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Consise Review on Cancer Disease

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ABSTRACT
Now a day's cancer is the most prevalent life threatening disease which is spreading because of the lifestyle we are living. Cancer is due to uncontrolled growth of cell which can be cured if diagnosed in early stage of life. Treatment of cancer depends on the various internal and external factors causing cancer. Cancer is screened by different screening tests and a number of treatments are now available these days such as gene therapy, chemotherapy, surgery, radiation therapy, immunotherapy etc. Cancer is characterized by proliferation of cells that have managed to evade central endogenous control mechanisms. Cancers are grouped according to their organ or tissue of origin, but increasingly also based on molecular characteristics of the respective cancer cells. Due to the rapid technological advances of the last years, it is now possible to analyze the molecular makeup of different cancer types in detail within short time periods. The accumulating knowledge about development and progression of cancer can be used to develop more precise diagnostics and more effective and/or less toxic cancer therapies. In the long run, the goal is to offer to every cancer patient a therapeutic regimen that is tailored to his individual disease and situation in an optimal way.
Keywords: cancer, anticancer; types, staging,pathophysiology,neuropathology, pharmacological and non pharmacological treatment of cancer.

I. INTRODUCTION

Cancer is a disease in which some of the body's cells grow uncontrollably and spread to other parts of the body.

Cancer can start almost anywhere in the human body, which is made up of trillions of cells. Normally, human cells grow and multiply (through a process called cell division) to form new cells as the body needs them. When cells grow old or become damaged, they die, and new cells take their place.

Sometimes this orderly process breaks down, and abnormal or damaged cells grow and multiply when they shouldn't. These cells may form tumors, which are lumps of tissue. Tumors can be cancerous or not cancerous (benign).

Cancerous tumors spread into, or invade, nearby tissues and can travel to distant places in the body to form new tumors (a process called metastasis). Cancerous tumors may also be called malignant tumors. Many cancers form solid tumors, but cancers of the blood, such as leukemia's, generally do not.

Benign tumors do not spread into, or invade, nearby tissues. When removed, benign tumors usually don't grow back, whereas cancerous tumors sometimes do. Benign tumors can sometimes be quite large, however. Some can cause serious symptoms or be life threatening, such as benign tumors in the brain.

- Cancer is the second leading cause of death worldwide. In 2015, 8.8 million deaths were attributed to cancer, and annual cases of cancer are expected to increase from 14 million in 2012 to 22 million over the next two decades. A total of 16,300 of deaths are men who typically have stomach, lung, prostate, or colorectal cancer or leukemia. The remaining 16,800 deaths are women who primarily suffer from cervical, stomach, breast, lung or colorectal cancer, the relative frequencies of the ten leading causes of cancer mortality from 2011-2015 in both sexes were stomach cancer (11.5%), lung cancer (11.0%), colorectal cancer (9.2%), breast cancer (8.3%), prostate cancer (7.9%), liver cancer (5.4%), lymphoma-myeloma (4.9%), pancreatic cancer (4.3%), leukemia (4.0%) or cervical cancer (3.8%).To improve patient quality of life, modern technological advances have led to the development of powerful drugs that increase life expectancy by curing or preventing the progression of diseases. However, the positive impact of these advances is diminished when patients do not follow medical

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recommendations. Therefore, it is important to evaluate diagnosed to treatment using an appropriate scale. However, oral therapeutic adherence in cancer is not usually measured, although scientific evidence suggests that lack of therapeutic adherence is a major problem among patients who are prescribed oral treatment for cancer. However, physicians do not use a validated scale for measurement. Given that cancer is a public health problem, it is important to conduct an overall study to identify the best-validated scale to evaluate cancer patients. This study will contribute to the formulation of new knowledge and ideas that enrich the intervention processes in cancer patients.

II. REVIEWS

Early studies

Early epidemiological studies: The earliest carcinogens to be identified were generally associated with specific occupations. Bernardino Ramazziniobserved in 1713 that nuns suffered from high rates of breast cancer which he attributed to their celibate life. Percivol Pott documented in 1775 that chimney sweeps frequently developed cancer of the scrotum which he deduced to be caused by their heavy exposure to soot. A century afterwards, reports emerged that a variety of other occupations were associated with increased rates of cancer. Richard von Volkmanndiagnosed three cases of scrotal cancer in 1875 among coal tar distillers in Germany, which was quickly followed by similar reports by other physicians.JosephBell.described two cases of scrotal cancer among shale oil workers in Scotland in 1876, and commented that the cancer was quite common among shale oil workers. Harting and Hesse documented in 1879 that miners in the Black Forest regions of Schneeberg in Germany and Joachimsthal in Czechoslovakia suffered from a high mortality due to lung cancer. Ludwig Rhenreported in 1895 that long term dye workers in Germany frequently perished of bladder cancer. Wilhelm Conrad Röntgendiscovered X-rays in 1895, which were heralded as a phenomenal discovery, because they permitted the painless visualization of bones. The early radiologists routinely tested the performance of their equipment by exposing their hands. Then a few days after a prolonged exposure, an extremely painful skin condition termed radiodermatitisdeveloped.A decade after Röntgen's discovery of X-rays, case reports began emerging from many diverse areas of the world, that radiologists were succumbing to skin cancers.

A few non-occupational agents were also identified during this period. John Hill[23] reported in 1761 that immoderate use of tobacco snuff was associated with the occurrence of nasal cancers[24]. Sir Johnathan Hutchinson[25] observed in 1881 that patients who used a tonic which contained arsenic for extended durations frequently developed keratosis lesions which sometimes progressed to skin cancer.

Early experimental studies: In the late 1800s, there were three fundamental theories of the cause of cancer[26-28]. Virchow proposed that cancer was a product of chronic irritation[28,29]; Lobstein and Recamier, and later Cohnheim hypothesized that cancer was the result of displaced embryonal tissue[28,29]; others surmised that cancer was caused by an infectious (or parasitic) agent[27,28,30]. Numerous researchers attempted to induce cancer in experimental animals, based on one of these theories. However, experiments to produce tumors with irritating chemicals produced only benign growths[31]. Work to prove Cohnheim's theory by transplanting embryonal or fetal tissue into adult hosts similarly failed to induce malignant growths[32]. A broad range of microbes were identified in cancerous growths. However attempts to extract the microbes and produce cancers, could not induce cancers reproducibly[28]. Experimental induction of cancer was considered to be important, because this was expected facilitate the development of preventative measures and effective treatments[32].

In 1908, Ellermann and Bang[33,34] reported that a cell-free filtrate caused a leukemia in chickens, and Peyton Rous[35,36] reported that a cell-free filtrate produced a sarcoma in chickens shortly afterwards. However, work with chickens seemed to be irrelevant to humans, so efforts to produce experimental cancer based on the other theories continued unabated.

2.1.Anti-Cancer

Anti-Cancer drugs are medicines formulated to treat wide range of cancer. Cancer is the uncontrolled growth of cells that interfere with the growth of healthy cells. The usual treatments of Cancer are surgery, chemotherapy (treatment with anticancer drugs), radiation, or some combination of these methods. Anti-Cancer drugs are targeted to control and treat various Cancer like, Breast cancer, Cervical cancer, Small cell lung cancer, Head and Neck cancer, Ovarian cancer, Hodgkin's and Non-Hodgkin's lymphoma, Oesteo-sarcoma,

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Seminomas of testis, Myeloblastic leukemia, Lymphoblastic leukemia etc. The use and application of drugs synthesized or procured from natural or synthetic sources for cancer inhibition and cure is known as "chemotherapy" and the drugs are more commonly named as chemotherapeutic drugs. As stated earlier, cancer can be defined as a state where cells or tissues of the body start to divide uncontrollably and evade the normal cell cycle as a result of which progression of large tumors occur, and the tumorous cells by the mechanism of metastasis may invade the neighboring normal tissues of the body causing serious implications. Keeping this in mind cancer drugs has been designed to slowly act on the cancerous cells and halt their progression by suppressing them through various molecular mechanisms.

