

Review

## An Overview of Theranostic Approaches to Cancer

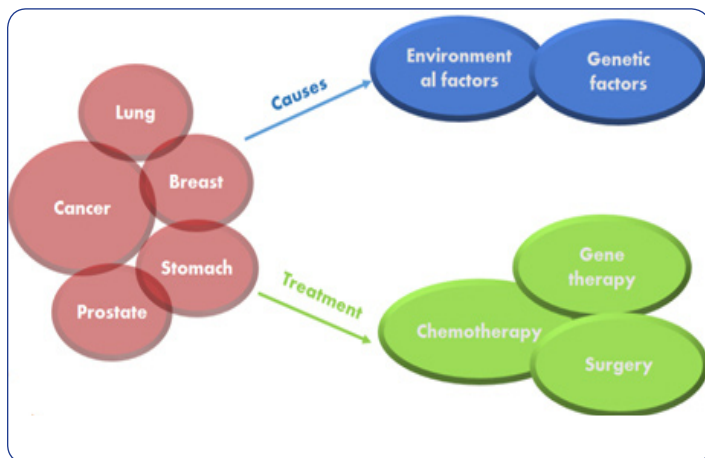
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### Abstract

DNA double helical structure carries the genetic blueprint of the cell and hence integrity of this biomolecule is crucial for all forms of life. Normal body cells grow, divide and die in a controlled manner for the proper functioning of the body. However, any alteration/mutation in the gene can alter the way in which a cell behaves and therefore, hampers the normal functioning of the body and may cause cancer. Cancerous cells are different from normal cell because they continue to grow in an uncontrolled fashion and do not die. Lung cancer, breast cancer, bladder cancer, kidney cancer, skin cancer, thyroid cancer, leukemia, prostate cancer, endometrial cancer, and pancreatic cancer are the most common types of cancer which affects a large number of mass across the world. This review is an attempt to summarize the causes of cancer along with the diagnostic tools employed for the treatment of this deadly disease.



**Keywords:** Cancer; Chemotherapy; Metastasis; Gene therapy; Tumor

### Introduction

Over many decades, scientists have been fascinated and stimulated by the fact that the study of nucleic acids is fundamental to knowledge of life. The study of structure and functions of this inscrutable molecule had a remarkable impact on science and medicine. Therefore, along with the key role it plays in the cellular processes, its applications in genetic engineering, biotechnology, molecular biology and cancer research is growing at a faster pace. In the recent time, a number of excellent reviews have addressed the diagnostic approaches employed for the treatment of cancer

cells [1-3]. Cancer is among the leading causes of death worldwide. In the year 2012, 8.2 million people were died due to cancer and more than ten million people get affected every year [4,5]. Normal cell grows in a controlled manner for the proper functioning of the body system. Cancer develops when there is uncontrolled/abnormal growth of the cells and it is not restricted to a particular organ but can also invade other tissues. Most of the time, cells can identify and correct/repair any damage to the DNA molecule. Normal cells have a tendency to destruct them when they are damaged. But sometimes, cell cannot repair itself, it undergoes apoptosis. There are many reasons due to which normal cells become cancerous, like mutations in a gene, inherited defects, environmental factors and sometimes poor life style choices such as smoking and heavy alcohol use etc [6]. An abnormal mass of cell is known as tumor. Tumor can be benign and malignant; benign tumor grows locally and does not spread whereas malignant tumor spread easily and invades other tissues in a process known as metastasis. Malignant tumor spread to other tissues like lungs, bones, liver, brain, and other site via blood stream or lymphatic system (Figure 1). Only some of the metastatic cancers are curable while others are not. In a recent report, anticancer activity of (')-Epigallocatechin-3-gallate (EGCG), a major bioactive constituent in green tea has been discussed [7].

