is the rarest bone cancer that mainly affects adults over the age of 40. Survival is higher because most of these tumors are low-grade lesions.[1]

INTRODUCTION

Primary bone cancer (PBC) is a rare bone malignancy that originates from primitive mesenchymal cells. It accounts for approximately 0.2% of all malignancies worldwide and is idiopathic in most cases. There are several subtypes, the most common of which are osteosarcoma, chondrosarcoma, and Ewing's sarcoma. Each is different in terms of demographics, visual appearance and biological behaviour. They are often aggressive and require early diagnosis by imaging and tissue biopsy. Surgery remains the mainstay of curative therapy, and chemotherapy and radiation therapy are often used together. [2]

Osteosarcoma is the most common primary malignant bone tumor in children and young adults.2 The average age of all patients with osteosarcoma is 20 years. In adults over 65 years of age, osteosarcoma develops as a secondary malignancy associated with Paget's disease of bone.16Osteosarcoma forms a family of lesions with different histological characteristics and natural histories. Osteosarcomas are broadly classified as intramedullary, superficial, and extraosseous.167 High-grade intramedullary osteosarcoma is the classic or common form and accounts for nearly 80% of osteosarcomas.167 It is a spindle cell tumor that produces osteoid or immature bone. The most common sites are the metaphyseal regions of the distal femur or proximal tibia, which are the sites of maximum growth. Low-grade intramedullary osteosarcoma accounts for less than 2% of all osteosarcomas, and the most common sites are similar to conventional osteosarcoma.168Parostic and periosteal osteosarcomas are cortical or superficial variants. Parosteal osteosarcomas are low-grade lesions that account for up to 5% of all osteosarcomas.168 The most common site is the posterior distal femur. This variant tends to metastasize later than the normal form. Transformation of a low-grade parosteal osteosarcoma to a high-grade sarcoma has been documented in 24–43 percent of cases.169 170 Periosteal osteosarcomas are intermediate-grade lesions that most often involve the femur, followed by the tibia.168 High-grade osteosarcomas. superficial osteosarcomas are rare. 171,172 Pain and swelling are the most common early symptoms. The pain is often intermittent at first, and thorough treatment is sometimes delayed because the symptoms can be confused with growing pains. Osteosarcoma spreads hematogenously, with the most common site of metastasis being the lungs.

SYMPTOMS

1. Bone pain
2. Swelling and tenderness near the affected area
3. Weakened bone, leading to fracture
4. Fatigue
5. Unintended weight loss

CLASSIFICATION

Osteosarcomas are divided into three groups: Osteoblastic, Chondroblastic and Fibroblastic, according to the dominant histologic feature. Osteosarcomas can be multifocal, synchronous or metachronous; they are also classified by the histologic grade of malignancy.

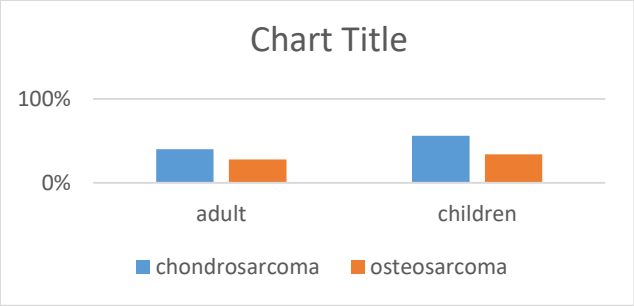
Osteogenic	Chondrogenic	Fibrogenic
Osteoid osteoma	Osteochondroma (Exostosis)	Non-ossifying fibroma
Osteoblastoma	Enchondroma	Fibrous dysplasia
	Chondroblastoma	
	Chondromyxoid fibroma	

ETIOLOGY

Genetic factors are interrelated. Germ cell abnormalities in hereditary cancer susceptibility syndromes increase the risk of later bone cancer because tumor suppressor genes are reduced, or oncogenes are increased. The TP53 tumor suppressor gene is frequently mutated in Li-Fraumen syndrome, where patients have an increased risk of developing osteosarcoma. Similarly, a mutation in the Rb1 gene, which causes hereditary retinoblastoma, is associated with osteosarcoma. Werner and Rothmund-Thomson syndromes are also associated with an increased risk of developing osteosarcoma. Early cancer treatment with radiation therapy is associated with a higher risk of developing PBC later in life, especially exposure to ionizing radiation during childhood.[3] Several benign conditions show the potential to develop into PBC. Paget's disease of bone is a condition characterized by impaired bone metabolism, particularly osteoclast function. These patients have a greater risk of developing osteosarcoma; however, this is a rare complication. Enchondroses and osteochondroses are benign cartilaginous tumors that can later develop into malignant chondrosarcoma.[4][5].

EPIDEMIOLOGY

Primary bone cancer remains rare, accounting for 0.2 percent of all malignancies and 5 percent of childhood malignancies. In the United States, approximately 3,600 new cases of PBC will be diagnosed in 2020, of which 1,720 will die, accounting for 0.3 percent of all cancer deaths. According to the National Cancer Institute, chondrosarcoma is most common in adults (40%), followed by osteosarcoma (28%). In children and adolescents, osteosarcoma is the most common (56%), followed by Ewing's sarcoma (34%).



Chordoma, undifferentiated pleomorphic sarcoma, adamantinoma, fibrosarcoma, and giant cell tumor of bone are also types of PBC; however, there are fewer of them. PBC predominates in men, with a global male-to-female osteosarcoma ratio of 1.43:1.[6][7].

PATHOPHYSIOLOGY

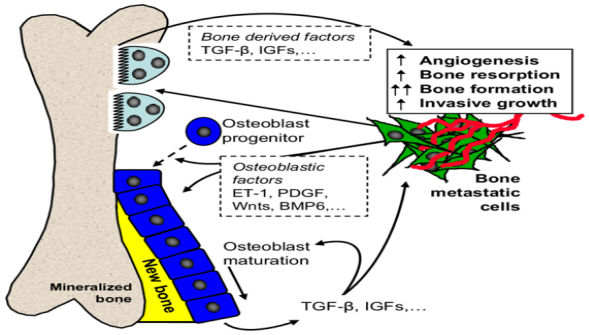
Primary bone cancer is a malignant connective tissue tumour of mesenchymal origin. The World Health Organization (WHO) has defined six categories: chondrogenic, osteogenic, notochordal, vascular, other malignant mesenchymal, and mixed (including Ewing's sarcoma). The pathophysiology varies considerably between groups and in some cases is poorly understood.[8] Osteosarcoma is a highly malignant osteogenic tumour that can develop in any bone. It tends to form in young patients near the metaphyses of long bones. The most common sites are the distal femur, proximal tibia, and proximal humerus, where bone turnover is high. Axial fractures are more common in adults, often associated with prior radiation or metabolic bone disease. Frequent genetic changes do not explain the growth of this type of tumor; However, 70% of cases show some degree of chromosomal abnormalities. Alterations in p53, Rb1, and DNA repair/surveillance genes occur in patients with Li-Fraumen, Bloom, and Rothmund-Thomson

syndromes and are all associated with an increased incidence of osteosarcoma.[8][9][10]. n Chondrosarcoma. is mainly a disease of adults, most often diagnosed between the ages of 30 and 60 years. They are usually slow-growing chondrogenic tumors of moderate malignancy, rarely metastatic. Chondrosarcoma arising de novo is classified as primary (> 85% of cases), while those arising from pre-existing benign osteochondrosis or enchondrosis are classified as secondary. The most common site of diagnosis is the long bones of the appendicular skeleton. Flat bones, including the pelvis, ribs and scapula, can also be affected. The exact pathogenesis of chondrosarcoma is unknown, although several genes have been implicated.

Cytogenic studies have identified structural and numerical chromosomal abnormalities. EXT1/2, TP53, Rb1, and IDH1/2 gene mutations have also been associated with malignant transformation of benign lesions.[8][9][10] Ewing sarcoma is an aggressive tumour of childhood and adolescence. usually occurs in bones, but also in soft tissues. The peak incidence is at the age of 15, with a male to female ratio of 1.5:1. The most common sites are the long bones of the lower limb, the pelvic bones, and the axial skeleton (ribs and spine). Unlike osteosarcoma, Ewing's sarcoma usually develops in the diaphysis. Ewing's sarcoma is genetically well characterized and characteristic chromosomal translocations have been identified. The translocation results in the fusion of the FET protein with an ETS transcription factor, most often FLI1 (>85% of cases). The result is fusion proteins that deregulate downstream genes and alter cell behavior.[11][12][13].

EVALUATION

Diagnostic methods for primary bone cancer include imaging, laboratory blood tests, and tissue biopsy. Plain film X-ray all patients should have an orthogonal plain film X-ray if PBC is suspected. Plain radiographs may show the following findings: Osteolytic, osteoblastic, or mixed changes. A moth-eaten appearance, suggesting destruction of bone by a rapidly expanding tumor within the bone, often seen in Ewing's sarcoma and telangiectasia osteosarcoma. Closure. bone appearance showing tumor progression through bone, with an ill-defined zone between the tumor and healthy bone, often seen in small cell tumors including Ewing's sarcoma"Onion peeling" in which the tumor elevates the partially formed periosteal bone classically seen For Ewing's. bones sarcoma."Codman triangle", in which the periosteum has been removed from the bone and bone tissue has been deposited."Sunburst" appearance, vertical osteoid calcification due to severe periostitis.[14][15] Magnetic resonance. Imaging (MRI)) MRI scanning remains the local gold standard for assessment of tumor extent. The entire anatomical section should be imaged with MRI, which is sensitive to bone and soft tissue lesions. Biopsy planning is crucial, and MR allows liasion of neurovascular structures. Modern techniques, including dynamic MRI, allow better characterization of high-grade tumor regions and have been used to assess tumor response to chemotherapy.[14][6][15] Computed tomography (CT)CT scans are used when the diagnosis remains unclear. MRI or after MRI is unclear. It remains the



method of choice for planning pelvic PBC and reconstructive surgery. Patients with confirmed PBC require staging, and although chest X-rays are still performed in many centers, chest CT is the gold standard for evaluation of metastatic lung disease.[14][6] Whole-body bone scintigraphy (Oscan)Whole-body bone scintigraphy is an isotope medical examination, where technetium-99m is used as an active ingredient, highlighting areas of osteoblastic activity. It can detect malignancy and is useful for diagnosing metastatic disease.[14] Positron Emission Tomography (PET)A PET scan is an isotopic medical test that takes advantage of the tumour's high metabolic rate. cells and measures cellular uptake. injected with radiolabeled F-18-fluorodeoxyglucose (FDG). PET scanning is used in some centers to early stage PBC, and studies have recommended it as a follow-up method when used together with CT scanning.[14][16] Laboratory blood tests Specific laboratory. blood tests are not used to diagnose PBC; however, they are part of the patient's work. In patients receiving chemotherapy, baseline urea, creatinine, and liver function tests allow assessment of baseline renal and liver function. Biochemical markers alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) offer some prognostic value and their levels can be monitored to assess disease

progression.[14][15] Close biopsy is required for definitive diagnosis of a lesion. which allows histopathological evaluation.and tumor classification. A biopsy should be performed with a surgical team, preferably in a specialized bone cancer center. This requires careful planning, and a suboptimal biopsy affects the final options for surgical treatment. Imaging should be performed prior to biopsy to help plan the approach and prevent tissue damage that can complicate radiologic evaluation. Percutaneous, incisional or surgical techniques are used. Ultrasound, X-ray and CT scans allow precise management. The track should be well marked so that surgery can be done during surgery, and the samples should be evaluated by a bone cancer specialist. Specific markers in immunohistochemical staining would help in diagnosis. More than 95% of Ewing sarcomas show extensive membranous expression of CD99. CD99 is not specific for Ewing's sarcoma, so that other markers are used in the immunohistochemistry panel [16][17].

TREATMENT

Treatment of primary bone cancer requires a multidisciplinary approach from a specialist bone cancer centre, including staff trained to provide age-appropriate care for children or young people. Treatment depends on several factors, including the type, stage and grade of the tumor, as well as patient preference. Surgical resection remains the cornerstone of PBC treatment. Neoadjuvant and adjuvant chemotherapy are also common in the treatment, and radiation therapy is used in certain cases and operation. The aim of the operation is to remove all the tumor tissue with a sufficient margin and preserve as much of the function of the limb as maybe the decision regarding limb salvage surgery or amputation is based on imaging, histopathology, response to adjuvant therapy, and patient preferences. Surgery often results in significant tissue loss, and an open discussion with the patient is essential. The potential risks, benefits, and expected long-term functional effects of surgery should be emphasized. Low-grade tumors that can be surgically removed usually require extensive surgery (removal of the involved bone part with a cuff of healthy tissue), high-grade tumors require radical surgery (removal of the diseased bone and related soft tissue of the anatomical part). section). .[7][18] Chemotherapy Many chemotherapy agents and regimens are used to manage PBC. It often consists of induction (neo-adjuvant) and postoperative combination therapy (adjuvant), and limb-salvage surgery rates and overall survival have improved since their introduction. Chemotherapy is part of the standard treatment for osteosarcoma and Ewing's sarcoma. Chondrosarcoma is still primarily treated with surgery, except for mesenchymal chondrosarcoma, where chemotherapy and radiation therapy are often used.[18][19] Neoadjuvant chemotherapy is used primarily to reduce the rate of further metastatic spread; however, studies have shown that it can also help control the primary tumour. A good response to neoadjuvant therapy is defined by an incidence of >90% histological necrosis, and a poor response often leads to changes in postoperative adjuvant therapy and shows worse outcomes.[19][20][21] Radiotherapy\ Radiotherapy is often used as adjunctive therapy for PBC. Ewing's sarcoma is a radiation-sensitive tumor, and radiation therapy is usually used as part of the definitive treatment plan. Preoperative radiotherapy is used when the response to neoadjuvant chemotherapy is poor, or the tumour is located in a problematic anatomical location where tumor volume reduction facilitates surgical resection. If sufficient tumor volume cannot be surgically removed or it would cause excessive disability, radiation therapy is used as local therapy. If adequate margins have not been removed, postoperative radiation therapy is used. Chondrosarcomas are relatively resistant to radiation, and radiation therapy is used only for tumors that have not been surgically removed or that have been incompletely removed. [22][23]

1. **Other Types of Tumor (malignant)**
   a. Metastases
   b. Lymphoma
   c. Multiple myeloma
2. **Other Types of Tumor (benign)**
   a. Giant cell tumor
   b. Osteoblastoma
   c. Enchondroma
   d. Chondromyxoid fibroma
   e. Cortical desmoid
3. **Infection**
   a. Osteomyelitis
4. **Trauma**

a. Fracture callus

5. **Other**

a. Aneurysmal bone cyst

b. Fibrous dysplasia [24]

TUMOR-RELATED COMPLICATIONS

- Pathological fracture
- Tumor recurrence
- Distant metastasis [25][26]

TREATMENT-RELATED COMPLICATIONS

- Surgery
  - Surgical site or periprosthetic infection
  - Implant failure
  - Non-union/fracture of biological implant [27]
- Chemotherapy
  - Short-term side effects include malaise, anaemia, nausea, vomiting, and alopecia.
  - Long-term side effects include cardiotoxicity, renal toxicity, hearing loss, and an increased risk of secondary malignancy.[27]
- Radiotherapy
- Side effects following radiation therapy are site-dependent, affecting the skin, pelvic organs, gastrointestinal tract, and lungs.
- Long-term, there is a small increased risk of developing a secondary malignancy.[26][27]

STAGING AND GRADING

Staging and grading a bone tumor allows doctors to decide on the best course of treatment and the most likely outlook.

Grading involves looking at the cells of the tumor under a microscope and assessing how they differ from healthy bone tissue.

A grade 1 tumor has cells that resemble bone tissue, while a grade 3 tumor has more abnormal cells that suggest a more aggressive cancer.

Staging a tumor indicates its size and spread. Several different characteristics can constitute the different stages, so each stage has two substages apart from stage 3.

Stage I:

The tumor measures either less or more than 8 centimeters (cm) across and has not spread from its original site. It is low grade, or the doctor has not been able to determine the grade through testing.

Stage 1 is the most treatable stage of bone cancer.

Stage 2:

A stage 2 tumour can be the same size as a stage I tumor, but the cancer is a higher grade. This means that it is more aggressive.

Stage 3:

Tumours have developed in at least two places in the same bone have not yet spread to the lungs or lymph nodes. A stage 3 bone tumor would have a high grade.

Stage 4:

This is the most advanced form of bone cancer. A stage 4 tumor will appear in more than one location and will have spread to either the lungs, lymph nodes, or other organs. The stage of the cancer will dictate the method of treatment and the overall outlook.

OUTLOOK

The outlook for a person with malignant bone cancer depends mainly on whether it has spread to other parts of the body.

The 5-year survival rate is the percentage of people with bone cancer (reported by stage) who are likely to survive to at least 5 years after diagnosis.

For example, a person with chondrosarcoma that has not spread has a 91% chanceTrusted Source of surviving for 5 years after diagnosis.

However, if the cancer spreads to distant sites, such as the lungs, the 5-year survival rate reduces to 33%. Taking all stages into account, the American Cancer Society puts the 5-year survival rate at 80%.

Early detection and treatment are key to improving the outlook.

CONCLUSION

Overall, advances in bone cancer treatment over the years have greatly improved patient outcomes. From traditional methods such as surgery and chemotherapy to more targeted treatments such as immunotherapy and precision medicine, the landscape of bone cancer treatment is constantly

evolving. Although challenges remain, including the risk of relapse and managing the side effects of treatment, continued research offers hope for new innovations in diagnosis and treatment. Through a multidisciplinary approach and continued collaboration between clinicians, researchers and patients, we are moving closer to more effective and personalized bone cancer treatments, ultimately improving the quality of life for those affected by this devastating disease.

Bone cancer can start in any bone in the body, but it most often affects the pelvis or the long bones of the arms and legs. Bone cancer is rare, accounting for less than 1 percent of all cancers. In fact, non-cancerous bone tumors are much more common than cancerous cells. The term "bone cancer" does not include cancers that start elsewhere in the body and spread (metastasize) to the bones. Instead, these cancers are named by where they start, such as breast cancer that has metastasized to the bones. Some types of bone cancer occur primarily in children, while others occur in adults. Surgical removal is the most common form of treatment, but chemotherapy and radiation therapy may also be used. The decision to use surgery, chemotherapy, or radiation therapy is based on the type of bone cancer being treated.

REFERENCES

1. Ferguson JL, Turner SP. Bone Cancer: Diagnosis and Treatment Principles. Am Fam Physician. 2018 Aug 15;98(4):205-213. PMID: 30215968.
2. Kube SJ, Blattmann C, Bielack SS, Kager L, Kaatsch P, Kühne T, Sorg B, Kevric M, Jabar S, Hallmen E, Sparber-Sauer M, Klingebiel T, Koscielniak E, Dirksen U, Hecker-Nolting S, Gerß JWO. Secondary malignant neoplasms after bone and soft tissue sarcomas in children, adolescents, and young adults. Cancer. 2022 May 01;128(9):1787-1800.
3. Hameed M, Mandelker D. Tumor Syndromes Predisposing to Osteosarcoma. Adv Anat Pathol. 2018 Jul;25(4):217-222
4. Berrington de Gonzalez A, Kutsenko A, Rajaraman P. Sarcoma risk after radiation exposure. Clin Sarcoma Res. 2012 Oct 04;2(1):18
5. Hansen MF, Seton M, Merchant A. Osteosarcoma in Paget's disease of bone. J Bone Miner Res. 2006 Dec;21 Suppl 2: P58-63.
6. Gerrand C, Athanasou N, Brennan B, Grimer R, Judson I, Morland B, Peake D, Seddon B, Whelan J., British Sarcoma Group. UK guidelines for the management of bone sarcomas. Clin Sarcoma Res. 2016; 6:7
7. Mirabello L, Troisi RJ, Savage SA. International osteosarcoma incidence patterns in children and adolescents, Middle Ages and elderly persons. Int J Cancer. 2009 Jul 01;125(1):229-34.
8. Messerschmitt PJ, Garcia RM, Abdul-Karim FW, Greenfield EM, Getty PJ. Osteosarcoma. J Am Acad Orthop Surg. 2009 Aug;17(8):515-27.
9. Morrow JJ, Khanna C. Osteosarcoma Genetics and Epigenetics: Emerging Biology and Candidate Therapies. Crit Rev Oncog. 2015;20(3-4):173-97.
10. Hayden JB, Hoang BH. Osteosarcoma: basic science and clinical implications. Orthop Clin North Am. 2006 Jan;37(1):1-7.
11. Whelan J, McTiernan A, Cooper N, Wong YK, Francis M, Vernon S, Strauss SJ. Incidence and survival of malignant bone sarcomas in England 1979-2007. Int J Cancer. 2012 Aug 15;131(4): E508-17.
12. Bernstein M, Kovar H, Paulussen M, Randall RL, Schuck A, Teot LA, Juergens H. Ewing's sarcoma family of tumors: current management. Oncologist. 2006 May;11(5):503-19.
13. Grünewald TGP, Cidre-Aranaz F, Surdez D, Tomazou EM, de Álava E, Kovar H, Sorensen PH, Delattre O, Dirksen U. Ewing sarcoma. Nat Rev Dis Primers. 2018 Jul 05;4(1):5.
14. Kundu ZS. Classification, imaging, biopsy and staging of osteosarcoma. Indian J Orthop. 2014 May;48(3):238-46
15. Plant J, Cannon S. Diagnostic work up and recognition of primary bone tumours: a review. EFORT Open Rev. 2016 Jun;1(6):247-253.
16. Amit P, Patro DK, Basu D, Elangovan S, Parathasarathy V. Role of dynamic MRI and clinical assessment in predicting histologic response to neoadjuvant chemotherapy in bone sarcomas. Am J Clin Oncol. 2014 Aug;37(4):384-90.
17. Kundu ZS. Classification, imaging, biopsy and staging of osteosarcoma. Indian J Orthop. 2014 May;48(3):238-46.
18. Ibrahim T, Mercatali L, Amadori D. Bone and cancer: the osteoncology. Clin Cases Miner Bone Metab. 2013 May;10(2):121-3.

19. Burgert EO, Nesbit ME, Garnsey LA, Gehan EA, Herrmann J, Vietti TJ, Cangir A, Tefft M, Evans R, Thomas P. Multimodal therapy for the management of nonpelvic, localized Ewing's sarcoma of bone: intergroup study IESS-II. J Clin Oncol. 1990 Sep;8(9):1514-24.

BREAST CANCER: A REVIEW

Mr. Somnath Gawali, Ms. Pallavi Gholap
Department of Pharmaceutics, Dr. D.Y Patil College of Pharmacy. Akurdi, Pune

ABSTRACT

Breast cancer is a prevalent malignancy primarily affecting women but can also occur in men, characterized by uncontrolled cell growth in breast tissue. Various factors influence its risk, including gender, age, hereditary predisposition, geography, ethnicity, obesity, alcohol consumption, and smoking. Early detection is crucial, often initiated through mammography, followed by clinical examination and imaging. Physical signs like lumps or skin changes may indicate cancer presence. Screening modalities include mammography, ultrasonography, and MRI. Breast cancer encompasses different types, including invasive ductal carcinoma, lobular carcinoma, and ductal carcinoma in situ, each with distinct characteristics. Pathophysiology involves DNA damage and genetic mutations influenced by estrogen exposure and hereditary factors. Treatment options include radiation therapy, surgery (lumpectomy, mastectomy), sentinel node biopsy, lymph node dissection, and breast reconstruction. Hormone therapy and chemotherapy are also employed based on tumor characteristics and risk factors.

BREAST CANCER

Breast cancer is a type of cancer that starts in the breast. It can start in one or both breasts. Cancer starts when cells begin to grow out of control. Breast cancer occurs almost entirely in women, but men can get breast cancer, too.

FACTORS AFFECTING BREAST CANCER RISK

1. **Gender**- Breast cancer is more prevalent among women due to heightened estrogen and progesterone stimulation, increasing their susceptibility compared to men.

2. **Age**- The risk of breast cancer escalates with age, with most cases diagnosed in women aged 50 and above, highlighting a correlation between advancing age and increased susceptibility.

3. **Heritable factors**- A personal history of breast cancer elevates the risk of developing the condition in the contralateral breast, while a first-degree family history, such as a mother, sister, or daughter with breast cancer, significantly heightens the risk. The presence of multiple first-degree relatives with breast cancer further amplifies the risk.

4. **Geography, Ethnicity, and Race**- Breast cancer incidence rates vary across regions, with higher rates observed in North America, North and West Europe, Australia, and New Zealand. In the United States, variations exist among racial groups, with white women exhibiting the highest overall incidence followed by black women.

5. **Obesity**- Obesity is associated with an overall increased risk of breast cancer. The link between increased Body Mass Index (BMI) and breast cancer is found primarily in post-menopausal women that form estrogen positive breast cancer. However, the relationship between obesity and risk of breast cancer differs based on menopausal status.

6. **Alcohol Consumption and Smoking**- A meta-analysis of over 100 studies revealed a positive correlation between breast cancer and both low alcohol intake (less than 3–4 drinks per week) and high intake (more than 20 drinks per week), compared to abstaining from alcohol. Additionally, a significant association between alcohol consumption and breast cancer risk was found in a comprehensive prospective study. Moderate consumption, ranging from 3 to 6 drinks per week, showed a slight increase in risk compared to abstainers, with a relative risk of 1.15 (95% CI 1.06–1.24). Moreover, the risk of breast cancer was found to be linearly related to lifetime alcohol consumption, with particular emphasis on

drinking habits in early and late adulthood. This link between alcohol consumption and breast cancer risk may be attributed to alcohol's impact on estrogen metabolism, leading to elevated levels of blood oestrogen.

7. Smoking has been shown by many studies to be associated with increased breast cancer risk. According to one meta-analysis of several prospective studies, the risk of breast cancer was higher among women with a history of smoking with a relative risk of 1.10 (95% CI 1.02–1.14). In one prospective study of more than 100,000 women, smoking was associated with a 5% increase in the risk of breast cancer particularly in women who started smoking as an adolescent.

Breast cancer can start from different parts of the breast. The breast is an organ that sits on top of the upper ribs and chest muscles. There is a left and right breast, and each one has mainly glands, ducts, and fatty tissue. In women, the breast makes and delivers milk to feed newborns and infants. The amount of fatty tissue in the breast determines the size of each breast After skin cancer, breast cancer is the most common cancer diagnosed in women in the United States. Breast cancer can spread when the cancer cells get into the blood or lymph system and then are carried to other parts of the body.

SIGNS AND SYMPTOMS OF BREAST CANCER MAY INCLUDE

DIAGNOSIS OF BREAST CANCER

Breast cancer is often first detected as an abnormality on a mammogram before it is felt by the patient or health care provider[4].

EVALUATION OF BREAST CANCER INCLUDES THE FOLLOWING:

- Clinical examination
- Imaging
- Needle biopsy

Physical examination:

The following physical findings should raise concern:

- Lump or contour change
- Skin tethering
- Nipple inversion
- Dilated veins
- Ulceration
- Eczema like rash or redness on the nipple or the surrounding area
- Nipple discharge

If a palpable lump is found and possesses any of the following features, breast cancer may be present:

- Hardness
- Irregularity
- Focal nodularity

Screening:

Early detection remains the primary defense in preventing advanced breast cancer[4]. Screening modalities include the following:

- Mammography with tomosynthesis
- Ultrasonography
- Magnetic resonance imaging (MRI) with and without contrast[4]

BREAST CANCER TYPES

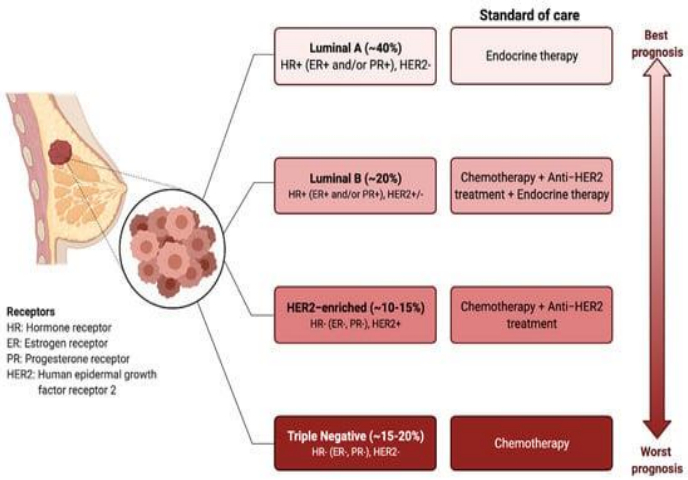
Common types of breast cancer include:

Invasive (infiltrating) ductalcarcinoma (IDC)	**Lobular breast cancer**	**Ductal carcinoma in situ (DCIS)**
This cancer starts in your milk ducts and spreads to nearby breast tissue. It's the most common type of breast cancer in the United States.	This breast cancer starts in the milk-producing glands (lobules) in your breast and often spreads to nearby breast tissue. It's the second most common breast cancer in the United States	Like IDC, breast cancer starts in your milk ducts. The difference is DCIS doesn't spread beyond your milk ducts.

PATHOPHYSIOLOGY

Breast cancer develops due to DNA damage and genetic mutations that can be influenced by exposure to estrogen. Sometimes there will be an inheritance of DNA defects or pro-cancerous genes like BRCA1 and BRCA2. Thus, the family history of ovarian or breast cancer increases the risk for breast cancer development[3]. In a typical person, the immune system targets cells exhibiting abnormal DNA or abnormal growth. However, in individuals with breast cancer, this defense mechanism falters, allowing tumors to develop and spread.[5]

Treatment Options in Past and Present



The main treatment options include:

1. Radiation Therapy
2. Surgery
3. Biological Therapy, Or Targeted Drug Therapy
4. Hormone Therapy
5. Chemotherapy

1. Radiation therapy:

A person may undergo radiation therapy around 1 month after surgery. It involves targeting the tumor with controlled doses of radiation that kill any remaining cancer cells.