Common Mechanism of Action of Anti-Cancer Drugs

- They may act by damaging the DNA of cancerous cells. The anticancer drugs cause single strand (SSB) and double strand (DSB) DNA breaks or may lead to manufacture of nonsense DNA or RNA. Examples of drugs in this category include Cisplatin, Mitomycin C, Daunorubicin, Doxorubicin and Etoposide..
- They inhibit the synthesis of new DNA to stop the cell from replicating because replication of cells leads to growth of tumor. These agents work in a number of different ways. DNA building blocks are folic acid, heterocyclic bases, and nucleotides, which are made naturally within cells. All of these agents work to block some step in the formation of nucleotides or deoxyribonucleotides (necessary for making DNA). When these steps are blocked, the nucleotides, which are the building blocks of DNA and RNA, cannot be synthesized. Thus the cells cannot replicate because they cannot make DNA without the nucleotides. Examples of drugs in this category include methotrexate, fluorouracil, hydroxyurea and mercaptopurine.
- They stop mitosis or the actual splitting of the original cells into cell into two new cells. Stopping mitosis stops cell division (replication) of the cancer cells and may ultimately halt the progression of the cancer.

Anti-Cancer agents can be divided into following several categories

*Alkylating agents (e.g., Mitomycin C, Cyclophosphamide),
*Antibiotics which affect nucleic acids (e.g., Doxorubicin, Bleomycin),
*Mitotic inhibitors (e.g., Vincristine, Vinblastine, Taxol),
*Platinum compounds (e.g., Cisplatin),
*Camptothecin derivatives (e.g., Topotecan),
*Antimetabolites (e.g., 5-fluorouracil),
*Biological response modifiers (e.g., Interferon) and
*Hormone therapy (e.g., Tamoxifen).

Example of some compounds

* Alkylating Agents (Mitomycin C) and Platinum Antitumor (Cisplatin) Compounds
* Mitotic inhibitors (e.g., Vincristine, Vinblastine, Taxol)
* Antimetabolites (e.g., 5-fluorouracil)
* Camptothecin derivatives (e.g., Topotecan)
*Hormone therapy (e.g., Tamoxifen)

III. CANCER DISEASE DIAGNOSTIC CRITERIA

If you have a symptom or a screening test result that suggests cancer, your doctor must find out whether it is due to cancer or some other cause. The doctor may start by asking about your personal and family medical history and do a physical exam. The doctor also may order lab tests, imaging tests (scans), or other tests or procedures. You may also need a biopsy, which is often the only way to tell for sure if you have cancer.

There are

- Lab tests
- Imaging tests
- Biopsy
- After cancer is diagnosed

➢ **Lab Tests**

High or low levels of certain substances in your body can be a sign of cancer. So, lab tests of your blood, urine, or other body fluids that measure these substances can help doctors make a diagnosis. However, abnormal lab results are not a sure sign of cancer. Learn more about laboratory tests and how they are used to diagnose cancer.

Some lab tests involve testing blood or tissue samples for tumor markers. Tumor markers are substances that are produced by cancer cells or by other cells of the body in response to cancer. Most tumor markers are made by normal cells and cancer cells but are produced at much higher levels by cancer cells. Learn more about tumor markers and how they are used to diagnose cancer.

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➢ **Imaging Tests**

Imaging tests create pictures of areas inside your body that help the doctor see whether a tumor is present. These pictures can be made in several ways:

➢ **CT Scan**

A CT scan uses an x-ray machine linked to a computer to take a series of pictures of your organs from different anglesDuring the CT scan, you will lie still on a table that slides into a donut-shaped scanner. The CT machine moves around you, taking pictures. Learn more about CT scans and how they are used to diagnose cancer.

. These pictures are used to create detailed 3-D images of the inside of your body.

Sometimes, you may receive a dye or other contrast material before you have the scan. You might swallow the dye, or it may be given by a needle into a vein. Contrast material helps make the pictures easier to read by highlighting certain areas in the body.

During the CT scan, you will lie still on a table that slides into a donut-shaped scanner. The CT machine moves around you, taking pictures. Learn more about CT scans and how they are used to diagnose cancer.

➢ **MRI**

An MRI uses a powerful magnet and radio waves to take pictures of your body in slices. These slices are used to create detailed images of the inside of your body, which can show the difference between healthy and unhealthy tissue.

When you have an MRI, you lie still on a table that is pushed into a long, round chamber. The MRI machine makes loud thumping noises and rhythmic beats.

Sometimes, you might have a special dye injected into your vein before or during your MRI exam. This dye, called a contrast agent, can make tumors show up brighter in the pictures.

➢ **Nuclear scan**

A nuclear scan uses radioactive material to take pictures of the inside of the body. This type of scan may also be called radionuclide scan.

Before this scan, you receive an injection of a small amount of radioactive material, which is sometimes called a tracer. It flows through your bloodstream and collects in certain bones or organs.

During the scan, you lie still on a table while a machine called a scanner detects and measures the radioactivity in your body, creating pictures of bones or organs on a computer screen or on film.

After the scan, the radioactive material in your body will lose its radioactivity over time. It may also leave your body through your urine or stool.

➢ **Bone Scan**

Bone scans are a type of nuclear scan that check for abnormal areas or damage in the bones. They may be used to diagnose bone cancer or cancer that has spread to the bones (also called metastatic bone tumors).

Before this test, a very small amount of radioactive material is injected into your vein. As it travels through the blood, the material collects in abnormal areas in the bone. Areas where the material collects show up on pictures taken by a special scanner. These areas are called “hot spots.”

➢ **PET scan**

A PET scan is a type of nuclear scan that makes detailed 3-D pictures of areas inside your body where glucose is taken up. Because cancer cells often take up more glucose than healthy cells, the pictures can be used to find cancer in the body.

Before the scan, you receive an injection of a tracer called radioactive glucose. During the scan, you will lie still on a table that moves back and forth through a scanner.

➢ **Ultrasound**

An ultrasound exam uses high-energy sound waves that people cannot hear. The sound waves echo off tissues inside your body. A computer uses these echoes to create pictures of areas inside your body. This picture is called a sonogram.

During an ultrasound exam, you will lie on a table while a tech slowly moves a device called a transducer on the skin over the part of the body that is being examined. The transducer is covered with a warm gel that makes it easier to glide over the skin.

X-rays use low doses of radiation to create pictures inside your body. An x-ray tech will put you in position and direct the x-ray beam to the correct part of your body. While the images are taken, you will need to stay very still and may need to hold your breath for a second or two.

Biopsy

In most cases, doctors need to do a biopsy to diagnose cancer. A biopsy is a procedure in which the doctor removes a sample of tissue. A pathologist looks at the tissue under a microscope

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and runs other tests to see if the tissue is cancer. The pathologist describes the findings in a pathology report, which contains details about your diagnosis. Pathology reports play an important role in diagnosing cancer and helping decide treatment options. Learn more about pathology reports and the type of information they contain.

The biopsy sample may be obtained in several ways:
With a needle: The doctor uses a needle to withdraw tissue or fluid. This method is used for bone marrow aspirations, spinal taps, and some breast, prostate, and liver biopsies.
With endoscopy: The doctor uses a thin, lighted tube called an endoscope to examine areas inside the body. Endoscopes go into natural body openings, such as the mouth or anus. If the doctor sees abnormal tissue during the exam, he will remove the abnormal tissue along with some of the surrounding normal tissue through the endoscope.

Examples of endoscopy exams include:

- **Colonoscopy**, which is an exam of the colon and rectum. In this type of exam, an endoscope goes through the anus, allowing the doctor to examine the rectum and colon. If the doctor sees polyps, she will remove them and send them to a lab for testing.
- **Bronchoscopy**, which is an exam of the trachea, bronchi, and lungs. In this type of exam, an endoscope goes through the mouth or nose and down the throat.

With surgery: A surgeon removes an area of abnormal cells during an operation. Surgery may be excisional or incisional.
In an excisional biopsy, the surgeon removes the entire area of abnormal cells. Often some of the normal tissue around these cells is also removed.
In an incisional biopsy, the surgeon removes just part of the abnormal area.

Some biopsies may require a sedative or anesthesia.
Sedatives are medicine that help you relax and stay very still or sleep during a biopsy.
Anesthesia keeps you from feeling pain. It refers to drugs or other substances that cause you to lose feeling or awareness. There are three types of anesthesia:

- **Local anesthesia**, which causes loss of feeling in one small area of the body
- **Regional anesthesia**, which causes loss of feeling in a part of the body, such as an arm or leg
- **General anesthesia**, which causes loss of feeling and a complete loss of awareness that seems like a very deep sleep

After Cancer Is Diagnosed
If the biopsy and other tests show that you have cancer, you may have more tests to help your doctor plan treatment. For instance, your doctor will need to figure out the stage of your cancer. for deciding on the best treatment. Your tumor may also be tested further for other tumor or geneticmarkers.

