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CURRENT ROLE OF ONCOS-12, PDT, PDL-1, AR SIGNALLING, HER2 AND IMMUNOTHERAPEUTIC APPROACHES IN DIVERGENT CANCERS

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Abstract: Cancer is characterized by uncontrolled cell growth and acquisition of metastatic properties. Some common forms include breast cancer, lung cancer, prostate cancer, colorectal cancer, and leukemia. Despite significant advances in research and treatment modalities, cancer remains a significant public health challenge, with millions of new cases diagnosed each year. For effective cancer therapy, it is necessary to improve and develop novel strategies for effective delivery of chemotherapeutics to cancer cells. Conventional chemotherapeutic agents accumulate both in normal and tumor cells due to non-specificity. The ultimate goal of cancer therapy is to reduce systemic toxicity and improve the quality of life. The landscape of cancer treatment has improved significantly over the past four decades. Novel treatment with ONCOS-102, developed by Targovax, is a genetically modified adenovirus designed to selectively infect cancer cells in lungs and stimulate anti-tumor immune responses has been developed in recent years. New approaches, such as Photodynamic therapy(PDT) is a minimally invasive treatment that utilizes a photosensitizing agent, light, and oxygen to selectively destroy oral cancer cells. One photosensitizer that has shown promise in oral cancer treatment is 5-aminolevulinic acid of oral cancer. Immune checkpoint inhibitors, such as anti-PD-1 or anti-PD-L1 antibodies, block this interaction, thereby reactivating T cell-mediated anti-tumor immune responses in Breast cancer. With the development of molecular biology and genomics, targeted therapy research has achieved a breakthrough development, including anti-angiogenesis, immune checkpoint inhibitors, and other treatments that are efficient for treatment of cervical cancer. a novel approach to the development of AR antagonists is to target the amino-terminus domain of the AR. The small molecule AR antagonist EPI-001 inhibits protein–protein interactions necessary for AR transcriptional activity. A promising novel approach for treating gastric cancer involves targeting the human epidermal growth factor receptor 2 (HER2), which is overexpressed in approximately 20% of gastric cancers.

Index Terms **– Photodynamic therapy, programmed death-ligand 1, human epidermal growth factor receptor 2, Androgen Receptor Signaling Pathway**

I. INTRODUCTION

Cancer is characterized by uncontrolled cell growth and acquisition of metastatic properties. In most cases, activation of oncogenes and/or deactivation of tumor suppressor genes lead to uncontrolled cell cycle progression and inactivation of apoptotic mechanisms (Sarkar *et al*., 2013). There are various types of cancer, each with its unique characteristics and behaviors. Some common forms include breast cancer, lung cancer, prostate cancer, colorectal cancer, and leukemia. Despite significant advances in research and treatment modalities, cancer remains a significant public health challenge, with millions of new cases diagnosed each

year (Bray *et al*., 2018)

The etiology of cancer is multifactorial, involving a complex interplay of genetic, environmental, and lifestyle factors. Risk factors such as tobacco use, exposure to carcinogens, unhealthy diet, physical inactivity, and certain infections contribute to the development of cancer. Additionally, genetic predisposition can also play a significant role, with certain individuals inheriting mutations that increase their susceptibility to specific types of cancer (Rahman *et al.*, 2018)

The hallmarks of cancer comprise six biological capabilities acquired during the multistep development of human tumors. The hallmarks constitute an organizing principle for rationalizing the complexities of neoplastic disease. They include sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis. Underlying these hallmarks are genome instability, which generates the genetic diversity that expedites their acquisition, and inflammation, which fosters multiple hallmark functions (Hanahan and Weinberg, 2011)

Early detection and diagnosis are crucial for improving cancer outcomes, as treatment efficacy is often higher in the early stages of the disease. Screening programs, advanced imaging technologies, and biomarker testing have facilitated earlier detection and intervention, leading to improved survival rates for many types of cancer (Crosby *et al*., 2022).

Treatment approaches for cancer vary depending on factors such as the type and stage of the disease, as well as the patient's overall health and preferences. Common treatment modalities include surgery, chemotherapy, radiation therapy, immunotherapy, targeted therapy, and hormone therapy. In recent years, there has been significant progress in the development of precision medicine approaches, which involve tailoring treatment strategies based on the individual characteristics of the tumor and the patient (Debela *et al*., 2021)

When cancer is detected at the earliest stages, treatment is more effective and survival drastically improves. Yet ~50% of cancers are still only detected at an advanced stage. Improved earlier detection of cancer could substantially increase survival rates. Although recent advances in early detection have saved lives, further innovations and development of early cancer detection approaches are needed. The field is evolving rapidly, owing to advances in biological understanding and an increasing pace of technological progress (Crosby *et al*., 2022)