2. Surgery:

If surgery is necessary, the type depends on the diagnosis and the person's preferences. Types of surgery include:

- **Lumpectomy:** This involves removing the tumor and a small amount of healthy tissue around it. A lumpectomy can help prevent the spread of cancer. This may be an option if the tumor is small and easy to separate from surrounding tissue.

- **Mastectomy:** A simple mastectomy involves removing the breast's lobules, ducts, fatty tissue, nipple, areola, and some skin. In some types, a surgeon also removes the lymph nodes and muscle in the chest wall.

- **Sentinel node biopsy:** If breast cancer reaches the sentinel lymph nodes, the first nodes to which it can spread, it can travel to other parts of the body through the lymphatic system. If the doctor does not find cancer in the sentinel nodes, it is usually not necessary to remove other nodes.

- **Axillary lymph node dissection:** If a doctor finds cancer cells in the sentinel nodes, they may recommend removing several lymph nodes in the armpit. This can prevent cancer from spreading.

- **Reconstruction:** Following a mastectomy, a surgeon can reconstruct the breast so that it looks more natural. This can help a person cope with the psychological effects of breast removal. The surgeon can reconstruct the

breast during the mastectomy or later. They may use a breast implant or tissue from another part of the body.

- **Hormone-blocking therapy**
  Doctors use hormone-blocking therapy to prevent hormone-sensitive breast cancers from returning after treatment. The therapy may help treat estrogen receptor-positive and progesterone receptor-positive cancers. administer it after surgery, though they may do so beforehand to shrink the tumour. Hormone-blocking therapy may be the only option for people who are not suitable candidates for surgery, chemotherapy, or radiotherapy.

Examples of hormone-blocking medications may include:

- Tamoxifen (Nolvadex)
- Aromatase inhibitors
- Ovarian ablation or suppression
- Goserelin (Zoladex)

- **Chemotherapy**
  A doctor may prescribe cytotoxic chemotherapy drugs to kill cancer cells if there is a high risk of recurrence or spread. When a person has chemotherapy after surgery, doctors call it adjuvant chemotherapy. Sometimes, a doctor may recommend chemotherapy before surgery to shrink the tumor and make it easier to remove. This is called neoadjuvant chemotherapy.

REFERENCE

1. Professional, C. C. M. (n.d.). Breast cancer. Cleveland Clinic. https://my.clevelandclinic.org/health/diseases/3986-breast-cancer
2. Breast cancer - Symptoms and causes - Mayo Clinic. (2024, February 10). Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/breast-cancer/symptoms-causes/syc-20352470
3. Alkabbani, F. M., & Ferguson, T. (2022, September 26). Breast cancer. StatPearls - NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK482286/#:~:text=Breast%20cancer%20develops%20due%20to,risk%20for%20breast%20cancer%20development.
4. "Breast cancer," *Medscape.com*, 21-Nov-2023. [Online]. Available: https://emedicine.medscape.com/article/1947145-overview?form=fpf. [Accessed: 14-Apr-2024].
5. C. Cilibrasi, P. Papanastasopoulos, M. Samuels, and G. Giamas, "Reconstituting immune surveillance in breast cancer: Molecular pathophysiology and current immunotherapy strategies," *Int. J. Mol. Sci.*, vol. 22, no. 21, p. 12015, 2021

KIDNEY CANCER

Kanchan Chaudhari, Dr. Sonali Mahaparale,
Department of Quality Assurance, Dr. D.Y.Patil College Pharmacy, Akurdi , Pune

ABSTRACT :

Around 2% of cancer cases worldwide are kidney cancer, with renal cell carcinoma being the most common type. Globally, the rates of occurrence and mortality are increasing by 2-3% every ten years. There are several known risk factors for kidney cancer, including cigarette smoking, obesity, acquired cystic kidney disease, and genetic vulnerability. For the small but significant minority of patients—that is, the 20% with good predictive characteristics—immunotherapy improves overall survival in metastatic renal cell carcinoma. Recent advances in the molecular biology of renal cell carcinoma have identified several pathways linked to the cancer's progression. Renal cell carcinoma pathology, immunohistochemistry, and genetics are becoming increasingly well understood. This has led to the identification of distinct tumour subtypes, some of which range from nonaggressive to highly aggressive and are linked to inherited tumour predisposition syndromes. These subtypes have a substantial impact on patient prognosis, treatment with targeted therapies, and counselling. Numerous tactics have been investigated to target these trails, and preliminary research has demonstrated significant clinical benefits. The burgeoning domain of radiogenomics holds the capability to revolutionise the function of imaging in the management of kidney cancer by means of noninvasively characterising the tumour histology and genetic microenvironment in isolated renal masses and/or secondary disease.

INTRODUCTION :

Renal cell carcinoma, which develops in the lining of the kidney's tiny tubes that filter blood and eliminate waste, and renal pelvis carcinoma, which grows in the kidney's core where urine accumulates, are two types of kidney cancer. Renal cancer ranks tenth among cancer-related deaths in males and is the seventh most frequent type of cancer overall. For women, it ranks as the sixth most frequent cause of cancer. [1] Histologically, renal cell carcinomas (RCCs) are categorized as collecting duct (<1%), chromophobe (5 - 10%), papillary (10 - 15%), and clear cell (60 - 80%). In the metastatic context, clear-cell histology is more closely associated with an improved product than papillary or chromophobe histology, but this is not the case for localized disease [3]. Moreover, RCC has a low prognosis and a high degree of resistance to chemotherapeutic treatment [4]. For individuals with RCC, targeted medications are increasingly advised as first- and second-line therapeutic options [5]. Previously thought to be a clinical diagnosis, kidney cancer is now predominantly diagnosed radiologically. The prevalence of kidney cancer has been steadily rising as a result of the widespread use of cross-sectional imaging. RCCs (renal cell carcinomas) are discovered by accident on cross-sectional imaging in about 70% of cases.[6] Lower-stage cancers have shown the largest increase in prevalence, which may indicate the benefit of early identification. [7] Early-stage detection can make the disease curable but metastatic kidney cancer is usually lethal. Kidney cancer tends to be “silent,” causing no symptoms until it has spread outside the kidneys. The most common form of kidney cancer in children is Wilms’ tumor, which also reveals distinctive genetic abnormalities and biologic activities. The initial part of present review mainly highlights general idea regarding cause, risks, and symptoms of kidney cancer. However, latter part focuses on the brief introduction about the efforts that have been taken for combating kidney cancer including various surgical and nonsurgical therapies. The new and emerging drugs and the combination therapy are found to be promising to defeat the kidney cancer.

Clinical study results have demonstrated the beneficial effects of targeted therapy, including sunitinib , sorafenib , temsirolimus , and bevacizumab with interferon . All of these medications have been approved for use in the treatment of RCC. Oral mammalian target of rapamycin inhibitors, such as everolimus, have also demonstrated efficacy in treating RCC, especially in patients who had acquired side effects from prior VEGF-targeted therapy [8].

TYPES OF KIDNEY CANCER

On the basis of microscopic view, the renal cell cancer (RCC) is having following subtypes:

1) **Clear cell renal cell carcinoma :** This is the RCC version that is most common. This type of cancer affects almost seven out of ten RCC patients. The cells that comprise clear cell RCC are exceedingly pale or clear when viewed under a microscope.

2) **Papillary renal cell carcinoma :** Approximately one in ten individuals with RCC have this subtype, which is the second most prevalent. Some, if not most, of the tumor is covered in tiny, finger-like projections known as papillae, caused by these malignancies. Because the cells pick up certain colors that are used to arrange the tissue so that it can be seen under a microscope, some doctors also refer to these as chromophilic tumors. The dye caused these cells to appear pink.

3) **Chromophobe renal cell carcinoma :** There aren't many RCC cases in this. Similar to clear cells, these malignancies also have pale cells, but they also have considerably larger cells and different behaviours.

4) **Collecting duct renal cell carcinoma :** This kind is quite rare. The primary feature is the cancer cells' capacity to create asymmetrical tubes.

5) **Unclassified renal cell carcinoma :** Renal cell tumors are sometimes labeled as "unclassified" because they do not fall into any of the preceding categories or because many cell types are present.

STAGES OF KIDNEY CANCER

Kidney cancer can be categorized into the following four phases based on the size of the tumor and its spread to other bodily parts. This classification may help determine the best course of therapy. Figure 1 shows the kidney tumor growth stages. [9]

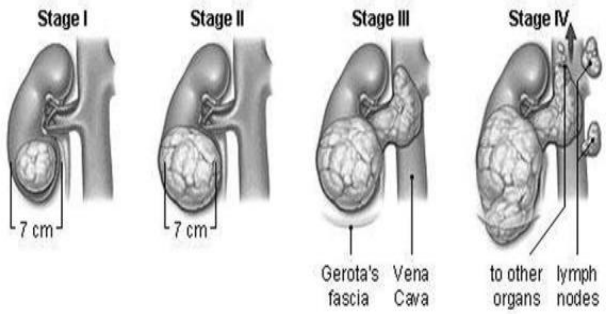


Figure 1. Stages of tumour growth in kidneys

Stage I : Less than 7 centimeters is the size of the tumor, and it has not grown outside the kidney.

Stage II : The size of the tumor exceeds 7 cm. Most frequently, radical or partial nephrectomy is used to surgically remove tumors in patients with stage I and II RCC. Following surgery for stage I or stage II RCC, further (adjuvant) chemotherapy, radiation treatment, or immunotherapy is not advised. [10]

Stage III : The tumor may have: 1) begun to grow outside of the kidney, into the surrounding adipose tissue; 2) traveled to a nearby lymph node; or 3) reached the kidney's main blood veins.
The most typical course of treatment for stage III RCC is radical nephrectomy.

Stage IV : The tumor has either extensively migrated to other parts of the body, such as the brain, bone, or lungs, or it has invaded several lymph nodes. Surgery is not an option for Stage IV RCC because it has gone too far from the kidney.

RISK FACTORS OF KIDNEY CANCER :

Kidney cancer's precise cause is uncertain. However, certain epidemiologic data indicates that kidney cancer risk factors include male gender, age over 50, and end-stage renal illness. The following are common risk variables that have previously been predicted:

1) **Lifestyle related and job-related risk factors :**

- **Smoking :** The risk of kidney cancer is increased by smoking. The danger seems to be correlated with the amount of smoke that a person consumes and decreases when they stop. [11]

- **Obesity :** An individual who is exceedingly overweight is more likely to develop kidney cancer.

- **Job hazards :** Numerous studies suggest that working with specific chemicals increases one's risk of developing kidney cancer. These include benzene, herbicides, asbestos, cadmium, and organic solvents, particularly trichloroethylene. [12]

- **Inherited Risk Factors :** Kidney cancer development may potentially be caused by a rare inherent disease. Although they account for a very tiny percentage of kidney cancer cases overall, people with these diseases have a substantially increased risk of developing kidney cancer. Here is a list of a few uncommon hereditary disorders. 1) the illness Von Hippel-Lindau. 2) Renal cell carcinoma, papillary. Hereditary. 3. Renal cell cancer with hereditary leiomyoma. 4, the Birt-Hogg-Dube condition. 5), Renal oncocytoma that is inherited.[13]

SIGNS AND SYMPTOMS OF KIDNEY CANCER

Renal cancer patients may experience:

1) Urinary tract bleeding.
2) Pressure or pain in the back or side.
3) A sore on the back or side.
4) Leg and ankle oedema
5) Elevated blood pressure.
6) Anaemia, or low red blood cell counts.
7) Tiredness and weakness.
8) Appetite loss.
9) Reduction of weight.

DIAGNOSIS OF KIDNEY CANCER

The expert may perform one or more of the following operations based on the patient's symptoms

1) **Physical exam :** The physician verifies typical health indicators and does tests for hypertension and fever. The abdomen and tumor site are also felt by the physician.

2) **Urine tests :** Blood and other illness indicators are looked for in urine analyses.

3) **Blood tests :** The purpose of this is to monitor kidney function. Increased levels of many chemicals, including creatinine, indicate that the kidneys are not functioning properly.

4) **CT scan :** An entire sequence of images of the kidneys could be taken with the use of an x-ray machine that was connected to a computer. When a dye is injected into the patient, kidney images can be seen clearly and used to anticipate the development of kidney cancer. CT scans of the abdomen and chest provide details on the main tumor's extension, the opposite kidney's morphology, and the assessment of any metastases.

5) **Ultrasound test :** An ultrasound is a test that uses high frequency sound waves to produce an image of the body part being scanned. The waves bounce off the kidneys, and a computer uses the echoes to create a picture called a sonogram. A solid tumor or cyst shows up on a sonogram.

6) **Biopsy :** A biopsy is the removal of tissue from suspected body part to look for cancer cells. A thin needle inserted through the skin into the kidney to remove a small portion of tissue. A pathologist uses a microscope to look for cancer cells in the tissue. Renal tumour biopsy is increasingly being used in diagnosis and is constantly designated previous to ablative and systemic therapy without earlier histopathology and in surveillance strategies to stratify follow-up[14]

CONCLUSION

The treatment of patients with advanced RCC has developed rapidly over the last decade. Several agents are now approved for use in many other countries, and patient viewpoint is significantly brighter. Making progress in the area of immunotherapy, targeted therapy and chemotherapy is necessary in order to significantly reduce morbidity and mortality related to advance RCC. The development of these agents with improved efficacy, of which, the kinase inhibitors have demonstrated the most significant activity. Progressively more

oncologists have choices concerning treatment selections for patients with renal cell carcinoma. Studies to date raise many queries with regard to scheduling, dose, duration, potential combinations and toxicity of treatment. A profound perceptive of the bond between the signalling pathways motivating tumor growth and their inhibition is needed in order to optimise the use of these agents and should recommend strategies to hinder or stop resistance and identify suitable therapeutic combinations. Current era is hopeful with regard to treatment for renal cell carcinoma with growing numbers of active agents. To understand these hopes, this is the major challenge to counterpart these agents with the biology of the tumors and their hosts.

REFERENCE

1. The American Cancer Society's publication, Cancer Facts & Figures 2010(website accessed on 27/04/2011.)

2. Beck SD, Patel MI, Snyder ME, Kattan MW, Motzer RJ, Reuter VE, Russo P. Effect of papillary and chromophobe cell type on disease-free survival after nephrectomy for renal cell carcinoma. *Ann Surg Oncol.* 2004;11(1):71–77. doi: 10.1007/BF02524349

3. Cheville JC, Lohse CM, Zincke H, Weaver AL, Blute ML. Comparisons of outcome and prognostic features among histologic subtypes of renal cell carcinoma. *Am J Surg Pathol.* 2003;27(5):612–624. doi: 10.1097/00000478-200305000-00005

4. Gupta K, Miller JD, Li JZ, Russell MW, Charbonneau C. Epidemiologic and socioeconomic burden of metastatic renal cell carcinoma (mRCC): a literature review. *Cancer Treat Rev.* 2008;34(3):193–205. doi: 10.1016/j.ctrv.2007.12.001.

5. Radulovic S, Bjelogrlic SK. Sunitinib, sorafenib and mTOR inhibitors in renal cancer. *J BUON.* 2007;12(Suppl 1):S151–162.

6. Atri M, Tabatabaeifar L, Jang HJ, et al: Accuracy of Contrast-enhanced US for Differentiating Benign from Malignant Solid Small Renal Masses. Radiology 276:900-8, 2015

7.Jinzaki M, Silverman SG, Akita H, et al: Renal angiomyolipoma: a radiological classification and update on recent developments in diagnosis and management. Abdom Imaging 39:588-604, 2014

8. Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, Grunwald V. et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. *Lancet.* 2008;372(9637):449–456. doi: 10.1016/S0140-6736(08)61039-9.

9. Hudes G, Carducci M, Tomczak P, Dutcher J, Figlin R, Kapoor A, Staroslawska E. et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med.* 2007;356(22):2271–2281. doi: 10.1056/NEJMoa066838.

10. Rini BI, Halabi S, Rosenberg JE, Stadler WM, Vaena DA, Ou SS, Archer L. et al. Bevacizumab plus interferon alfa compared with interferon alfa monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206. *J Clin Oncol.* 2008;26(33):5422–5428.

11. Hu J, Ugnat AM. Active and passive smoking and risk of renal cell carcinoma in Canada. *Eur J Cancer.* 2005;41(5):770–778. doi: 10.1016/j.ejca.2005.01.003.

12. Mattioli S, Truffelli D, Baldasseroni A, Risi A, Marchesini B, Giacomini C, Bacchini P. et al. Occupational risk factors for renal cell cancer: a case—control study in northern Italy. *J Occup Environ Med.* 2002;44(11):1028–1036.

13. Sanz-Ortega J, Olivier C, Perez Segura P, Galante Romo I, San Jose Manso L, Saez M. Hereditary renal cancer. *Actas Urol Esp.* 2009;33(2):127–133. doi: 10.4321/S0210-48062009000200005.

14. Israel GM, Bosniak MA. Pitfalls in renal mass evaluation and how to avoid them. *Radiographics : a review publication of the Radiological Society of North America, Inc.* 2008;28(5):1325–1338.

LUNG CANCER

Mrs. Bhavana Kapse
Department of Pharmaceutics, Dr. D.Y.Patil College Pharmacy, Akurdi , Pune

INTRODUCTION

The history of Lung Cancer dates back centuries, with smoking recognized as a significant risk factor for the disease. Here are some key points in the history of Lung Cancer:

1. **Early observations:** Reports of lung cancer-like symptoms date back to ancient Egypt and Greece, but the link to tobacco was not established until much later.

2. **Rise in smoking:** The 20th century saw a significant increase in smoking rates, leading to a surge in lung cancer cases.

3. **Recognition of smoking as a risk factor:** In the mid-20th century, research definitively linked smoking to lung cancer, leading to public health campaigns to curb tobacco use.

4. **Advances in treatment:** Over the years, advancements in surgery, chemotherapy, radiation therapy, and targeted therapies have improved outcomes for some lung cancer patients.

5. **Screening and prevention efforts:** Lung cancer screening programs for high-risk individuals and public health initiatives promoting smoking cessation have been instrumental in reducing lung cancer incidence and mortality rates.

6. **Ongoing research:** Current research focuses on personalized medicine, immunotherapy, and early detection methods to further improve lung cancer outcomes.

7. Throughout history, Lung Cancer has evolved from a poorly understood disease to one where risk factors are well-established, treatment options have expanded, and prevention strategies are actively promoted.

ANATOMY AND PHYSIOLOGY OF THE LUNGS:

Structure of Lung:

The structure of the lungs is complex and crucial for respiratory function. Here is an overview of the main components of the lungs:

- **Trachea:** Also known as the windpipe,it connects the larynx to the bronchi, allowing air to pass in and out of the lungs.
- **Bronchi:** The trachea divides into two main bronchi, which further branch into smaller bronchioles within each lung.
- **Bronchioles:** These smaller airways branch off the bronchi and continue to divide, leading to the alveoli.
- **Alveoli:** These are tiny air sacs where gas exchange occurs. Oxygen from inhaled air diffuses into the bloodstream, and carbon dioxide moves from the blood into the alveoli to be exhaled.
- **Diaphragm**: A dome-shaped muscle below the lungs that contracts and relaxes to help with breathing. When it contracts, the chest cavity expands, allowing air to enter the lungs.
- **Pleura:** The double-layered membrane that surrounds each lung. The inner layer (visceral pleura) covers the lungs, while the outer layer (parietal pleura) lines the chest cavity.
- **Lobes:** The right lung has three lobes (upper, middle, lower) while the left lung has two (upper and lower) to accommodate the heart.

Understanding the structure of the lungs is essential for comprehending how air moves through the respiratory system, reaches the alveoli for gas exchange, and supports vital functions like oxygenation of the blood and removal of carbon dioxide.

Anatomy:

The lungs are a pair of spongy, cone-shaped organs located in the chest.

They are surrounded by a protective membrane called the pleura.

The right lung has three lobes, while the left lung has two lobes to accommodate the

heart.

Air enters the lungs through the trachea, which branches into the bronchi,

bronchioles, and ultimately into alveoli (air sacs).

Physiology:

1. **Respiration:** The primary function of the lungs is to facilitate gas exchange. Oxygen from the air we breathe enters the bloodstream, and carbon dioxide is removed from the body.

2. **Alveoli:** These tiny air sacs are where gas exchange occurs. Oxygen moves from the alveoli into the blood, while carbon dioxide moves from the blood into the alveoli to be exhaled.

3. **Diaphragm:** This muscle plays a crucial role in breathing. When it contracts, the chest cavity expands, allowing air to enter the lungs. When it relaxes, air is expelled.

4. **Surfactant:** A substance produced by the lungs that helps reduce surface tension in the alveoli, preventing them from collapsing.

Understanding the anatomy and physiology of the lungs is essential for comprehending how these organs facilitate oxygen exchange, support breathing, and maintain overall respiratory function in the body.

PHARMACOLOGY OF LUNG CANCER:

1. Chemotherapy: Traditional cytotoxic drugs like cisplatin, paclitaxel, and docetaxel are commonly used to kill cancer cells. Newer agents like pemetrexed and gemcitabine are also utilized.

2. Targeted Therapy: Drugs like Erlotinib, Gefitinib, and Crizotinib target specific genetic mutations in cancer cells, such as EGFR or ALK mutations.

3. Immunotherapy: Checkpoint inhibitors like Pembrolizumab and Nivolumab boost the immune system's ability to recognize and destroy cancer cells.

4. Angiogenesis Inhibitors: Drugs like Bevacizumab target blood vessel growth in tumours to cut off their blood supply.

5. Combination Therapies: Often, a combination of chemotherapy, targeted therapy, and immunotherapy is used to treat advanced lung cancer effectively.

Understanding the pharmacology of Lung Cancer involves recognizing the various drug classes and mechanisms of action used to target cancer cells, inhibit tumour growth, and improve patient outcomes.

CAUSES OF LUNG CANCER:

1. **Smoking:** The primary cause, responsible for the majority of lung cancer cases. Second-hand smoke exposure: Non-smokers exposed to tobacco smoke are at risk.

2. **Environmental factors:** Exposure to radon, asbestos, arsenic, and other carcinogens increase risk.

RISK FACTORS:

- **Smoking:** The most significant risk factor.
- Family history of lung cancer.
- Exposure to secondhand smoke, radon, asbestos, or other carcinogens.
- Air pollution.
- Personal or family history of lung disease.

PREVENTION:

- Quit smoking and avoid second-hand smoke.
- Test homes for radon.
- Minimize exposure to carcinogens like asbestos.
- Maintain a healthy lifestyle with a balanced diet and regular exercise.
- Consider lung cancer screening for high-risk individuals.

TREATMENT OPTIONS

- **Surgery:** Removes the tumour and surrounding tissue.
- **Chemotherapy:** Uses drugs to kill cancer cells.

- **Radiation therapy:** Uses high-energy rays to destroy cancer cells.
- **Immunotherapy:** Boosts the body's immune system to fight cancer.
- **Targeted therapy:** Targets specific genetic mutations in cancer cells.

OUTCOMES:

- Prognosis varies based on cancer stage, type, and individual factors.
- Early detection improves survival rates.
- Treatment outcomes can range from successful remission to palliative care for advanced cases.
- Supportive care focuses on symptom management and improving quality of life for patients.

REFERENCES:

1. Kelloff, G.J., Crowell, J.A., Steele, V.E., Lubet, R.A., Malone, W.A., Boone, C.W., Kopelovich, L., Hawk, E.T., Lieberman, R., Lawrence, J.A., Ali, I., Viner, J.L., Sigman, C.C. Progress in cancer chemoprevention: development of diet-derived chemopreventive agents. Journal of Nutrition 2000; 130 (2): 467S–471S.

2. Greenwald, P. Cancer chemoprevention. British Medical Journal 2002; 324 (7339): 714– 718.

3. Corner, J. What is cancer? In: Cancer Nursing Care in Context (eds J. Corner and C. Bailey), Blackwell Publishing; Oxford.; 2001.

4. Yarbro, C., Frogge, M. and Goodman, M. Cancer Nursing: Principles and Practice, 6th edn, Jones and Bartlett Publishers, Boston, MA; 2005.

5. V. Sankar Lung Cancer - A Review, International Journal of Health Sciences and Research, Vol.13; Issue: 10; October 2023.

6. http://www.news-medical.net

7. Araujo LH, Horn L, Merritt RE, Shilo K, XuWelliver M, Carbone DP. Ch. 69 - Cancer of the Lung: Non-small cell lung cancer and small cell lung cancer. In: Niederhuber JE, Armitage JO, Doroshow JH, Kastan MB, Tepper JE, eds. Abeloff's Clinical Oncology. 6th ed. Philadelphia, Pa: Elsevier; 2020.

8. Siddiqui F, Siddiqui AH. Cancer, Lung.: Stat Pearls [Internet]. Treasure Island (FL): Stat Pearls Publishing; 2020.

LIVER CANCER: A REVIEW

Ms. Bhumika Zade, Ms. Anju Kalyankar

Department of Pharmaceutical Chemistry, Dr. D.Y Patil College of Pharmacy, Akurdi, Pune

ABSTRACT

The most common type of liver cancer is hepatocellular carcinoma, which begins in the main type of liver cell (hepatocyte).The main risk factors for Liver Cancer include chronic excessive alcohol use, non-alcoholic fatty liver disease linked to diabetes and obesity, and hepatitis C infection. When liver cells experience DNA alterations, or mutations, cancer in the liver results. Liver cancer can be easily diagnosed by ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET).

INTRODUCTION

Primary liver cancer, or hepatocellular carcinoma (HCC), is the fifth most common cancer in males and the seventh most common cancer in females and is the third leading cause of cancer-related death worldwide[1]. (Ferlay et al. 2010; Jemal 2011). Liver metastases most often arise from primary tumours in colon, breast, lung, pancreas and stomach [2]. 80-90% percent of primary LC cases are caused by hepatocellular carcinoma (HCC), a frequent kind of LC. The main risk factor for primary LC is the presence of chronic inflammatory etiologies .Chronic inflammation can be brought on by persistent viral infections, persistent exposure to poisons or parasites, alcoholic and non-alcoholic steatohepatitis, diabetes, and obesity.

INCIDENCE AND PREVALENCE

Liver cancer accounts for 788,000 fatalities annually, and 1.16 million deaths overall, ranking it as the eleventh and sixteenth most common causes of death, respectively. A couple of years ago, reported on the global burden of liver cancer by 2015 using Global Burden of Disease data. The number of incident liver cancer cases in 2015 was 854,000, whereas the number of deaths and disease adjusted life year(DALYs) were 810,000 and 20,578,000, respectively. The number of incident cases increased by 75% between 1990 and 2015, mostly because of changes in population age structures and population growth [3]. GLOB0CON 2020 predicted that the incidence of liver cancer would increase by 55.0% and the number of deaths would increase by 56.4% between 2020 and 2040 [4]. HCC has a male proponderance, male:female ratios that vary from 0.7:1 in Paraguay to 6.4:1 in the Bas Rhin area of France. In the United States the ratio is 2:1. The incidence of HCC increases with age. The median age at diagnosis is 53 years in Asia and 62 years in United States [5].

SIGNS AND SYMPTONS

Loss of weight, appetite decline ,vomiting or feeling queasy ,n enlarged liver, Abdominal swelling or accumulation of fluid (belly) and Jaundice are some of the primary symptoms of liver cancer. The risk factors for liver cancer include gender, race, chronic viral hepatitis, cirrhosis, inherited metabolic diseases, alcohol drinking, smoking, obesity, type 2 diabetes, and exposure to carcinogenic substances such as aflatoxins [6]. Liver cancer could be prevented by reducing the prevalence of these modifiable risk factors, including hepatitis vaccination and lifestyle changes [7]. Research has also demonstrated that the prevalence of liver cancer brought on by the hepatitis B and hepatitis C viruses varies geographically (HCV)

DIAGNOSIS

1. Computed Tomography:

Benefits of CT are easy access due to wide availability and patient-friendly protocols allowing even a chest–abdomen–pelvis CT examination in a less then 20-s breath hold using multidetector CT technology[8,9]. contrast-enhanced CT study since CT has high sensibility (93%) and specificity (100%) for detecting hepatic metastases[8]. computed tomography (CT) is widely used in clinical practice because of its three-dimensional (3D) measurements of liver volume and tumour volume and evaluations of metastasis to other organs such as the lungs and bones.

2. Magnetic Resonace Imaging:

If radiographic contrast media cannot be administered due to iodine allergy or renal insufficiency, the accuracy of CT is poor and an MRI should be performed to fully evaluate the liver. MRI should be performed in the presence of fatty infiltration of the liver since liver metastases can be obscured when hepatic steatosis is present [10]. The detection rate of smaller (<2 cm) tumors, in particular, was noted to have improved from 55.6% in 2006 to 87.5% in 2010, largely secondary to technology updates related to graded improvements in MR sequence design and hardware[11].

3. Ultrasonography:

The most used imaging test for the liver is abdominal ultrasonography because of its convenience, versatility, visibility, non-invasiveness, and ease of use. However, reports indicate highly variable sensitivity for the detection of HCC with US, ranging from 33% to 96% [12]. Comparatively less expensive initially per study when compared to CT and MRI. Contrast ultrasonography visualizes the hemodynamic changes within the liver cancer and facilitates the differentiation and diagnosis of different kinds of liver cancer[13].

4. Positron Emission Tomography:

Also referred to as Nuclear Medical Imaging. The advantages of whole-body ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET)/CT are evident for the following: (1) tumour staging; (2) re-staging after treatment; (3) response evaluation; (4) guidance of biological target volume delineation for radiation therapy and puncture biopsy sites (evidence level 2) [14,15] and (5) evaluation of the extent of malignancy and prognosis of the tumour (evidence level 2)[16-18].