### Causes of Cancer

Different theories were put forward by different scientist to determine the causes of cancer in late 1800s [6]. Lobstein and Recamier, and later Cohnheim postulated cancer as the result of displaced embryonal tissue, whereas Virchow suggested that chronic irritation was a main cause of cancer [8,9]. Later on few experimental evidences established viruses as one among the other important causes of cancer [10]. All these studies proposed that

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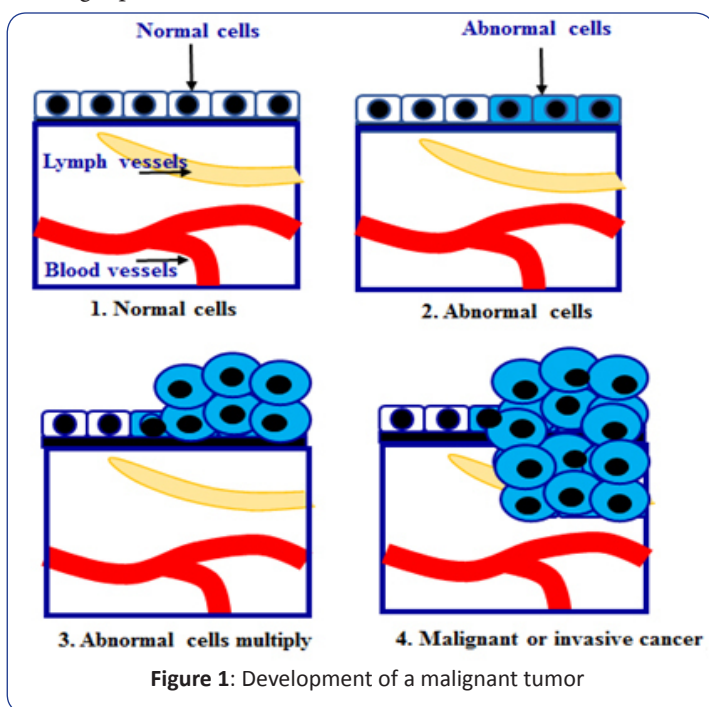
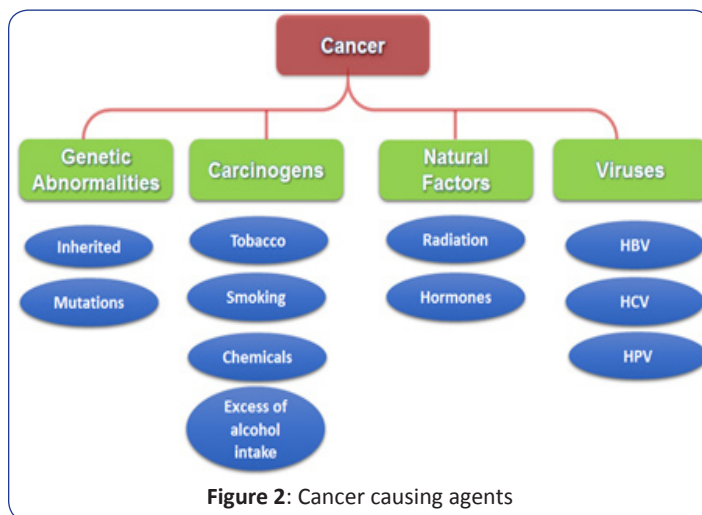
**Rec Date:** July 16, 2016, **Acc Date:** August 3, 2016, **Pub Date:** August 3, 2016.

**Citation:** Shikha Kaushik and Anju Singh (2016) An Overview of Theranostic Approaches to Cancer. BAOJ Cancer Res Ther 2: 024.