II TYPES OF CANCERS

1. Breast Cancer: Breast cancer is one of the most common cancers affecting women worldwide. It typically originates in the milk ducts or lobules of the breast tissue and can spread to nearby lymph nodes and other parts of the body. Risk factors include family history, genetic mutations (such as BRCA1 and BRCA2), hormonal factors, and lifestyle choices. Treatment may involve surgery, chemotherapy, radiation therapy, hormone therapy, and targeted therapy (DeSantis *et al*., 2019).
2. Lung Cancer: Lung cancer is a leading cause of cancer-related deaths globally, with smoking being the primary risk factor. It arises from the cells lining the airways and lungs and is often diagnosed at advanced stages. Lung cancer can be categorized into two main types: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Treatment options include surgery, chemotherapy, radiation therapy, immunotherapy, and targeted therapy (Hirsch *et al*., 2016).
3. Prostate Cancer: Prostate cancer develops in the prostate gland, which is part of the male reproductive system. It is the most common cancer in men, with age being the primary risk factor. Prostate cancer often grows slowly and may not cause symptoms in the early stages. Treatment options include active surveillance, surgery, radiation therapy, hormone therapy, chemotherapy, and immunotherapy (Siegel *et al*., 2020)
4. Colorectal Cancer: Colorectal cancer affects the colon or rectum and usually develops from precancerous polyps in the lining of the intestine. Risk factors include age, family history, inflammatory bowel disease, diet high in red and processed meats, obesity, and lack of physical activity. Screening tests such as colonoscopy can help detect colorectal cancer early when it is most treatable. Treatment may involve surgery, chemotherapy, radiation therapy, targeted therapy, and immunotherapy (Keum *et al*., 2019)
5. Leukemia: Leukemia is a type of cancer that affects the blood and bone marrow, leading to the overproduction of abnormal white blood cells. There are several types of leukemia, including acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), and chronic myeloid leukemia (CML). Risk factors vary depending on the type of leukemia but may include exposure to radiation, certain chemicals, genetic factors, and some viral infections. Treatment options include chemotherapy, targeted therapy, radiation therapy, stem cell transplantation, and immunotherapy (Arber *et al*., 2016).

6. Melanoma: Melanoma is a type of skin cancer that originates in the pigment-producing cells called melanocytes. It is often associated with exposure to ultraviolet (UV) radiation from sunlight or tanning beds. Risk factors include fair skin, a history of sunburns, family history of melanoma, and having numerous moles or atypical moles. Treatment options may include surgery, chemotherapy, radiation therapy, immunotherapy, and targeted therapy (Schadendorf *et al*., 2018).

7. Ovarian Cancer: Ovarian cancer develops in the ovaries, which are part of the female reproductive system. It is often diagnosed at an advanced stage because early-stage ovarian cancer may not cause noticeable symptoms. Risk factors include age, family history, inherited genetic mutations (such as BRCA1 and BRCA2), and certain reproductive factors. Treatment options include surgery, chemotherapy, targeted therapy, and radiation therapy (Reid *et al*., 2014).

8. Pancreatic Cancer: Pancreatic cancer arises in the tissues of the pancreas, an organ located behind the stomach. It is often diagnosed at an advanced stage and has a poor prognosis. Risk factors include smoking, obesity, family history, chronic pancreatitis, and certain genetic syndromes. Treatment options may include surgery, chemotherapy, radiation therapy, targeted therapy, and immunotherapy (Rahib *et al*., 2014).

9. Bladder Cancer: Bladder cancer develops in the lining of the bladder, which stores urine. It is often characterized by blood in the urine and frequent urination. Risk factors include smoking, exposure to certain chemicals, chronic bladder inflammation, and older age. Treatment options depend on the stage and may include surgery, chemotherapy, immunotherapy, radiation therapy, and targeted therapy (Cumberbatch *et al*., 2018).

10. Brain Cancer (Glioblastoma Multiforme): Glioblastoma multiforme is a type of brain cancer that originates in the glial cells, which support and nourish the neurons in the brain. It is highly aggressive and difficult to treat due to its location and invasive nature. Risk factors are not well understood, but exposure to ionizing radiation may increase the risk. Treatment typically involves surgery, radiation therapy, chemotherapy, and targeted therapy (Stupp *et al*., 2005)

III LUNG CANCER

Lung cancer is a malignant tumor that starts in the cells of the lung. It is the leading cause of cancer-related deaths worldwide for both men and women. Lung cancer typically arises from the epithelial cells lining the airways and may spread (metastasize) to other parts of the body, such as the lymph nodes, bones, brain, or liver.

There are two main types of lung cancer: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC is the most common type, accounting for approximately 85% of all cases, while SCLC accounts for about 15% of cases. These types are further classified based on histological subtypes, including adenocarcinoma, squamous cell carcinoma, and large cell carcinoma for NSCLC, and small cell carcinoma for SCLC. Several factors contribute to the development of lung cancer, with smoking being the most significant risk factor. Other risk factors include exposure to secondhand smoke, occupational exposures (such as asbestos, radon, and certain chemicals), air pollution, genetic predisposition, and family history of lung cancer.

Lung cancer often does not cause noticeable symptoms in its early stages, and symptoms may vary depending on the type and location of the tumor. Common symptoms may include persistent cough, coughing up blood, shortness of breath, chest pain, hoarseness, unexplained weight loss, fatigue, and recurrent respiratory infections.

Diagnosis of lung cancer typically involves imaging tests such as chest X-rays, CT scans, or PET scans, followed by biopsy to confirm the presence of cancer cells and determine the type and stage of the disease. Staging is crucial for determining the most appropriate treatment approach and prognosis.