TREATMENT

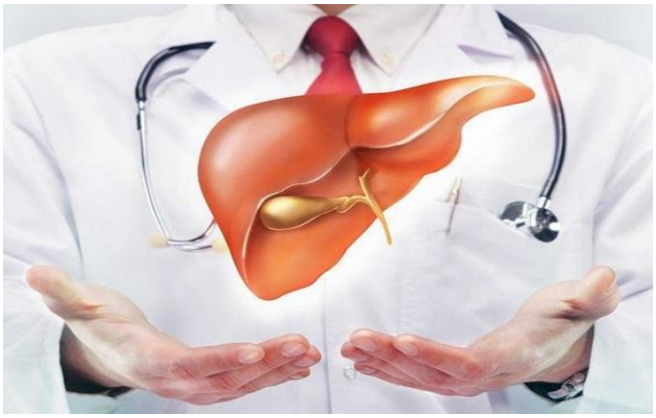
1. Immunotherapy:

Immunotherapy has become a viable treatment option and is being studied for a number of malignancies, including liver cancer. The immune

system can identify cancer cells, and mobilizing the immune response is able to eliminate cancer. Treatment of immunotherapy-induced hepatitis by and large consists of wrangling in and quieting down the immune system activation induced by these therapies. Liver injury may not become apparent after the first dose of therapy and may occur only after additional cycles. While many instances of mild liver test elevations will resolve spontaneously, ongoing liver injury necessitates treatment [19] Their role in normal liver function is to prevent acute response to bacterial agents in order to avoid unnecessary tissue damage [20]. As a result, liver sinusoidal endothelial cells express immunosuppressive molecules, such as programmed cell death ligand-1 (PD-L1). Another important cell type, Kupffer cells, are specialized liver-located macrophages that remove bacteria and produce immunosuppressive cytokines, such as IL-10 and prostaglandins.

2. Liver transplant:

Patients with acute and chronic end-stage liver disease can benefit greatly from liver transplantation (LT), a proven operation that can save their lives. It increases lifespan by fifteen years and restores regular health and lifestyle. LT is recommended for individuals experiencing acute liver failure, hepatocellular carcinoma (HCC) in progress, and end-stage liver disease. Cirrhosis is the most frequent cause of end-stage liver disease in people that warrants LT. When significant cirrhosis problems including variceal hemorrhage, ascites, hepatorenal syndrome, and encephalopathy manifest, patients ought to be referred to transplant centers.



REFERENCE:

1.(Ferlay et al. 2010; Jemal 2011).

2. Ackerman NB, Lien WM, Kondi ES, et al. The blood supply of experimental liver metastases. Distribution of hepatic artery and portal vein blood to ‘small’ liver metastases. Distribution of hepatic artery and portal vein blood to ‘small’ and ‘large’ tumors. *Surgery*. 1969;**66**:1067–72. [PubMed] [Google Scholar]

3. Akinyemiju T, Abera S, Ahmed M, Alam N, Alemayohu MA, Allen C, et al.Global Burden of Disease Liver Cancer Collaboration The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level: Results from the global burden of disease study 2015. *JAMA Oncol*. 2017;3:1683–1691. [PMC free article] [PubMed] [Google Scholar]

4. Rumgay H, Arnold M, Ferlay J, Lesi O, Cabasag CJ, Vignat J, et al. Global burden of primary liver cancer in 2020 and predictions to 2040. *J Hepatol*. 2022;77:1598–1606. [PMC free article] [PubMed] [Google Scholar]

5. Chen, M.W. Yu, Y.F. LiawEpidemiological characteristics and risk factors of hepatocellular carcinoma J Gastroenterol Hepatol, 12 (1997), p. S294

6. Yang JD, Hainaut P, Gores GJ, Amadou A, Plymoth A, Roberts LR. A global view of hepatocellular carcinoma: trends, risk, prevention and management. *Nat Rev Gastroenterol Hepatol*. 2019 Oct;16((10)):589–604. [PMC free article] [PubMed] [Google Scholar] [Ref list]

7. Jemal A, Center MM, DeSantis C, Ward EM. Global patterns of cancer incidence and mortality rates and trends. *Cancer Epidemiol Biomarkers Prev*. 2010 Aug;19((8)):1893–907. [PubMed] [Google Scholar] [Ref list]

8. Hopper KD, Singapuri K, Finkel A. Body CT and oncologic imaging. *Radiology*. 2000;**215**:27–40. [PubMed] [Google Scholar].

9. Kulinna C, Helmberger T, Kessler M, Reiser M. Improvement in diagnosis of liver metastases with the multi-detector CT. *Radiologe*. 2001;**41**:16–23. [PubMed] [Google Scholar] [Ref list]

10. Zhao X, Wu N, Ouyang H. Imaging manifestations of tumors metastasized in fatty liver. *Zhonghua Zhong Liu Za Zhi*. 1998;**20**:132–4. [PubMed] [Google Scholar]

11. Becker-Weidman DJ, Kalb B, Sharma P, et al. Hepatocellular carcinoma lesion characterization: single-institution clinical performance review of multiphase gadolinium-enhanced MR imaging--comparison to prior same-center results after MR systems improvements. *Radiology*. 2011;261:824–833. [PubMed] [Google Scholar] [Ref list]

12. Digumarthy SR, Sahani DV, Saini S. MRI in detection of hepatocellular carcinoma (HCC) *Cancer Imaging*. 2005;5:20–24. [PMC free article] [PubMed] [Google Scholar] [Ref list]

13. Salvatore V, Gianstefani A, Negrini G, Allegretti G, Galassi M, Piscaglia F: Imaging diagnosis of hepatocellular carcinoma: recent advances of contrast-enhanced ultrasonography with SonoVue®. Liver Cancer 2016; 5: 55–66.

14. Boellaard R, Delgado-Bolton R, Oyen WJ, Giammarile F, Tatsch K, Eschner W, Verzijlbergen FJ, Barrington SF, Pike LC, Weber WA, Stroobants S, Delbeke D, Donohoe KJ, Holbrook S, Graham MM, Testanera G, Hoekstra OS, Zijlstra J, Visser E, Hoekstra CJ, Pruim J, Willemsen A, Arends B, Kotzerke J, Bockisch A, Beyer T, Chiti A, Krause BJ; European Association of Nuclear Medicine: FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. Eur J Nucl Med Mol Imaging 2015; 42: 328–354.

15.Boellaard R, O'Doherty MJ, Weber WA, Mottaghy FM, Lonsdale MN, Stroobants SG, Oyen WJ, Kotzerke J, Hoekstra OS, Pruim J, Marsden PK, Tatsch K, Hoekstra CJ, Visser EP, Arends B, Verzijlbergen FJ, Zijlstra JM, Comans EF, Lammertsma AA, Paans AM, Willemsen AT, Beyer T, Bockisch A, Schaefer-Prokop C, Delbeke D, Baum RP, Chiti A, Krause BJ: FDG PET and PET/CT: EANM procedure guidelines for tumour PET imaging: version 1.0. Eur J Nucl Med Mol Imaging 2010; 37: 181–200.

16. Ferda J, Ferdova E, Baxa J, Kreuzberg B, Daum O, Treska V, Skalicky T: The role of 18F-FDG accumulation and arterial enhancement as biomarkers in the assessment of typing, grading and staging of hepatocellular carcinoma using 18F-FDG-PET/CT with integrated dual-phase CT angiography. Anticancer Res 2015; 35: 2241–2246.

17.Lee JW, Oh JK, Chung YA, Na SJ, Hyun SH, Hong IK, Eo JS, Song BI, Kim TS, Kim do Y, Kim SU, Moon DH, Lee JD, Yun M: Prognostic significance of 18F-FDG uptake in hepatocellular carcinoma treated with transarterial chemoembolization or concurrent chemoradiotherapy: a multicenter retrospective cohort study. J Nucl Med 2016; 57: 509–516.

18.Hyun SH, Eo JS, Lee JW, Choi JY, Lee KH, Na SJ, Hong IK, Oh JK, Chung YA, Song BI, Kim TS, Kim KS, Moon DH, Yun M: Prognostic value of 18F-fluorodeoxyglucose positron emission tomography/computed tomography in patients with Barcelona Clinic Liver Cancer stages 0 and A hepatocellular carcinomas: a multicenter retrospective cohort study. Eur J Nucl Med Mol Imaging, Epub ahead of print.

19. Gangadhar TC, Vonderheide RH. Mitigating the toxic effects of anticancer immunotherapy. Nat Rev Clin Oncol. 2014;11(2):91–9.

20. Jenne, C.N.; Kubes, P. Immune surveillance by the liver. *Nat. Immunol.* **2013**, *14*, 996–1006. [**Google Scholar**] [**CrossRef**]

ORAL CANCER WITH DIAGNOSIS AND PERSPECTIVES IN INDIA

Mr. Siddharth Topale, Ms. Pooja Palandurkar
Department of Pharmaceutics, Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune

ABSTRACT:

Oral cancer is the sixth most prevalent type of cancer worldwide, with India accounting for about one-third of cases and ranking second in terms of the number of instances. Oral squamous cell carcinoma (OSCC), which is also acknowledged as a detectable pre-clinical phase of mouth cancer, predominates in all cases of oral cancer with potentially malignant abnormalities. Some risk factors for the incidence of oral cancer include smoking, especially smokeless tobacco, chewing betel guid, excessive alcohol use, unclean oral conditions, and persistent viral infections, including the human papillomavirus. A broad range in the worldwide incidence and a higher death rate are indicated by ignorance, differences in environmental exposure, and behave oral risk factors. In this overview, many risk factors associated with the incidence of mouth cancer are discussed, along with data on the disease's distribution by virtue throughout India and socioeconomic status. Along with cutting-edge methods, the many traditional diagnostic methods that are frequently employed to identify oral cancer are covered. The innovative methods created by Indian researchers that have great promise for use in the diagnosis of oral cancer are also the subject of this review.

INTRODUCTION:

Cancer is the term for any unchecked cell proliferation that invades another tissue and damages it. A little, strange, inexplicable growth or sore appears in the mouth, encompassing the lips, cheeks, sinuses, tongue, hard and soft palate, and the area from the base of the mouth to the oropharynx. This is the first sign of oral cancer. Oral cancer is the sixth most common type of cancer worldwide.

India accounts for one-third of the global oral cancer burden and the greatest number of instances of the disease. For countries going through economic transition, oral cancer is a major health concern [1]. About one-fourth of all cases worldwide roughly 77,000 new cases and 52,000 deaths are recorded in India each year [2]. Given that oral cancer is one of the most prevalent cancer types in India, the rising number of instances of this disease should raise the greatest concerns for community health [3]. Approximately 70% of instances of oral cancer in India are said to be in advanced stages, making it a far more serious worry than in the west (American Joint Committee on Cancer, Stage III-IV). The likelihood of a cure is extremely low nearly non-existent due to late-stage identification; five-year survival rates are about 20% [4]. An impressive 84–97% of oral cancer is caused by oral squamous cell carcinoma (OSCC). Normal epithelial linings or possibly malignant lesions are the common causes of OSCC. PMDs, or potentially malignant disorders, have been identified as markers of oral cancer preclinical stage. These include fibrosis, erythroplakia, leukoplakia, candidal leukoplakia, dyskeratosis congenital, and lichen planus [5]. Smokeless tobacco (SLT) use, chewing betel quid, binge drinking, bad dental hygiene, a diet lacking in nutrients, and persistent viral infections, i.e. Ocular cancer can occur due to a number of factors, including the human papillomavirus (HPV). There is significant diversity in the incidence across the globe, which can be indicated by behavioral risk factors, exposure to extreme environmental circumstances, and lack of understanding. Infections of the periodontal system are also a high-risk factor for oral cancer, and they are more common in the Indian population, where the practice of chewing paan is the primary cause of oral cancer [2]. Tumorigenesis is significantly influenced by inflammation, which is also a result of bacterial and viral infections and inflammatory bowel disorders, both of which increase the risk of cancer. Cancer can result from a variety of socioecological and behavioral factors, including exposure to smoke, silica, asbestos, and other carcinogenic substances [2]. Tobacco consumption (in any form) is a leading cause of cancer, particularly in underdeveloped countries. Aside from tobacco, chewing paan containing piper betel

leaves mixed with areca nut, lime, catechu, cinnamon, and other ingredients is a prominent cause of oral cancer, particularly in north-eastern India, which has the highest cancer incidence in the country [6].

THE CURRENT STATUS OF ORAL CANCER IN INDIA:

Oral cancer is a significant health concern in India because it is one of the most common types of cancer, affecting a big population. Low-income people are most vulnerable because they are exposed to a wide range of risk factors. Tobacco usage has been the leading cause of mouth cancer. Tobacco usage in various forms, such as gutka, zarda, mawa, kharra, khaini, cigarettes, bidi, hookah, and so on, is a major cause of oral cavity tumor formation in both young and adult Indians.

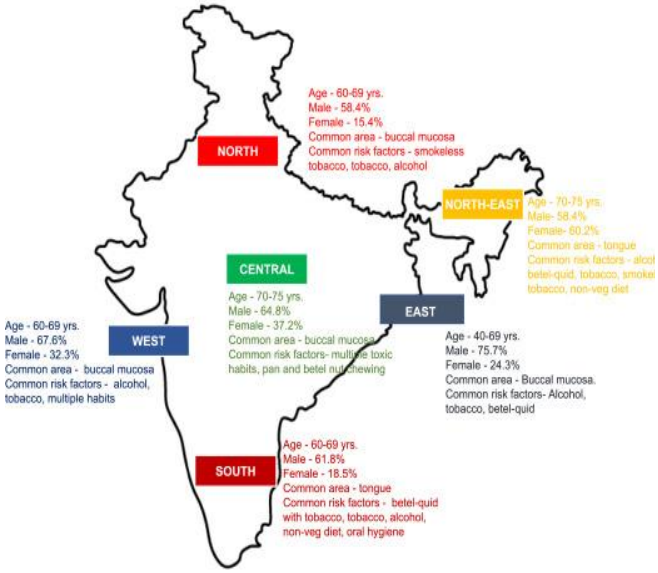


Fig1: The spread of oral cancer in India. [16]

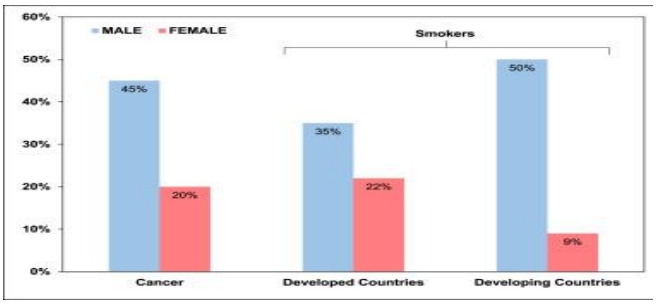


Fig:- Tobacco-related malignancies are distributed according on gender and among smokers.[16]

METHODS EMPLOYED IN THE DIAGNOSIS OF ORAL CANCER:

In order to lower the death rate for patients with oral cancer, early detection is crucial. As a result, there is a great need for quick, simple, and non-invasive methods of diagnosing oral cancer. A doctor must first correctly evaluate any oral lesions in the mouth in order to diagnose oral cancer. When cancer is detected, the patient is referred to an oral or maxillofacial surgeon, who performs the necessary testing.

Fig:- Symptoms of oral cancer

Different techniques for diagnosis are as follows:

1. Physical examination
2. Histopathological examination
3. Vital staining techniques
4. Biopsy
5. Imaging techniques
6. Optical and radiological techniques
7. Biomarker detection and biosensor

Synopsis and prospective views

Given that it bears a third of the global burden of oral cancer, India is regarded as the global center for cases of the disease. The highest incidence rate of oral cancer in women both in India and globally is seen in the southern regions of the country. The two main factors that most influence the incidence of oral cancer are genetic and epigenetic. A number of variables, including oral thrust, mouthwash use, radiation, alcohol, immunosuppression, tobacco, food, and nutrition, are significant contributors to occurrence. Two more important risk factors for oral cancer include poor oral hygiene and HPV infection. The cost of treating oral cancer is very exorbitant for the patient, and the majority of patients discontinue therapy in the middle, which raises the death rate even further. The location, size, and viability of organ preservation in patients are

the primary determinants of the course of treatment for oral cancer. Surgery and radiation therapy are advised treatments for mouth cancer in its early stages. Preventive measures, prompt diagnosis, and prompt treatment are essential components in addressing the oral cancer epidemic in India. People need to be made aware of the risks and causes of oral cancer as well as the significance of abstaining from alcohol and tobacco use and practicing good dental hygiene. realizing how important early detection of oral cancer is, many research teams worldwide are developing methods to help with this process. In addition to a physical examination, the following tests are advised: 1) X-rays; 2) CT; 3) PET; 4) MRI; and 5) endoscopy. In addition, the most often used techniques for diagnosing oral cancer in India are histological examination, vital staining methods, brush biopsy biopsies, biomarker detection using biosensors or immunohistochemistry, radiography, and optical imaging systems. In order to meet the needs of a sizable and diversified population, medical and technology research institutions in India have been collaborating to develop and offer novel technologies. There have been reports of a number of diagnostic methods that can distinguish between benign and malignant tumors. The traditional methods of diagnosis are pricy, time-consuming, necessitate skilled experts, and can involve surgery, among other drawbacks. There has been much promise for integrating biosensor-based oral cancer biomarker sensing approaches into diagnostic procedures, as reported recently. Despite the publication of several research, India still lacks non-invasive, portable, simple, quick, and affordable methods that do not call for a trained expert to process, evaluate, and interpret test data. In order to incorporate newly developed, commercialized procedures into clinical diagnostic practices, professionals must support them.

REFERENCES:

1. Gupta B., Bray F., Kumar N., Johnson N.W. Associations between oral hygiene habits, diet, tobacco and alcohol and risk of oral cancer: a case–control study from India. *Cancer Epidemiol.* 2017;51:7–14. doi: 10.1016/j.canep.2017.09.003. [PubMed] [CrossRef] [Google Scholar]

2. Laprise C., Shahul H.P., Madathil S.A., Thekkepurakkal A.S., Castonguay G., Varghese I., Shiraz S., Allison P., Schlecht N.F., Rousseau M.C., Franco E.L., Nicolau B. Periodontal diseases and risk of oral cancer in Southern India: results from the HeNCe Life study. *Int. J. Canc.* 2016;139:1512–1519. doi: 10.1002/ijc.30201. [PubMed] [CrossRef] [Google Scholar]

3. Sharma S., Satyanarayana L., Asthana S., Shivalingesh K.K., Goutham B.S., Ramachandra S. Oral cancer statistics in India on the basis of first report of 29 population-based cancer registries. *J. Oral Maxillofac. Pathol.* 2018;22:18–26. doi: 10.4103/jomfp.JOMFP_113_17. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

4. Veluthattil A., Sudha S., Kandasamy S., Chakkalakkoombil S. Effect of hypofractionated, palliative radiotherapy on quality of life in late-stage oral cavity cancer: a prospective clinical trial. *Indian J. Palliat. Care.* 2019;25:383. doi: 10.4103/IJPC.IJPC_115_18. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

5. Ajay P., Ashwinirani S., Nayak A., Suragimath G., Kamala K., Sande A., Naik R. Oral cancer prevalence in Western population of Maharashtra, India, for a period of 5 years. *J. Oral Res. Rev.* 2018;10:11. doi: 10.4103/jorr.jorr_23_17. [CrossRef] [Google Scholar]

6. Singh M., Prasad C.P., Singh T.D., Kumar L. Cancer research in India: challenges & opportunities. *Indian J. Med. Res.* 2018;148:362–365. doi: 10.4103/ijmr.IJMR_1711_18. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

7. Varshitha A. Prevalence of oral cancer in India. *J. Pharmaceut. Sci. Res.* 2015;7:845–848. [Google Scholar]

8. Gupta S., Gupta R., Sinha D.N., Mehrotra R. Relationship between type of smokeless tobacco & risk of cancer: a systematic review. *Indian J. Med. Res. Suppl.* 2018;148:56–76. doi: 10.4103/ijmr.IJMR_2023_17. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

9. Asthana S., Patil R.S., Labani S. Tobacco-related cancers in India: a review of incidence reported from population-based cancer registries. *Indian J. Med. Paediatr. Oncol.* 2016;37:152–157.

doi: 10.4103/0971-5851.190357. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

10. Kadashetti V., Shivakumar K., Chaudhary M., Patil S., Gawande M., Hande A. Influence of risk factors on patients suffering from potentially malignant disorders and oral cancer: a case-control study. *J. Oral Maxillofac. Pathol.* 2017;21:455–456. doi: 10.4103/jomfp.JOMFP_236_14. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

11. Malik A., Mishra A., Garg A., Shetty R., Mair M., Chakrabarti S., Nair D., Balasubramaniam G., Chaturvedi P. Trends of oral cancer with regard to age, gender, and subsite over 16 years at a tertiary cancer center in India. *Indian J. Med. Paediatr. Oncol.* 2018;39:297. doi: 10.4103/ijmpo.ijmpo_6_17. [CrossRef] [Google Scholar]

12. Murugesan A. Sabarinath, Sivapathasundharam, Awareness of oral cancer among medical students in Chennai. *J. Med. Radiol. Pathol. Surg.* 2016;2:18–22. doi: 10.15713/ins.jmrps.58. [CrossRef] [Google Scholar]

13. Singh V., Singh A.K., Dutta K.D., Kumar N., Kumari A. Evaluation of quality of life and the nutritional status of oral cancer treated patients as compared with the control group in Varanasi district: a cross sectional study. *Int. J. Community Med. Public Heal.* 2019;6:4804. doi: 10.18203/2394-6040.ijcmph20195059. [CrossRef] [Google Scholar]

14. Thavarool S.B., Muttath G., Nayanar S., Duraisamy K., Bhat P., Shringarpure K., Nayak P., Tripathy J.P., Thaddeus A., Philip S., Satheesan B. Improved survival among oral cancer patients: findings from a retrospective study at a tertiary care cancer centre in rural Kerala, India. *World J. Surg. Oncol.* 2019;17:1–7. doi: 10.1186/s12957-018-1550-z. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

15. Oral cancer screening in Mumbai, India by primary health care workers. https://clinicaltrials.gov/ct2/show/NCT00655421 Full Text View - ClinicalTrials.gov, (n.d.)

16. Vivek Borse, Aditya Narayan Konwar, Pronamika Buragohain. Oral cancer diagnosis and perspectives in India. Elsevier – PMC COVID- 19. 2020. doi: 10.1016/j.sintl.202

RETINOBLASTOMA

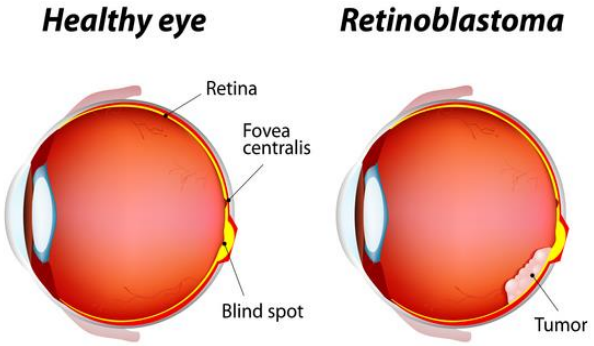
Ms. Sharayu Buchude, Dr. Ramesh Katedeshmukh
Department of Pharm D : Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune.

ABSTRACT

Retinoblastoma is the most common neoplasm of the eye in childhood and represents 3% of all childhood malignancies. Retinoblastoma is a cancer of eye found in very young children; two-thirds of these children are diagnosed before 2 years of age and 95% before 5 years of age. Retinoblastoma is present in two distinct clinical forms: (1) a bilateral or multi-focal, heritable form which is found in almost 25% of all the cases characterized by the presence of germline mutations of the RB1 gene; and (2) a unilateral or uni-focal form which comprises about 75% of the cases, 90% of which are nonhereditary. *RB1* deficiency makes the retinoblastoma cell-of-origin extremely susceptible to cancerous transformation, and the tumor cell-of-origin appears to depend on the developmental stage and species. Mutations or changes in the retinoblastoma 1 (RB1) gene is the most important risk factor for retinoblastoma.The earliest and most common symptom of retinoblastoma is the pupil of your eye appearing white (leukocoria) or pale-coloured in certain settings, especially seen in photos taken in dim places that also use a flash for illumination. It can happen in one or both eyes. Common *retinoblastoma treatments* include chemotherapy, cold therapy and laser therapy. Radiation therapy may be another option. The treatment of retinoblastoma is multidisciplinary and is designed primarily to save life and preserve vision.

INTRODUCTION

Retinoblastoma (An eye cancer that begins in the back of the retina) is a malignant tumour of the developing retina that occurs in children, usually before five years of age. It is an uncommon type of malignancy occurring in 1 per 18000 (0.0056%) childbirths. It is the most commonly encountered primary intraocular malignancy of childhood and accounts for 3% of cases of all childhood cancers. It is also the second most prevalent intraocular malignant tumour after uveal melanoma. About 60% of affected individuals have unilateral retinoblastoma with a mean age of diagnosis of 24 months and about 40% have bilateral retinoblastoma with a mean age of diagnosis of 15 months. It affects the light sensitive cell and optic nerve invasion can occur with the spread of tumour in subarachnoid space and into the brain. Metastatic spread occurs in regional lymph nodes, liver, lungs, bones, and brain.[1][3]



HISTORY

Pawius of Amsterdam is credited as the first to recognize retinoblastoma in an autopsy of a young child in 1597. In 1809, Wardrop referred to the tumour as fungus hematodes and suggested enucleation as the primary mode of management. The introduction of the ophthalmoloscope in 1851 facilitated the recognition of specific clinical features of retinoblastoma. Initially thought to be derived from the glial cells, it was called a glioma of the retina by Virchow (1864). Flexner (1891) and Wintersteiner (1897) believed it was a neuroepithelioma because of the presence of rosettes. Later, the consensus was reached that the tumor originated from the retinoblasts and subsequently the American Ophthalmological Society officially accepted the term retinoblastoma in 1926. Early tumor recognition aided by indirect ophthalmoscopy and refined enucleation techniques contributed to improved survival from 5% in 1896 to 81% in 1967. Advances in external beam radiotherapy in the 1960s and 1970s and further progress in planning and delivery provided an excellent alternative to enucleation, that enabled salvaging the eye. Focal therapeutic measures such as cryotherapy, photocoagulation and plaque

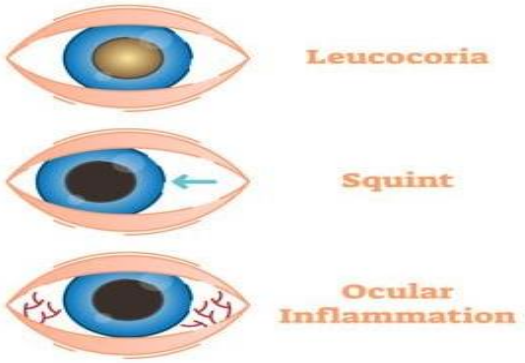
brachytherapy allowed targeted treatment of smaller tumors that saved vision.

ETIOLOGY

Retinoblastoma occurs as a result of a mutation in the RB1 tumour suppressor gene located at the long arm of chromosome 13 at locus 14. This gene is responsible for regulating the cell cycle so that cell augmentation proceeds in a planned and controlled fashion. It also helps to control cell survival, programmed cell death and cell differentiation.[2]*RB1* mutations lead to the wild and erratic division of a single cell in the retina, which becomes a retinoblastoma. This may be influenced by other genetic changes which facilitate the persistence of this cancerous change.

HERITABLE

Every cell in the body has germinal mutations, which can be inherited or spread.These cells lack one normal *RB1* gene already, having been derived



from a parent with one abnormal copy of the gene. This is called autosomal dominant inheritance. only 25% of children with heritable mutations have a positive family history. Merely 25% of offspring possessing heritable mutations exhibit a favorable familial background. The remaining ones result from a de novo germline mutation, which is the result of inheriting an RB1 gene copy that is faulty from a parent who did not get the illness.[5]

NON-HERITABLE

Non-germinal mutations are found in 60% of retinoblastomas and occur only in the cancerous cells. They are therefore not passed on to succeeding generations. There is no family history of the disease. In these individuals as well, the cells are initially normal. Early in life, both normal copies of the *RB1* gene undergo mutation within the retinal cells, rendering the genes useless. The tumor usually develops in one eye.[4]

EPIDEMEOLOGY

Retinoblastoma represents 3% of all children's tumors and is the most frequently occurring primary intraocular tumor. It is also the second most common intraocular malignant tumour. The number of retinoblastoma cases ranges from 1 in 14000 to 1 in 20000 live births.[7] Three hundred new cases occur in the US per year. Retinoblastoma occurs equally in both sexes, and there is no sexual preference. Ninety percent of the cases present before the age of three years. The disease has varying incidence throughout different geographic regions. According to research, there are four instances per million in the US and six cases per million in Mexico. Incidence is higher in Africa and India.[6]

TYPES OF RETINOBLASTOMA

1. **Unilateral**: This means "one-sided," so it affects one eye only.
2. **Bilateral**: This means "two-sided," so it affects both eyes.
3. **Trilateral**: This means you have cancer in three places. Each eye reflects one of those places. The third place is in the pineal gland inside your brain. [2]

CLINICAL PRESENTATION

- White or red pupil instead of the normal black.
- Misaligned eyes looking toward the ear or nose.
- Reddened, painful eye.
- Enlarged pupil.
- Different-coloured irises.
- Poor vision.