IV. CANCER DISEASE NEUROPATHOLOGY

Standard therapeutic options for brain tumors include surgery, radiation, and chemotherapy. Unfortunately, these same therapies pose risks of neurotoxicity, the most common long-term complications being radiation necrosis, chemotherapy-associated leukoencephalopathy, and secondary neoplasm. These side effects remain difficult to predict, but are associated with risk factors that include patient age, therapeutic modality and dosage, genetic background, and idiosyncratic predispositions. Experimental treatments designed to enhance efficacy and to minimize neurotoxicity include molecularly targeted, genetic, stem cell, and immune therapies. Newer modifications in radiation and drug delivery include stereotactic radio surgery, interstitial therapy such as intracavitary brachytherapy and gliadel wafer placement, 3D conformal radiation, boron neutron capture therapy, radio sensitizers, blood–brain barrier disrupting agents, and convection enhanced delivery. Toxicities associated with these newer modalities have yet to be fully investigated and documented. Additionally, a number of recently implemented radiographic techniques such as PET and SPECT imaging have enhanced the ability to distinguish recurrent tumor from radiation necrosis. Nevertheless, post-therapeutic brain biopsies and autopsies remain the gold standard for assessing neurotoxicity, therapeutic efficacy, tumor progression, and the development of secondary neoplasm. At the same time, treatment-associated changes such as tumor necrosis, vasculopathy, inflammation, and cytologicatypia can pose significant diagnostic pitfalls, particularly if the pathologist is not provided a detailed therapeutic

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history. Therefore, it is critical to recognize the full spectrum of cancer therapy-associated neuropathology, the topic of the current review.

V. STAGES OF CANCER DISEASE

Staging helps your doctor plan the best treatment. This may include choosing a type of surgery and whether or not to use chemotherapy or radiation therapy. Knowing the cancer stage lets your entire health care team talk about your diagnosis in the same way.

Doctors can also use staging to:

- Understand the chance that the cancer will come back or spread after the original treatment.
- Help forecast the prognosis, which is the chance of recovery
- Help determine which cancer clinical trials may be open to you.
- See how well a treatment worked
- Compare how well new treatments work among large groups of people with the same diagnosis

When is cancer staging done?

Staging of a cancer can be done at different times in a person's medical care. Here are some information on when and how staging is done. You will notice that these descriptions refer to the "TNM category." This refers to the TNM system of cancer staging, which is explained in more detail further in this article.

Clinical staging. Clinical staging is staging that is done before any treatment begins. Your doctor uses information from physical exams, your medical history, and any x-rays, imaging, scans, or diagnostic tests that you had. They will also use the results of any biopsy that has been done of the cancer, lymph nodes, or other tissue. Clinical staging helps you and your doctor plan the initial steps in your treatment. Clinical staging is indicated with a small"c" before the TNM category.

Pathological staging. Pathological staging is based on the same information as clinical staging, plus any new information gained during surgery if surgery was the first treatment for the cancer. Pathological staging is indicated with a small "p" before the TNM category.

Post-therapy staging. Post-therapy staging is used in cases where surgery is not the first treatment, but other treatments are given before surgery. These treatments can include radiation therapy or drug treatments like chemotherapy, immunotherapy, or hormone therapy. These treatments may be used before surgery to shrink the tumor to make surgery easier. It can also help doctors learn how well treatments work for the cancer to plan further treatment. Post-therapy staging is indicated with a "y" before the TNM category.

When doctors determine the stage of the cancer using the TNM system (see below), every cancer should be staged with clinical staging. After surgery or initial treatments before surgery, pathological staging and post-therapy staging should be used as well. Clinical staging is very important to help plan initial treatment, but pathological staging or post-therapy staging give the most information. This can help your health care team understand your prognosis.

What is the TNM staging system for cancer?

Doctors use the TNM staging system for most types of cancer. The TNM system uses letters and numbers to describe the tumor (T), lymph nodes (N), whether or not the cancer has spread or metastases (M). Each letter and number tell you something about the cancer. The specific definitions for each category are different for each type of cancer that is staged using this system. Learn more specific staging information for each **type of cancer**.

Tumor (T): The letter T and the number after it describe the tumor by answering these questions:

- How large is the primary tumor?
- Where is it located?
- Does it go into other tissues or organs in the same area?

The letter T is followed by a letter, number, or combination of letters after it. This gives additional information about the tumor. The different letters and numbers that may see include:

- **TX** means that there is no information about the tumor or it cannot be measured.
- **T0** means that there is no evidence of a tumor.
- **Tis** refers to a tumor "in situ." This means that the tumor is only found in the cells where it started. It has not spread to any surrounding tissue.
- **T1-T4** describe the size and location of the tumor, on a scale of 1 to 4. A larger tumor or a tumor that has grown deeper into nearby tissue will get a higher number.

For some types of cancer, the T stage can be broken down into subcategories for even more detail. This is noted with a lowercase letter, like an "a" or "b", such as "T2b". What these letters mean depends on the type of cancer. A lowercase "m"

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can also be used to show that there are multiple tumors.

Node (N): The letter N and the number after it describe if cancer has affected the lymph nodes. The lymph nodes are small, bean-shaped organs that help fight infection. They are a common spot where cancer first spreads. This part of the staging system answers these questions:

- Has the tumor spread to the lymph nodes? If so, which lymph nodes and how many?

Lymph nodes near where the cancer started are called regional lymph nodes. Lymph nodes in other parts of the body are called distant lymph nodes. The N category only refers to lymph nodes near the cancer (regional lymph nodes). Distant lymph nodes elsewhere in the body are included in the "M" category (see below).

After the letter N, there will be a number from 0 (zero) to 3. N0 means there are no lymph nodes with cancer. Most often, the more lymph nodes with cancer, the larger the number. But for some tumors, the location of the lymph nodes with cancer may determine the "N" category.

Metastasis (M): The letter M and the number after it describes if the cancer has spread. It answers these questions:

- Has the cancer spread to other parts of the body?
- If so, where and how much?

If cancer has not spread, the stage is M0. If the cancer has spread to other parts of the body, it is stage M1.

What other factors are used in cancer staging?

For some cancer types, factors other than the TNM categories can be included in the cancer's stage. They may include:

Grade: The grade describes how much cancer cells look like healthy cells. A pathologist will look at the cancer cells under a microscope. A pathologist is a doctor who specializes in evaluating cells, tissues, and organs to diagnose disease. They will compare the cancer tissue with healthy tissue. Healthy tissue often contains many types of cells groups together.

If the cancer looks like healthy tissue and has different cell groupings, it is called a differentiated or a low-grade tumor. If the cancer looks very different from healthy tissue, it is called a poorly differentiated or a high-grade tumor. The cancer's grade may help predict how quickly cancer will spread.

Cancer grade is recorded by the pathologist using the letter "G" with a number from 1 to 3 for most cancers and from 1 to 4 in some. In general, the lower the tumor's grade, the better the prognosis. Different types of cancer have different methods to assign a cancer grade.

Biomarkers: Biomarkers, also called tumor markers, are substances found in higher-than-normal levels in the cancer itself, or in blood, urine, or tissues of some people with cancer. Biomarkers can help figure out how likely some types of cancer are to spread. They can also help doctors choose the best treatment. For some cancers, certain tumor markers may be more helpful for staging than treatment planning. Learn more about testing forbiomarkers.

Tumor genetics. Researchers have found ways to figure out the genes involved in many types of cancer. These genes may help predict if a cancer will spread or what treatments will work best. This information may help doctors target treatment to each person's cancer. Learn more about personalized and targeted therapies.

What is cancer stage grouping?

The information collected to determine the TNM stage is used to give a cancer stage specific to you. Most types of cancer have four stages: stage I (1) to IV (4). Some cancers also have a stage 0 (zero). Here is a general description of cancer stage groupings. (Please see the guide for a specific type of cancer for details about its detailed staging system.