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cancer is a multifactorial illness as there is a complete web of cause and there is no single factor known for any type of cancer (Figure 2). Some of the factors responsible for damaging DNA and known to cause cancer are:

1. Mutations in a gene
2. Environmental factors, mainly exposure to UV radiations and air pollutants
3. Certain microbial infections (Epstein-Barr virus, Helicobacter pylori (H. pylori), Human papillomavirus (HPV)), Hepatitis B virus (HBV) and Hepatitis C virus (HCV)
4. Poor Lifestyle (exposure to chemicals, high alcohol intake, smoking, tobacco use, obesity)
5. Poor immune system
6. Intake of nonsteroidal anti-inflammatory drugs (NSAID) for longer period



### Types of Cancer

Cancer can be categorized on the basis of the body part from which they are originated. More than 200 types of cancer are identified till date, however, some body parts contains different tissues. So, NCI has classified this disease into several categories on the type of cell. These include:

**Carcinoma** – Cancer that originates in the skin and in tissues that form lining over internal organs. These cancerous cells invade the nearby tissues and organs. The common types of cancer which fall in this category are lung, breast, prostate and colon cancer.

**Sarcoma** – Cancers which arises from connective tissues (i.e. bone, fat, muscle, nerves and cartilage) are included in this class. The most common forms of sarcoma are leiomyosarcoma, liposarcoma

and osteosarcoma.

**Leukemia** – This class of cancer instigates from white blood, bone marrow and tissues that form blood cells and is the most common in children.

**Lymphoma** – This is a form of cancer that starts from the infection fighting cells of the immune system. Lymphoma (also called lymphatic cancer) can occur anywhere in the body. Table 1 shows the common types of cancer, factors responsible for them and the tissue affected.

### Diagnostic Techniques for Cancer

With advancement of technologies a number of diagnostic tools are present which can help to detect cancer. However, in some cases, particular types of cancer such as lymphomas are hard to diagnose even for an expert in the field. Some important types of diagnostic tools are explained here and summarized in Figure 3.

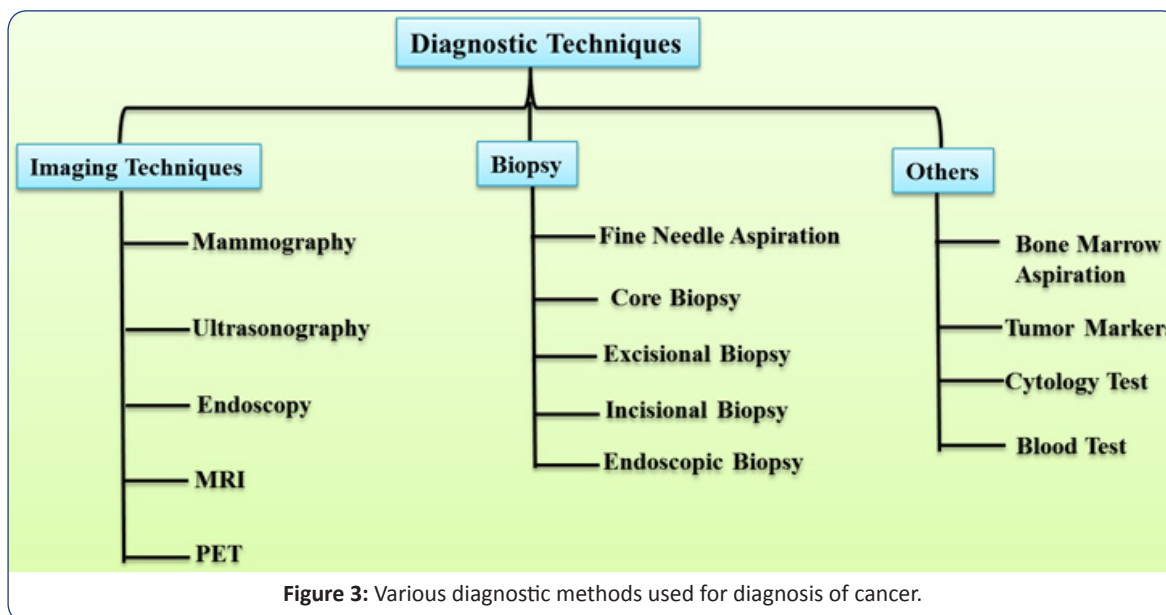
**Imaging Techniques:** This technique is basically used for screening, detection and diagnosis for various types of cancers. There are various imaging techniques used for the diagnosis of cancerous cells in the body which includes mammography, ultrasonography, endoscopy, MRI and PET. A brief about all the imaging diagnostic techniques are given here:

(i) **X-ray:** The most common imaging technique is X-ray which can be made more specific by using barium. Barium studies are specifically used to diagnose stomach and small intestinal growth and cancer while mammogram is used for diagnosis of breast lumps and growths [11,12]. It is used specifically for screening at early stages of breast cancer and it reduces mortality rate caused by breast cancer in various cases. Along with providing adequate visualization, this diagnostic technique is capable of depicting subtle calcification [13].