EVALUATION

- **Direct Ophthalmoscopy**: Red reflex testing with a direct ophthalmoscope is the simplest test, and leukocoria is easily observable. This method serves as a simple screening test. [8]
- **Examination Under Anaesthesia** : Examination under anaesthesia is necessary

for measuring the corneal diameter, for tonometry, anterior chamber examination with a hand-held slit lamp, fundoscopy, cycloplegic refraction, and documenting all findings.

- **Ultrasound: to** assess the size of the tumour, to observe calcifications, and it also helps to rule out similar conditions like coats disease.
- **Wide-Field Photography**: Wide-field photography is used for analysis, documentation, and helps in the management of retinoblastoma.
- **CT SCAN:** CT scans help in the detection of calcifications, but due to radiation risks, it is avoided upon making the primary diagnosis.
- **MRI:** MRI is useful in the evaluation of optic nerve, extraocular extension, pineoblastoma, and to exclude similar diseases.[9]
- **Systemic Assessment: This** includes physical examination, MRI orbit and brain, bone scan, bone marrow aspiration, and lumbar puncture.
- **Genetic Studies**: Genetic studies of blood samples and tumour tissue from patient and relatives.[3][8]

TREATMENT

- **CHEMOTHERAPY**: Intravenous carboplatin, etoposide, and vincristine are used in three to six cycles depending upon the grade of retinoblastoma. Single carboplatin or dual agent therapy can also be used and has shown favourable results in selective patients such as bridging therapy to avoid aggressive measures. Intravitreal melphalan is used in cases of vitreous seeding although it carries a small risk of extraocular dissemination.

- **TTT (Transpupillary Thermal Therapy):** It is used mostly for focal consolidation after chemotherapy; however, it can be used as an isolated treatment. TTT has a direct effect but also augments the effects of chemotherapy.[4]

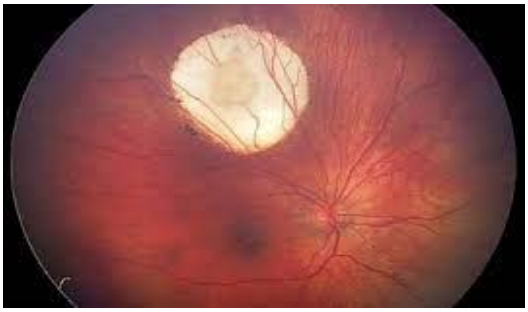
- **CRYOTHERAPY:** The triple freeze-thaw technique is an option for pre-equatorial tumours without deeper invasion or vitreous seedings.

- **BRACHYTHERAPY:** It is used for an anterior tumour when there is no vitreous seeding and in cases of resistance to chemotherapy.

- **RADIOTHERAPY:** It should be avoided, when possible, especially in the case of heritable retinoblastoma because it can result in a second malignancy. Retinoblastomas are radiosensitive, but adverse effects include cataract, radiation neuropathy, radiation retinopathy, and hypoplasia of orbit. [10]

- **SURGERY:** Enucleation is performed when there is infiltration of the anterior chamber, neovascular glaucoma, invasion of the optic nerve, and if the tumour comprises more than half of the vitreous volume. Additionally, it is helpful in situations of diffuse retinoblastoma, which has a poor visual prognosis and a significant chance of recurrence, and when chemotherapy has failed.

- **EXTRAOCULAR EXTENSION:** Adjuvant chemotherapy for 6 months is given following enucleation when there is retrolaminar or massive choroidal spread. When the extension of the tumour is up to the cut end of the optic nerve at enucleation, or it is through the sclera, then external beam radiation is used.[9]



PROGNOSIS

Patients with intraocular retinoblastoma, particularly those who have access to modern health care facilities, have an excellent prognosis and an overall survival rate of more than 95% in developed countries. The most critical risk factor associated with poor prognosis is extraocular extension either through the sclera or through the invasion of the optic nerve. Patients who survive bilateral retinoblastoma are at an increased risk of developing non-ocular malignancies later in life, the

latent period for the development of the second tumor is usually 9 months. External beam radiotherapy decreases the latent period and increases the risk of the second malignancy in the first 30 years of life. The most prevalent type of second malignancy is a sarcoma. The survival of patients who have developed sarcoma is less than 50%.

REFERENCES

1. Mattosinho CCS, Moura ATMS, Oigman G, Ferman SE, Grigorovski N. Time to diagnosis of retinoblastoma in Latin America: A systematic review. Pediatr Hematol Oncol. 2019 Mar;36(2):55-72. [PubMed]

2. Alkatan HM, Al Marek F, Elkhamary S. Demographics of Pediatric Orbital Lesions: A Tertiary Eye Center Experience in Saudi Arabia. J Epidemiol Glob Health. 2019 Mar;9(1):3-10. [PMC free article] [PubMed]

3. Kletke SN, Feng ZX, Hazrati LN, Gallie BL, Soliman SE. Clinical Predictors at Diagnosis of Low-Risk Histopathology in Unilateral Advanced Retinoblastoma. Ophthalmology. 2019 Sep;126(9):1306-1314. [PubMed]

4. Zahn J, Chan MP, Wang G, Patel RM, Andea AA, Bresler SC, Harms PW. Altered Rb, p16, and p53 expression is specific for porocarcinoma relative to poroma. J Cutan Pathol. 2019 Sep;46(9):659-664. [PubMed]

5. House RJ, Hsu ST, Thomas AS, Finn AP, Toth CA, Materin MA, Vajzovic L. Vascular Findings in a Small Retinoblastoma Tumor Using OCT Angiography. Ophthalmol Retina. 2019 Feb;3(2):194-195. [PMC free article] [PubMed]

6. Darwich R, Ghazawi FM, Rahme E, Alghazawi N, Burnier JV, Sasseville D, Burnier MN, Litvinov IV. Retinoblastoma Incidence Trends in Canada: A National Comprehensive Population-Based Study. J Pediatr Ophthalmol Strabismus. 2019 Mar 19;56(2):124-130. [PubMed]

7. Liu Z, Yang Q, Cai N, Jin L, Zhang T, Chen X. Enigmatic Differences by Sex in Cancer Incidence: Evidence From Childhood Cancers. Am J Epidemiol. 2019 Jun 01;188(6):1130-1135. [PubMed]

8. Shafiq A. Seeing red in young children: the importance of the red reflex. Br J Gen Pract. 2015 Apr;65(633):209-10. [PMC free article] [PubMed]

9. Jenkinson H. Retinoblastoma: diagnosis and management--the UK perspective. Arch Dis Child. 2015 Nov;100(11):1070-5. [PubMed]

10. Elaraoud I, Ch'ng S, Karl D, Kalogeropoulos D, Chavan R, Sharma A. Management of retinal detachment in retinoblastoma with globe conserving treatment. J Curr Ophthalmol. 2019 Mar;31(1):43-48. [PMC free article] [PubMed]

MYELODYSPLASTIC SYNDROME

Ms. Gauri Gawande, Ms Dhanashri Sonavane, Dr. Devendra Shirode

Department of Pharmacology, Dr D Y Patil College of Pharmacy Akurdi, Pune

ABSTRACT

Myelodysplastic anaemia is a clonal hematopoietic stem cell disease characterized by peripheral cytopenia, bone marrow (BM) dysplasia, and inefficient hematopoiesis, as well as a predisposition to leukemia. They are frequently found in the elderly, with the median age upon diagnosis ranging between 60 and 75 years in most series. The natural history of these diseases varies from relatively benign clonal bone marrow abnormalities (refractory anemias with or without ring sideoblasts) to variants that rapidly progress to AML (Acute myeloid leukemia). Basically, this illness is caused by a variety of factors, including the acquisition of distinctive chromosomal abnormalities, aging, exposure to dangerous chemicals, and cancer therapy. The main methods of diagnosis include CBC count, bone marrow aspiration and biopsy, and immunochemistry. Currently, the FDA has granted authorization for Azacitidine, decitabine, and lenalidomide for MDS. Other therapeutic options include transfusion therapy, bone marrow transplant, stem cell transplant, and erythropoiesis-stimulating drugs. Treatment outcomes and innovative treatment techniques employing immune regulation, as well as the role of the immune system in potential pathways responsible for genetic instability in MDS. The primary aims of treatment myelodysplastic syndromes are to alleviate symptoms, prevent the condition from progressing, and avoid complications.

Medications to increase the synthesis of red blood cells and blood transfusions are common interventions. It may be necessary in some circumstances to replace your own bone marrow with healthy bone marrow from a donor through a bone marrow transplant, sometimes referred to as a stem cell transplant.

MYELODYSPLASTIC SYNDROMES

Myelodysplastic syndromes are cancers caused by immature bone-marrow blood cells that do not grow into healthy cells. Alternatively known as "bone marrow failure disorder"[1]. MDS is a diverse collection of hematologic neoplasms that are typically defined as a clonal disease of hematopoietic stem cells that causes dysplasia and inefficient hematopoiesis in the bone marrow.[6]

Myelodysplastic syndromes are a collection of conditions brought on by malformed or malfunctioning blood cells and abnormalities in the bone marrow, the spongy substance found inside your bones that is where blood cells are created.[3]

Acute myeloid leukemia (AML) can develop from myelodysplastic syndromes (MDS), which are clonal hematopoietic stem cell illnesses characterized by peripheral cytopenia, bone marrow (BM) dysplasia, and inefficient hematopoiesis. The pathobiology of MDS is a complicated condition with a diverse molecular base, and the molecular processes behind it are currently poorly understood. Genetic variants (GVs) in the genes known to be connected to the onset of MDS are present in about 90% of patients. On the other hand, single nucleotide variants (SNVs) are typically reported in genetic research on MDS, although insertions and deletions (indels) are seldom reported.

A myelodysplastic syndrome occurs when blood stem cells (immature cells) in the bone marrow do not mature into grow red blood cells, white blood cells, or platelets. These immature blood cells, known as blasts, do not function properly and perish either in the bone marrow or shortly after entering the bloodstream. This reduces the capacity of the bone marrow to produce healthy white blood cells, red blood cells, and platelets. Infection, anemia, or easy bleeding may result from a lack of healthy blood cells.[1]

The bone marrow produces immature blood stem cells, which eventually develop into adult blood cells in a healthy individual.

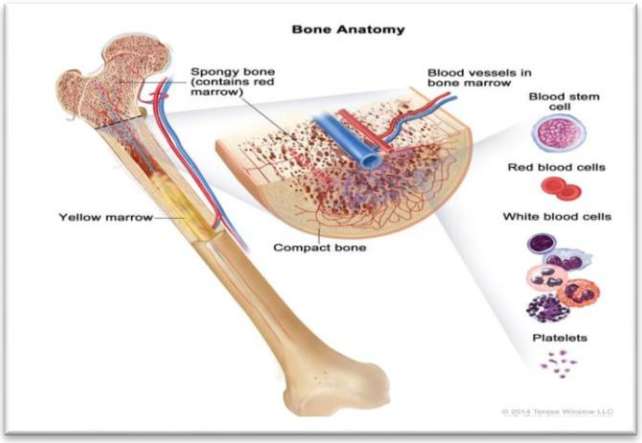


Fig:1

The structure of bones. The bone is made up of bone marrow, spongy bone, and compact bone. Spiky bones, which are often found close to the extremities of bones, can display red marrow. Bone marrow, found in most bones, is densely packed with blood vessels. There are two types of bone marrow: red and yellow. Red marrow contains blood stem cells, which can differentiate into platelets, white blood cells, or red blood cells. The main component of yellow marrow is fat.[1]

CAUSES

MDS is caused by DNA abnormalities in blood cells, often known as mutations. Most people do not inherit these modifications. They happen over a person's lifetime, not all at once.
The exact reason why some people experience these changes whereas others do not is unknown. some circumstances enhance a person's chances of having MDS. We refer to them as risk factors.
Even if there is a little increase in risk owing to these variables, anybody can have MDS, and it is not your fault. The majority of MDS patients do not have an identified cause or trigger.[9]

1. **Age**: MDS can be diagnosed at any age, although it is more frequent in those over the age of 75. Nine out of ten individuals over 50 have MDS and it is uncommon in young adults and children.

2. **Prior cancer therapy:** Previous radiation or chemotherapy treatments may have damaged the bone marrow, contributing to MDS. We call this therapy-related or secondary MDS.

3. **Inherited illnesses**: MDS can occasionally be caused by another rare genetic disorder or be inherited. If doctor believes MDS is hereditary, he or she will refer you to a genetics agency to determine the risk that additional family members will also have the disease. However, MDS is not an inherited genetic disorder, and it is seldom passed down to kids.

4. **Additional blood disorders:**
a. Clonal hemopoiesis of unclear significance (CHIP) is a disorder in which genetic changes occur in otherwise healthy blood cells.
b. Idiopathic cytopenia of uncertain significance (ICUS) is a disorder in which one or more blood cell types are absent without a clear explanation.
c. Clonal cytopenia of unknown significance (CCUS) is a disorder characterized by genetic changes in blood cells as well as low amounts of one or more blood cell types that have no obvious reason.

5. **Exposure to harmful substances:**
Extended exposure to certain substances may raise the chance of developing MDS. Tobacco smoke contains benzene. Benzene is also utilized in several manufacturing process, however regulations now prohibit workers from being exposed to dangerously high concentrations of the chemical.[9]
MDS has been related to a variety of environmental and iatrogenic causes, including radiation, chemotherapy (particularly alkylating medications).

6. Researchers can currently find one or more driver mutations in 80% to 90% of patients, with the most common being SF3B1, TET2, SRSF2, ASXL1, DNMT3A, RUNX1, U2AF1, TP53, and EZH2. RUNX1, for example, is a recognized mutation that affects normal hematopoiesis. MDS has around 100 recurrently changed genes that encode spliceosome components, chromatin remodeling proteins, epigenetic pattern modulators, and transcription factors. These driver mutations have been associated with a wide range of clinical characteristics, including cytopenia severity, blast percentage, cytogenetics, and overall survival.

PATHOPHYSIOLOGY:

- MDS can be caused by environmental exposure to toxins like benzene, radiation, or past treatment to chemotherapeutic medicines. It can also be idiopathic, particularly in the elderly. Bone marrow failure disorders such as acquired aplastic anemia and Fanconi anemia increase the likelihood of developing MDS and can occasionally resemble it. MDS can develop spontaneously or as a result of other causes, which is referred to as treatment-related MDS. Chemotherapeutic drugs like as alkylators and topoisomerase II inhibitors have been identified as recognized causes of MDS, which typically occurs 2 to 7 years following exposure.

- More than 80% of patients exhibit cytogenetic abnormalities, such as translocations or, more typically, aneuploidy (chromosome loss or increase). The most prevalent aberrant karyotype is deletion of the long arm of chromosome 5 (5q), which may be classified into two types: treatment-related MDS with 5q deletion, which is typically associated with exposure to alkylating drugs, and de novo isolated 5q deletion. Patients with 5q deletion caused by past chemotherapeutic drugs are more likely to have additional cytogenetic abnormalities and TP53 mutations, which typically indicate a bad prognosis. Isolated 5q deletion without additional cytogenetic abnormalities results in a much better prognosis. Other frequent cytogenetic anomalies are normal karyotype, deletion 7q (-7), trisomy 8, and -Y.

- Over 100 somatic point mutations have been linked to MDS, and there is considerable overlap with AML. The most prevalent somatic mutations are in TET2, SF3B1, ASXL1, DNMT3A, SRSF2, RUNX1, TP53, U2AF1,EZH2, ZRSR2, STAG2, CBL, NRAS, JAK2, SETBP1, IDH1, IDH2, and ETV6. These mutations have been found to connect with a variety of characteristics. TP53 mutations are associated with complicated cytogenetics and poor overall survival. RUNX1 and TP53 are associated with poorer thrombocytopenia. TET2 mutations respond well to hypomethylating drugs.[2]

SYMPTOMS:

Individuals with myelodysplastic syndromes may not initially exhibit symptoms.

In time, myelodysplastic syndromes might cause:

- Fatigue
- Shortness of breath.
- Unusual paleness (pallor) caused by decreased red blood cell count (anemia)
- Low blood platelet count (thrombocytopenia) causes easy or uncommon bruising and bleeding.
- Petechiae are pinpoint-sized red patches beneath the skin produced by bleeding.
- Frequent infections caused by a low white blood cell count (leukopenia).
- Feeling weak or exhausted.[9]

TYPES OF MYELODYSPLASTIC SYNDROMES

The World Health Organization classifies myelodysplastic syndromes into subcategories based on the kind of blood cells involved (red cells, white cells, and platelets).

Myelodysplastic syndrome subgroups include the following categorization of MDS by WHO (2016):

1. **MDS with dysplasia** of anyone blood cell, such as platelets, red blood cells, or white blood cells.

2. **Myelodysplastic disorders with multilineage dysplasia:** This subtype have two or three aberrant blood cell types.

3. **Myelodysplastic syndromes with ring sideoblasts:** This subtype include a small number of one or more blood cell types. One distinguishing aspect is the presence of extra iron rings in existing red blood cells in the bone marrow.

4. **Myelodysplastic disorders with a single del(5q) chromosomal defect:** People with this subtype have a low amount of red blood cells, which contain a unique mutation in their DNA.

5. **Myelodysplastic disorders with excessive blasts:** In this subtype, any of the three kinds of blood cells red blood cells, white blood cells, or platelets may be low and seem abnormal under a microscope. The blood and bone marrow contain very young blood cells known as blasts.

6. **Myelodysplastic disorders unclassifiable:** This subtype has a lower amount of one or more kinds of mature blood cells, and the cells may seem aberrant under a microscope. Sometimes blood cells look normal, but investigation may reveal DNA alterations linked with myelodysplastic syndromes.

7. **Myelodysplastic/myeloproliferative neoplasm, unclassifiable:** There are also many other overlap syndromes with myeloproliferative and myelodysplastic features, such as chronic myelomonocytic leukemia (CMML), atypical chronic myeloid leukemia (CML), and juvenile myelomonocytic leukemia (JMML)[2]

RISK FACTORS

1) **Older age.** Mostly older than 60 are affected

2) **Previous treatment with chemotherapy or radiation.** Chemotherapy or radiation treatmen itelf may risk of myelodysplastic syndromes.

3) **Exposure to certain chemicals.** Chemicals, including benzene, have been linked to myelodysplastic syndromes [9]. Exposure with tobacco smoke, fertilizers also cause MS.

4) **Exposure to heavy metals** like Mercury and Lead [10]

5) Cancer therapy: You can get this condition 1 to 15 years after having specific types of chemotherapy or radiation. Doctor or nurse may refer to this as "treatment-related MDS." Patient may be more prone to develop MDS after being treated for acute lymphocytic leukemia in infancy, Hodgkin's disease, or non-Hodgkin's lymphoma.[11]

6) Cancer medications associated to MDS include:

- Chlorambucil (Leukeran)
- Cyclophosphamide
- Doxorubicin (Adriamycin)
- Etoposide (Etopophos)
- Ifosfamide (Ifex)
- Mechlorethamine (Mutagen)
- Melphalan (Alkeran)
- Procarbazine (Matulane)
- Teniposide

7) Inherited problems: Certain disorders passed down from parents and enhance risk of developing myelodysplastic syndrome. This includes:

- Down syndrome: Also known as trisomy 21, children with this condition are born with an extra chromosome, which can impair mental and physical development.
- Fanconi anemia: This disorder occurs when the bone marrow fails to produce adequate amounts of all three kinds of blood cells.
- Bloom syndrome: People with this ailment are rarely taller than 5 feet and are prone to skin rashes from sunshine.
- Ataxia telangiectasia: This has an effect on both the neurological and immunological systems. Children who have it have difficulty walking and maintaining balance.
- Schwachman–Diamond syndrome: This prevents the body from producing enough white blood cells.

8) Blood disorders: Individuals who have a history of blood disorders are more susceptible to MDS. Among them are:

- Paroxysmal nocturnal hemoglobinuria: This potentially fatal condition affects platelets, which aid in blood clotting, white blood cells, which fight infection, and red blood cells, which deliver oxygen.
- Congenital neutropenia: Individuals with this condition are more susceptible to infections

because they are deficient in a certain type of white blood cell.[11]

COMPLICATIONS

Complications of myelodysplastic syndromes include:

1. **Anaemia:** Anaemia, which is characterized by a decrease in red blood cell counts, might make patient feel exhausted.

2. **Recurrent infections:** Patient run a higher risk of developing serious infections if patient white blood cell count is low.

3. **Uncontrollably bleeding:** Excessive bleeding may result from a lack of platelets in the blood to halt the bleeding.

4. **An elevated cancer risk:** Certain individuals with myelodysplastic syndromes may eventually develop leukemia, or cancer of the blood and bone marrow.[9]

DIAGNOSIS

A physical exam, medical history and tests might be used if doctor suspects that you have a myelodysplastic syndrome. Tests might include In addition to asking about personal and family health history and doing a physical exam, doctor may perform the following tests and procedures:

1. **Complete blood count with Differential (CBC):** A procedure in which a sample of blood is drawn and checked for the following:

   - Red blood cells and platelets count.
   - The kind and quantity of white blood cells
   - How much of the oxygen-carrying protein hemoglobin is present in red blood cells.[1]

2. **Peripheral blood smear:** A process where a sample of blood is examined to look for abnormalities in the quantity, kind, size, and shape of blood cells as well as for excessive iron levels in the red blood cells.[1]

3. **Cytogenetic analysis:** a lab test where cells in a bone marrow or blood sample have their chromosomes counted and examined for any abnormalities, such as damaged, missing, altered, or additional chromosomes. Cytogenetic analysis is a useful tool for cancer diagnosis, treatment planning, and monitoring response to therapy. [1]

4. **Blood chemistry studies**: A process where a blood sample is examined to determine the levels of specific chemicals released into the blood by the body's organs and tissues, like vitamin B_{12} and folate. A substance's unexpected concentration either higher or lower than usual may indicate a medical condition. [1]

5. **Bone marrow aspiration and biopsy:** Myelodysplastic disorders are diagnosed by blood and bone marrow tests.: a small area of skin is numbed; a bone marrow needle is inserted into the patient's hip bone. Bone, blood and bone marrow samples are collected for aspiration and biopsy.

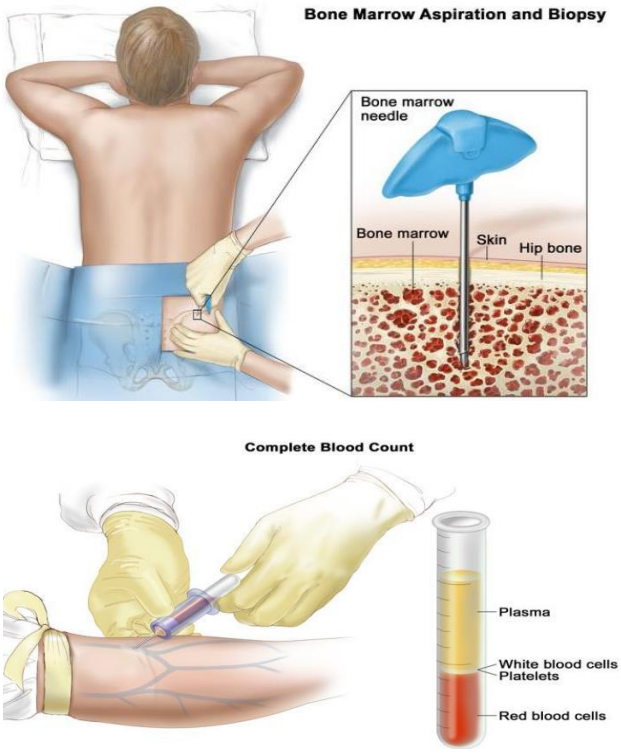


Fig: 3.1The removal of bone marrow, blood, and a tiny piece of bone using a hollow needle inserted into the hipbone or breastbone. A pathologist examines the bone marrow, blood, and bone using a microscope to check for aberrant cells. Removing bone marrow for testing. During a bone marrow biopsy and aspiration, a tiny needle is used to remove (aspirate) a little quantity of liquid bone

marrow, often from the back of hipbone. Then a little piece of bone with its marrow is extracted (biopsy). [1]

6. **Blood tests**. Doctor may request blood tests to count the quantity of red cells, white cells, and platelets, as well as to search for unexpected changes in the size, shape, and appearance of different blood cells.

7. **Blood and bone marrow samples are sent for laboratory analysis.** Specialized tests can identify the exact properties of cells, which will aid in evaluating the kind of myelodysplastic syndrome prognosis, and treatment choices.[1]

THE FOLLOWING TESTS MAY BE DONE ON THE SAMPLE OF TISSUE THAT IS REMOVED:

1. **Immunocytochemistry:** A laboratory test that employs antibodies to detect certain antigens (markers) in a patient's bone marrow. Antibodies are typically coupled to enzymes or fluorescent dyes. After the antibodies attach to the antigen in the patient's cell sample, the enzyme or dye is triggered, allowing the antigen to be viewed under a microscope. This sort of test is used to identify cancer and distinguish between myelodysplastic syndromes, leukemia, and other diseases. [1]

2. **Immunophenotyping:** A laboratory test that employs antibodies to detect cancer cells based on the antigens or markers present on their surfaces[1].

3. **Flow cytometry:** A laboratory test that determines the number of cells in a sample, the proportion of living cells, and cell properties such as size, shape, and the presence of tumor (or other) markers on the cell surface. Cells from a patient's blood, bone marrow, or other tissue are dyed with a fluorescent dye, suspended in a fluid, and passed one at a time via a light beam. The test results are based on how fluorescently dyed cells react to light. This test is used to help identify and treat some forms of cancer, including leukaemia and lymphoma.[1]

FISH (Fluorescence In Situ Hybridization): A lab test used to examine and quantify genes or chromosomes in cells and tissues. Laboratory-created fluorescent dye-containing DNA is added to a sample of a patient's cells or tissues. When these colored DNA fragments bind to certain genes or chromosomal regions in the sample, they glow up under a fluorescent microscope. The FISH test helps identify cancer and arrange therapy.[1]

TREATMENT

Drug therapy, supportive care and stem cell transplantation is require treating myelodysplastic syndromes. Supportive care is provided to patients with myelodysplastic syndrome who experience low blood count symptoms. In some cases, intensive therapy with chemotherapy followed by stem cell transplant from a donor can cure the disease.

The following types of treatment are used:

1. **Transfusion therapy**: Transfusion therapy (blood transfusion) is the process of replacing red blood cells, white blood cells, or platelets that have been damaged by disease or treatment. A red blood cell transfusion is administered when the red blood cell count is low and signs or symptoms of anemia, such as shortness of breath or extreme fatigue, arise. A platelet transfusion is often administered when a patient is bleeding, undergoing a surgery that may induce bleeding, or has a very low platelet count.

2. Patients who get a large number of blood cell transfusions may experience tissue and organ damage as a result of iron overload. These individuals may be treated with iron chelation treatment to eliminate excess iron from their bloodstream.[9]

3. **Erythropoiesis-stimulating agents**: Erythropoiesis-stimulating agents (ESAs) can be used to enhance the amount of mature red blood cells produced by the body and reduce the symptoms of anemia. Granulocyte colony-

stimulating factor (G-CSF) is occasionally used in conjunction with ESAs to improve therapy efficacy.

4. Medications:

- **Increase the quantity of blood cells in body:** These drugs, known as growth factors, are artificial copies of chemicals present naturally in your bone marrow. Growth hormones that encourage bone marrow to produce more red blood cells can help you avoid frequent blood transfusions. Growth factors that increase white blood cell production may lower your risk of infection.

- **Encourage blood cells to develop:** Medications that increase the maturation of blood cells can lessen the need for frequent blood transfusions in persons who do not benefit from growth factors. Some of these medications may also lessen the likelihood that the condition may proceed to leukaemia.

- **Suppress immune system:** Certain myelodysplastic syndromes are treated with medications that inhibit or regulate the immune system, reducing the requirement for red blood cell transfusions.

- **Assist persons with a certain genetic abnormality:** If your myelodysplastic syndrome is linked to a gene mutation known as isolated del(5q), doctor may prescribe lenalidomide (Revlimid).

- **Treat infections:** If disease creates infections, patient will be treated for them. [9]

5. Bone Marrow Transplant:

A bone marrow transplant, also known as a stem cell transplant, is the only therapy that has the potential to cure myelodysplastic disorders. However, because of the high risk of catastrophic consequences, this treatment is normally reserved for patients who are in good enough condition to tolerate it.

During a bone marrow transplant, heavy dosages of chemotherapy medications are utilized to remove faulty blood cells from bone marrow. The defective bone marrow stem cells are then replaced with healthy donor cells (allogeneic transplantation).

In certain cases, less aggressive chemotherapy medicines can be used to lessen the hazards of bone marrow transplantation in older persons and those who would not normally be candidates for this treatment.[9,1,8.]

6. Drug Therapy:

1. Lenalidomide: Lenalidomide reduces the requirement for red blood cell transfusions in MDS[1]

7. Immunosuppressive therapy: Anti thymocyte globulin (ATG) suppresses or weakens the immune system. It helps to reduce the need for red blood cell transfusions.

2. Azacitidine and decitabine

Azacitidine and decitabine treat myelodysplastic syndromes by targeting quickly dividing cells. They also help genes involved in cell proliferation to function properly. Azacitidine and decitabine can decrease the development of myelodysplastic syndromes to acute myeloid leukemia.

8. Chemotherapy used in acute myeloid leukemia (AML):

Patients with myelodysplastic syndrome and a large number of blasts in their bone marrow are more likely to develop acute leukemia. They may get the same treatment regimen as individuals with acute myeloid leukemia.[6]

9. Chemotherapy with stem cell transplant:

To eliminate cancer cells, chemotherapy is administered. Stem cell transplant is a therapy that replaces blood-forming cells. Stem cells (immature blood cells) are harvested from the patient's or donor's blood or bone marrow and frozen for storage. After chemotherapy, the stored stem cells are thawed and returned to the patient via an infusion. These reinfused stem cells develop into (and replenish) the body's blood cells.