Treatment options for lung cancer depend on the type, stage, and molecular characteristics of the tumor but may include surgery, radiation therapy, chemotherapy, targeted therapy, immunotherapy, or a combination of these modalities. Advances in precision medicine have led to the development of targeted therapies and immunotherapies that can specifically target cancer cells while sparing normal cells, resulting in improved outcomes and quality of life for some patients. Despite advancements in treatment, the prognosis for lung cancer remains generally poor, particularly for advanced-stage disease. Prevention efforts focused on smoking cessation, reducing exposure to carcinogens, and early detection through screening programs are critical in reducing the burden of lung cancer and improving patient outcomes.

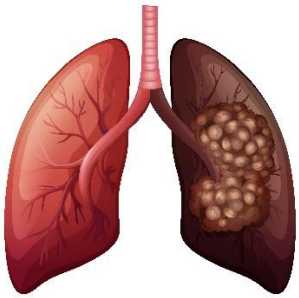

Figure 1: Lung cancer

Novel approaches for lung cancer treatment

❖ Utilizing oncolytic viruses as a therapeutic strategy. Oncolytic viruses are viruses that selectively infect and replicate within cancer cells, leading to their destruction while sparing normal cells. One such oncolytic virus showing promise in lung cancer treatment is the adenovirus-based therapy known as **ONCOS-102.**

ONCOS-102, developed by Targovax, is a genetically modified adenovirus designed to selectively infect cancer cells and stimulate anti-tumor immune responses. The virus is armed with a GM-CSF (granulocyte-macrophage colony-stimulating factor) transgene, which enhances the activation and recruitment of immune cells to the tumor microenvironment.

The mechanism of action of ONCOS-102 involves several steps:

- Selective Infection: ONCOS-102 is engineered to selectively infect cancer cells that often overexpress specific receptors, such as CD46, which the virus utilizes for cell entry.
- Viral Replication and Cell Lysis: Once inside the cancer cell, ONCOS-102 replicates, leading to the lysis (bursting) of infected cancer cells. This process releases viral particles and tumor-associated antigens.
- Immune Activation: The release of tumor-associated antigens from lysed cancer cells triggers an immune response. The GM-CSF transgene carried by ONCOS-102 further enhances this response by stimulating the maturation and activation of dendritic cells, which are crucial for initiating adaptive immune responses.
- Tumor-Specific Immune Response: Activated dendritic cells present tumor antigens to T cells, leading to the activation of tumor-specific cytotoxic T lymphocytes (CTLs) that recognize and kill cancer cells.
- Tumor Microenvironment Modulation: ONCOS-102 also helps modulate the tumor microenvironment by promoting the infiltration of immune cells, such as T cells and natural killer (NK) cells, and reducing immunosuppressive factors, thus creating a more favorable environment for anti-tumor immune responses (Wang *et al*., 2022).

❖ The use of chimeric antigen receptor (CAR) T-cell therapy. CAR T-cell therapy is a type of immunotherapy that involves genetically modifying a patient's own T cells to express chimeric antigen receptors, which enable them to recognize and attack cancer cells with specific antigens

Mechanism of Action:

- T Cell Collection: The process begins with the collection of T cells from the patient's blood through leukapheresis.
- Genetic Modification: The collected T cells are then genetically modified in the laboratory to express CARs specific to antigens present on the surface of lung cancer cells. These CARs are typically composed of an antigen-recognition domain, a hinge region, a transmembrane domain, and one or more intracellular signaling domains.
- Expansion and Activation: The modified T cells are expanded in culture to generate a large population of CAR T cells. They are also activated to become cytotoxic against cancer cells.
- Infusion: Once a sufficient number of CAR T cells have been produced, they are infused back into the patient's bloodstream.
- Recognition and Killing: The infused CAR T cells traffic to the tumor site, where they recognize lung cancer cells expressing the target antigen through their CARs.
- Cytotoxic Activity: Upon antigen recognition, CAR T cells become activated and release cytotoxic molecules, such as perforin and granzymes, to induce apoptosis (cell death) in the cancer cells.
- Persistence and Memory: Some CAR T cells may persist in the patient's body as memory cells, providing long-term surveillance against cancer recurrence (Martinez *et al.,* 2019) (Xio *et al.,* 2021)

IV. ORAL CANCER

Oral squamous cell carcinoma (OSCC) is a combination of highly malignant tumors that may emerge from the epithelium's surface, submucosal tissue, or small salivary glands. Almost 85% 95% of all oral cancer is OSCC. Oral cancer is still the sixth cause of death in the world despite all advanced methods used for detection and treatment because of its relapses, resistance, and post-treatment failure. Like any other disease, diagnosis of oral cancer is an important step starting with biopsy of the concerning area then investigation with computerized tomography (CT), Magnetic resonance imaging (MRI), positron emission tomography (PET) scan to determine if the tumor has metastases to distant parts depending on the grade or size of the tumor. Oral cancer involves the rapid growth of cells besides the ability of these cells to secrete enzymes, angiogenetic factors, growth factors, invasion factors, and many other elements that encourages the disease to disseminate. The traditional treatment of oral cancer includes several approaches such as surgery, radiotherapy, and chemotherapy.