- **Stage 0.** This stage describes cancer in situ. In situ means "in place." Stage 0 cancers are still located in the place they started. They have not spread to nearby tissues. This stage of cancer is often curable. Surgery can usually remove the entire tumor.
- **Stage I.** This stage is usually a cancer that has not grown deeply into nearby tissues. It also has not spread to the lymph nodes or other parts of the body. It is often called early-stage cancer.
- **Stage II and Stage III.** In general, these 2 stages are cancers that have grown more deeply into nearby tissue. They may have also spread to lymph nodes but not to other parts of the body.
- **Stage IV.** This stage means that the cancer has spread to other organs or parts of the body. It may be also called advanced or metastatic cancer.

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What is cancer restaging?

The stage of a cancer given at the time of diagnosis and initial treatments does not change. This is so doctors can understand a person's medical progress, help understand the prognosis, and learn how treatment affects many people. However, if the cancer comes back or spreads, restaging can be done. This is described with a small "r." For example, rN1 is restaging of the lymph nodes. Usually some of the same tests that were done when the cancer was first diagnosed will be done again. After this, the doctor can assign the cancer a restage or "r stage."

What other staging systems are there?

The TNM staging is mainly used to describe cancers that form solid tumors, such as breast, colon, and lung cancers. Doctors use other staging systems to classify other types of cancer, such as:

- **Central nervous system tumors (brain tumors):**Cancerous brain tumors do not normally spread outside the brain and spinal cord. Therefore, only the "T" description of the TNM system applies. No single staging system exists for central nervous system tumors. Learn more about brain tumor staging and prognostic factors.
- **Childhood cancers:**The TNM system does not include childhood cancers. Doctors stage most childhood cancers using systems that are specific to that cancer.
- **Blood cancers:**The TNM system does not describe blood cancers, such as leukemia, lymphoma, or multiple myeloma. That is because they usually do not form solid tumors. Each blood cancer has its own staging system.

VI. ETIOLOGY AND PATHOPHYSIOLOGY OF CANCER DISEASE

Etiological agents that induce cancer

1.Environmental factors:

- tobacco, smokes, diets, environmental pollutants etc
- Heavy smoking cause lung, oral cavity and oesophagus cancer.
- Excessive intake of alcohol cause liver cancer.

2. Chemical carcinogen

- Nickel compounds, cadmium, arsenic, nitrosamines, trichloroethylene, arylamines, benzopyrene, aflatoxins, reactive oxygen radicals etc

3. Physical carcinogen

- UV rays (ultraviolet), ionizing radiation (x-rays and gamma rays)

❖ **Biological carcinogen**

- **Virus**
- Virus has also been associated with various types of cancers. These viruses are called oncoviruses
- Rous sarcoma virus (RSV) is the first discovered retro-virus causing cancer.
- **(Oncovirus)**; Human papilloma virus (HPV), Epstein-BarrVirus, (EBV),
- Hepatitis B virus, Herpes virusHepatitis B and C virus is casually related with hepato-cellular carcinoma.
- Cytomegalovirus (CMV) is associated with kaposi's sarcoma.Human papilloma virus (HPV) is a chief suspect of cervix cancer.
- **Bacteria**; Helicobacter pylori,

4. **Endogenous factors**

- Mutations, change in DNA replication, metabolic reactions generating, reactive oxygen radicals, Immune system defects, Ageing

❖ **Cancer pathophysiology**

- Regardless of difference in types of cancer histologically and physiologically, there is existence of a common pathophysiological process of malignant tumors or cancer development in the organism.
- The commonly accepted basis of the pathogenesis of cancer is the damage to the genetic
  apparatus of cells (such as mutation, disturbance of gene expression, activation of tumor promoter gene, inactivation of tumor suppressor genes, etc.)
- It is believed that damage to the genetic apparatus of the cell along with inactivation of anti-tumor genes takes place and is essential for the development of malignant tumors. But it should be noted that the inactivation of tumor suppressor gene is one of the natural physiological reactions of the organism, and when this reaction becomes pathophysiological condition of an organism**.**
- At the cellular level, the development of cancer is viewed as a multi-step process involving mutation and selection for cells with progressively increasing capacity for proliferation, survival, invasion, and metastasis.

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First step: Mutation andtumor initiation

- Genetic alteration leads to mutation in a single cell which results into abnormal proliferation of that cell known as tumor cell.

Second step: Cell proliferation and Tumor progression

- Tumor progression continues as additional mutations occur within cells of the tumor population.
- The mutated cells have some selective advantage over normal cell as such cells shows rapid growth and division. The descendants of a cell bearing such additional mutation will consequently become dominant within the tumor population.

Third step: Clonal selection and malignancy

- Cell proliferation of tumor then leads to new clone of tumor cells with increased growth rate or other properties (such as survival, invasion, or metastasis) that confer a selective advantage. The process is called clonal selection.
- Clonal selection continues throughout tumor development, so tumors continuously become more rapid-growing and increasingly malignant.

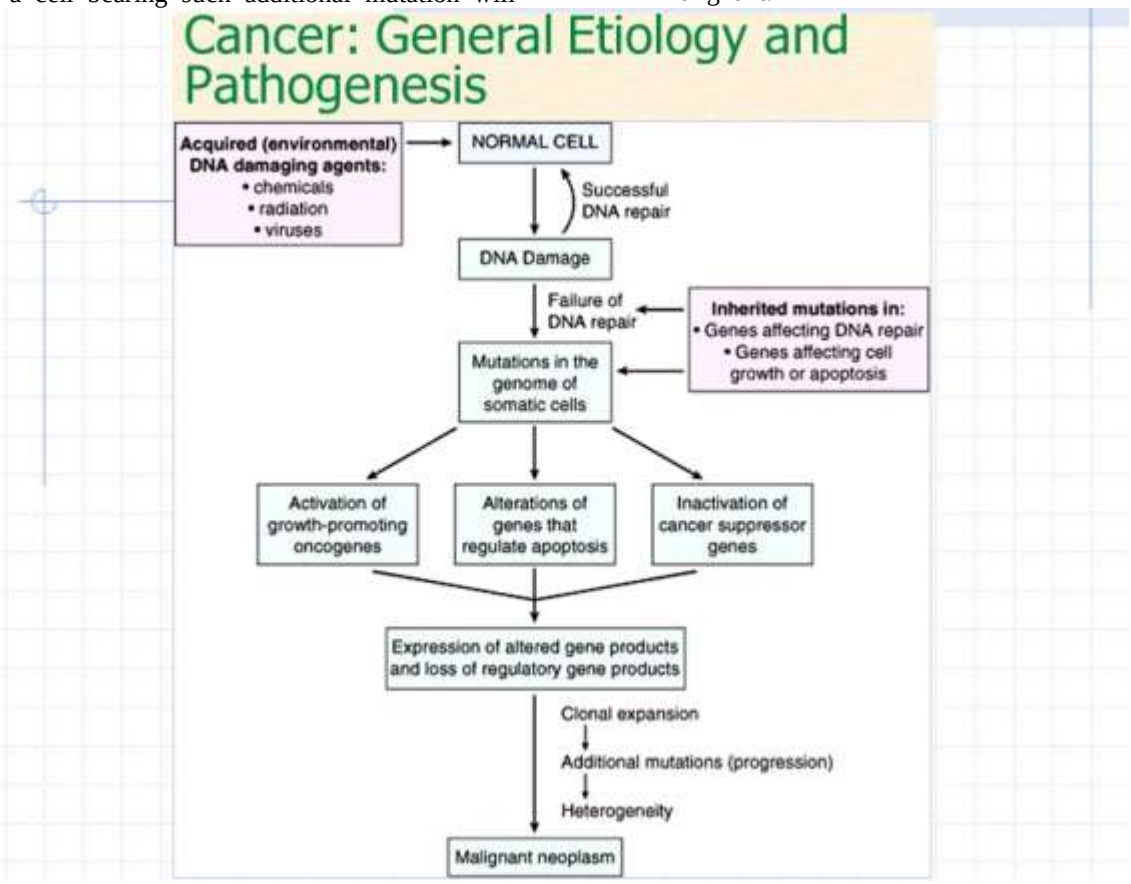

Figure1.Pathogenesis of cancer

- **For example:** In colon cancer, the earliest stage in tumor development is increased proliferation of colon epithelial cells. A clonal selection occurs in which, a single cell within these proliferative cell population give rise to a small benign neoplasm. Further rounds of clonal selection lead to the growth of benign neoplasm with increase in size and proliferative potential resulting in malignant carcinoma. The cancer cells then continue to proliferate and spread through the connective tissues of the colon wall. Eventually the cancer cells penetrate the wall of the colon and invade other abdominal organs, such as the bladder or small intestine. In addition, the cancer cells invade blood and lymphatic vessels, allowing them to metastasize throughout the body.