10. Donor stem cell transplant: (Step 1): Medication is implemented for donor prior 4-5 days of collection of stem cell from donor. The blood-forming stem cells are then harvested from the donor via a major vein in their arm. The blood passes through an apheresis machine, which extracts the stem

cells. The remaining blood is returned to the donor through a vein in their other arm. (Step 2): Cancer cells are eradicated using chemotherapy for adaptation of stem cell in receiver body. The patient may additionally be subjected to radiation therapy (not depicted). (Step 3): The patient gets an infusion of donor stem cells.[7]

11. **Tibsovo (ivosidenib)** has been granted by the FDA for the treatment of adult patients with relapsed or refractory (R/R) myelodysplastic syndromes (MDS) who have an isocitrate dehydrogenase-1 (IDH1) mutation as discovered by an FDA-approved test.[13]

REFERENCE:

1. https://www.cancer.gov/types/myeloproliferative/patient/myelodysplastic-treatment-pdq
2. Dotson JL, Lebowicz Y. Myelodysplastic Syndrome. [Updated 2022 Jul 18]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK534126/
3. https://www.mayoclinic.org/diseases-conditions/myelodysplastic-syndrome/symptoms-causes/syc-20366977
4. Bandara M, Goonasekera H, Dissanayake V. Identification of Novel Insertions and Deletions in Hematopoietic Stem/Progenitor Cells in de novo Myelodysplastic Syndromes. Int J Mol Cell Med. 2021 Summer;10(3):228-233. doi: 10.22088/IJMCM.BUMS.10.3.227. Epub 2022 Jan 10. PMID: 35178361; PMCID: PMC8800462.
5. https://emedicine.medscape.com/article/207347-overview?form=fpf#a5
6. Garcia-Manero, G., McCloskey, J., Griffiths, E. A., Yee, K. W. L., Zeidan, A. M., Al-Kali, A., Deeg, H. J., Patel, P. A., Sabloff, M., Keating, M. M., Zhu, N., O'Connell, C. L., Roboz, G. J., Busque, L., … Savona, M. R. (2024). Oral decitabine-cedazuridine versus intravenous decitabine for myelodysplastic syndromes and chronic myelomonocytic leukemias (ASCERTAIN): a registrational, randomized, crossover, pharmacokinetics, phase 3 study. *The Lancet. Hematology*, *11*(1), e15–e26. https://doi.org/10.1016/S2352-3026(23)00338-1
7. https://www.mayoclinic.org/diseases-conditions/myelodysplastic-syndrome/symptoms-causes/syc-20366977
8. https://my.clevelandclinic.org/health/diseases/6192-myelodysplastic-syndrome-myelodysplasia
9. https://bloodcancer.org.uk/understanding-blood-cancer/myelodysplastic-syndromes-mds/what-is-mds/what-causes-mds/
10. Alessandrino, Emilio Paolo, et al. "Myelodysplastic syndromes: recent advances." *hematological* 86.11 (2001): 1124-1157.
11. Gangat, Naseema, Mrinal M. Patnaik, and Ayalew Tefferi. "Myelodysplastic syndromes: contemporary review and how we treat." *American journal of hematology* 91.1 (2016): 76-89.
12. Greenberg, Peter L., Neal S. Young, and Norbert Gattermann. "Myelodysplastic syndromes." *ASH Education Program Book* 2002.1 (2002): 136-161.
13. Sochacka-Ćwikła, Aleksandra, Marcin Mączyński, and Andrzej Regiec. "FDA-approved drugs for hematological malignancies—the last decade review." *Cancers* 14.1 (2021): 87.

SKIN CANCER: CAUSES, SYMPTOMS, AND PREVENTION

Mr. Bhagwat Patil, Dr. Pallavi Chaudhari
Department of Pharmaceutics, Dr. D.Y. Patil College of Pharmacy, Akurdi, Pune

ABSTRACT

Skin cancer is one of the most common cancers worldwide, and its incidence has been steadily increasing over the last few decades. This article provides an overview of skin cancer, including its definition, types, risk factors, signs and symptoms, diagnosis, treatment, prevention, and new treatments. It emphasizes the importance of awareness about skin cancer and explores various ways to combat the disease, including drug therapy, herbal remedies and nanotechnology interventions. By understanding the causes and mechanisms of skin cancer, as well as effective prevention and treatment strategies, we can work to reduce its burden on public health.

INTRODUCTION

Skin cancer is a growth in skin cells due to irreparable DNA damage, usually due to exposure to ultraviolet (UV) electricity. It is the most common type of cancer worldwide, with millions of patients diagnosed every year. Despite major prevention efforts, breast cancer remains a major public health problem due to factors such as increased exposure to sunlight, lifestyle changes, and lack of awareness about prevention. [1][5]

This article focuses on various aspects of skin cancer, including its definition, types, risk factors, symptoms and causes, symptoms, diagnosis, treatment, prevention strategies, and new treatments. By spreading awareness about skin cancer, we hope to inspire people to take the necessary steps to prevent this disease and to seek research and treatment when necessary. [2]

SKIN CANCER DEFINITION AND MEANING

Skin cancer refers to abnormal growth of the skin, usually resulting from changes in the skin's DNA. These changes cause skin cells to multiply rapidly and form malignant tumors. There are many types of cancer; the most common are basal cell carcinoma, squamous cell carcinoma, and melanoma. Although some types of skin cancer are benign and easily treated if caught early, other types of skin cancer, such as melanoma, can still be very serious and life-threatening if not diagnosed and treated quickly. [3][4][5]

CAUSES SKIN CANCER

The main cause of skin cancer is long-term exposure to ultraviolet (UV) radiation from the sun or products such as a tanning bed. UV radiation can damage DNA in cells, causing mutations that can lead to cancer. Other risk factors for breast cancer include light skin and hair color, history of heat stroke, family medical history, and some genetic factors. [6]

TYPES OF SKIN CANCER

Skin cancer is generally divided into three types of cancer: basal cell carcinoma, squamous cell carcinoma, and melanoma. Basal cell carcinoma and squamous cell carcinoma are more common and often occur on areas of skin exposed to sunlight, such as the face, neck, and arms. Although melanoma is less common, it is more serious and can spread to other parts of the body if not treated early. Each type of cancer has different characteristics and treatments. [7][8][9]

1. BASAL CELL CARCINOMA

Basal cell carcinoma is the most common type of skin cancer, accounting for approximately 80% of all cases. It usually appears as a small, pearly or waxy bump on the skin and often shows veins. Basal cell carcinoma usually occurs in sun-exposed areas such as the face, neck, and hands, but it can occur anywhere on the body. Although basal cell carcinoma rarely spreads to other parts of the body, it can cause local tissue damage if left untreated. [8]

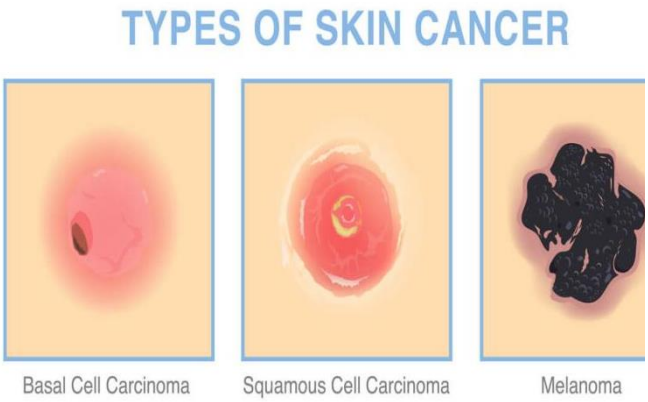
2. SQUAMOUS CELL CARCINOMA

Squamous cell carcinoma is the second most common type of skin cancer, accounting for approximately 20% of cases. It most often appears on the skin as red, scaly patches or hard, raised nodules, often with a crusty surface. Squamous cell carcinoma usually occurs in sun-exposed areas such as the face, ears, lips, and hands, but it can also occur on mucous membranes and scars. Although squamous cell carcinoma is less serious than

melanoma, it can metastasize to other parts of the body if left untreated. [9]

3. MELANOMA

Melanoma is the least common but most dangerous type of skin cancer, accounting for the majority of skin cancers. It originates from melanocytes, which are cells that produce melanin, the pigment that determines skin color. Melanoma usually appears as a new mole or as a variant of an existing mole that has irregular edges, uneven color, and is larger in size than the original. If not detected and treated early, melanoma can spread to other parts of the body, making treatment difficult and potentially fatal. [10]



MECHANISM OF PROGRESSION OF SKIN CANCER

1. Ultraviolet Radiation Exposure:

Ultraviolet (UV) radiation from sunlight is a major environmental risk factor for skin aging.

Ultraviolet radiation can damage DNA in cells, cause genetic mutations, and disrupt cell growth and division. Exposure to UV rays can cause skin changes. Key genes involved in cell cycle regulation, DNA repair, and apoptosis predispose cells to malignant transformation. [11][12]

2. Activation of oncogenic pathways:

Mutations in key genes such as BRAF, NRAS and PTEN can activate oncogenic signaling pathways that promote cell proliferation and survival. The MAPK signaling pathway, which is often dysregulated in melanoma, is activated by changes in the BRAF and NRAS genes, causing uncontrolled cell growth and tumor formation. The PI3K/AKT/mTOR pathway is regulated by PTEN and other tumor suppressor factors and plays a role in cell survival, metabolism and growth. [13]

3. Tumor suppressor gene inactivation:

Tumor suppressor genes play an important role in controlling cell growth, differentiation and apoptosis. Loss-of-function mutations or epigenetic silencing of tumor suppressor genes such as p53, CDKN2A (p16), and PTEN can promote uncontrolled cell proliferation and tumor growth. Inactivation of p53, known as the "genome guardian," "allows cells with DNA damage to escape apoptosis and accumulate further mutations, resulting in genome instability and negative mutations." leading to genomic instability and malignant transformation.[14][15][16]

4. Control of the cell cycle:

Changes in the cell cycle are tightly regulated by cyclin-dependent kinases (CDKs) and their inhibitors (CKIs) (such as p16 and p21). loss of CKI function can lead to uncontrolled cell proliferation and tumor formation, stimulating the existing vascular system to form new blood vessels. Angiogenesis provides the tumor with oxygen and nutrients necessary for growth and survival and promotes tumor spread to distant sites. [17][18]

5. Immune defense and tumor microenvironment:

tumor cells can inhibit the immune system by expressing antibodies such as PD-L1, inhibiting T cell activation and promoting immunity. The tumor microenvironment is characterized by immune cells such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) that limit the immune response of the tumor. The immune system allows cancer cells to escape from the damage caused by the immune system and develop an immune system. Permissive microenvironment for tumor growth and metastasis. [19]

6. Epithelial-mesenchymal transition (EMT):

Epithelial-mesenchymal transition (EMT) is a cellular process that provides mobility and effect to tissues. cancer. During EMT, epithelial cells lose intercellular adhesion and polarity and acquire a mesenchymal phenotype characterized by increased motility and invasiveness. EMT allows cancer cells to leave the tumor, invade surrounding tissue, and metastasize to distant organs, thereby promoting tumor growth and spread. [20]

RISK FACTORS

Some factors increase the risk of skin cancer, for example:

1. **Sun exposure**:

Prolonged exposure to ultraviolet (UV) rays Electricity is a major risk factor for skin diseases. UV radiation can damage DNA in cells, causing mutations that can lead to cancer. People who spend long periods outdoors without adequate sun protection are at greater risk of skin cancer. [21]

2. **Light skin and light hair:**

People with light skin, hair, and blue or green eyes have less melanin, the pigment that provides some protection against ultraviolet radiation. As a result, they are exposed to more sunlight than dark-skinned people and have a higher risk of developing cancer.

3. **Family History of Skin Cancer:**

Having a family history of skin cancer increases a person's risk of developing this disease. Genetic factors and genetic mutations can predispose some people to cancer, so regular skin examinations and early diagnosis are important for early intervention and treatment. [22]

SIGNS AND SYMPTOMS

It is important to know the signs and symptoms of skin cancer so that it can be diagnosed early and treated quickly. Signs and symptoms include:

1. **Changes in moles or birthmarks:**

A mole, also known as a nevus, is a skin growth that usually appears during childhood or adolescence. Although most moles are harmless, changes in their appearance may indicate the presence of skin cancer. It is important to monitor moles regularly and know the ABCDEs of melanoma: [23]

- **Asymmetry:** One half of the mole does not match the other half.
- **Irregular border**: The edges of the mole are irregular, jagged or blurred.
- **Color:** The color of the mole is not uniform, brown, black, red, white or blue.
- **Diameter**: The mole is more than 6 mm in diameter (about the size of a pencil) or continues to grow.
- **Evolution:** The size, shape, color or height of a mole changes.

If you notice a birthmark or birthmark change in the size, shape, color or texture of the mole, such as itching, tenderness or bleeding, you should consult a doctor for a dental examination. A dermatologist may perform a skin biopsy to determine whether these changes indicate cancer. [24]

2. **New growth or pain:**

New growth or pain that does not heal may be a sign of cancer. These growths may appear as nodules, bumps, or patches on the skin and may vary in size, shape, and color. They may also have ragged edges and bleed or scratch easily.

Types of skin cancer, such as basal cell carcinoma and squamous cell carcinoma, usually appear as new growths or lesions on areas of the body exposed to sunlight, such as the face, neck, hands and arms. These growths may start small but gradually grow larger over time.

If you notice a new growth or a sore that does not improve for several weeks, it is important to be evaluated by a doctor. dermatologist can perform a biopsy to determine if the growth is cancerous and recommend appropriate treatment if necessary.[25]

3. **Itching, Pain, or Bleeding:**

Skin cancer lesions may cause symptoms such as itching, pain, tenderness, or bleeding. These symptoms can vary depending on the type and location of the cancerous growth.

Basal cell carcinoma, for example, may cause itching or tenderness in the affected area, while squamous cell carcinoma may cause pain or discomfort. Melanoma lesions may be prone to bleeding, especially if they are irritated or traumatized.

It's essential not to ignore any unusual symptoms associated with skin lesions, as they may indicate a more serious underlying condition. If you experience persistent itching, pain, tenderness, or bleeding associated with a skin lesion, it's important to seek medical attention promptly. A dermatologist or oncologist can evaluate the symptoms and recommend appropriate diagnostic tests and treatment options.[26]

By being vigilant about changes in moles or birthmarks, monitoring new growths or sores, and paying attention to symptoms such as itching, pain, or bleeding, individuals can help detect skin cancer early and improve their chances of successful

treatment. Regular skin examinations by a healthcare professional are also recommended, especially for individuals with risk factors for skin cancer, such as a history of sun exposure or a family history of the disease.[27]

DIAGNOSIS AND TREATMENT

Early diagnosis and treatment are critical for the successful management of skin cancer. Common diagnostic and treatment modalities include.

1. Skin Biopsy:

A skin biopsy is the definitive method for diagnosing skin cancer. During this procedure, a dermatologist or surgeon numbs the area with a local anesthetic and removes a small sample of suspicious skin tissue. There are several types of skin biopsies, including:

- **Punch biopsy:** A circular tool is used to remove a small cylinder of skin tissue.
- **Shave biopsy:** A thin slice of tissue is shaved off the surface of the skin.
- **Excisional biopsy:** The entire suspicious area, along with a margin of surrounding healthy tissue, is removed.

The biopsy sample is then sent to a pathology laboratory, where it is examined under a microscope by a pathologist. The pathologist analyzes the tissue to determine if it contains cancer cells, the type of skin cancer present, and its characteristics, such as depth of invasion and involvement of surrounding tissue. The results of the biopsy help guide treatment decisions and determine the prognosis for the patient.[28]

2. Surgical Removal:

Surgical removal, or excision, is the primary treatment for most cases of skin cancer. During this procedure, the dermatologist or surgeon removes the cancerous lesion along with a margin of healthy tissue surrounding it. The amount of tissue removed depends on the size, location, and type of skin cancer, as well as other factors such as the patient's age and overall health.

Mohs micrographic surgery is a specialized technique used to remove skin cancer with high precision while preserving as much healthy tissue as possible. During Mohs surgery, the surgeon removes thin layers of tissue one at a time and examines each layer under a microscope immediately after removal. This process continues until no cancer cells are detected, ensuring complete eradication of the tumor while minimizing damage to surrounding healthy tissue.

After surgical removal, the wound is typically closed with stitches or left to heal on its own, depending on the size and location of the lesion. Patients may experience some discomfort and swelling after surgery, but complications are rare. Follow-up appointments are scheduled to monitor the surgical site and assess for any signs of recurrence.[29]

3. Radiation Therapy:

Radiation therapy may be used to treat skin cancer in cases where surgery is not feasible or to target cancer cells that remain after surgery. It involves delivering high-energy radiation beams to the affected area to destroy cancer cells and shrink tumors. Radiation therapy may be used alone or in combination with surgery or other treatments, depending on the type, size, and location of the skin cancer, as well as the patient's overall health and treatment goals.[30]

There are different types of radiation therapy techniques used to treat skin cancer, including external beam radiation therapy, brachytherapy (internal radiation therapy), and electron beam therapy. The choice of radiation therapy technique depends on factors such as the depth of the tumor, its proximity to critical structures, and the patient's individual treatment plan.

Radiation therapy is typically administered over several sessions, spaced out over a period of weeks. Side effects may include skin irritation, redness, and changes in skin pigmentation, which usually resolve after treatment. Regular follow-up appointments are scheduled to monitor the response to radiation therapy and assess for any signs of recurrence or complications.[30]

DRUG COMBINATION THERAPIES FOR SKIN CANCER

In recent years, drug combination therapies have emerged as a promising approach for treating skin cancer, particularly advanced melanoma and other aggressive forms of the disease. These therapies involve the simultaneous use of multiple drugs that target different molecular pathways involved in cancer progression. By targeting multiple pathways, combination therapies can potentially

improve treatment outcomes, overcome drug resistance, and reduce the risk of disease recurrence.

One example of a successful drug combination therapy for melanoma is the combination of BRAF and MEK inhibitors. BRAF inhibitors, such as vemurafenib and dabrafenib, target the BRAF gene mutation commonly found in melanoma cells, while MEK inhibitors, such as trametinib and cobimetinib, block the MEK protein, which is downstream of BRAF in the MAPK signaling pathway. Clinical trials have shown that combining BRAF and MEK inhibitors can significantly improve progression-free survival and overall survival in patients with BRAF-mutant melanoma compared to monotherapy with either drug alone.[31]

HERBAL DRUGS IN SKIN CANCER

In addition to conventional treatments, herbal remedies and alternative therapies are being explored for their potential role in managing skin cancer. Several plant-derived compounds have shown promise in preclinical studies for their anti-cancer properties. For example:

- **Green tea polyphenols:** Green tea contains polyphenolic compounds such as epigallocatechin-3-gallate (EGCG), which have antioxidant and anti-inflammatory properties. Studies have shown that EGCG inhibits tumor growth and induces apoptosis (cell death) in skin cancer cells.
- **Curcumin:** Curcumin, the active ingredient in turmeric, has anti-inflammatory and anti-cancer effects. Preclinical studies have demonstrated that curcumin inhibits tumor proliferation, angiogenesis (formation of new blood vessels), and metastasis in skin cancer models.
- **Resveratrol:** Resveratrol is a polyphenolic compound found in grapes, red wine, and certain berries. It has antioxidant and anti-inflammatory properties and has been shown to inhibit tumor growth and induce apoptosis in skin cancer cells.

While these herbal drugs hold promise as adjunctive therapies for skin cancer treatment, more research is needed to validate their efficacy and safety in clinical settings. Clinical trials are ongoing to evaluate the potential benefits of herbal drugs in combination with standard treatments for skin cancer. [28] [31]

NANOTECHNOLOGICAL APPROACHES TO TACKLE SKIN CANCER

Nanotechnology offers innovative solutions for the diagnosis, imaging, and treatment of skin cancer. Nanoparticle-based drug delivery systems can improve the efficacy and specificity of anti-cancer drugs by enhancing their stability, solubility, and targeted delivery to tumor cells. For example, liposomal formulations and polymer-based nanoparticles can encapsulate chemotherapy drugs or targeted therapies and deliver them directly to the tumor site, minimizing systemic toxicity and enhancing therapeutic efficacy. [32]

Nanomaterials such as gold nanoparticles and quantum dots are also being investigated for their potential applications in photothermal therapy (PTT) and photodynamic therapy (PDT) for skin cancer. In PTT, gold nanoparticles absorb near-infrared light and convert it into heat, causing localized hyperthermia and thermal ablation of cancer cells. In PDT, photosensitizing agents are delivered to the tumor site and activated by light of a specific wavelength, generating reactive oxygen species that selectively destroy cancer cells. [32]

Furthermore, nanotechnology-based imaging modalities, such as nanoparticle-enhanced magnetic resonance imaging (MRI) and nanoparticle-based contrast agents, enable non-invasive detection and visualization of skin cancer lesions with high sensitivity and resolution.

Overall, nanotechnological approaches hold great promise for improving the diagnosis, imaging, and treatment of skin cancer by enhancing the efficacy, specificity, and safety of anti-cancer therapies while minimizing side effects and improving patient outcomes.[32]

LIST OF DRUGS APPROVED BY FDA FOR SKIN CANCER TREATMENT

The U.S. Food and Drug Administration (FDA) has approved several drugs for the treatment of skin cancer, including melanoma, basal cell carcinoma, and squamous cell carcinoma. These drugs target specific molecular pathways involved in cancer growth and progression, and they have revolutionized the management of advanced skin cancer.

1. **Targeted therapies:** Drugs such as vemurafenib, dabrafenib, and encorafenib target the BRAF gene mutation commonly found in melanoma cells. Other targeted

therapies, such as cetuximab and vismodegib, inhibit the epidermal growth factor receptor (EGFR) and the Hedgehog signaling pathway, respectively, in advanced squamous cell carcinoma and basal cell carcinoma. [33]

2. **Immune checkpoint inhibitors:** Pembrolizumab, nivolumab, and ipilimumab are immune checkpoint inhibitors that block the PD-1/PD-L1 and CTLA-4 pathways, thereby enhancing the immune system's ability to recognize and destroy cancer cells. These drugs have shown remarkable efficacy in treating advanced melanoma and have significantly improved survival rates for patients with metastatic disease.

3. **Conventional chemotherapy agents:** Dacarbazine and paclitaxel are conventional chemotherapy agents that have been used for the treatment of advanced melanoma and other forms of skin cancer. While these drugs may have limited efficacy and significant side effects, they are still used in certain cases, particularly when targeted therapies or immunotherapies are not suitable. [33]

IMPORTANCE OF SKIN CANCER AWARENESS

Skin cancer awareness is crucial for several reasons. Firstly, it helps individuals understand the risk factors associated with the disease, such as sun exposure, fair skin, and family history, allowing them to take proactive steps to protect themselves. Secondly, awareness campaigns educate the public about the signs and symptoms of skin cancer, encouraging early detection and prompt treatment. Early diagnosis significantly improves the prognosis and reduces the likelihood of complications associated with advanced disease. Additionally, skin cancer awareness fosters a culture of prevention, promoting sun-safe behaviors such as sunscreen use, wearing protective clothing, and avoiding tanning beds. By raising awareness and promoting preventive measures, we can reduce the burden of skin cancer on individuals, families, and healthcare systems. [33]

CONCLUSION

In conclusion, skin cancer is a significant public health concern with rising incidence rates worldwide. However, through increased awareness, prevention efforts, early detection, and advancements in treatment modalities, significant progress has been made in combating this disease. By adopting sun-safe behaviors, undergoing regular skin examinations, and staying informed about the latest developments in skin cancer research and treatment, individuals can reduce their risk of developing skin cancer and improve their chances of successful outcomes if diagnosed. Continued research into novel therapies, including drug combinations, herbal drugs, and nanotechnological approaches, holds promise for further improving the prognosis and quality of life for patients with skin cancer. Together, we can work towards a future where skin cancer is no longer a major health threat.

REFERENCES

1. Apalla Z, Lallas A, Sotiriou E, Lazaridou E, Ioannides D. Epidemiological trends in skin cancer. Dermatol Pract Concept. 2017;7(2):1-6.

2. Rogers HW, Weinstock MA, Feldman SR, Coldiron BM. Incidence estimate of nonmelanoma skin cancer (keratinocyte carcinomas) in the U.S. population, 2012. JAMA Dermatol. 2015;151(10):1081-1086.

3. Guy GP Jr, Machlin SR, Ekwueme DU, Yabroff KR. Prevalence and costs of skin cancer treatment in the U.S., 2002-2006 and 2007-2011. Am J Prev Med. 2015;48(2):183-187.

4. American Cancer Society. Cancer Facts & Figures 2021. Atlanta: American Cancer Society; 2021.

5. Cancer Council Australia. Skin cancer statistics. https://www.cancer.org.au/about-cancer/types-of-cancer/skin-cancer/statistics.html. Accessed April 6, 2024.

6. Armstrong BK, Kricker A. How much melanoma is caused by sun exposure? Melanoma Res. 1993;3(6):395-401.

7. Narayanan DL, Saladi RN, Fox JL. Ultraviolet radiation and skin cancer. Int J Dermatol. 2010;49(9):978-986.

8. Gordon R. Skin cancer: an overview of epidemiology and risk factors. Semin Oncol Nurs. 2013;29(3):160-169.

9. Wu S, Han J, Laden F, Qureshi AA. Long-term ultraviolet flux, other potential risk factors, and skin cancer risk: a cohort study. Cancer

Epidemiol Biomarkers Prev. 2014;23(6):1080-1089.

10. Perera E, Gnaneswaran N, Staines C, Win AK, Sinclair R. Incidence and prevalence of non-melanoma skin cancer in Australia: a systematic review. Australas J Dermatol. 2015;56(4):258-267.

11. El Ghissassi F, Baan R, Straif K, et al. A review of human carcinogens--part D: radiation. Lancet Oncol. 2009;10(8):751-752.

12. Berman B, Cockerell CJ. Pathobiology of basal cell carcinoma. J Am Acad Dermatol. 2006;54(1):1-16.

13. Alam M, Ratner D. Cutaneous squamous-cell carcinoma. N Engl J Med. 2001;344(13):975-983.

14. Schadendorf D, Fisher DE, Garbe C, et al. Melanoma. Nat Rev Dis Primers. 2015;1:15003.

15. Wong JR, Harris JK, Rodriguez-Galindo C, Johnson KJ. Incidence of childhood and adolescent melanoma in the United States: 1973-2009. Pediatrics. 2013;131(5):846-854.

16. World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Expert Report 2018. Diet, Nutrition, Physical Activity and Skin Cancer. https://www.wcrf.org/dietandcancer/exposures/sun-exposure. Accessed April 6, 2024.

17. Watts CG, Madronio CM, Morton RL, et al. Clinical features associated with individuals at higher risk of melanoma: a population-based study. JAMA Dermatol. 2017;153(1):23-29.

18. Armstrong BK, Cust AE. Sun exposure and skin cancer, and the puzzle of cutaneous melanoma: a perspective on Fears et al. Mathematical models of age and ultraviolet effects on the incidence of skin cancer among whites in the United States. Am J Epidemiol. 2018;187(2):237-240.

19. Korgavkar K, Xiong M, Weinstock M. Changing incidence trends of cutaneous melanoma among US white Hispanics/Latinos. JAMA Dermatol. 2016;152(7):766-769.

20. Caini S, Boniol M, Botteri E, et al. The risk of developing a second primary cancer in melanoma patients: a comprehensive review of the literature and meta-analysis. J Dermatol Sci. 2014;75(1):3-9.

21. McLaughlin JM, Fisher JL, Paskett ED. Marital status and stage at diagnosis of cutaneous melanoma: results from the Surveillance Epidemiology and End Results (SEER) program, 1973-2006. Cancer. 2011;117(9):1984-1993.

22. Youlden DR, Baade PD, Soyer HP, Youl PH, Kimlin MG, Aitken JF. Anatomic distribution of skin cancers in Australia: a population-based study. J Am Acad Dermatol. 2018;78(2):325-332.e1.

23. Koh HK, Geller AC, Miller DR, Grossbart TA, Lew RA. Prevention and early detection strategies for melanoma and skin cancer. Curr Status Dermatol. 1996;29(1):151-172.

24. Dennis LK, Vanbeek MJ, Beane Freeman LE, Smith BJ, Dawson DV, Coughlin JA. Sunburns and risk of cutaneous melanoma: does age matter? A comprehensive meta-analysis. Ann Epidemiol. 2008;18(8):614-627.

25. Gandini S, Sera F, Cattaruzza MS, et al. Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. Eur J Cancer. 2005;41(1):45-60.

26. Cust AE, Armstrong BK, Goumas C, et al. Sunbed use during adolescence and early adulthood is associated with increased risk of early-onset melanoma. Int J Cancer. 2011;128(10):2425-2435.

27. O'Sullivan DE, Brenner DR, Demers PA, et al. Indoor tanning and skin cancer in Canada: a meta-analysis and attributable burden estimation. Can J Public Health. 2019;110(5):580-589.

A REVIEW ON THYROID CANCER

Dr. Smeeta Sadar, Ms. Gauri Gawande, Mr. Ajay Lokhande
Department of Pharmacology, D Y Patil College of Pharmacy, Akurdi, Pune

ABSTRACT

The seventh most frequent type of cancer worldwide is thyroid canver[1]. The most common type is differentiated, which typically requires surgery followed by radioactive iodine or observation. Well-differentiated thyroid cancer is among the least morbid types of solid carcinomas, and patients typically experience long-term survival. Thyroid cancer shows increased risk of extrathyroidal extension, lymph node metastasis, recurrence, and mortality. Researchers have differing opinions on thyroid cancer surgery, with some favoring whole and partial thyroidectomies, while others suggest preventive dissection of the central cervical lymph nodes. There are six types of thyroid cancer: Palillary carcinoma, Follicular carcinoma, hurtle carcinoma, Anaplastic carcinoma, Medullary carcinoma, and differentiates thyroid cancer. Genes play a role in thyroid cancer development, with somatic Ras mutations in follicular thyroid carcinomas being an early event. Somatic RET and TRK rearrangements are mostly observed in PTC and can be detected early. Hereditary medullary thyroid cancer is caused by germline RET missense mutations, while the role of somatic RET mutations in sporadic MTC is unclear. p53 is essential for the dedifferentiation process of thyroid cancer, and the function of PTEN is still unknown. Radiation is the only known external agent that can cause thyroid cancer, primarily PTC. Early diagnosis is crucial for a cure, and surgery can be combined with chemotherapy, radioiodine, or external radiation.