Nanotechnology is a field of research used for detecting and targeting a single cancerous cell, delivering and releasing drugs in a regulated manner, with enormous specificity and sensitivity so, it holds vast power for defeating many obstacles related to traditional methods: problems in detection, treatment, and diagnosis of cancer. Nanodentistry deals with materials whose size <100 nm in at least one dimension, therefore, have a much surface area/unit mass compared to greater particles. Many nanoparticles are used in the diagnosis and treatment of oral cancer such as carbon nanotubes, nanoshells, polymeric nanoparticles, dendrimers, quantum dots, and polynucleotide nanoparticles (Sabea *et al.*, 2023).

Figure 2: Oral cancer

Novel approaches for oral cancer treatment

- ❖ Photodynamic therapy (PDT): Photodynamic therapy is a minimally invasive treatment that utilizes a photosensitizing agent, light, and oxygen to selectively destroy cancer cells. One photosensitizer that has shown promise in oral cancer treatment is 5-aminolevulinic acid (5-ALA (Biel *et al*., 2006)

The mechanism of action of photodynamic therapy with 5-ALA involves several steps:

- Administration of Photosensitizer: Patients are administered 5-aminolevulinic acid (5-ALA) orally or topically. 5-ALA is a precursor molecule in the heme biosynthesis pathway and is selectively taken up by rapidly dividing cells, including cancer cells.
- Conversion to Porphyrins: Within the cancer cells, 5-ALA is metabolized to protoporphyrin IX (PpIX), a photosensitizing molecule. PpIX accumulates preferentially in cancer cells due to their higher metabolic activity and reduced ability to excrete the photosensitizer compared to normal cells.
- Activation by Light: After a sufficient amount of time for accumulation, the cancerous tissue is exposed to light of a specific wavelength that corresponds to the absorption peak of PpIX. Typically, a laser or LED light source is used for this purpose.
- Generation of Reactive Oxygen Species (ROS): When activated by light, PpIX in the cancer cells undergoes a photochemical reaction that leads to the production of reactive oxygen species (ROS), such as singlet oxygen and free radicals. These ROS cause oxidative damage to cellular components, including proteins, lipids, and DNA, ultimately leading to cell death.
- Selective Destruction of Cancer Cells: The generated ROS selectively destroy the cancer cells in the illuminated area while sparing surrounding healthy tissues (Malik, 2020)

- ❖ Green Tea Extract
  - The extract of Green tea contains polyphenol epigallocatechin 3- gallate (EGCG) in great amounts that regulate apoptosis, arrests cells in the G0/G1 phase, and blocks angiogenesis over inhibition the secretion of vascular endothelial growth factor receptor (VEGFR) in tumor cells and phosphorylation of VEGFR showed that partial or complete relapse among oral premalignant lesions patients received green tea extract in phase II randomized, placebo-controlled. However, this study demonstrated that

high doses of the green tea extract give a great response than the low doses of it and this may refer to downregulation of stromal VEGF expression in patients taking higher doses of the extract and a potential effect of green tea extract resulting in angiogenesis inhibition (Tsao *et al*., 2009).

- Curcumin has been determined as an effective agent in the chemoprevention of breast, colon, prostate, and oral cancers (Sabea *et al*., 2023). Many studies in vitro have determined its ability to inhibit the cyclooxygenase-2 (COX-2) and nuclear factor-kappa B (NF-κB) gene expression in oral premalignant cancer. Chronic exposure to mutagens developed the reactive oxygen species and inflammation resulting in irregular activation of NF-κB and development of OSCC (Fang *et al*., 20178) (Al-Sharifi *et al*., 2019). The antioxidant activity of curcumin by oral leukoplakia, increasing salivary as well as serum concentrations of vitamin C and E in lichen planus and submucous fibrosis patients. The biotransformation of curcumin in the gut and enterohepatic cycling of metabolites result in the poor bioavailability of curcumin and make it more difficult to use as a chemoprevention agent. Many studies are recommended to determine the potential use of curcumin as a chemoprevention agent in oral cancer (Sabea *et al*., 2023)

V. BREAST CANCER :

Breast cancer is the most common cause of cancer in women and the second most common cause of cancer death in women in the U.S. Breast cancer refers to cancers originating from breast tissue, most commonly from the inner lining of milk ducts or the lobules that supply the ducts with milk. Breast cancer can manifest as various types, with some being more aggressive than others. The most common types include invasive ductal carcinoma, which starts in the milk ducts and then invades nearby tissue, and invasive lobular carcinoma, which begins in the lobules and can spread to other parts of the breast (Sharma *et al*., 2010).

Several risk factors can increase the likelihood of developing breast cancer, including age, gender, family history, genetics (mutations in BRCA1 and BRCA2 genes), hormonal factors (early menstruation, late menopause, hormone replacement therapy), lifestyle factors (obesity, alcohol consumption), and exposure to radiation or certain chemicals (Sun *et al.,* 2017).