Fourth step: Metastasis

- **Metastasis** is a complex process in which cancer cells break away from the primary tumor and circulate through the bloodstream or lymphatic system to other sites in the body.

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- At new sites, the cells continue to multiply and eventually form additional tumors comprised of cells that reflect the tissue of origin.
- The ability of tumors, such as pancreatic cancer and uveal (iris, ciliary body, or choroid of eye) cancers, to metastasize contributes greatly to their lethality.
- Many fundamental questions remain about the clonal structures of metastatic tumors, phylogenetic relationships among metastases, the scale of ongoing parallel evolution in metastatic and primary sites, how the tumor disseminates, and the role that the tumor micro-environment plays in the determination of the metastatic site.

VII. CAUSES AND RISK FACTOR OF CANCER CELL

How Does Cancer Develop?

Cancer is a genetic disease—that is, it is caused by changes to genes that control the way our cells function, especially how they grow and divide.

Genetic changes that cause cancer can happen because:

- Errors that occur as cells divide.
- Damage to DNA caused by harmful substances in the environment, such as the chemicals in tobacco smoke and ultraviolet rays from the sun. (Our Cancer Causes and Prevention section has more information.)
- They were inherited from our parents.
- The body normally eliminates cells with damaged DNA before they turn cancerous. But the body's ability to do so goes down as we age. This is part of the reason why there is a higher risk of cancer later in life.
- Each person's cancer has a unique combination of genetic changes. As the cancer continues to grow, additional changes will occur. Even within the same tumor, different cells may have different genetic changes.

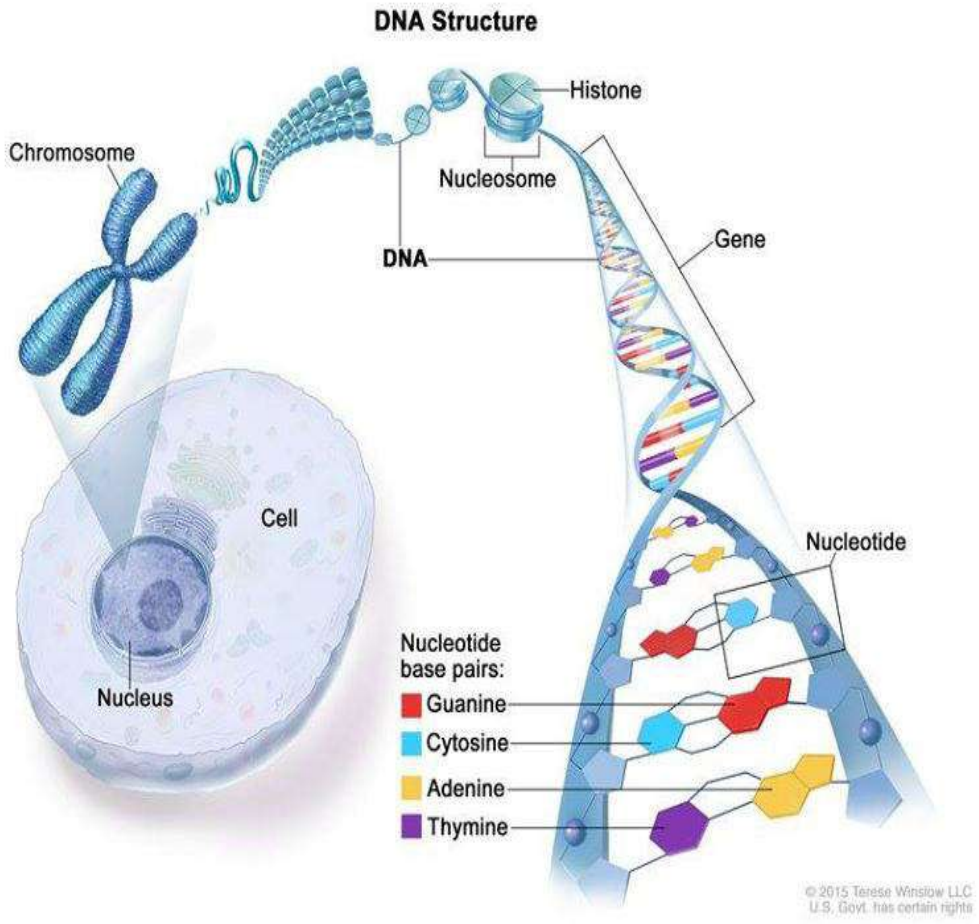

Figure 2

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Cancer is caused by certain changes to genes, the basic physical units of inheritance. Genes are arranged in long strands of tightly packed DNA called chromosomes.

Types of Genes that Cause Cancer

The genetic changes that contribute to cancer tend to affect three main types of genes—proto-oncogenes, tumor suppressor genes, and DNA repair genes. These changes are sometimes called "drivers" of cancer.

Proto-oncogenes are involved in normal cell growth and division. However, when these genes are altered in certain ways or are more active than normal, they may become cancer-causing genes (or oncogenes), allowing cells to grow and survive when they should not.

Tumor suppressor genes are also involved in controlling cell growth and division. Cells with certain alterations in tumor suppressor genes may divide in an uncontrolled manner.

When Cancer Spreads

A cancer that has spread from the place where it first formed to another place in the body is called metastatic cancer. The process by which cancer cells spread to other parts of the body is called metastasis.

Metastatic cancer has the same name and the same type of cancer cells as the original, or primary, cancer. For example, breast cancer that forms a metastatic tumor in the lung is metastatic breast cancer, not lung cancer.

Under a microscope, metastatic cancer cells generally look the same as cells of the original cancer. Moreover, metastatic cancer cells and cells of the original cancer usually have some molecular features in common, such as the presence of specific chromosome changes.

In some cases, treatment may help prolong the lives of people with metastatic cancer. In other cases, the primary goal of treatment for metastatic cancer is to control the growth of the cancer or to relieve symptoms it is causing. Metastatic tumors can cause severe damage to how the body functions, and most people who die of cancer die of metastatic disease.

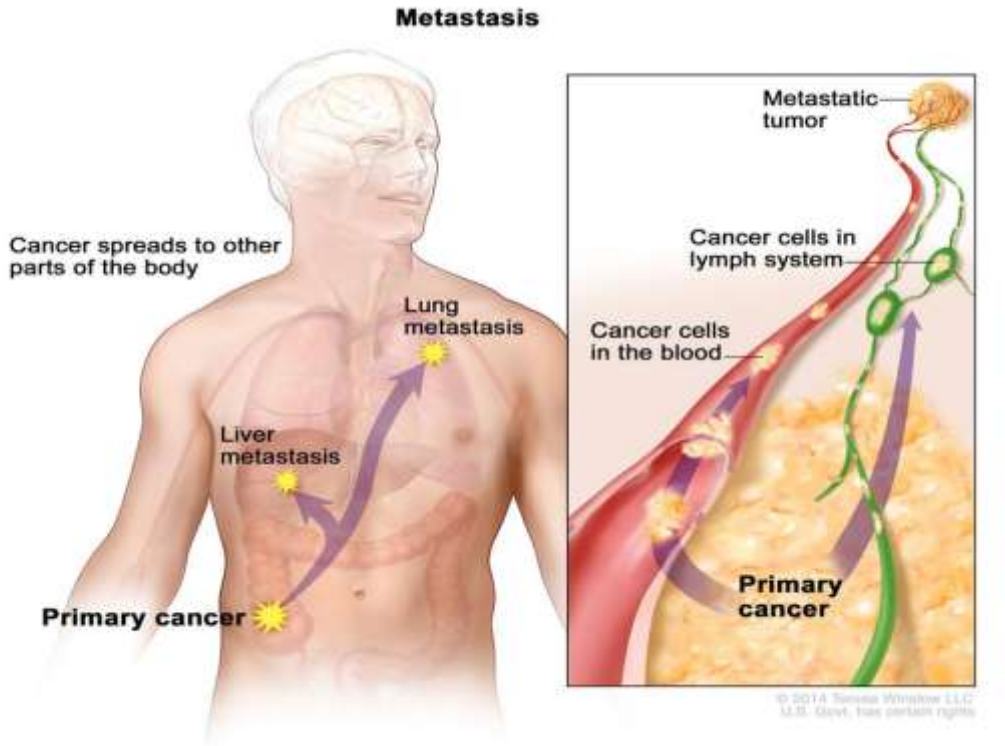

Figure 3.