(ii) **Ultrasonography:** Ultrasonography technique was proposed as the effective diagnostic technique adopted for diagnosis of breast diseases by Wild and Neal in 1952 [14]. An ultrasonography is also used to find tumor in body as well as it can also help in biopsies by showing the exact location of any tumor. It is a very effective

Table 1

Cancer Type	Causes	Part (Tissue) Affected
Bladder Cancer	Smoking, Prolonged contact with chemicals (Aromatic Amines, Metals such as Arsenic)	Urinary Bladder
Breast Cancer	Environmental factors, genetic	Breast Tissue (milk ducts & lobules)
Colon Cancer	Hereditary Factors, Poor diet (high in fat and low in fiber content)	Large intestine
Lung Cancer	Tobacco smoking, Exposure to radiation and chemicals	Any part of the respiratory system
Endometrial/ Uterine Cancer	Obesity, certain inherited conditions, and taking estrogen alone (without progesterone)	Tissue coating the uterus
Kidney/ Renal Cancer	Smoking, Obesity, use of NSAID and inherited disorders	Kidney
Thyroid Cancer	Genetic factors, exposure to radiation	Thyroid Gland
Leukemia (Blood Cancer)	Genetic diseases, exposure to radiation	Bone Marrow
Prostate Cancer	Intake of inflammatory drugs, obesity in some cases	Prostate gland
Pancreatic Cancer	Hereditary factors, intake of alcohol	Pancreas
Melanoma	Exposure to UV rays	Melanocytes (Skin)



imaging modality and pictures of internal organ can be produced using high frequency sound waves. The sound waves generate different echo sound while bouncing off from abnormal tissues and healthy tissue which helps doctor to detect a potential tumor [15].

(iii) **Endoscopy:** It is also an imaging technique used to see the parts of the body, which we cannot see by any other technique. Endoscopy is frequently done for screening, detection and diagnosis of various types of cancer. Colonoscopy and sigmoidoscopy are used to screen the colon and rectal cancer [16]. Endoscopy can help in prevention of cancer by letting the doctor find and remove polyps or abnormal growth that might become cancerous at later stage.

(iv) **Magnetic Resonance Imaging (MRI):** MRI is a powerful imaging technique used for the screening and diagnosis of various types of cancer. It uses a strong magnetic field to generate a

complete computer image of the body's soft tissues, blood vessels and other major internal organs. MRI has been proved to be an effective technique in diagnosis and localize the prostate cancer as well as breast cancer [17].

(v) **Positron-Emission Tomography (PET):** Positron-Emission Tomography is used to screen, diagnose and locate new areas of cancer spread in bones. It is also effective in diagnosis of brain tumor, neck tumors, colorectal cancers and lymphomas [18]. PET scans use a special kind of radioactive sugars and on the basis of growth rate body cells absorb radioactive sugars. The cancerous cells usually take up a large amount of radioactive sugars in comparison to the normal cells. The sugars give off tiny positrons which in turn in body to electrons thereby produce gamma rays. A special kind of camera captures these gamma rays as they are coming out from body and turns into images.



**Biopsy:** A biopsy is a method or procedure by which removal of small amount of tissue from suspected organ takes place to test presence of cancer cells. Various types of biopsies are possible which are as follows [19]:

(i) **Fine Needle Aspiration (FNA):** In this biopsy, a fine tipped needle is used to collect the tissue sample. FNA is used for thyroid cancer.