Early-stage breast may not cause any noticeable symptoms and may only be identified with a routine screening mammogram. But it can cause a range of symptoms including: Lump or mass in the breast, which is usually painless, Changes in shape or size of the breast, Changes to skin of breast (reddening, thickening, or dimpling of skin), Warm breast, Swollen lymph nodes in armpit or above collarbone, Nipple changes, including discharge, blistering, pain, and inversion, Breast pain (Yale medicine). Imaging modalities for diagnosis and staging of breast cancer comprise mammography, digital breast tomosynthesis (DBT), ultrasound, contrast-enhanced mammography (CEM), and magnetic resonance imaging (MRI) (Gilbert *et al*., 2019)

Treatment options vary depending on the type and stage of breast cancer but may include surgical resection is either lumpectomy or mastectomy in combination with axillary assessment, chemotherapy, radiotherapy, endocrine therapy, targeted therapy, immunotherapy, gene therapy, and other innovative treatment strategies in early-stage and metastatic breast cancer (Wang *et al*., 2023)

Novel approaches for breast cancer treatment

- A novel approach for breast cancer treatment involves the use of immune checkpoint inhibitors, particularly those targeting the programmed death-ligand 1 (PD-L1)/programmed cell death protein 1 (PD-1) pathway. This approach aims to harness the body's immune system to recognize and eliminate cancer cells. Here's a brief overview of the mechanism of action:

  1. **Immune Checkpoint Inhibition:** Cancer cells often exploit immune checkpoint pathways, such as the PD-L1/PD-1 pathway, to evade immune surveillance. PD-L1, expressed on cancer cells, interacts with PD-1 receptors on T cells, leading to T cell exhaustion and immune tolerance. Immune checkpoint inhibitors, such as anti-PD-1 or anti-PD-L1 antibodies, block this interaction, thereby reactivating T cell-mediated anti-tumor immune responses.\

  2. **Tumor Cell Recognition and Destruction:** In breast cancer, immune checkpoint inhibitors can enhance the recognition and elimination of cancer cells by the immune system. By blocking the PD-L1/PD-1 pathway, these inhibitors restore T cell activity, allowing T cells to recognize and attack cancer cells more effectively.

3. Tumor Microenvironment Modulation: Immune checkpoint inhibitors can also modulate the tumor microenvironment by promoting the infiltration of immune cells, such as cytotoxic T lymphocytes (CTLs), into the tumor bed. This leads to a more favorable immune milieu, conducive to anti-tumor immune responses.

- A novel approach for breast cancer treatment involves the use of poly (ADP-ribose) polymerase (PARP) inhibitors. PARP inhibitors have emerged as promising therapeutic agents, particularly in breast cancers with deficiencies in DNA damage repair pathways, such as those with mutations in BRCA1 and BRCA2 genes. Here's a brief overview:

  1. Exploiting Synthetic Lethality: PARP inhibitors exploit the concept of synthetic lethality, particularly in breast cancers with mutations in BRCA1 and BRCA2 genes. These genes play essential roles in DNA repair via homologous recombination (HR). In cells with intact HR pathways, PARP inhibition leads to the accumulation of single-strand DNA breaks. However, these breaks can be efficiently repaired. In contrast, in cells with defective HR pathways (e.g., BRCA-mutated cells), the inability to repair single-strand DNA breaks results in the conversion of these breaks into double-strand breaks during DNA replication. This ultimately leads to genomic instability and cell death.

  2. Induction of Apoptosis: The accumulation of unrepaired DNA damage, particularly double-strand breaks, triggers apoptosis (programmed cell death) in cancer cells, resulting in tumor regression.

  3. Enhancing Sensitivity to DNA-Damaging Agents: PARP inhibitors can also sensitize cancer cells to DNA-damaging agents, such as chemotherapy or radiation therapy, by further impairing DNA repair mechanisms, thus enhancing the cytotoxic effects of these treatments (Meneze *et al*., 2022)

VI CERVICAL CANCER :

Cervical cancer is a type of cancer that occurs in the cells of the cervix, the lower part of the uterus that connects to the vagina. It is primarily caused by persistent infection with high-risk strains of the human papillomavirus (HPV), a sexually transmitted infection. HPV infection is very common, but in most cases, the immune system clears the virus without causing any health problems. However, persistent infection with high-risk HPV types can lead to changes in cervical cells that may progress to cancer over time. Cervical cancer is one of the most preventable and treatable forms of cancer, primarily due to the availability of screening tests such as the Pap test (Papanicolaou smear) and HPV testing. These tests can detect precancerous changes or early-stage cancer in the cervix, allowing for early intervention and treatment.

Despite the availability of screening programs, cervical cancer remains a significant global health concern, particularly in low- and middle-income countries where access to screening and healthcare services may be limited. Factors such as lack of awareness, limited resources, cultural barriers, and inadequate vaccination coverage against HPV contribute to the burden of cervical cancer in these regions.

Symptoms of cervical cancer may include abnormal vaginal bleeding, pelvic pain, pain during intercourse, and unusual vaginal discharge. However, early-stage cervical cancer may not cause any symptoms, underscoring the importance of regular screening for early detection.