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In metastasis, cancer cells break away from where they first formed and form new tumors in other parts of the body.

Tissue Changes that Are Not Cancer

Not every change in the body's tissues is cancer. Some tissue changes may develop into cancer if they are not treated, however. Here are some examples of tissue changes that are not cancer but, in some cases, are monitored because they could become cancer:

- **Hyperplasia** occurs when cells within a tissue multiply faster than normal and extra cells build up. However, the cells and the way the tissue is organized still look normal under a microscope. Hyperplasia can be caused by several factors or conditions, including chronic irritation.
- **Dysplasia** is a more advanced condition than hyperplasia. In dysplasia, there is also a buildup of extra cells. But the cells look abnormal and there are changes in how the tissue is organized. In general, the more abnormal the cells and tissue look, the greater the chance that cancer will form. Some types of dysplasia may need to be monitored or treated, but others do not. An example of dysplasia is an abnormal mole (called a dysplastic nevus) that forms on the skin. A dysplastic nevus can turn into melanoma, although most do not.
- **Carcinoma in situ** is an even more advanced condition. Although it is sometimes called stage 0 cancer, it is not cancer because the abnormal cells do not invade nearby tissue the way that cancer cells do. But because some carcinomas in situ may become cancer, they are usually treated.

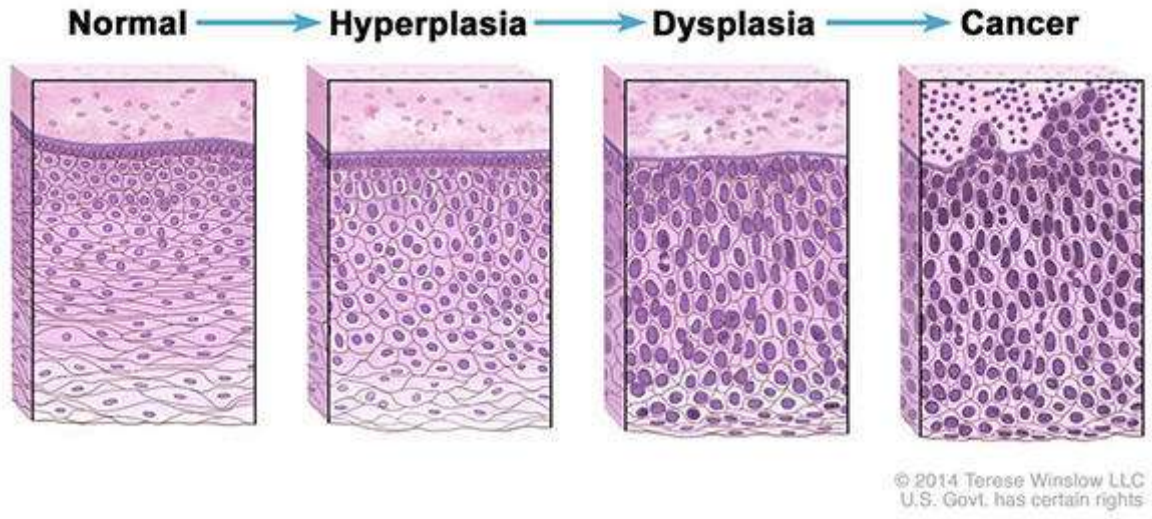

Figure 4.

Normal cells may become cancer cells. Before cancer cells form in tissues of the body, the cells go through abnormal changes called hyperplasia and dysplasia. In hyperplasia, there is an increase in the number of cells in an organ or tissue that appear normal under a microscope. In dysplasia, the cells look abnormal under a microscope but are not cancer. Hyperplasia and dysplasia may or may not become cancer.

Differences between Cancer Cells and Normal Cells

Cancer cells differ from normal cells in many ways. For instance, cancer cells:

- grow in the absence of signals telling them to grow. Normal cells only grow when they receive such signals.
- ignore signals that normally tell cells to stop dividing or to die (a process known as programmed cell death, or apoptosis).
- invade into nearby areas and spread to other areas of the body. Normal cells stop growing when they encounter other cells, and most normal cells do not move around the body.tell blood vessels to grow toward tumors. These blood vessels supply tumors with oxygen and nutrients and remove waste products from tumors.

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- hide from the immune system. The immune system normally eliminates damaged or abnormal cells.
- trick the immune system into helping cancer cells stay alive and grow. For instance, some cancer cells convince immune cells to protect the tumor instead of attacking it.
- accumulate multiple changes in their chromosomes, such as duplications and deletions of chromosome parts. Some cancer cells have double the normal number of chromosomes.
- rely on different kinds of nutrients than normal cells. In addition, some cancer cells make energy from nutrients in a different way than most normal cells. This lets cancer cells grow more quickly.

Many times, cancer cells rely so heavily on these abnormal behaviors that they can't survive without them. Researchers have taken advantage of this fact, developing therapies that target the abnormal features of cancer cells. For example, some cancer therapies prevent blood vessels from growing toward tumors, essentially starving the tumor of needed nutrients.

VIII. TYPES OF CANCER

There are more than 100 types of cancer. Types of cancer are usually named for the organs or tissues where the cancers form. For example, lung cancer starts in the lung, and brain cancer starts in the brain. Cancers also may be described by the type of cell that formed them, such as an epithelial cell or a squamous cell.

Here are some categories of cancers that begin in specific types of cells:

8.1. Carcinoma

Carcinomas are the most common type of cancer. They are formed by epithelial cells, which are the cells that cover the inside and outside surfaces of the body. There are many types of epithelial cells, which often have a column-like shape when viewed under a microscope.

Carcinomas that begin in different epithelial cell types have specific names:

Adenocarcinoma is a cancer that forms in epithelial cells that produce fluids or mucus. Tissues with this type of epithelial cell are sometimes called glandular tissues. Most cancers of the breast, colon, and prostate are adenocarcinomas.

Basal cell carcinoma is a cancer that begins in the lower or basal (base) layer of the epidermis, which is a person's outer layer of skin.

Squamous cell carcinoma is a cancer that forms in squamous cells, which are epithelial cells that lie just beneath the outer surface of the skin. Squamous cells also line many other organs, including the stomach, intestines, lungs, bladder, and kidneys. Squamous cells look flat, like fish scales, when viewed under a microscope. Squamous cell carcinomas are sometimes called epidermoid carcinomas.

Transitional cell carcinoma is a cancer that forms in a type of epithelial tissue called transitional epithelium, or urothelium. This tissue, which is made up of many layers of epithelial cells that can get bigger and smaller, is found in the linings of the bladder, ureters, and part of the kidneys (renal pelvis), and a few other organs. Some cancers of the bladder, ureters, and kidneys are transitional cell carcinomas.

8.2. Sarcoma

Sarcomas are cancers that form in bone and soft tissues, including muscle, fat, blood vessels, lymph vessels, and fibrous tissue (such as tendons and ligaments).

Osteosarcoma is the most common cancer of bone. The most common types of soft tissue sarcoma are leiomyosarcoma, Kaposi sarcoma, malignant fibrous histiocytoma, liposarcoma, and dermatofibrosarcoma protuberans.