INTRODUCTION

Thyroid cancer is the seventh most common cancer throughout the world[1]. The most common type is differentiated, which typically requires surgery followed by radioactive iodine or observation[2]. Medullary and anaplastic thyroid cancers require experienced doctors for treatment. Targeted therapies for differentiated and medullary thyroid tumours offer longer progression-free survival but should only be used for patients with progressing or exhibiting symptoms[3]. Thyroid cancer can be divided into three types: well-differentiated (WDTC), poorly differentiated (PDDT), and anaplastic (ATC). PDTCs and ATC are believed to be the result of differentiated tumors that do not accumulate radioiodine and have poor response to medical and surgical procedures. Approximately 70% of PTCs have mutations in the RET, TRKA, RAS, and BRAF genes, which can be developed from existing WDTCs[5].

NATURAL HISTORY AND PROGNOSIS

Well-differentiated thyroid cancer is among the least morbid types of solid carcinomas, and patients typically experience long-term survival. This is generally true. Regional lymph node exhibits a significant difference in their correlation with overall survival, but they do consistently correlate with local frequency[9] when compared to other solid tumors. At presentation, approximately two-thirds of patients have gross disease localized to the thyroid. Those with papillary carcinomas smaller than 1.0 cm are considered to have either minimal or occult PTC (papillary microcarcinoma). At the time of diagnosis, a tiny percentage of individuals had distant metastatic hematogenous illness and 1% to 22% of PTC and 2% to 5% of FTC patients had metastases outside the neck or mediastinum. The majority of patients with recurrent disease have local cervical recurring episodes in their lymph nodes or the thyroid bed, and a small percentage of them exhibit distant metastases to the lung, bone and liver. Some studies have linked BRAF mutations to an increased risk of extrathyroidal extension, lymph node metastasis, recurrence, and mortality. However, not all studies share the same gene.

CLINICAL PRESENTATION

1. Thyroid nodules

Thyroid nodules are now more commonly detected in clinical settings through the use of diagnostic

imaging. Investigations using new high-resolution imaging techniques are now revealing previously undetectable thyroid nodules. Non-palpable or pallatable lesions are present in some patients, but they may be malignant despite being benign and not palpably noticeable; they will never develop into clinically important tumours. Determining whether malignant thyroid nodules, particularly those that may cause illness if left undiagnosed, is of great importance. In order to differentiate between low-risk and high- risk patient subsets, a thorough history and physical examination, laboratory testing, neck ultrasonography, and fine-needle aspiration (FNA) are necessary.

2. Genetics of thyroid cancer:

The majority of thyroid malignancies have a hereditary foundation, according to research on DNA sequencing of thyroid cancer. The cellular signalling system of mitogen-activated protein kinase (MAPK) is mutated in the majority of thyroid malignancies (figure 1). This route is essential for controlling cellular proliferation as it carries growth signals from the plasma membrane to the nucleus.

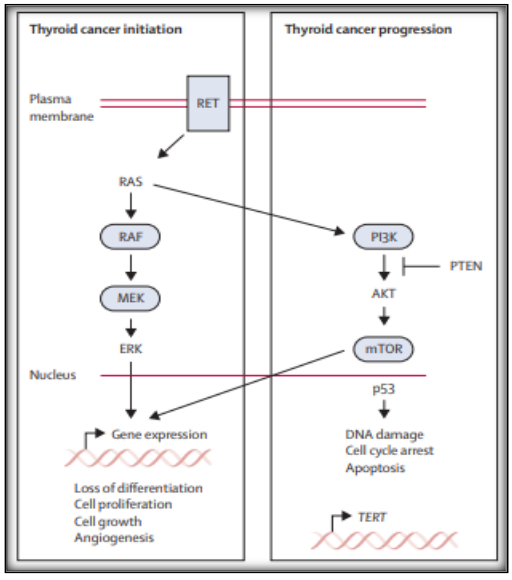


Fig 1: Thyroid cancer pathways

TYPES OF THYROID CANCER[2,3,4,8]:

1) Papillary carcinoma:

Unfavorable prognostic factors include age over 45, tumour size, thyroid invasion, distant metastasis, vascular invasion (inferior histology), and poorly differentiated findings. The nuclei in this variation lack typical PTC characteristics, such as a rare nuclear groove. The FVPTC can be classified as either encapsulated or diffuse/invasive (infiltrative). There are two types: the diffuse/invasive subtype and the clinical features of PTC that are common. However, the absence of invasion or incomplete nuclear features in the subtype (which has been encapsulated) makes its diagnosis very disputed. The presence of unfavorable prognostic elements, such as older age at the diagnosis stage, thyroidal invasion during treatment, and accelerated mitosis frequency, is frequently linked to this variation. Though this form of PTC die very rarely, it usually has later thyroidal growth and subsequent metastases in the lymph nodes adjacent to the body upon diagnosis, which reduces survival by a factor of recurrence.

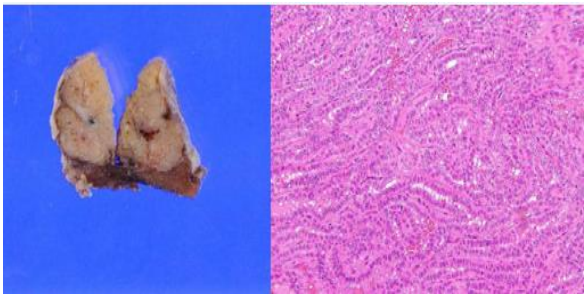


Fig 2: Typical image of papillary carcinoma

2) Follicular carcinoma

Between 5-15% of thyroid cancer cases have FTC, which is characterized by follicular differentiation but lacks papillary nuclear features. Vascular invasion has a worse prognosis than only capsular infiltration. The majority of FTCs exhibit minimal tumour capsular infiltration (Figure. These less invasive FTCs resemble follicular adenomas in appearance and aren't often associated with distant metastases. Due to the difficulty in distinguishing between a minimally invasive FTC and follicular accretion, it can only be detected after undergoing cytology or frozen section.

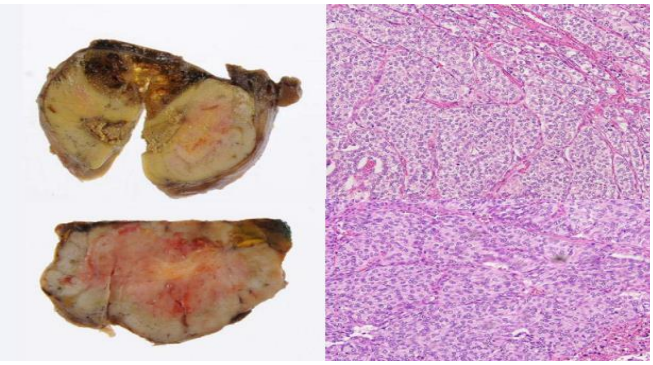


Fig 3: Papillary carcinoma

3) Hurthle cell carcinoma

Although Hürthle cell carcinoma, also known as oxyphilic cell carcinoma, is believed to be a kind of FTC, its prognosis is believed to be worse than that of FTC in general. There is a rare variation of papillary carcinoma with a prognosis comparable to that of FTC. Hürthle cell tumours contain more than 75% of follicular cells that exhibit oncocytic features. Polygonal form, eosinophilic granular cytoplasm, hyperchromatic or vesicular nuclei with big nucleolus, and an abundance of mitochondria are characteristics of oxyphilic or oncocytic cells.

4) Anaplastic carcinoma

ATC, an aggressive undifferentiated tumor, accounts for 40% of thyroid cancer deaths, despite 70% being female. About half of ATC patients have had differentiated thyroid carcinoma (DTC), causing refractoriness to radioiodine treatment. ATCs are typically incurable but can be surgically removed for better results. Anaplastic thyroid cancer, 1%, manifests as a neck lump that grows rapidly and can coexist with differentiated thyroid carcinoma. Patients with a history of differentiated thyroid carcinoma should be referred to a center with experience treating anaplastic thyroid cancer due to their poor prognosis. Clinical trials are testing promising medicines for survival.

5) Medullary carcinoma

Less than 5% of thyroid carcinomas are medullary thyroid carcinomas (MTCs), a neuroendocrine tumor derived from C cells of the neural crest's ultimobranchial body. Family MTCs are categorized as multiple endocrine neoplasia 2A (MEN2A), multiple endocrine neoplasia 2B (MEN2B), and familial medullary thyroid cancer (FMTC). They typically have firm, solid tumors with a large proportion of C cells. MTCs can be gray-tan, spindle, polyhedral, or circular to oval shapes, and have a background of C cell hyperplasia. Medullary thyroid cancer, which makes up 1-2% of all thyroid cancer cases, typically presents as a single thyroid nodule in individuals aged four to six.

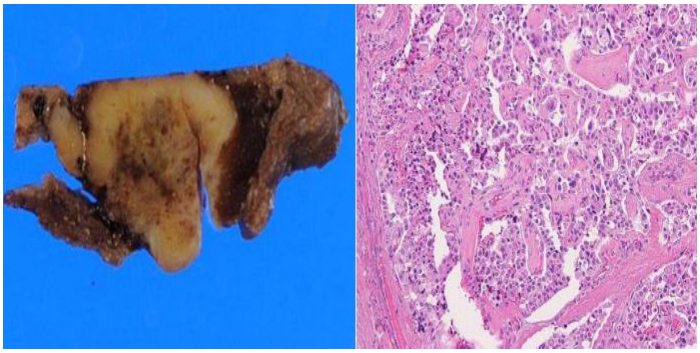


Fig 4: Medullary thyroid carcinoma

6) Differentiated thyroid cancer

With about 95% of cases, differentiated thyroid carcinoma is the most common type of thyroid cancer.8 Thyroid follicular epithelial cells are the source of this malignancy. Papillary thyroid cancer, follicular thyroid cancer, and Hurthle cell thyroid cancer fall within the category of well-differentiated thyroid cancers. Compared to differentiated thyroid cancer, poorly differentiated thyroid cancer is a more aggressive follicular-derived thyroid cancer. The most prevalent subtype of thyroid cancer has the greatest overall prognosis, which is papillary thyroid cancer. Most frequently, cervical lymph nodes and less frequently, the lungs, are the sites of metastases. High-risk thyroid tumours that are prone to spread to distant areas, including the lung and bones, include follicular thyroid cancer, Hurthle cell thyroid cancer, and poorly differentiated thyroid cancers. The current staging approach for differentiated thyroid tumours is based on age, with patients who are older (≥45 years) exhibiting worse outcomes.

DIAGNOSIS AND PATHOLOGY[3]:

Thyroid cancer diagnosis is often based on the presence of nodules, physical examination, or neck imaging for other conditions. A higher chance of developing carcinoma is indicated by lymphadenopathy, the size of the nodules, stiffness, and movement in the neck upon examination. Along with the clinical examination, high-resolution ultrasonography can be used to diagnose thyroid nodules and other unidentifiable nodes as well as to perform an FNA analysis and detect abnormalities in cervical lymph node. Cytologic diagnosis with FNA is highly sensitive, taking into account the expertise of both individuals conducting the biopsy and the chemist interpreting it, with values between 70% and 17% when thyroid FAN is administered. The prevalence of papillary thyroid cancer in developed countries with a high iodine diet is estimated to be around. The primary tumor's insignificance may be a secondary manifestation of thyroid papillary carcinoma, which is often the latter. These tumors account for around 10-15% of all thyroid cancer cases (15%).

ASSESSMENT AND TREATMENT OF THYROID NODULES [4]:

1) Sonographic features that require FNA biopsy:

The size of a thyroid nodule is primarily determined by its size, but other sonographic findings may also provide important clues about whether or not the nodal malignancy has been diagnosed. The list comprises of irregular borders, microcalcifications, hypoechogenicity, a rigid internal structure, taller-than-wide oblongation, and symptoms of cervical lymphadenopathy or extrathyroidal extension, or both. FNA cytology can be delayed by the smallness of the nodule, provided there are no other characteristics associated with it. These factors are predominantly associated with papillary thyroid carcinoma. Regardless of the appearance, FNA can be evaluated in subsequent situations. Notwithstanding all these factors, the 2015 guidance states that biopsy is only recommended for nodules larger than 1 cm.do. ATA guidelines.

2) Use of FNA cytology to tailor treatment:

The Bethesda system comprises six diagnostic categories for thyroid cytopathology reporting. Forty Benign nodules fall under diagnostic which can be safely treated with routine neck ultrasonography. Malignant typically require surgery.The nodule needs to be re-aspirated if the cytology results are nondiagnostic. Depending on clinical risk factors, ultrasound patterns, and patient choices, indeterminate results can be handled surgically or with close monitoring.

TREATMENT

1) Surgical treatment :[4]

For well differentiated papillary microcarcinoma, multifocal distribution, lymph-node involvement, and limited surgery were found to be associated with an increased risk of local recurrence. Studies indicate that local recurrence rates are significantly lower after thyroidectomy, with most studies indicating a significant decrease in incidence. Thyroidectomy for high-risk tumours reduces local recurrence and improves survival. According to most experts, a total thyroidectomy is recommended for Hurthle-cell carcinomas as it minimizes the risk of local recurrence, particularly since the tumour cannot concentrate radioactive Iodine. Despite the acceptance of surgery as the preferred treatment for thyroid carcinoma, there's still controversy surrounding the extent of thyroidectomy and lymph node dissection. There are conflicting prognostic factors for lymph nodes dissecting uniformly, leading to inconsistent results. Due to its multifocal nature, MTC is not susceptible to radioiodine ablation, making the overall recommendation for a total thyroidectomy fair. Generally, it is recommended to examine the areas that are clearly linked to LNM.

2) Treatment of recurrent and metastatic disease

In 5-23% of patients with differentiated thyroid carcinoma, contrasting metastases are observed; these metstatic changes are typically found in lung and bone tumors but not frequently in the liver or brain. Moreover, some patients with significant

thyroglobulin levels, which may indicate a negative diagnosis, exhibit evidence of uptake in the posttreatment scan. Univariate and multivariable analyses have revealed an adverse prognostication bias in survival among older individuals during the discovery of metastases. Younger patients with limited-volume disease, mainly in the lungs, who achieve a complete response to radioiodine have the best prognosis, with 15-year survival of 89%.16. In comparison, iodine has a less favorable outcome for older patients and those with larger metastases or bone involvement, leading to ill-fated prognosis. In patients with microscopic foci, 82% of those who had uptake in lung metastases not detected on chest radiography were found to have complete response, while only 15% of individuals with visible macronodules reported full response. A low response rate to radioiodine is associated with bone lesions, so it is recommended to try to excision the area where it becomes feasible or to add external radiotherapy.

3) Radiotherapy and chemotherapy

The controversy surrounding external-beam radiation therapy in differentiated thyroid carcinomas stems from the difficulty in interpreting available data. Radiotherapy is not recommended for young patients with good iodine uptake or prognostic characteristics. Postoperative radiation therapy improves local control in patients with advanced tumors and persistent microscopic disease. Radiotherapy is prescribed for older patients with locally advanced tumors and macroscopic or microscopic disease after surgery. Chemotherapy is reserved for patients with progressing, symptomatic incurable illness that does not concentrate iodine, with Doxorubicin being the most successful drug, but with only partial, transient responses and no positive impact on survival.

4) Management of anaplastic carcinoma[8]

Anaplastic carcinoma is a rapidly progressive thyroid cancer with a poor prognosis, with a median survival of only 6 months. Surgical excision is rare, and response is seen in less than 45% of patients. Despite attempts to improve local control, most patients spend a significant part of their remaining life undergoing treatment and recovering from toxic effects. Combining chemotherapy and radiotherapy, particularly in a hyper fractionated schedule, has been reported to improve response rates, but at the cost of increased morbidity.

5) Management of medullary cancer

Total thyroidectomy is the best surgical treatment for medullary thyroid cancer, as it is the most effective in multifocal and bilateral cases. However, postoperative calcitonin concentrations can persist in many patients, and the location of the tumour may not be apparent. Ultrasonography, computed tomography, magnetic resonance imaging, radionuclide scanning, and selective venous catheterisation may assist in tumour localisation. Medullary thyroid cancer has an indolent course, with 90% and 86% overall survival at 5 years and 10 years, respectively. Postoperative radiotherapy is controversial due to a lack of prospective studies. Adjuvant irradiation is recommended for patients with locally advanced disease at presentation, and radiotherapy should be considered for bulky inoperable tumors. Chemotherapy is considered for unresectable progressive and symptomatic disease. The clinical course of medullary thyroid cancer varies widely, with overall 10-year survival rates ranging from 65% to 90%.

6) Non-surgical treatment modalities[4,7]

In Europe, patients with diffuse thyroid carcinoma (DTC) are often treated with radioiodine postoperatively, while in the US, it is less common. Radioiodine is effective in ablation of small thyroid remnants and pulmonal metastases, but bone metastases are less likely to respond. Retinoc acid may induce redifferentiation of less-differentiated thyroid carcinoma. Routine use of external radiation should be avoided, and remission can only be achieved in single patients. In UTC, radioiodine is of no value, but external radiation may be helpful in controlling the local tumor burden. Hyperfractionated radiotherapy is reputed to be more effective than conventional radiotherapy with less toxicity. Chemotherapy is the only available treatment for disseminated distant metastases.

Reexpression of p53 in thyroid cancer cell lines has been shown to inhibit proliferation and restore differentiation. Radioiodine therapy in MTC is not indicated, but radioimmunotherapy with iodine-131-labelled antiCEA antibodies might be useful in non-resectable cases or bone metastases.

7) Radioactive Iodine Ablation and Treatment[5]

131I therapy is a crucial treatment for thyroid cancer, used alongside thyroidectomy to completely ablate the thyroid gland and eradicate residual cancer postoperatively. It works by entering thyroid cells via sodium iodide transporters and emitting short-wavelength beta rays, causing acute cell death. 131I is particularly useful for differentiated thyroid cancer, with a 10-year survival rate of 90%-95%. Patients are initially placed on a low-iodine diet or have their urine iodine level adjusted.

8) Tyrosine Kinase Inhibitors[5,6]

Radioactive iodine therapy is the primary treatment for thyroid cancers, but in patients whose cancer no longer responds, a new treatment option is needed. Tyrosine kinase signaling pathways, including RET, RAF, and RAS, are linked to VEGF syntheses. Gain-of-function mutations in the BRAF oncogene are common in papillary thyroid cancer. Drugs targeting these pathways could control disease progression.

i) Vandetanib:

In 2011, the FDA approved vandetanib, targeting RET, EGFR, and VEGF receptors, for treating patients with symptomatic or progressive medullary thyroid cancer. The study showed a significant prolongation of progression-free survival with vandetanib compared to a placebo. Adverse events occurred in over 30% of patients, and 8 out of 19 patients developed protocol-defined QTc prolongation.

ii) Cabozantinib:

In 2012, the FDA approved cabozantinib, a second TKI targeting MET, VEGF receptor 2, and RET pathways in medullary thyroid cancer. The study showed cabozantinib prolonged progression-free survival to 11.2 months compared to a placebo. However, it had significant side effects like diarrhea, hand-foot syndrome, fatigue, and hypertension. 79% of patients had dose reductions, and 16% discontinued treatment. Grade 5 lethal toxicities occurred in 7% of patients.

iii) Combination of Vandetanib & Cabozatinib:

Though levels of calcitonin and carcinoembryonic antigen drop significantly when using vandatetanib and cabozantinib, these drugs have demonstrated a considerable prolongation of progression-free survival; thus far, however, these trials have not demonstrated an overall survival advantage. Because of these medications' diverse adverse effects, each patient must be treated differently, necessitating extensive clinical judgment before prescribing them.

iv) Sorafenib:

Sorafenib, a multikinase inhibitor, was approved by the FDA in 2013 for treating 131I-refractory, locally recurrent or metastatic, progressive, differentiated thyroid cancer. The DECISION study, a phase 3, multicenter, randomized, double-blind, placebo-controlled clinical trial, showed a significant prolongation in median progression-free survival of 10.8 months with sorafenib compared to 5.8 months with a placebo. Adverse events occurred in 98.6% of patients receiving sorafenib, with hand-foot skin reactions, diarrhea, alopecia, and rash or desquamation being the most common. Sorafenib can prolong the QT/corrected QT interval and increase the risk of ventricular arrhythmias. Combination with carboplatin and paclitaxel is contraindicated in patients with squamous-cell lung cancer.

9) External Beam Radiation Therapy[5]:

Only individuals with advanced or incurable thyroid cancer are treated palliatively with

external beam radiation therapy.5 Patients with grossly evident extrathyroidal extension and a high risk of residual disease after surgery are typically the ones who are evaluated for it. These patients are usually older than 45.5. Additionally, it is saved for cancers that don't respond to 131I therapy.

POSTTREATMENT MANAGEMENT[2,5]:

The use of SH suppression medication is recommended after 131I therapy and surgery because differentiated thyroid tumours exhibit HC-triggered receptors. Levothyroxine at supraphysiologic doses can be used to suppress TSH to less than 0.1 mU/L, or up to 0.5 mU/L in patients at lesser risk.5. It is recommended to conduct a test on serum thyroglobulin levels every 6 to 12 months in the same laboratory as those who produce antithreonal antibodies (THG) and have inaccurate reductions of these levels from 25% duets.

References:

1) Katoh, Hiroshi, et al. "Classification and general considerations of thyroid cancer." Ann Clin Pathol 3.1 (2015): 1045
2) Cabanillas, Maria E., David G. McFadden, and Cosimo Durante. "Thyroid cancer." The Lancet 388.10061 (2016): 2783-2795.
3) Carling, Tobias, and Robert Udelsman. "Thyroid cancer." Annual review of medicine 65 (2014): 125-137.
4) Gimm, Oliver. "Thyroid cancer." Cancer letters 163.2 (2001): 143-156.
5) 4. Katoh, Hiroshi, et al. "Classification and general considerations of thyroid cancer." Ann Clin Pathol 3.1 (2015): 1045.
6) 5. Nguyen, Quang T., et al. "Diagnosis and treatment of patients with thyroid cancer." American health & drug benefits 8.1 (2015): 30.
7) Guarino, Valentina, et al. "Thyroid cancer and inflammation." Molecular and cellular endocrinology 321.1 (2010): 94-102.
8) Vini, Louiza, and Clive Harmer. "Management of thyroid cancer." The Lancet Oncology 3.7 (2002): 407-414.
9) Lundgren CI, Hall P, Dickman PW, et al. 2006. Clinically significant prognostic factors for differentiated thyroid carcinoma: a population-based, nested case-control study. Cancer 106:524–31

THYROID CANCER

Mr. Siddharth Topale, Mr. Mukesh Mohite
Department of Pharmaceutical Chemistry, Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune

ABSTRACT

One type of cancer that develops from the thyroid parenchymal cells is thyroid carcinoma. Globally, its incidence is rising steadily, although during the last few years, the death rate has stayed constant. Thyroid cancers range widely in their clinical behavior from slow-growing, indolent tumors to extremely aggressive tumors with significant fatality rates. While there is evidence to suggest that overtreatment of low-risk thyroid malignancies is not beneficial, there are a number of novel, state-of-the-art treatment options available for advanced thyroid cancer. Thus, giving the patient the right treatment requires a complete grasp of the many forms of thyroid cancer and how to treat it. The incidence, etiology, pathophysiology, diagnosis, and treatment of thyroid cancer are reviewed in this activity, which also emphasizes the need of interprofessional communication in maximizing the patient's care.

INTRODUCTION

A tumor of the thyroid parenchymal cells is called thyroid cancer. Thyroid follicular cells, which give rise to differentiated thyroid cancer (DTC), and parafollicular or C-cells, which give rise to medullary thyroid carcinoma (MTC), make up the two main cell types that make up the thyroid parenchyma. DTC includes follicular thyroid cancer (FTC), Hurthle cell cancer, and papillary thyroid cancer (PTC), which together make up 90–95% of thyroid cancer cases. Anaplastic thyroid carcinoma makes up fewer than 1% of all thyroid malignancies, while MTC makes up between 1% and 2%[1].

ETIOLOGY

For PTC and FTC, the familial occurrence of thyroid cancer is about 5%, whereas for MTC, it is between 15% and 30%.[2] Papillary thyroid cancer incidence has increased globally over the past few decades, primarily as a result of early detection and sophisticated imaging technology that carries the danger of overdiagnosis.The genetic basis of the majority of thyroid malignancies has been linked to mutations and translocations in the genes encoding the cellular signaling pathway known as mitogen-activated protein kinase (MAPK).[4]

The following are some examples of frequent mutations:

PTC- The most frequent mutation causing PTC (29 to 69%) and PTC-associated anaplastic thyroid carcinoma (0 to 12%) is a point mutation in the BRAF gene that results in BRAF V600E mutant kinase.[5] Approximately 7% of PTCs have translocation of the RET-papillary thyroid carcinoma (RET/PTC).RAS proto-oncogene mutations affect 10–20% of follicular variant PTC (FVPTC).[2]

FTC- FTC patients most frequently have mutations in the RAS proto-oncogene (40–50%). In approximately 30 to 35% of FTC, translocation in PAX8-peroxisome proliferator-activated receptor γ (PPARγ) has been detected.[7]

Anaplastic- In around 50 to 80% of instances of anaplastic thyroid carcinoma, inactivating mutations of the p53 tumor suppressor gene have been found in addition to early inactivating alterations.[8][9][10] Furthermore, mutations in the CTNNB1 gene have been found to be present in 66% of anaplastic thyroid tumors.[5] Additionally, 20 to 40 percent of anaplastic thyroid tumors are linked to RAS mutations.

RISK FACTORS

The main risk factors for DTC include female sex, a family history of thyroid cancer, and radiation exposure to the thyroid gland as a kid.[14][15][16] Thyroid cancer affects men and women equally, according to autopsy reports, however it may be found in women more often than in men, according to a recent study. The disparity can be attributed to medical care accessibility.[17]

EPIDEMIOLOGY

Thyroid cancer is the sixth most prevalent cancer in women in the United States, accounting for 1% to 4% of all cancer cases.[14] It has a roughly 3:1

female to male ratio.[18] Thyroid cancer incidence has been steadily increasing worldwide; in particular, throughout the past three decades, there has been a 240% increase in PTC detection.[19] It is believed that a rising trend in the rate of diagnostic imaging is the main cause of this incidence increase, which has been seen across all racial and gender groups.[11][19] PTC is the most prevalent endocrine cancer, accounting for 96% of newly diagnosed cases and 66.8% of endocrine cancer-related fatalities.[14] As was previously established, the follicular epithelium is the source of the majority of thyroid malignancies, with PTC and FTC being significantly more common than anaplastic thyroid cancer.[2][4]

EVALUATION

The best initial assessment for a patient with a thyroid nodule is a thyroid function panel. A lower risk of cancer is frequently associated with hyperthyroidism; in these patients, a radionuclide uptake scan is recommended. The general recommendation is to avoid fine-needle aspiration biopsy (FNAB) if the nodule or nodules are found to be hyperfunctioning. This is due to the fact that the FNAB results for hyperfunctioning nodules are frequently erroneous and that these nodules are rarely cancerous.[3] A high-resolution diagnostic thyroid ultrasound should be performed before evaluating the thyroid nodule in patients who are biochemically hypothyroid or euthyroid. This can assist in evaluating the nodules for high-risk characteristics, finding more nodules not felt during a physical examination, determining whether there are any neck lymph nodes, and directing FNAB if necessary.

A considerable rise in size from previous imaging, hypoechogenicity, uneven borders, a size that is taller than wide, microcalcifications, a solid internal structure, extra-thyroidal extension, and central vascularity are among the high-risk characteristics on ultrasound. Peripheral vascularity, spongiform appearance, comet tail shadowing, and solely cystic nodule are the characteristics linked to a lower risk of cancer. The Thyroid Imaging Reporting and Data System (TIRADS) or American Thyroid Association (ATA) criteria should be consulted when deciding whether to submit a nodule for FNAB. Clinical indications should always take precedence over imaging criteria.[3][14][19]

THERAPY

Papillary and Follicular Thyroid Cancers

Surgical Treatment

The primary treatment for both FTC and PTC is still surgical excision, which is followed by thyroid hormone suppression therapy and, when necessary, radioiodine ablation (RAI ablation).[7][9] In severe cases that are resistant to traditional techniques, systemic radiation and chemotherapy may be utilized, but they rarely have a substantial impact on the course of treatment. Surgery is advised to reduce the risk of sequelae, including hypoparathyroidism and recurrent laryngeal nerve injury. This procedure should be carried out by qualified, "high-volume" thyroid surgeons.[7]

The pre-operative ultrasonography of the neck plays a crucial role in selecting the right surgical technique. Hemithyroidectomy or complete thyroidectomy, with or without dissection of lymph nodes, are the two types of surgical resections. The size of the tumor, the existence of lymph node metastases, extra-thyroidal extension, the patient's age, and the existence or absence of co-morbid disorders all influence the surgical option. It is recommended that patients with locally advanced illness undergo further neck imaging.

Thyroid lobectomy is the chosen treatment for unilateral DTC < 1 cm, provided that there is no invasion of lymph nodes or extra-thyroidal region, unless there are clear reasons for complete thyroidectomy, such as a significant family history of thyroid cancer or childhood head and neck radiation.