Treatment options for cervical cancer depend on the stage of the disease but may include surgery (such as hysterectomy or removal of lymph nodes), radiation therapy, chemotherapy, targeted therapy, or a combination of these modalities. Advances in treatment approaches, including minimally invasive surgery and precision medicine, have improved outcomes and quality of life for cervical cancer patients. Preventive measures for cervical cancer include HPV vaccination, regular screening with Pap tests and HPV tests, practicing safe sex, and avoiding tobacco use. Public health efforts to increase vaccination rates, improve access to screening and treatment services, and raise awareness about cervical cancer and its prevention are essential in reducing the global burden of this disease (Arbyn *et al.*, 2020)

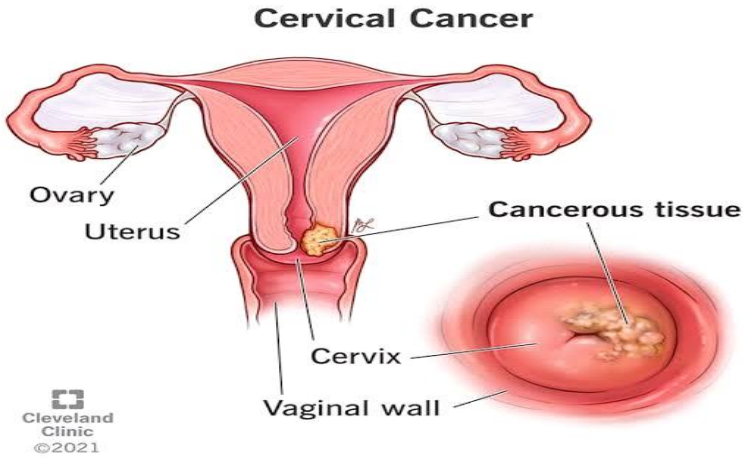

Figure 3: Cervical Cancer

Novel approaches for cervical cancer treatment

- A novel approach for cervical cancer treatment involves the use of immune checkpoint inhibitors, particularly those targeting the programmed death-ligand 1 (PD-L1)/programmed cell death protein 1 (PD-1) pathway. Here's a brief overview of the mechanism of action:

  1. Immune Checkpoint Inhibition: Cancer cells often exploit immune checkpoint pathways, such as the PD-L1/PD-1 pathway, to evade immune surveillance. PD-L1, expressed on cancer cells, interacts with PD-1 receptors on T cells, leading to T cell exhaustion and immune tolerance. Immune checkpoint inhibitors, such as anti-PD-1 or anti-PD-L1 antibodies, block this interaction, thereby reactivating T cell-mediated anti-tumor immune responses.

  2. Enhanced Tumor Cell Recognition and Destruction: In cervical cancer, immune checkpoint inhibitors can enhance the recognition and elimination of cancer cells by the immune system. By blocking the PD-L1/PD-1 pathway, these inhibitors restore T cell activity, allowing T cells to recognize and attack cancer cells more effectively.

  3. Tumor Microenvironment Modulation: Immune checkpoint inhibitors can also modulate the tumor microenvironment by promoting the infiltration of immune cells, such as cytotoxic T lymphocytes (CTLs), into the tumor bed. This leads to a more favorable immune milieu, conducive to anti-tumor immune responses (Xie *et al*., 2022).

- A novel approach for cervical cancer treatment involves the use of therapeutic vaccines targeting human papillomavirus (HPV), the primary cause of cervical cancer. These vaccines aim to stimulate the patient's immune system to recognize and eliminate HPV-infected cells, thus preventing the development of cervical cancer or targeting existing cancer cells. Here's a brief overview:

1. Vaccine Design: Therapeutic HPV vaccines are designed to target specific HPV antigens, such as E6 and E7 oncoproteins, which are expressed in HPV-infected and HPV-associated cancer cells. These antigens play essential roles in promoting HPV-associated carcinogenesis by interfering with cell cycle regulation and promoting cellular proliferation and survival.

2. Immune Activation: Therapeutic HPV vaccines contain antigenic components derived from HPV, which are presented to the immune system to stimulate the production of cytotoxic T lymphocytes (CTLs) and other immune effector cells. CTLs are capable of recognizing and killing HPV-infected or HPV-transformed cells expressing the targeted HPV antigens, including cancer cells.

3. Tumor Cell Destruction: Activated CTLs infiltrate the tumor microenvironment and recognize HPV-infected or HPV-transformed cells expressing the targeted antigens. Upon recognition, CTLs release cytotoxic molecules, such as perforin and granzymes, leading to the destruction of cancer cells through apoptosis (programmed cell death) or necrosis.

4. Induction of Immune Memory: Therapeutic HPV vaccines also aim to induce long-lasting immune memory against HPV-infected cells, providing ongoing surveillance and protection against recurrence or progression of cervical cancer (Ferrall *et al*., 2021).

VII PROSTATE CANCER:

Prostate cancer is a prevalent malignancy that originates in the prostate gland, a walnut-sized organ located below the bladder and in front of the rectum in men. It arises from the abnormal growth of cells within the prostate tissue, leading to the formation of tumors. Prostate cancer is one of the most common cancers diagnosed in men, particularly in older individuals, and represents a significant health concern globally. Risk factors for prostate cancer include advanced age, family history of the disease, African ancestry, and certain genetic mutations, such as mutations in the BRCA1 and BRCA2 genes. Early-stage prostate cancer often grows slowly and may not cause noticeable symptoms. However, as the disease progresses, symptoms may include urinary difficulties, such as frequent urination, weak or interrupted urine flow, blood in the urine, erectile dysfunction, and pain in the pelvis or lower back.

Screening for prostate cancer typically involves a combination of a digital rectal examination (DRE) and a prostate-specific antigen (PSA) blood test. Diagnosis is confirmed through a prostate biopsy, where tissue samples are collected from the prostate gland and examined under a microscope.