(ii) **Core Biopsy:** A larger hollow needle is used in core biopsy to extract a column of tissue in suspected area of tumor.

(iii) **Excisional Biopsy:** In this biopsy, whole organ or whole lump area is removed and good candidates for excisional biopsy are spleen and sometimes breast lumps.

(iv) **Incisional Biopsy:** In this type of biopsy a small portion of tumor or lump is removed. This biopsy is specifically used for tumors of soft and connective tissue, muscle. It is also used to differentiate benign tumor from malignant tumor.

(v) **Endoscopic Biopsy:** Endoscopic biopsy is the common technique of biopsy used for tumor diagnosis in urinary bladder, abdominal cavity, joint cavity either through natural orifice or small surgical incision in body.

**Other Diagnostic Technique:** In addition to imaging and biopsy techniques, some other advanced procedures are also employed to screen and diagnose cancer in various organs. Some of these are discussed below:

(i) **Bone Marrow Aspiration:** This is an important procedure employed for the diagnosis of blood disorders like leukemia, lymphoma and multiple myeloma. Bone marrow aspiration is different from biopsy because in aspiration procedure, a sample of liquid portion of the bone marrow is taken for examination in contrast to the solid piece in biopsy.

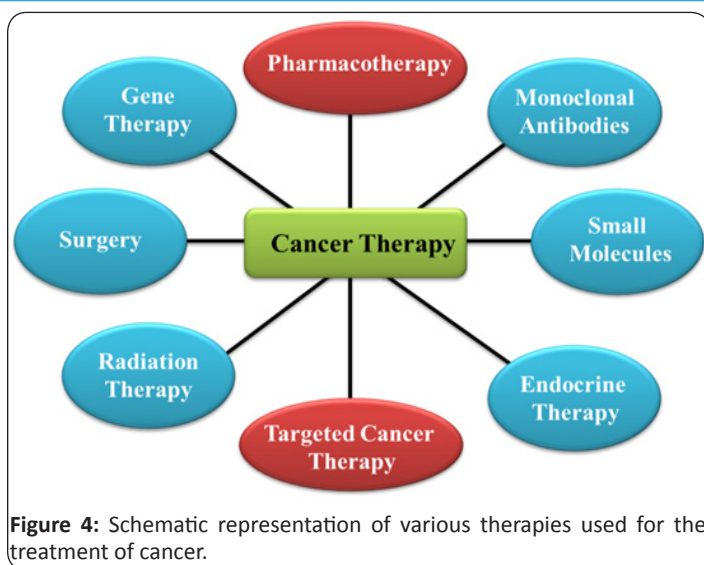
(ii) **Tumor Markers:** Tumor markers are the biomarkers used for the detection of certain types of cancer in the body. Most of the tumor markers are protein. These substances are found in higher amount than normal in the blood, urine, stool or body fluids. A drop in the amount of a tumor marker or its retention at the normal level is an indication that cancerous cells are responding well to the treatment. Some examples of tumor markers are CA15-3, PSA, CEA and CA19-9.

(iii) **Cytology Test:** This technique includes diagnosis of tumors by looking at single cell or small cluster of cells. This type of cytology test of sample cell is known as pap test. In this technique, a brush or spatula is used to take sample from cervix for pap test. It is a very simple method and comfortable for patients also.

(iv) **Blood Test:** A complete blood count (CBC) test is a common test to diagnose cancer. This technique is useful in screening and diagnosis of leukemia and lymphoma by observing high count of white blood cells which play a key role in defense mechanism of body by engulfing foreign bodies, bacteria and viruses in body.

### The Possible Treatment of Cancer

The word cancer dictates its meaning by unusual and abnormal growth of cells in body. Since tumors have wide variety of



**Figure 4:** Schematic representation of various therapies used for the treatment of cancer.

background of origination and different causative organism not a single technique or therapy is sufficient for the complete eradication of cancer [20]. Different pathogenesis is sensitive to varied anticancer drugs and therapies. Treatment can vary from patient to patient and type of cancer, depending upon the stage of the tumor growth, physiological condition of patient and sensitivity towards the anticancer drugs and therapy. The goal of the treatment is cure and the eradication of cancer from the root and prolonged survival. Various techniques can be applied in single or in combination for the treatment of cancer (Figure 4).