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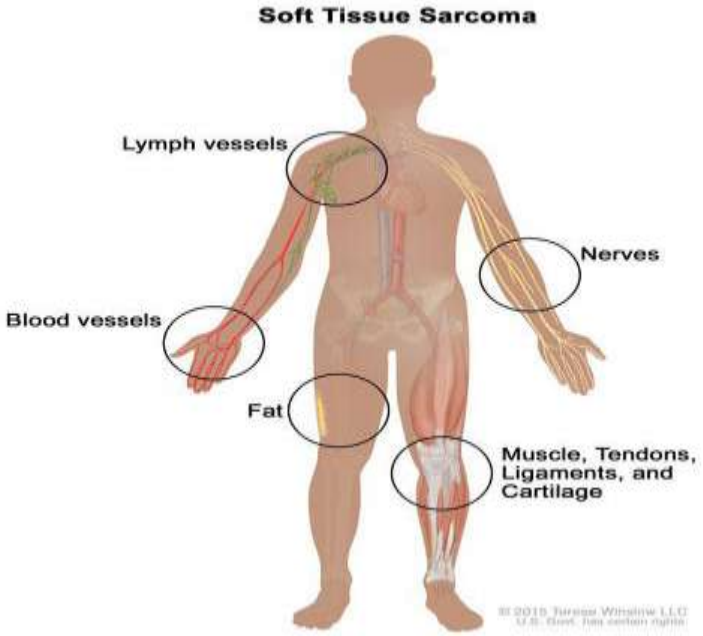

Figure 5.

Soft tissue sarcoma forms in soft tissues of the body, including muscle, tendons, fat, blood vessels, lymph vessels, nerves, and tissue around joints.

8.3. Lymphoma

Lymphoma is cancer that begins in lymphocytes (T cells or B cells). These are disease-fighting white blood cells that are part of the immune system. In lymphoma, abnormal lymphocytes build up in lymph nodes and lymph vessels, as well as in other organs of the body.

There are two main types of lymphoma:

Hodgkin lymphoma – People with this disease have abnormal lymphocytes that are called Reed-Sternberg cells. These cells usually form from B cells.

Non-Hodgkin lymphoma – This is a large group of cancers that start in lymphocytes. The cancers can grow quickly or slowly and can form from B cells or T cells.

8.4. Multiple Myeloma

Multiple myeloma is cancer that begins in plasma cells, another type of immune cell. The abnormal plasma cells, called myeloma cells, build up in the bone marrow and form tumors in bones all through the body. Multiple myeloma is also called plasma cell myeloma and Kahler disease.

IX. RISK FACTOR OF CANCER

- Tobacco consumption
- Physical Activity
- Weight Control and Obesity Prevention
- Dietary Improvements
- Limitation of Alcohol Use
- Safer Sex and Control of Oncogenic viruses
- Screening
- Sun Protection
- Medications

X. TREATMENT OF CANCER

10.1. Pharmacological Treatment

Table 1. First-Line, Second-Line and Beyond Second-Line Treatment Recommendations for Neuropathic Pain

Neuropathic Pain		
First-Line	**Second-Line**	**Beyond Second-Line**
Gabapentin	Other Antiepileptic Drugs (AEDs)	Capsaicin

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Neuropathic Pain		
First-Line	**Second-Line**	**Beyond Second-Line**
	Lamotrigine	Clonidine
	Carbamazepine	Dextromethorphan
	Levetiracetam	Mexiletine
	Oxcarbazepine	
	Tiagabine	
	Topiramate	
	Zonisamide	
5% Lidocaine patch	Other Antidepressants	
Opioid analgesics	Paroxetine	
Tramadol hydrochloride	Citalopram	
Tricyclic Antidepressants (TCAs)	Bupropion Hydrochloride	
hydrochloride Nortryptiline	Venlafaxine Hydrochloride	
hydrochloride Desipramine		

Table 2. EFNS Guidelines on Pharmacological Treatment of Neuropathic Pain

First Line	Second Line	Third Line
Pregabalin	Topical lidocaine (PHN)	Strong opioids
Gabapentin	Tramadol	
TCAs (tricyclic antidepressants)	Venlafaxine	
	Duloxetine (especially for PDN)	

Table 3. Recommendations for the Pharmacolocical Management of Neuropathic Pain

First Line	Second Line	Third Line
Pregabalin	Tramadol	NMDA antagonists,
Gabapentin	Strong opioids	Mexiletine
TCAs		Topical capsaicin
SNRIs		

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First Line	Second Line	Third Line
Topical lidocaine for PHN		

Table 4. Guidelines on Pharmacological Treatment of Neuropathic Pain

Pharmacological Treatment	
First Line for various conditions	Second Line
TCAs (25 to 150 mg/day)	Tramadol (200 to 400mg/day)
Gabapentin (1200 to 3600 mg/day)	
Pregabalin (150 to 600mg/day)	
First Line for restricted conditions	Second or Third Line
Lidocaine plaster (up to three plasters/day): PHN	Opioids
PDN Duloxetine (60 to 120mg/day)	
PDN Venlafaxine (150 to 225mg/day)	
Capsaicin 8% patch: PHN, HIV neuropathies	
Cannabinoids: MS	
Pregabalin SCI	
First Line for neuropathic cancer pain	
Gabapentin	
Tramadol, TCAs level B of evidence	
Combination therapy	
Gabapentin & TCAs	
Gabapentin & opioids	

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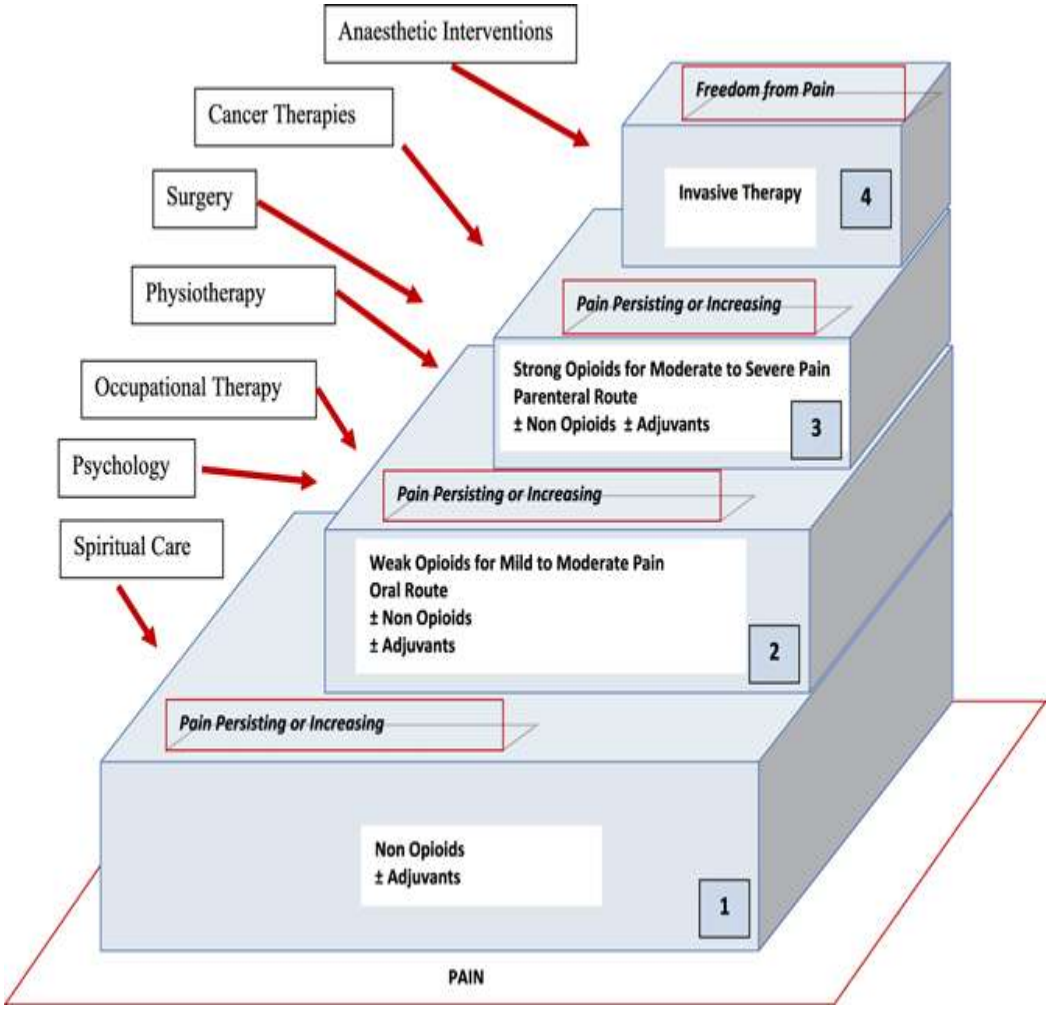

Figure 6

10.2. Non-pharmacological

In cancer pain management. It is considered that these therapies help the standard pharmacological treatment in pain management. While medical drugs are being used for treating the somatic (physiological and emotional) dimension of the pain non-pharmacological therapies aim to treat the affective.