Treatment options for prostate cancer vary depending on factors such as the stage and aggressiveness of the tumor, as well as the patient's overall health and preferences. Active surveillance, surgery (prostatectomy), radiation therapy (external beam or brachytherapy), hormone therapy, chemotherapy, and immunotherapy are among the main treatment modalities used either alone or in combination. Research into novel treatment approaches, including targeted therapies and immunotherapies, continues to advance our understanding and management of prostate cancer (Siegel *et al*., 2020) (Mohler *et al*., 2021)

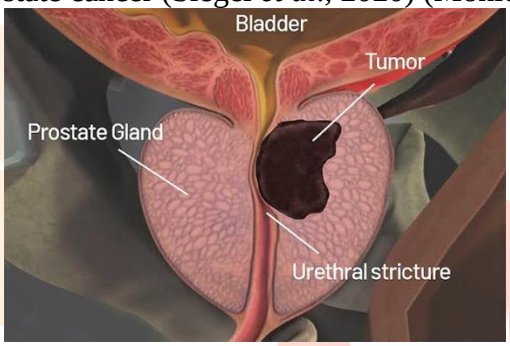

Figure 4: Prostate cancer

Novel Approach of Prostate Cancer Targeting Androgen Receptor Signaling Pathway

- A novel approach in treating prostate cancer involves targeting the androgen receptor (AR) signaling pathway, which plays a crucial role in the development and progression of prostate cancer. Androgens, such as testosterone and dihydrotestosterone (DHT), bind to the AR, leading to the activation of downstream signaling pathways that promote cancer cell proliferation and survival. In advanced prostate cancer, this pathway remains a key driver of disease progression, even in cases where androgen deprivation therapy (ADT) initially suppresses tumor growth.

  One emerging strategy is the development of next-generation androgen receptor inhibitors, such as enzalutamide and apalutamide, which exhibit higher affinity for the AR and increased potency compared to traditional anti-androgens. These agents not only block the binding of androgens to the AR but also inhibit AR nuclear translocation, DNA binding, and recruitment of coactivators, thereby more effectively suppressing AR-mediated transcriptional activity.

  Another promising approach involves targeting the androgen biosynthesis pathway to reduce intratumoral androgen levels. Abiraterone acetate inhibits the enzyme CYP17A1, which is involved in androgen synthesis, leading to decreased production of testosterone and DHT. This approach has demonstrated efficacy in both metastatic castration-resistant prostate cancer (mCRPC) and earlier stages of the disease when combined with ADT. Furthermore, emerging therapies aim to disrupt AR signaling at various points in the pathway, including targeting AR splice variants that lack the ligand-binding domain and are constitutively active, as well as modulating AR cofactors and downstream signaling pathways.

  By targeting the AR signaling pathway through these novel approaches, researchers aim to overcome resistance mechanisms that develop during ADT and improve outcomes for patients with advanced prostate cancer (Attard *et al*., 2016).

❖ **Innovative Immunotherapy Approaches for Prostate Cancer**

A cutting-edge approach in prostate cancer treatment involves harnessing the power of the immune system to target and destroy cancer cells. Immunotherapy has emerged as a promising strategy, particularly for advanced prostate cancer cases that are resistant to conventional therapies.

- One innovative immunotherapy approach utilizes immune checkpoint inhibitors, such as pembrolizumab and nivolumab, which target proteins like PD-1 and CTLA-4 that inhibit T-cell activity. By blocking these checkpoint proteins, these drugs unleash the immune system to recognize and attack cancer cells more effectively.
- Another exciting avenue of research involves therapeutic cancer vaccines designed to stimulate the immune system to recognize and target prostate cancer cells. Sipuleucel-T, an autologous cellular immunotherapy, is the first FDA-approved vaccine for prostate cancer. It involves harvesting a patient's own immune cells, stimulating them to target prostate cancer antigens, and then reinfusing them into the patient to mount an immune response against the cancer.
- Furthermore, chimeric antigen receptor (CAR) T-cell therapy, a groundbreaking form of immunotherapy, is being investigated for its potential in treating prostate cancer. CAR T-cell therapy involves genetically engineering a patient's T cells to express receptors that specifically target prostate cancer cells, enhancing their ability to seek out and destroy tumors.
- Additionally, combination approaches incorporating immunotherapy with other treatment modalities, such as chemotherapy, radiation therapy, and targeted therapy, are being explored to enhance treatment efficacy and overcome resistance mechanisms.
- While immunotherapy holds great promise for improving outcomes in prostate cancer, challenges remain, including identifying predictive biomarkers to select patients who are most likely to benefit and managing immune-related adverse events. Nonetheless, ongoing research and clinical trials are continually advancing our understanding of immunotherapy's role in prostate cancer treatment, offering hope for improved outcomes and prolonged survival for patients with this challenging disease (Sharma *et al*., 2015)

VIII GASTRIC CANCER

Gastric cancer, commonly referred to as stomach cancer, is a malignancy originating in the lining of the stomach. It ranks among the top cancers worldwide in terms of incidence and mortality rates, posing a significant public health concern. Gastric cancer presents a complex interplay of genetic, environmental, and lifestyle factors contributing to its development. The primary risk factors for gastric cancer include chronic infection with Helicobacter pylori, a bacterium implicated in gastric inflammation and subsequent carcinogenesis. Other risk factors include a diet high in salt and smoked or pickled foods, tobacco use, obesity, genetic predisposition, and certain medical conditions such as pernicious anemia and gastric polyps. Clinically, gastric cancer may manifest with a variety of symptoms, ranging from nonspecific gastrointestinal discomfort to more alarming signs such as unintentional weight loss, abdominal pain, nausea, vomiting (sometimes with blood), difficulty swallowing, and anemia.Diagnostic modalities for gastric cancer include endoscopic examination with biopsy, imaging studies such as CT scan and MRI, and staging procedures to assess the extent of the disease. The TNM staging system, based on tumor size, lymph node involvement, and distant metastasis, guides treatment decisions and prognosis.