There has also been a recent tendency toward only active surveillance rather than immediate surgery, although more research is required to see whether this has an impact on prognosis and outcomes.[19] Depending on patient preferences and risk factors, a complete thyroidectomy or lobectomy may be the preferred operation for tumors between 1 and 4 cm in size that do not exhibit extrathyroidal or lymphatic invasion. The patient should be informed of the possibility that, depending on pathology findings, a complete thyroidectomy may be required at the time of this decision. A total thyroidectomy is the recommended surgical

approach for tumors larger than 4 cm or those involving invasion of lymph nodes or the extrathyroidal region, as these cancers have an increased risk of multifocal carcinoma. It also aims to make future surveillance using thyroglobulin as a tumor marker and RAI ablation easier.

Individual patient decisions should be made about lymph node dissection, and there is ongoing debate on the efficaciousness of prophylactic node dissection in terms of survival. Nevertheless, a comprehensive evaluation of the central and lateral necks should be performed on all patients with confirmed or suspected PTC to rule out nodal metastases. When performing a thyroidectomy, the lateral neck compartments should not be regularly penetrated. Instead, they should be evaluated beforehand using ultrasound and, if lymphatic spread is a concern, FNAB. An ipsilateral neck dissection should be performed if pathologic nodes are verified, and formal clearing of specific lymph node compartments should be performed rather than isolated "berry-picking" of diseased nodes. Because of their placement, the lymph nodes in the middle neck are challenging to evaluate before surgery. At the time of operation, the central neck should be carefully examined and palpated. If any aberrant nodes are discovered, the compartmental neck should be dissected.[19]

DISTINCTIVE DIAGNOSIS

- Benign thyroid nodule
- Toxic nodular goiter
- Primary thyroid lymphoma
- Cervical lymphadenopathy

FORECAST

Thyroid cancer prognosis varies widely based on the type of cancer, size of the tumour, number of metastases, age of the patient, and resection amenability. For patients of all ages and races, the prognosis is generally favorable, with a 5-year survival rate of up to 95%. Large tumor size, extra-thyroidal expansions or metastases, advanced age, or unfavorable tumor forms including undifferentiated carcinoma are all considered poor prognostic factors.[1][19]

COMPLICATION

Thyroid cancer that is left untreated has the potential to locally invade the esophagus, airways, or other surrounding neurovascular tissues. The lung, bone, and other soft tissue structures are the most often affected organs in distant metastases. Neurovascular injuries are possible during both thyroid lobectomy and total thyroidectomy; the most common injury is to the recurrent laryngeal nerve, which can result in hoarseness of voice and, in cases of bilateral injuries, respiratory failure. Pregnancy problems did not significantly increase with thyroid cancer treatment, which primarily involved thyroidectomy.[2][8][14]

CONSULTATION

- Thyroid surgeon
- Endocrinologist
- Radiologist
- Pathologist

IMPROVING THE RESULTS OF HEALTHCARE TEAMS

As previously mentioned, thyroid cancer can present in a wide range of ways, from a low-risk, clinically indolent condition that can be treated with active surveillance to a very aggressive, metastatic condition that requires major surgical resection and either systemic chemotherapy or no chemotherapy at all.

As a result, treating a patient with thyroid cancer is a very personalized procedure that considers the patient's preferences as well as their chance of recurrence (after the patient has been informed about the various treatment options and the advantages and disadvantages of each).

To provide the best possible treatment for the patient without going overboard, the interprofessional team—which includes, but is not limited to, the thyroid surgeon, the endocrinologist, the pathologist, the radiologist, and possibly the oncologist—must work closely together. Every

stage of the process, from pre-operative planning to treatment and postoperative monitoring, should involve the patient and be comfortable for them, according to nursing staff. A dedicated oncology pharmacist is also a beneficial addition to the interprofessional team when undergoing chemotherapy. [19]

References:

1.Noone AM, Cronin KA, Altekruse SF, Howlader N, Lewis DR, Petkov VI, Penberthy L. Cancer Incidence and Survival Trends by Subtype Using Data from the Surveillance Epidemiology and End Results Program, 1992-2013. Cancer Epidemiol Biomarkers Prev. 2017 Apr;26(4):632-641.

2.Nikiforov YE, Nikiforova MN. Molecular genetics and diagnosis of thyroid cancer. Nat Rev Endocrinol. 2011 Aug 30;7(10):569-80.

3. Miranda-Filho A, Lortet-Tieulent J, Bray F, Cao B, Franceschi S, Vaccarella S, Dal Maso L. Thyroid cancer incidence trends by histology in 25 countries: a population-based study. Lancet Diabetes Endocrinol. 2021 Apr;9(4):225-234.

4. Fagin JA. How thyroid tumors start and why it matters: kinase mutants as targets for solid cancer pharmacotherapy. J Endocrinol. 2004 Nov;183(2):249-56.

5. Carling T, Udelsman R. Thyroid cancer. Annu Rev Med. 2014;65:125-37.

6. Cancer Genome Atlas Research Network. Integrated genomic characterization of papillary thyroid carcinoma. Cell. 2014 Oct 23;159(3):676-90.

7.Raman P, Koenig RJ. Pax-8-PPAR-γ fusion protein in thyroid carcinoma. Nat Rev Endocrinol. 2014 Oct;10(10):616-23.

8. Nikiforova MN, Wald AI, Roy S, Durso MB, Nikiforov YE. Targeted next-generation sequencing panel (ThyroSeq) for detection of mutations in thyroid cancer. J Clin Endocrinol Metab. 2013 Nov;98(11):E1852-60.

9. Santarpia L, El-Naggar AK, Cote GJ, Myers JN, Sherman SI. Phosphatidylinositol 3-kinase/akt and ras/raf-mitogen-activated protein kinase pathway mutations in anaplastic thyroid cancer. J Clin Endocrinol Metab. 2008 Jan;93(1):278-84.

10. Hou P, Liu D, Shan Y, Hu S, Studeman K, Condouris S, Wang Y, Trink A, El-Naggar AK, Tallini G, Vasko V, Xing M. Genetic alterations and their relationship in the phosphatidylinositol 3-kinase/Akt pathway in thyroid cancer. Clin Cancer Res. 2007 Feb 15;13(4):1161-70.

11. Leboulleux S, Baudin E, Travagli JP, Schlumberger M. Medullary thyroid carcinoma. Clin Endocrinol (Oxf). 2004 Sep;61(3):299-310.

12. Landa I, Ganly I, Chan TA, Mitsutake N, Matsuse M, Ibrahimpasic T, Ghossein RA, Fagin JA. Frequent somatic TERT promoter mutations in thyroid cancer: higher prevalence in advanced forms of the disease. J Clin Endocrinol Metab. 2013 Sep;98(9):E1562-6.

13. Malchoff CD, Malchoff DM. Familial nonmedullary thyroid carcinoma. Cancer Control. 2006 Apr;13(2):106-10.

14. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin. 2015 Jan-Feb;65(1):5-29.

15. Galanti MR, Ekbom A, Grimelius L, Yuen J. Parental cancer and risk of papillary and follicular thyroid carcinoma. Br J Cancer. 1997;75(3):451-6.

16. Robbins J, Schneider AB. Thyroid cancer following exposure to radioactive iodine. Rev Endocr Metab Disord. 2000 Apr;1(3):197-203.

PROSTATE CANCER

Mr. Sanket Palve, Dr. Prafulla kadam
Department of PharmD, Dr. D.Y. Patil College of Pharmacy Akurdi, Pune.

INTRODUCTION

Postate cancer (PCa) is a prevalent malignancy affecting men globally. It is the second most common cancer in men, with significant implications for health and quality of life. In the United States alone, an estimated 34,130 deaths were attributed to prostate cancer in 2021.[1]The prostate gland, a walnut-sized organ located below the bladder, plays a crucial role in male reproductive function.[2] Prostate cancer arises from the uncontrolled growth of cells within the prostate tissue. Although the exact etiology remains multifactorial, risk factors include age, family history, and genetic predisposition.[3]Advancements in research have shed light on various aspects of prostate cancer, including its genetics, diagnosis, and treatment options.[1] Scientific investigations have explored genes and mutations associated with disease onset and progression. Additionally, novel diagnostic techniques, biomarkers, and therapeutic modalities have emerged, aiming to improve patient outcomes.[4]As researchers increasingly focus on prostate cancer-associated exosomes, the field witnesses growing attention.[5] Notably, exosomes—small extracellular vesicles—have been implicated in tumour progression, metastasis, and drug delivery.[6] Collaborations among institutions worldwide have fuelled research endeavours, with notable contributions from institutions such as Harvard Medical School, Cedars Sinai Medical Center, and Johns Hopkins University.[1]The lifetime risk of developing prostate cancer is almost 16%; the lifetime risk of dying from prostate cancer is 2.8% [7]; and 85% of prostate cancers are clinically localized at the time of diagnosis [8].

EPIDEMIOLOGY

Based on GLOBOCAN 2018 estimates, we have evaluated worldwide prostate cancer incidence and mortality rates, as well as analysed incidence and mortality, temporal trends and survival rates [11].

1. Incidence

The incidence rate of prostate cancer varies across the regions and populations (Fig. 1) [13]. In 2018, 1,276,106 new cases of prostate cancer were registered worldwide, representing 7.1% of all cancers in men [12]. Prostate cancer incidence rates are highly variable worldwide. The age-standardized rate (ASR was highest in Oceania (79.1 per 100,000 people) and North America (73.7), followed by Europe (62.1). Conversely, Africa and Asia have incidence rates that are lower than those from developed countries (26.6 and 11.5, respectively) [13]. Differences in incidence rates were 190-fold between the populations at the highest rate (France, Guadeloupe, 189.1), and the populations with the lowest rate (Bhutan, 1.0). Prostate cancer incidence increases with age [13]. Although only 1 in 350 men under the age of 50 years will be diagnosed with prostate cancer [14], the incidence rate increases up to 1 in every 52 men for ages 50 to 59 years. The incidence rate is nearly 60% in men over the age of 65 years. The reason for these differences among the countries is not entirely clear.

The worldwide variations in prostate cancer incidence might be attributed to PSA testing [15]. For example, 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 estimated in 2018 [16]. While in the USA, prostate cancer is the second most common cancer accounting for 9.5% of all new cancer cases (164,690 new cases of prostate cancer) registered in 2018 [17]. According to recently conducted research studies, around 20-40% of the prostate cancer cases in the USA and Europe

could be due to overdiagnosis through extensive PSA testing [15, 18, 19].

ETIOLOGY OF PROSTATE CANCER

Prostate cancer (PCa) is a multifaceted disease influenced by a complex interplay of genetic, environmental, and lifestyle factors. Understanding its etiology is crucial for effective prevention, early detection, and targeted therapeutic interventions.

1. TMPRSS2:ERG Fusion and Etiologic Differences:

The TMPRSS2:ERG gene fusion is the most common somatic alteration in primary prostate cancer and an early event in carcinogenesis.

- Emerging data highlight etiologic differences in prostate cancer based on TMPRSS2:ERG status.
- A systematic review synthesized evidence from epidemiologic studies, focusing on prostate cancer risk factors for tumour with and without the TMPRSS2:ERG fusion [24].

Key findings include:

- Taller height and higher total and free circulating testosterone levels tend to be associated with a higher risk of ERG-positive prostate cancer.
- CAG repeat length in the androgen receptor (AR) gene, inversely related to transcriptional activity, is associated with a lower risk of ERG-positive prostate cancer.

2. Genomic Research and Non-Coding RNAs:

- Cutting-edge genomic research sheds light on prostate cancer.
- Genome alterations, cancer immunology, and non-coding RNAs play pivotal roles in PCa.

- Understanding these molecular mechanisms provides insights into disease progression and potential therapeutic targets [26].

3. Risk Classification, Imaging, and Biomarkers:

- Advances in risk classification methods, imaging techniques, and biomarkers enhance prostate cancer diagnosis [27].

- Researchers explore novel approaches to improve early detection and personalized treatment strategies [28].

HISTOPATHOLOGY OF PROSTATE CANCER

Histopathologically, prostate cancer is characterized by the presence of malignant epithelial cells within the prostate glandular tissue. The histological features of prostate cancer include architectural patterns such as acinar, cribriform, papillary, and solid growth patterns, as well as cellular characteristics like nuclear atypia, prominent nucleoli, and increased mitotic activity (Epstein et al., 2016; Humphrey, 2016). The Gleason grading system, a widely used histological grading system for prostate cancer, evaluates the architectural patterns and cellular differentiation to assign a Gleason score that correlates with the aggressiveness of the tumour (Mottet et al., 2021). Additionally, immunohistochemical markers such as prostate-specific antigen (PSA), AMACR (alpha-methylacyl- CoA racemase), and p63 are commonly used in conjunction with histopathology to aid in the diagnosis and classification of prostate cancer subtypes (Humphrey et al., 2014; Lotan et al., 2017). Understanding the histopathological features of prostate cancer is essential for accurate diagnosis, prognostication, and guiding treatment decisions in clinical practice.

Histological features:

The histological features of prostate cancer encompass various architectural patterns that play a crucial role in its diagnosis and classification. These patterns include acinar, cribriform,

papillary, and solid growth patterns, each with distinct characteristics indicative of different subtypes of prostate cancer [31].

1. Acinar Pattern:

- Description: The acinar pattern is the most common histopathological subtype of prostate cancer, constituting approximately 93% of cases. It is characterized by the presence of glandular structures resembling normal prostate glands but with malignant features [32].

2. Cribriform Pattern:

- Description: The cribriform pattern involves the formation of glandular structures with a cribriform tuft attached to the gland wall.

3.Papillary Pattern:

- Description: The papillary pattern is characterized by finger-like projections of malignant cells growing into gland lumina.

Histopathologic Grade (G)

GX: Grade cannot be assessed [12]

G1: Well, differentiated (slight anaplasia) (Gleason 2 to 4) [12]

G2: Moderately differentiated (moderate anaplasia) (Gleason 5 to 6) [12]

G3-4: Poorly differentiated or undifferentiated (marked anaplasia) (Gleason 7 to 10)

Diagnosing prostate cancer from biopsy samples can sometimes present challenges, especially when the biopsy sample is small. However, accurate diagnosis and grading is critical since prognosis depends heavily on the grade and differentiation of the tumour.

HISTORY AND PHYSICAL

Patient history plays a crucial role in identifying risk factors for prostate cancer. Family history of prostate cancer is a significant predictor of the disease, with a positive family history associated with an increased risk of developing prostate cancer [45, 46, 47, 48]. Specifically, having a father or brother(s) diagnosed with prostate cancer increases the risk [49]. Other factors such as age, ethnicity, hypertension, diabetes, obesity, and severe lower urinary tract symptoms have also been associated with an increased risk of prostate cancer. However, certain factors like BMI, hypertension, diabetes, and positive family history of cancer are not predictive of prostate cancer detection. It is important to consider patient history, including family history and other risk factors, to identify individuals who may be at a higher risk of developing prostate cancer and to tailor screening and diagnostic strategies accordingly.

ROLE OF PATIENT HISTORY IN IDENTIFYING RISK FACTORS FOR PROSTATE CANCER

Prostate cancer (PCa) is a multifactorial disease influenced by a complex interplay of genetic, environmental, and lifestyle factors. Understanding the patient's history is pivotal in identifying risk factors and tailoring preventive strategies.

1. **Family History and Genetic Predisposition**:
   - **Family history** of prostate cancer has consistently emerged as a significant risk factor.
   - Numerous studies have demonstrated that men with a first-degree relative (father, brother) diagnosed with prostate cancer face an elevated risk [50, 51, 52].
   - **Genetic susceptibility**, including specific gene variants (e.g., BRCA1, BRCA2, HOXB13), contributes to familial clustering.
   - Integrating family history with polygenic risk scores enhances risk stratification, identifying individuals at higher risk of aggressive disease [51].
2. Age as a Key Determinant:
   - **Age** remains a critical risk factor for prostate cancer.
   - Incidence rises significantly after age 50, with the majority of cases occurring in men over 65 [52].
   - Longitudinal studies underscore the importance of age-related risk assessment [53].
3. **Ethnic and Geographical Variations**:

- **Race/ethnicity** plays a role in prostate cancer risk.
- African American men exhibit the highest incidence rates globally, followed by Caribbean and African men.
- **Geographical location** influences risk due to variations in lifestyle, diet, and environmental exposures.

4. **Hormonal Factors**:
   - **Androgens**, particularly testosterone, influence prostate cancer development.
   - Studies highlight the association between elevated androgen levels and increased risk.
   - **Obesity**, which affects hormonal balance, also contributes to risk.
5. **Dietary Patterns and Environmental Exposures**:
   - **Diet** plays a crucial role.
   - High intake of **red meat**, **processed meats**, and **dairy products** correlates with increased risk.
   - **Vitamin D deficiency**, exposure to **heavy metals**, and **pesticides** are potential environmental risk factors.
6. **Screening and Health Literacy**:
   - Patient history informs screening decisions.
   - **Prostate-specific antigen (PSA)** testing and digital rectal examination (DRE) are common screening methods.
   - However, health literacy barriers, cultural beliefs, and socioeconomic factors affect screening uptake [54].
7. **Communication and Shared Decision-Making**:
   - Effective communication between patients and healthcare providers is crucial.
   - Shared decision-making regarding screening, risk assessment, and lifestyle modifications empowers patients.detection, it has limitations in specificity, leading to false-positive results and overdiagnosis.
   - Invasiveness: The PSA test is minimally invasive, involving a simple blood draw, making it a convenient initial screening tool.
   - Accuracy: While the PSA test is widely used for early screening tool for prostate cancer. Description: The PSA test measures the levels of prostate-specific antigen in the blood, serving as a standard

TRANSRECTAL ULTRASOUND (TRUS):

Description: TRUS involves using ultrasound imaging to visualize the prostate gland and guide biopsies for tissue sam Accuracy: TRUS aids in targeting suspicious areas for biopsy, enhancing the accuracy of tissue sampling and diagnosis.provide valuable insights into the various diagnostic approaches utilized in clinical practice.

Diagnostic Methods for Prostate Cancer:
Prostate-Specific Antigen (PSA) Test:accuracy and invasiveness, each offering unique advantages and considerations in the detection andtechniques that differ in terms of characterization of the disease. prostate cancer encompass a range of Scientific research and review articles
Invasiveness: TRUS-guided biopsies are moderately invasive, involving the insertion of needles through the rectum to obtain tissue samples.

DIAGNOSIS OF PROSTATE CANCER

Current diagnostic methods for

TREATMENT

Management options for men with localized prostate cancer are stratified by cancer severity risk group. Active surveillance is recommended for men at very low- and low-risk. Standard treatment options for intermediate and high-risk are radical prostatectomy or radiotherapy plus androgen deprivation therapy (ADT).

Treatment options for men with locally advanced prostate cancer are external beam radiotherapy (EBRT) with or without hormonal therapy, brachytherapy, hormonal manipulations, radical prostatectomy with or without EBRT, and watchful waiting/active surveillance. Modalities that may be used to improve local disease control and manage symptoms include radiation therapy, hormonal manipulation, palliative surgery (transurethral resection of the prostate [TURP]), and brachytherapy combined with EBRT; alternative forms of radiation therapy and ultrasound-guided percutaneous cryosurgery are under clinical evaluation.

Treatment options for metastatic prostate cancer include hormonal manipulations, hormonal manipulations plus chemotherapy, bisphosphonates, EBRT with or without hormonal therapy, palliative radiation therapy, palliative TURP, and watchful waiting/active surveillance; radical prostatectomy with immediate orchiectomy is under clinical evaluation.

There are a variety of treatment options for men with castration-resistant prostate cancer. Despite resistance to initial ADT, most men respond to second-line hormonal therapies. The standard of care is to maintain castrate testosterone levels, even with castration-resistant disease. Preventive treatment for fractures and skeletal-related events (eg, supplemental calcium, vitamin D) are recommended for all patients, and either denosumab or zoledronic acid may be considered in patients with metastatic castration-resistant prostate cancer with bony metastases.

DRUG THERAPY

Luteinizing Hormone Releasing Hormone Agonists Indications for Androgen Deprivation Therapy (ADT)

Localized Prostate Cancer :

- Very Low Risk: Not recommended
- Low Risk: Not recommended as adjunct for radiotherapy unless necessary to reduce prostate size for brachytherapy.
- Intermediate Risk: Radiotherapy plus ADT or radical prostatectomy are standard treatment options. The addition of ADT to radiotherapy usually increases the risk and severity of sexual dysfunction and may cause other systemic side effects.
- High Risk: Radiotherapy plus ADT for 24 to 36 months or radical prostatectomy are standard treatment options.

Locally Advanced Prostate Cancer :

Orchiectomy or LHRH agonists are appropriate treatments for stage III prostate cancer.

Evidence that compared immediate hormonal therapy (orchiectomy or LHRH analog) with hormonal therapy at progression is conflicting, but the largest randomized trial (N=985; median age, 73 years) failed to show noninferiority of deferred treatment versus immediate treatment with regards to overall survival (6.5 vs 7.4 years).

Intermittent ADT was noninferior to continuous ADT with regards to overall survival. There was no significant difference in prostate cancer-specific survival or progression-free survival in men with advanced or recurrent prostate cancer, according to a systematic review and meta-analyses of 15 studies, 14 of which were at high risk of bias.

If external beam radiotherapy (EBRT) is the selected treatment option, ADT (luteinizing

hormone-releasing hormone [LHRH] agonist or orchiectomy) should be considered, especially in men without underlying moderate or severe comorbidities.

Metastatic Prostate Cancer :

The primary treatment for metastatic prostate cancer is hormonal manipulation. Hormonal manipulations that were effective as initial therapy were orchiectomy alone or with androgen blocker, LHRH agonists (with consideration of concomitant antiandrogens in specific patients), and estrogens. The two-year overall survival was similar with LHRH agonists compared with orchiectomy.

A cure is unlikely, but most patients achieve a subjective or objective response. It is uncommon for men to achieve an objective response with an alternative hormonal manipulation after progression on the initial form.

Evidence for immediate hormonal therapy versus delayed hormonal therapy at disease progression is inconclusive.

Intermittent androgen deprivation therapy (ADT) compared with continuous ADT was noninferior with regards to overall survival, and there was no significant difference in prostate cancer-specific survival or progression-free survival in men with advanced or recurrent prostate cancer, according to a systematic review and meta-analyses of 15 studies, 14 of which were at high risk of bias.

The addition of chemotherapy to hormonal therapy improved overall survival in randomized trials. The addition of docetaxel to hormonal manipulations improved 4- year overall survival by 9%, according to a systematic review and meta-analysis of 3 randomized trials (N=3206).

If EBRT is used for an attempted cure in highly selected stage patients with no radiographic evidence of metastases, the addition of hormonal therapy should be considered. Castration-Resistant Prostate Cancer Observation with continued ADT is a treatment option for men with nonmetastatic castration-resistant prostate cancer.

Castration-Resistant Prostate Cancer :

Observation with continued ADT is a treatment option for men with nonmetastatic castration-resistant prostate cancer.

REFERENCE

[1] Frontiers | Research trends and hotspots in prostate cancer associated .... https://www.frontiersin.org/journals/oncology/articles/10.3389/fonc.2023.1270104/full.

[2] Prostate Cancer Review: Genetics, Diagnosis, Treatment Options, and https://mdpi-

res.com/d_attachment/molecules/molecules-27-05730/article_deploy/molecules-27-05730-v2.pdf?version=1662455892.

[3] The Diagnosis and Treatment of Prostate Cancer : A Review - JAMA Network. https://jamanetwork.com/journals/jama/fullarticle/2633921.

[4] Cancers | Free Full-Text | Diagnosis and Treatment of Prostate ... - MDPI. https://www.mdpi.com/2072-6694/13/15/3660.

[5] Prostate Cancer Research Articles - NCI. https://www.cancer.gov/types/prostate/research/articles.

[6] https://doi.org/10.3389/fonc.2023.1270104.

[7] Moyer VA: Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2012; 157(2):120-134. PubMed Abstract: http://www.ncbi.nlm.nih.gov/...

[8] Greene KL. American Lirological Association. Prostate specific antigen best practice statement: 2009 update. JUrol. 2013;189:S2-11.

[9] The Current Status of Prostate Cancer* Mukund S. Joshi President, NAMS, Ann Natl Acad Med Sci (India), 54(4): 179-193, 2018

COMPREHENSIVE REVIEW OF OVARIAN CANCER

Mr. Rushikesh Chaudhari, Ms. Poonam Mulay, Ms Tejashree Deokule

Department of Pharmaceutical Chemistry, Dr. D.Y. Patil College of Pharmacy Akurdi, Pune.

ABSTRACT

Ovarian cancer is a significant health challenge for women globally, characterized by its high mortality rates and challenges in early detection. This comprehensive review aims to explore the epidemiology, etiology, risk factors, clinical presentation, diagnostic methods, molecular subtypes, and evolving treatment strategies for ovarian cancer. Understanding the complexities of ovarian cancer is crucial for improving patient outcomes and reducing the burden of this disease on women's health.

INTRODUCTION

Ovarian cancer encompasses a diverse group of malignancies arising from various cell types within the ovaries. It is the seventh most common cancer in women worldwide and ranks as the eighth leading cause of cancer-related deaths among women. The prognosis of ovarian cancer is often poor due to late-stage diagnosis, with the disease frequently metastasizing beyond the ovaries by the time of detection. The etiology of ovarian cancer is multifactorial, with genetic, hormonal, and environmental factors contributing to disease development. Notably, women with germline mutations in BRCA1 and BRCA2 genes have a significantly increased risk of developing ovarian cancer [6]. Other risk factors include a family history of ovarian or breast cancer, endocrine factors (such as early menarche or late menopause), obesity, and smoking. Advances in understanding ovarian cancer subtypes, molecular pathways, and treatment approaches have led to improved outcomes for some patients. However, challenges remain in early detection and effective management of advanced disease [18].

INCIDENCE AND PREVALENCE

The incidence of ovarian cancer varies geographically, with higher rates observed in developed countries such as North America and Europe. In the United States, ovarian cancer is the fifth leading cause of cancer-related deaths among women, with approximately 21,000 new cases and 14,000 deaths annually. Age is a significant risk factor for ovarian cancer, with the highest incidence rates observed in women aged 55 years and older. However, ovarian cancer can affect women of all ages, including young adults and adolescents. Approximately 20% of ovarian cancer cases occur in women under the age of 55 [12] ; [13]. The prevalence of specific histological subtypes of ovarian cancer varies, with epithelial ovarian tumours comprising the majority of cases. High-grade serous carcinoma (HGSC) is the most common subtype and is associated with aggressive clinical behaviour and poor outcomes. Other histological subtypes include endometrioid carcinoma, clear cell carcinoma, mucinous carcinoma, and low-grade serous carcinoma, each with distinct clinical and molecular characteristics[20].

RISK FACTORS AND ETIOLOGY

Several risk factors contribute to the development of ovarian cancer, including genetic predisposition, reproductive factors, hormonal factors, and lifestyle factors.

1. **Genetic Predisposition :**

Inherited mutations in BRCA1 and BRCA2 genes significantly increase the lifetime risk of developing ovarian cancer. Women with BRCA1 mutations have a 39% to 46% lifetime risk of ovarian cancer, while those with BRCA2 mutations have a 12% to 20% lifetime risk. Other genetic syndromes associated with ovarian cancer

Inherited mutations in BRCA1 and BRCA2 genes significantly increase the lifetime risk of developing ovarian cancer. Women with BRCA1 mutations have a 39% to 46% lifetime risk of ovarian cancer, while those with BRCA2 mutations have a 12% to 20% lifetime risk. Other genetic syndromes associated with ovarian cancer risk include Lynch syndrome (hereditary nonpolyposis colorectal cancer) and mutations in other DNA repair genes (e.g., RAD51C, RAD51D)[1].

2. Reproductive factors :

Reproductive factors that impact hormonal levels, such as early menarche, late menopause, nulliparity (never giving birth), and infertility, are associated with an increased risk of ovarian cancer [17]. Conversely, factors that reduce lifetime ovulatory cycles, such as pregnancy, breastfeeding, and oral contraceptive use, are protective against ovarian cancer.

3. Hormonal Factors :

Exposure to exogenous hormones, such as estrogen replacement therapy (ERT) and fertility treatments, may increase ovarian cancer risk. The use of hormonal contraceptives, however, is associated with a decreased risk of developing ovarian cancer.

4. Lifestyle Factors :

Obesity, tobacco smoking, and dietary factors (such as high-fat diets) have been implicated in ovarian cancer development. Obesity is associated with chronic inflammation, insulin resistance, and altered sex hormone levels, contributing to cancer progression [4] ; [6].

CLINICAL PRESENTAION AND SYMPTOMS

Ovarian cancer is sometimes called the "silent killer" because its early symptoms are not specific, and it is often diagnosed at a late stage. The clinical presentation of ovarian cancer varies depending on the disease stage and histological subtype.

1. Early-Stage Symptoms :

In the early stages, ovarian cancer may be asymptomatic or present with mild, nonspecific symptoms that can be mistaken for other benign conditions. Common early-stage symptoms include:

- Abdominal bloating or swelling
- Pelvic discomfort or pain
- Changes in bowel habits (constipation or diarrhoea)
- Urinary urgency or frequency
- Unexplained weight loss
- Fatigue and lethargy

These symptoms are often attributed to benign conditions, leading to diagnostic delays and advanced-stage presentation.

2. Advanced-Stage Symptoms :

As ovarian cancer progresses, symptoms may become more pronounced and may include:

- Persistent abdominal or pelvic pain
- Ascites (fluid buildup in the abdomen)
- Palpable abdominal or pelvic mass
- Bowel obstruction
- Pleural effusion (fluid in the lungs)
- Generalized symptoms of cancer-related cachexia (weight loss, fatigue, anorexia)

Recognizing the subtle signs and symptoms of ovarian cancer is critical for prompt diagnosis and timely intervention.