.• Decrease the feeling of weakness.

• Improves the activity level and functional capacity.

.• Reduces stress and anxiety.

• Reduces the pain behavior and focused pain level.

• Reduces the needed dosage of analgesic drugs thus decreasing the side effects of the.

• It may increase the number of methodsthat the patient uses to manage. It requires an experiencedtherapist. Skin Stimulation/Coetaneous Stimulation (superficial hot-cold application and massage) .

• It may reduce muscle spasms,inflammation and pain. It can be used more likely as an adjuvanttherapy together with other methods.

• It may increase the controlling ability ofpain feeling of the patient.

• It is so easy to use. It may be applied by the patients orfamilies.

• It is a cheap method.

• Hot application can increase the bleeding or edema after acute injuries.

• Cold application is contraindicate for the situations such as uritcaria/hypersensitivity, hypertension, Reynaud's phenomenon and sickle cell anemia which are related to cold.

• Transcutaneous Electrical Nerve Stimulation (TENS). It reduces the pain without having any drug-related side effects.

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- It can be used more likely as an adjuvant therapy together with other methods. It gives the feeling of pain management to the patient. It requires an experiencedtherapist.
- There is a risk for bleeding and infection.
- There are no reliable results for use in cases of pregnant women. It has an analgesic effect
- Aromatherapy: It has a sedative and relaxing effect. It may cause hypersomnia
- Some herbs should not be used with other antidepressants and alcohol.
- Acupuncture: It may provide pain reduction without any side effects.
- It can be used more likely as an adjuvant therapy together with other methods.
- It requires an experienced therapist.

XI. DISCUSSION

India exhibits heterogeneity in cancer. The incidence rates of Aizawl district were observed to be 7 times and 4 times that of Osmanabad and Beed district PBCRs in males and females, respectively. The highest cancer incidence rate was observed in the NE region (6 PBCRs for males and 4 PBCRs for females) than other areas in the country. The leading sites of cancer in the NE region were nasopharynx, hypo pharynx, esophagus, stomach, liver, gallbladder, larynx, lung, breast, and cervix uteri. The NE region lacks required infrastructure with respect to specialized treatment facilities, human resources, as seen by the low 5-year survival of breast, cervix, and head and neck cancer compared with rest of India. A substantial proportion of patients with cancer from the NE region are traveling outside the NE for treatment and cancer care.Local cultural factors and lifestyle choices may have contributed to the heterogeneity in cancer incidence pattern and differences in India, as was seen in Thailand.

Lung (9 PBCRs), mouth (9 PBCRs), esophagus (5 PBCRs), stomach (4 PBCRs), and nasopharynx (1 PBCR) cancers were the most common cancers in men. Lung cancer was the leading site in metropolitan cities and the southern region, whereas mouth cancer was the leading site in the West and Central regions. Lung cancer and oral/mouth cancer were the most common cancers among males in the Indian subcontinent. Cancers of the esophagus, stomach, and nasopharynx were the leading sites in the NE region of India. Here, the cancer incidence pattern is different from the rest of India. There are similarities in the cancer incidence pattern with the Southeast Asian region. Overall, these findings on patterns of cancer were similar to previously published reports under NCRP.

Cancer of the breast (19 PBCRs) and cervix uteri (7 PBCRs) were the most common cancers in women. The highest burden of breast cancer was observed in metropolitan cities. There is an increase in the trend of incidence of breast cancer, whereas cervix uteri cancer is on the decline. A steady increase in breast cancer in most of the PBCRs including newer PBCRs, poses a great health challenge to women in India. Presently, breast cancer and cervix uteri are the leading sites of cancer among women in India, posing an important public health problem that needs important input from various health and other agencies to tackle. A multidisciplinary approach to breast cancer, including awareness programs, preventive measures, screening programs for early detection, and availability of treatment facilities, are vital for reducing both incidence and mortality of cancer in Indian women.

The incidence rate of thyroid cancer among women is increasing, and it is most common in the districts of Thiruvananthapuram and Kollam in Kerala. The high burden of thyroid cancer in Kerala could be due to overdiagnosis, as was observed even in high-income and low- and middle-income countries.AAR in Barshi rural is almost one third of urban PBCRs (males, 50.6 v 147.0; females, 61.0 v 146.8), and the increase in APC was less compared with urban PBCRs. This needs additional investigation.

There are cancers of several anatomic sites known to be associated with the use of tobacco.Based on PBCR data, almost one third of the cancers were known to be associated with the use of tobacco in India. India state-level disease burden initiative cancer collaborators estimated that tobacco use was the highest contributing risk factor for cancer in India. In India, lung cancer can be attributed to tobacco use and air pollution, which are the leading risk factors.Approximately 70% of cancers in India were potentially preventable through modifiable risk factors.

Because it is difficult to obtain information on the clinical extent of disease and treatment from PBCRs, the hospital database was used for such analysis. The majority of breast and cervix uteri cancers were diagnosed at a locally advanced stage. Chemoradiation was the most common type of treatment of cancer cervix uteri. A multi-institutional study from India on cervix cancer showed significantly better survival with chemo radiation than radiation alone in the locally advanced stage. A study from Chennai showed that

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concurrent chemoradiation for locally advanced cervical cancer resulted in the best disease-free survival.Two thirds of the patients with cancer were diagnosed at the locoregional stage for head and neck cancers from HBCRs. Similar to that, a low proportion of patients with head and neck cancer presented in the early stage, and a high proportion (88.1%) were seen in Uttarakhand.Multimodality was the most common treatment given for breast and head and neck cancers. A multi-institutional study estimated that 65% of new head and neck cancers with locally advanced disease did not receive the benefit of optimal treatment, resulting in poor survival.

Less than one fifth of lung and stomach cancers were diagnosed as localized only. Systemic therapy was the most common type of treatment given for lung and stomach cancer. A previous report on HBCR results showed similar findings. A hospital-based study from northern India showed that 90% of patients with lung cancer were diagnosed at an advanced stage of the disease, and there was a delay in diagnostic evaluation and treatment. Creating cancer awareness, preventing risk factors, and improving access to care among people would result in down staging of cancer.

The measure of validity, MV%, was above 77% for all the PBCRs. Varying patterns of DCO% and M:I% were observed among PBCRs which were dependent on the quality of death registration and certification. Efforts to improve the quality are always underway. In some registries, low DCO% (< 1%) is due to nonavailability of all-cause mortality data and incomplete/incorrect certification of cause of death. Some registries had an efficient trace back procedure by house visit/phone. Data from PBCRs were regularly published in successive volumes of Cancer Incidence in Five Continents (CI-5) by WHO-IACR/IARC. The incidence data from 15 PBCRs under NCRP (India) were published in Cancer Incidence in Five Continents, Volume XI, by WHO-IACR/IARC.

XII. CONCLUSION:

A plan for the diagnosis and treatment of cancer is a key component of any overall cancer control plan. Its main goal is to cure cancer patients or prolong their life considerably, ensuring a good quality of life. In order for a diagnosis and treatment programmed to be effective, it must never be developed in isolation. It needs to be linked to an early detection programme so that cases are detected at an early stage, when treatment is more effective and there is a greater chance of cure. It also needs to be integrated with a palliative care programme, so that patients with advanced cancers, who can no longer benefit from treatment, will get adequate relief from their physical, psychosocial and spiritual suffering. Furthermore, programmes should include a awareness-raising component, to educate patients, family and community members about the cancer risk factors and the need for taking preventive measures to avoid developing cancer.

Where resources are limited, diagnosis and treatment services should initially target all patients presenting with curable cancers, such as breast, cervical and oral cancers that can be detected early. They could also include childhood acute lymphatic leukaemia, which has a high potential for cure although it cannot be detected early. Above all, services need to be provided in an equitable and sustainable manner. As and when more resources become available, the programme can be extended to include other curable cancers as well as cancers for which treatment can prolong survival considerably.

This module on diagnosis and treatment is intended to evolve in response to national needs and experience. WHO welcomes input from countries wishing to share their successes in diagnosis and treatment.

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