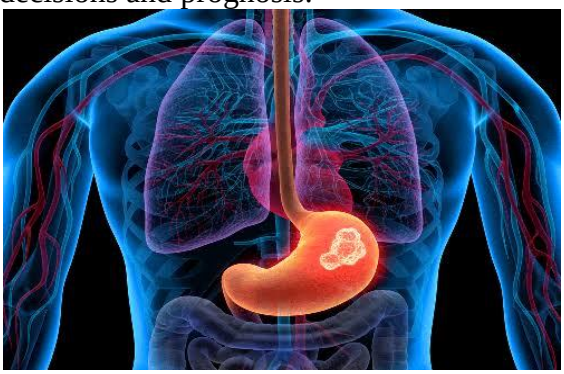

Figure 5: Gastric cancer

Gastric cancer represents a significant global health burden with diverse etiological factors and complex management challenges. Continued research efforts aimed at understanding the molecular mechanisms underlying gastric carcinogenesis and developing novel therapeutic approaches are essential for improving outcomes and reducing the morbidity and mortality associated with this disease (Ferro *et al*., 2011).

Novel Approach for Gastric Cancer:

- **Targeting HER2:** A promising novel approach for treating gastric cancer involves targeting the human epidermal growth factor receptor 2 (HER2), which is overexpressed in approximately 20% of gastric cancers. HER2 overexpression is associated with aggressive tumor behavior and poorer prognosis in gastric cancer patients. The mechanism of action of HER2-targeted therapy involves the use of monoclonal antibodies such as trastuzumab and pertuzumab, which specifically bind to the HER2 receptor on cancer cells, inhibiting downstream signaling pathways involved in cell proliferation and survival. Trastuzumab works by blocking HER2 signaling and inducing antibody-dependent cellular cytotoxicity (ADCC), leading to the destruction of HER2-overexpressing cancer cells. Pertuzumab acts synergistically with trastuzumab by targeting a different domain of the HER2 receptor, thereby further inhibiting HER2-mediated signaling pathways. Clinical trials have demonstrated the efficacy of HER2-targeted therapy in improving outcomes for patients with HER2-positive gastric cancer, both in the metastatic and adjuvant settings. Combination regimens incorporating trastuzumab with chemotherapy, such as fluoropyrimidine and platinum-based regimens, have shown significant improvements in overall survival and progression-free survival compared to chemotherapy alone.

  Additionally, ongoing research is exploring the potential of novel HER2-targeted agents, including antibody-drug conjugates (ADCs) and small molecule inhibitors, as well as investigating biomarkers to identify patients most likely to benefit from HER2-targeted therapy. Overall, HER2-targeted therapy represents a promising and effective novel approach for the treatment of HER2-positive gastric cancer, offering improved outcomes and survival for patients with this aggressive disease (Bang *et al*., 2010).

- **Immune Checkpoint Inhibitors**
  - Another innovative approach in the treatment of gastric cancer involves the use of immune checkpoint inhibitors, which aim to harness the body's immune system to target and destroy cancer cells. Immune checkpoint inhibitors work by blocking proteins on immune cells or cancer cells that inhibit the immune response, thereby unleashing the immune system to attack the tumor.
- One of the key immune checkpoint pathways targeted in gastric cancer is the programmed cell death protein 1 (PD-1) pathway. PD-1 is expressed on the surface of activated T cells, and its ligands, PD-L1 and PD-L2, are often upregulated in gastric cancer cells, allowing them to evade immune surveillance. By blocking the interaction between PD-1 and its ligands, immune checkpoint inhibitors such as pembrolizumab and nivolumab enhance the activity of T cells, leading to tumor cell death.
- Clinical trials evaluating immune checkpoint inhibitors in gastric cancer have shown promising results, particularly in patients with advanced or metastatic disease who have progressed on standard chemotherapy. These agents have demonstrated durable responses and improved overall survival rates compared to chemotherapy alone, leading to their approval for the treatment of advanced gastric cancer in certain settings.
- Combination strategies incorporating immune checkpoint inhibitors with other immunotherapies, chemotherapy, targeted agents, or radiation therapy are also being explored to enhance treatment efficacy and overcome resistance mechanisms. Additionally, biomarker studies are underway to identify predictive markers of response to immune checkpoint inhibitors, allowing for more personalized treatment approaches.
- While immune checkpoint inhibitors represent a promising treatment option for gastric cancer, challenges remain, including identifying patients who are most likely to benefit from immunotherapy and managing immune-related adverse events. Ongoing research efforts are focused on addressing these challenges and further optimizing the use of immune checkpoint inhibitors in the treatment of gastric cancer (Fuchs *et al*., 2018)

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CONFLICT OF INTEREST

All authors have no conflicts of interest to declare.

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