PATHOPHYSIOLOGY OF OVARIAN CANCER

Ovarian cancer originates from epithelial cells lining the ovarian surface or within the fallopian tubes, although rare subtypes arise from germ cells or stromal cells.

1. Epithelial Ovarian Cancer (EOC)

Epithelial ovarian cancer (EOC) accounts for approximately 90% of all ovarian cancers and includes high-grade serous carcinoma (HGSC), endometrioid carcinoma, clear cell carcinoma, and mucinous carcinoma. HGSC is the most common subtype and is characterized by TP53 mutations, genomic instability, and defects in homologous recombination DNA repair pathways.

2. High-Grade Serous Carcinoma (HGSC) [21]

High-grade serous carcinoma (HGSC) is the archetype of epithelial ovarian cancer and is characterized by rapid growth, extensive intraperitoneal spread, and frequent mutations in TP53 tumour suppressor gene. TP53 mutations impair DNA repair mechanisms, leading to chromosomal instability and aggressive tumour behaviour. Additional genomic alterations, such as BRCA1/2 mutations and CCNE1 amplifications, drive tumorigenesis and therapeutic resistance.

3. Endometrioid Carcinoma

Endometrioid carcinoma is associated with endometriosis and is characterized by mutations in PTEN, CTNNB1 (β-catenin), and ARID1A genes. Aberrant activation of the PI3K/AKT/mTOR signalling pathway promotes cell proliferation and survival, contributing to tumour progression [12].

4. Clear Cell Carcinoma

Clear cell carcinoma is frequently associated with ARID1A mutations and is prevalent in women with endometriosis. Dysregulated cellular metabolism, including increased glucose uptake and lipid accumulation, supports tumour growth and survival in a hypoxic microenvironment.

5. Mucinous Carcinoma

Mucinous carcinoma is characterized by KRAS mutations and is often diagnosed at earlier stages. However, its histological similarity to metastatic gastrointestinal tumours poses diagnostic challenges. Aberrant mucin production and mucin-mediated signalling pathways promote tumour growth and dissemination.

6. Germ Cell Tumours and Sex Cord-Stromal Tumours

Germ cell tumours, including teratomas, dysgerminomas, and yolk sac tumours, arise from pluripotent germ cells within the ovary. These tumours typically occur in young women and adolescents and are associated with favourable prognosis, especially when diagnosed early.

Sex cord-stromal tumours originate from specialized cells (granulosa cells, Sertoli cells) within the ovarian stroma and account for a small percentage of ovarian malignancies [5] ; [19]. These tumours are often hormonally active and may produce oestrogen or androgens, leading to endocrine manifestations.

CLINICAL PRESENTATION AND SYMPTOMS

The clinical presentation of ovarian cancer is often insidious, with nonspecific symptoms that can be attributed to other benign conditions. Early-stage ovarian cancer may be asymptomatic, leading to delayed diagnosis and advanced-stage presentation.

Recognizable symptoms of ovarian cancer include:

- Abdominal or pelvic pain
- Bloating or abdominal distension
- Changes in bowel habits (constipation or diarrhoea)
- Urinary urgency or frequency
- Unexplained weight loss

DIAGNOSIS

The diagnosis of ovarian cancer requires a systematic approach integrating medical history, physical examination, imaging studies, tumour markers, and histopathological analysis.

1. Medical History and Physical Examination :

A thorough medical history helps identify risk factors, family history of cancer, and presenting symptoms suggestive of ovarian cancer. Physical examination may reveal abdominal or pelvic masses, ascites, or signs of metastatic disease.

2. Imaging Studies :

Imaging modalities play a crucial role in evaluating suspected ovarian masses, assessing disease extent, and detecting metastases. Transvaginal ultrasound is often the initial imaging test of choice for assessing adnexal (ovarian) masses and characterizing their features[10]. Computed tomography (CT) scans, magnetic resonance imaging (MRI), and positron emission tomography (PET) scans are utilized for further evaluation and staging of ovarian cancer.

3. Tumour Markers :

Serum tumour markers, such as cancer antigen 125 (CA-125), are commonly used in the evaluation of ovarian cancer. CA-125 is elevated in the majority of epithelial ovarian cancers, although it lacks sensitivity and specificity, particularly in early-stage disease. Other tumour markers, including human epididymis protein 4 (HE4), CA 19-9, and carcinoembryonic antigen (CEA), may be utilized in conjunction with CA-125 to improve diagnostic accuracy and monitor disease progression[16] ; [20].

4. Histopathological Examination :

Definitive diagnosis of ovarian cancer requires histopathological confirmation through tissue biopsy or cytology. This is typically achieved via surgical exploration, either through laparoscopy or laparotomy, allowing for tissue sampling (biopsy) and staging of the disease [15]. Histological analysis identifies the specific subtype of ovarian cancer, guides treatment decisions, and informs prognosis.

MOLECULAR SUBTYPES OF OVARIAN CANCER

Ovarian cancer comprises a heterogeneous group of tumours characterized by distinct molecular profiles, histological features, and treatment responses. The classification of ovarian cancer subtypes has evolved with advances in genomic sequencing and molecular profiling techniques.

1. High-Grade Serous Carcinoma (HGSC) :

High-grade serous carcinoma (HGSC) is the most common and aggressive subtype of epithelial ovarian cancer, accounting for approximately 70% of cases. HGSC is characterized by TP53 mutations, genomic instability, and homologous recombination deficiency (HRD). Targeted therapies, such as PARP inhibitors, have shown efficacy in patients with HRD-positive HGSC.

2. Endometrioid Carcinoma :

Endometrioid carcinoma is characterized by mutations in PTEN, CTNNB1, and ARID1A genes and is associated with endometriosis. This subtype is often diagnosed at earlier stages and has a more favourable prognosis compared to HGSC [19].

3. Clear Cell Carcinoma :

Clear cell carcinoma is characterized by ARID1A mutations and is associated with endometriosis and insulin resistance. It tends to present at advanced stages and is less responsive to conventional chemotherapy [22] – [24].

4. Mucinous Carcinoma :

Mucinous carcinoma is characterized by KRAS mutations and is often diagnosed at earlier stages. It is typically less aggressive than other subtypes but may present diagnostic challenges due to its histological similarity to metastatic gastrointestinal tumours.

5. Low-Grade Serous Carcinoma :

Low-grade serous carcinoma is characterized by MAPK pathway alterations and is associated with a less aggressive clinical course compared to HGSC. Targeted therapies, such as MEK inhibitors, are being investigated for this subtype.

STAGING AND PROGNOSIS

The staging of ovarian cancer is based on the International Federation of Gynaecology and Obstetrics (FIGO) system, which considers the extent of tumour involvement, lymph node metastasis, and distant spread. Ovarian cancer is staged from I to IV, with higher stages indicating more advanced disease[3].

Prognosis in ovarian cancer varies widely depending on the stage at diagnosis, histological subtype, molecular characteristics, and response to treatment. The five-year survival rates range from over 90% for localized disease (Stage I) to less than 30% for advanced-stage disease with distant metastases (Stage IV).

TREATMENT STRATEGIES

The management of ovarian cancer is complex and multidisciplinary, involving surgery, chemotherapy, targeted therapy, immunotherapy, and, in selected cases, radiation therapy.

1. Surgery:

Surgical debulking (cytoreduction) is a cornerstone of ovarian cancer treatment and aims to achieve optimal tumour removal while minimizing residual disease. Surgical procedures may include:

- Total abdominal hysterectomy (removal of the uterus)
- Omentectomy (removal of omentum)
- Lymph node dissection (sampling or removal of lymph nodes)

The extent of surgical resection impacts prognosis and determines the need for adjuvant therapies.

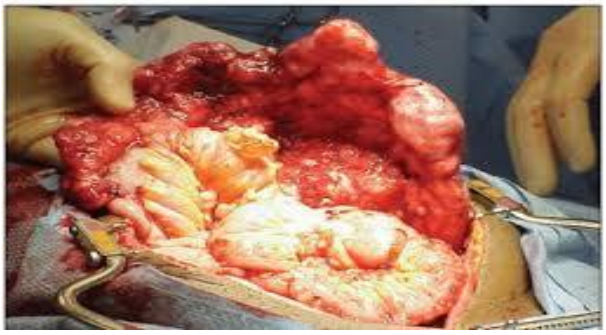


Figure 1 : Surgery

2. Chemotherapy : [11]

Chemotherapy is essential for adjuvant (post-surgical) and neoadjuvant (pre-surgical) treatment of ovarian cancer. Platinum-based chemotherapy regimens, such as carboplatin and paclitaxel, are standard first-line therapies for EOC.

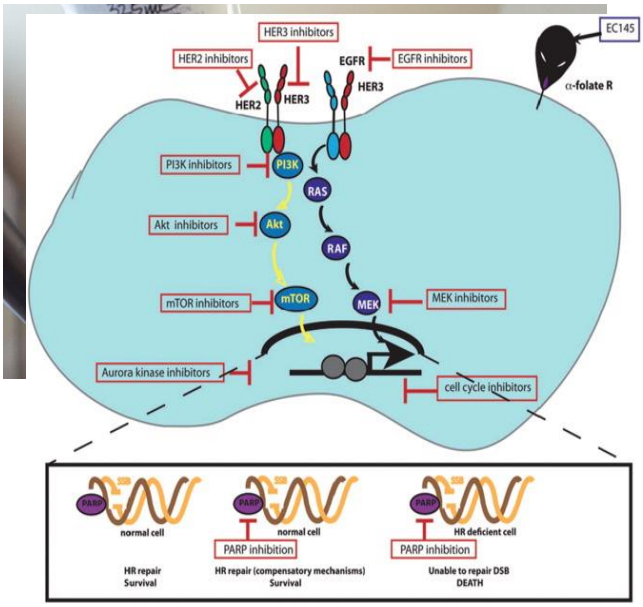


Figure 2 : Chemotherapy

3. Targeted Therapy :

Targeted therapies have transformed the treatment landscape for ovarian cancer, particularly in patients with specific molecular subtypes. Poly (ADP-ribose) polymerase (PARP) inhibitors, such as Olaparib and niraparib, have shown efficacy in patients with germline or somatic BRCA mutations and HRD-positive tumours.

Figure 3 : Targeted Therapy

4. Immunotherapy :

Immunotherapy, including immune checkpoint inhibitors targeting PD-1/PD-L1, is being investigated for ovarian cancer. Preliminary studies have shown promising results in a subset of patients with immunogenic tumours.

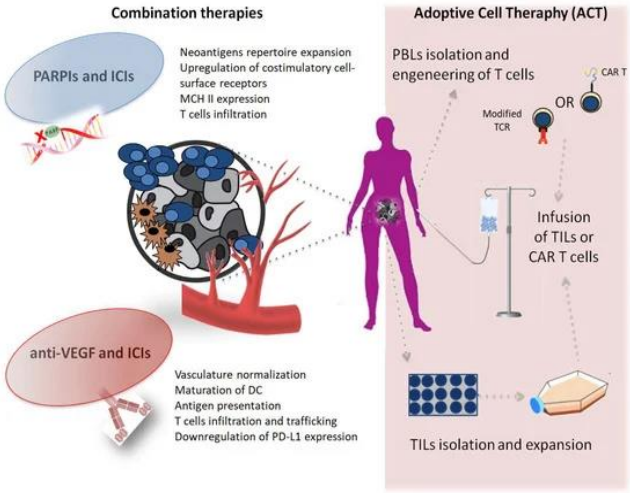
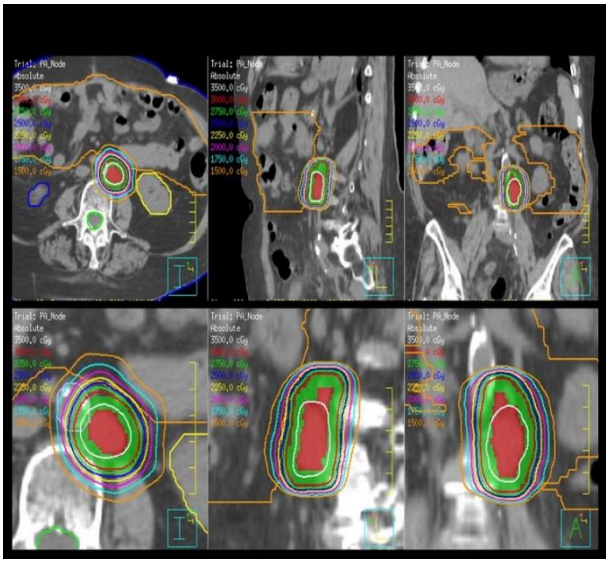


Figure 4: Immunotherapy

5. Radiation Therapy: [9]

Radiation therapy may be employed for palliation



of symptoms or localized disease recurrence. Techniques such as external beam radiation and intraperitoneal radioisotope therapy may be utilized based on individual patient needs and disease characteristics.

Figure 5 : Radiation Therapy

EMERGING THERAPIES AND FUTURE DIRECTIONS

Ovarian cancer research is rapidly evolving, with ongoing efforts to identify novel therapeutic targets, improve early detection methods, and enhance personalized treatment approaches.

1. Immunotherapy :

Immunotherapy, particularly immune checkpoint inhibitors targeting programmed cell death protein 1 (PD-1) and programmed cell death ligand 1 (PD-L1), is being investigated for ovarian cancer. Preliminary studies have shown promising results in a subset of patients with immunogenic tumors [17].

2. Biomarker-Driven Therapies :

Advances in genomic profiling and biomarker identification have led to the development of biomarker-driven therapies for ovarian cancer. Molecular testing is increasingly used to guide treatment decisions and identify patients likely to benefit from targeted therapies.

3. Precision Medicine :

Precision medicine approaches aim to tailor treatment strategies based on individual patient characteristics, including molecular subtypes, genetic mutations, and treatment responses. Integrated molecular profiling may facilitate the identification of optimal therapeutic combinations for patients with refractory disease.

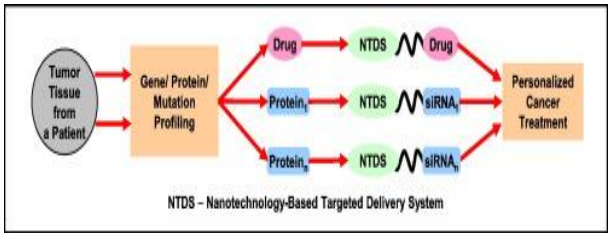
PROGNOSIS AND SURVIVORSHIP

Prognosis in ovarian cancer depends on multiple factors, including disease stage, histological subtype, molecular characteristics, and treatment response. The overall five-year survival rate for ovarian cancer is approximately 47% but varies widely based on disease stage at diagnosis.

Long-term survivorship and quality of life issues are important considerations in ovarian cancer care. Survivorship programs focus on addressing physical, emotional, and psychosocial needs, including fertility preservation, menopausal

symptoms, sexual health, and psychological support.

GRAPHICAL ABASTRACT



REFERENCES

1. Bast Jr RC, Hennessy B, Mills GB. The biology of ovarian cancer: new opportunities for translation. Nature Reviews Cancer. 2009;9(6):415-428.

2. Kurman RJ, Shih IM. The origin and pathogenesis of epithelial ovarian cancer: a proposed unifying theory. American Journal of Surgical Pathology. 2011;34(3):433-443.

3. Bowtell DD, Böhm S, Ahmed AA, et al. Rethinking ovarian cancer II: reducing mortality from high-grade serous ovarian cancer. Nature Reviews Cancer. 2015;15(11):668-679.

4. Cannistra SA. Cancer of the ovary. New England Journal of Medicine. 2004;351(24):2519-2529.

5. Vaughan S, Coward JI, Bast Jr RC, et al. Rethinking ovarian cancer: recommendations for improving outcomes. Nature Reviews Cancer. 2011;11(10):719-725.

6. Permuth-Wey J, Sellers TA. Epidemiology of ovarian cancer. Methods in Molecular Biology. 2009;472:413-437.

7. Patch AM, Christie EL, Etemad Moghadam D, et al. Whole-genome characterization of chemo resistant ovarian cancer. Nature. 2015;521(7553):489-494.

8. Bowtell DD. The genesis and evolution of high-grade serous ovarian cancer. Nature Reviews Cancer. 2010;10(11):803-808.

9. Lheureux S, Gourley C, Vergote I, Oza AM. Epithelial ovarian cancer. The Lancet. 2019;393(10177):1240-1253.

10. Cannistra SA. Is there a “best” choice of second-line agent in the treatment of recurrent, potentially platinum-sensitive ovarian cancer? Journal of Clinical Oncology. 2004;22(7):1125-1126.

11. Suh DH, Kim JW, Kang S. Current management of ovarian cancer. Korean Journal of Obstetrics and Gynaecology. 2014;57(2):93-113.

12. Jelovac D, Armstrong DK. Recent progress in the diagnosis and treatment of ovarian cancer. CA: A Cancer Journal for Clinicians. 2011;61(3):183-203.

13. Bowtell DD, Australian Ovarian Cancer Study Group. The genesis and evolution of high-grade serous ovarian cancer. Nature Reviews Cancer. 2015;10(11):803-808.

14. Matulonis UA, Sood AK, Fallowfield L. Howitt BE, Shukla SA, Sholl LM, et al. Association of somatic mutations in women with breast and ovarian cancers with human papillomavirus-related cervical disease. JAMA Oncology.

15. Bell DA. Origins and molecular pathology of ovarian cancer. Modern Pathology. 2005;18(S2):S19-S32.

16. Kobel M, Kalloger SE, Huntsman DG, et al. Differences in tumour type in low-stage versus high-stage ovarian carcinomas. International Journal of Gynaecological Pathology. 2008;27(3):380-384.

17. Gilks CB, Ionescu DN, Kalloger SE, et al. Tumour cell type can be reproducibly diagnosed and is of independent prognostic significance in patients with maximally debulked ovarian carcinoma. Human Pathology. 2008;39(8):1239-1251.

18. Verhaak RG, Tamayo P, Yang JY, et al. Integrative Genomics Analysis of Serous Ovarian Cancer. Cancer Cell. 2013;24(5):707-720.

19. Shih IM, Kurman RJ. Ovarian tumorigenesis: a proposed model based on morphological and molecular genetic analysis. American Journal of Pathology. 2004;164(5):1511-1518.

20. Karam A, Ledermann JA, Kim JW, Sehouli J, Lu K, Gourley C. Fifth Ovarian Cancer Consensus Conference: individualized therapy and patient factors. Annals of Oncology. 2019;30(4):644-646.

21. Tew WP, Mahdi H. Targeted therapy for ovarian cancer. American Journal of Obstetrics and Gynaecology. 2015;213(3):251-257.

22. Torre LA, Trabert B, DeSantis CE, et al. Ovarian cancer statistics, 2018. CA: A Cancer Journal for Clinicians. 2018;68(4):284-296.

23. Mutch DG. The role of genetic testing in gynaecologic cancer. JAMA. 2014;312(6):594-595.

24. Lim AW, Mesher D. Adjuvant therapy in early-stage epithelial ovarian cancer. Current Treatment Options in Oncology. 2015;16(8):38.

PANCREATIC CANCER

Ms. Rajashree Shinde, Mr. Omkar Shendge, Ms. Ankita Dudhal
Department of Pharmacology , Dr. D.Y. Patil College of Pharmacy Akurdi, Pune.

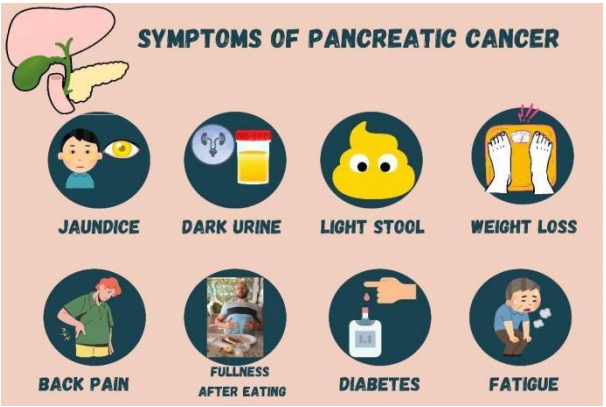
INTRODUCTION:

Pancreatic cancer is characterized by the first cell growth in the pancreas. Located behind the pancreas is the lower part of the stomach. It generates enzymes to help with food digestion and hormones to help control blood sugar.

What is most common among pancreatic cancers is pancreatic ductal adenocarcinoma. The cells around the pancreatic ducts, which carry digesting enzymes, are the starting point for this sort.

When there is the highest chance of a cure, pancreatic cancer is seldom found in its early stages. This is because it often takes longer for symptoms to manifest until the illness has spread to other organs. The level of your pancreatic cancer is taken into consideration by your healthcare team while

developing your treatment plan. chemotherapy, surgery, and radiation treatment.



ETIOLOGY

The most well acknowledged risk factor for pancreatic cancer is tobacco use. The following are additional factors:

- Being overweight
- Diabetes type I
- Prolonged pancreatitis
- History of pancreatic cancer in the family
- Genetic syndromes
- Elements related to lifestyle

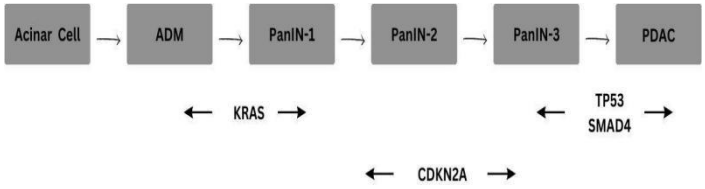
The underlying cause of chronic pancreatitis is unrelated to less than 5% of pancreatic cancer cases. Unless it is linked to chronic pancreatitis, alcohol use does not seem to be a risk factor for pancreatic cancer on its own.

It has been debatable whether having a hepatitis B infection increases the risk of pancreatic cancer. Recent evidence, however, point to a connection between the two illnesses.

PATHOPHYSIOLOGY

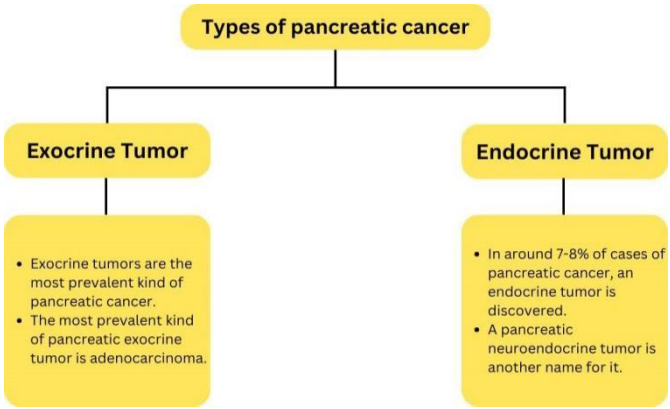
From non-neoplastic to non-invasive precursor, the pancreatic epithelium experiences a gradual accumulation of genetic alterations. tumours, to malignant growths. The process of pancreatic cancer involves several steps in its growth and progression. Intraepithelial Pancreatic Mucinous Neoplasms (IPMNs) and Pancreatic Intraepithelial Neoplasia (PanIN) are precursor lesions for pancreatic cancer. PanIN, the most prevalent antecedent lesion of pancreatic cancer, develops in the ductulus and tiny ducts. From PanIN lesions, pancreatic cancer develops into an invasive carcinoma. Lesions classified as low-grade (PanIN-1A/B) to high-grade (PanIN-3) based on cellular and nuclear abnormalities are called PanIN lesions. A number of alterations are collected that affect important genes (KRAS, CDKN2, TP53, SMAD4/DPC4, BRCA2). mRNAs, stromal associated factors, and dysregulated signalling pathways all contribute to the development of pancreatic cancer. In PanIN-1 lesions, oncogenic miRNAs are overexpressed, KRAS is mutated, and stromal associated factors are activated. In PanIN-2 lesions, inactivating mutations in the p16/CDKN2A gene are detected, and mucin 1 is overexpressed. TP53, BRCA2, and SMAD4

inactivating mutations are also linked to PanIN-3



lesions.

TYPES



DIAGNOSIS

When a patient's symptoms lead to concerns about pancreatic cancer, imaging and biopsies are utilized to confirm the diagnosis. The initial testing may include an abdominal ultrasound or CT scan; however, these procedures only yield a limited amount of information because they depend on internal body structures.

On the other hand, an IV contract-based ACT pancreas angiography scan provides more precise data and the ability to identify small cancers.

It can also show whether the illness has spread to other organs and how much of the blood vessels are affected.

Additionally, an MRI scan might clarify the kind of pancreatic tumour.

Endoscopic ultrasonography is another increasingly used imaging modality that uses endoscopy to examine tumours straight from the stomach or small intestine using a tiny probe.

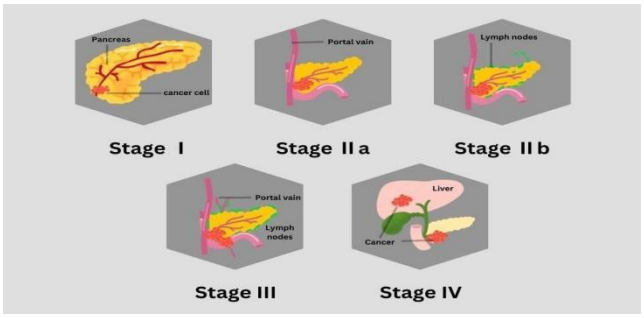
In parallel, a biopsy known as a fine needle aspiration (FN) can be carried out by introducing a tubelike a small needle into the tumour. The cells extracted are subsequently examined to determine whether the tumour is malignant.

Based on the side of the tumour and whether the illness has spread to neighbouring tissues, primarily blood vessels and organs, the stage of the cancer is identified after imaging.

Stage I & II denotes limited illness, such as tiny, localized tumours, that may only be verified by pathologic investigation following surgery. Tumours of stage I & II can be observed with or without the involvement of lymph nodes.

Stage III tumours are sometimes referred to as locally progressed since they may have wrapped around significant arteries and veins, making surgical removal impossible.

In stage IV, the cancer has progressed to other organs, most commonly the liver, the lungs, lymph nodes, or, less frequently, the bones.



TREATMENT

The course of treatment for pancreatic cancer is determined by the patient's personal preferences, overall health, and the stage of the disease. The primary goal is to eliminate the illness; but, if that isn't possible, the focus may change to improving quality of life and preventing further harm. Treatment options include chemotherapy, radiotherapy, surgery, or a combination of these.

Surgery may not always be the best course of action for advanced pancreatic cancer, thus other treatments like chemotherapy may be performed prior to surgery.

1. **Chemotherapy**: Chemotherapy is a powerful treatment for pancreatic cancer, using powerful medications to kill cells. It can be used alone or

in combination and can be administered intravenously or combined with radiation treatment. Specialty hospitals provide treatment, eliminate cancer cells post-surgery, control cancer that has spread, and relieve symptoms like pain.

2. **Radiation therapy**: Radiation therapy uses high-powered beams to target cancer cells, often following chemotherapy. It can be used before or after surgery and can help reduce symptoms like discomfort when the disease spreads to other body areas. Combining chemotherapy and radiation therapy may be the first line of treatment.
3. **Immunotherapy**: Immunotherapy is a medical intervention that stimulates the immune system to eradicate cancerous cells from the body. The immune system targets bacteria and other foreign cells in the body to prevent illness. Cancer cells steer clear of the immune machine with a view to live. Immunotherapy aids withinside the immune system's capacity to become aware of and do away with cancerous cells. If your pancreatic cancer contains certain DNA alterations that increase the likelihood that the disease may respond to these therapies, immunotherapy may be a possibility for you.

4. **Clinical trials:** Research on novel therapies is done through clinical trials. The possibility to check the latest healing procedures is obtainable with the aid of using those studies. Possible negative consequences may not be known. Find out from your medical provider if you qualify for a clinical study.

5. **Palliative care**: Palliative care is a medical strategy that aims to lessen discomfort and symptoms while offering patients with life-threatening diseases comfort and support. In order to improve the patient's quality of life, a group of medical professionals, including doctors and nurses, work together with them and the healthcare team.

REFERENCE

1. https://www.mayoclinic.org/diseases-conditions/pancreatic-cancer/symptoms-causes/syc- 20355421

2. https://www.cancer.org/cancer/types/pancreatic-cancer/detection-diagnosis-st aging/signs-and- symptoms. htmlfile:///C:/Users/Dell/Downloads/admin,+Rikarni.pdf

3. https://www.hopkinsmedicine.org/health/conditions-and-diseases/pancreatic-cancer/pancreatic-cancer-types

4. https://www.animatedpancreaspatient.com/en-pancreas/home

5. https://www.mayoclinic.org/diseases-conditions/pancreatic-cancer/diagnosis-treatment/drc- 20355427

6. https://www.researchgate.net/figure/Pancreatic-cancer-pathogenesis-The-sche matic-and-mouse-histology-demonstrate-step-wise_fig1_346882775

7. https://www.cancer.gov/types/pancreatic/hp/pancreatic-treatment-pdq

8. https://www.cancer.gov/types/pancreatic/patient/pancreatic-treatment-pdq#:~:text=Pancreatic%20cancer%20is%20a%20type,is%20difficult%20to%20dia

OUR SOCIAL MEDIA PLATFORMS

Facebook:
https://www.facebook.com/Dypcopakurdipune/
+76 Instagram:
https://www.instagram.com/dypcopakurdipune/
Twitter:
https://twitter.com/Dypcopharmacy
LinkedIn:
https://www.linkedin.com/in/dypcop-akurdi-949413b1/

Dr. D. Y. Patil College of Pharmacy, D. Y. Patil Educational Complex, Sector 29, Nigidi Pradhikaran, Akurdi, Pune 411044.