(i) **Pharmacotherapy:** Cytotoxic agents are the main basis of all types of therapies used to treat cancer or tumor growth. The pattern of growth of cancerous cells may affect the tumor behavior to a greater extent and their response to various types of cancer therapies used. Cell has four steps of growth phase in cell cycle namely  $G_1$ ,  $G_2$ , S and M phase respectively. In which  $G_1$ ,  $G_2$  phases deal with growth of the cell whereas S phase deals with synthesis or replication of DNA followed by M phase in which cell growth is halted till active division of cell takes place. Various checkpoints are there in cell cycle which allows another growth phase after successful accomplishment of division but these checkpoints become abnormal in cancerous cells. Various types of anticancer agents can work at the specific points of cell cycle [21]. Antimetabolites such as methotrexate are more active towards the synthesis phase which deals with synthesis of purines and pyrimidines whereas alkylating agents like cisplatin and doxorubicin act on DNA synthesis and binding. Chemotherapeutic agents are used at the initial stage for the treatment of advanced diseases.

(ii) **Monoclonal Antibodies:** These antibodies specifically bind to the antigens produced by the cancerous cells and thus immune reaction is induced against cancer cells. Different types of monoclonal antibodies have been synthesized and effectively used against the various oncogenic disorders [22]. Clinical trials of various monoclonal antibodies are already approved and some are under process.

(iii) **Small Molecules:** Various small molecules have been

synthesized and some naturally occurring small molecules are used for treatment of cancer by interacting in the intracellular molecular pathways and thereby exert anti-tumor effect [23]. Small molecules such as abiraterone, crizotinib and many more are presently used for the treatment of the cancer.

**(iv) Endocrine Therapy:** Endocrine therapy or hormonal therapy is used since century ago for the treatment of cancers, specifically the breast cancer. Manipulation in endocrine hormones can successively check or halt the cancer cell growth by hormone deprivation or by blocking hormone receptor [24].

**(v) Targeted Cancer Therapy:** The biggest challenge in treatment of cancer is development of resistance towards drugs by multiple drug resistance (MDR) as well as the destruction of normal cells along with cancerous cells. Targeted therapy aims at delivering the drugs specifically to the neoplastic cells or genes and proteins whichever is the main cancer causing agent [25]. Targeted therapy deals with development of drugs that check the cancer cells, promote cell cycle regulation, induction of apoptosis and autophagy. It can be used in combination with therapies like monoclonal antibodies and small molecules.

**(vi) Radiation Therapy:** This therapy is used for the destruction of the cancer cells by damaging the genetic material e.g. DNA of cells by high energy beam of radiation which block their ability to divide and proliferate. Radiation therapy is used along with the surgery to eradicate the small lumps of cancer or tumor growth [26]. The drawback of radiation therapy is that it also kills the normal cells along with the abnormal cells but normal cells have a tendency to repair very fast while cancer cells are not so efficient to repair the damage, and ultimately results in cell death.

**(vii) Surgery:** Surgery plays a pivotal role in screening, diagnosing, prevention, cure and eradication of cancer. In many cases small tumor growth is surgically removed for the prevention and to check further progression of cancer in other neighboring cells. Even though late stage cancer is treated with chemotherapy, surgery may be used to offer alleviation of cancer in advance stage.

**(viii) Genetic Therapy:** Cancer gene therapy is based on the fact that many cancers are caused by genetic aberrations and genetic alterations, successively lead to the cause of malignant change in tissues. Gene therapy basically deals with genetic modification of cancer cell by transferring the genetic material for the alteration of cellular phenotype transiently or permanently. The genetic material introduced in the patient can be a gene, a segment of gene or oligonucleotide. Viruses are preferably very potential vector for the gene transfer [27].

**(ix) Antiangiogenic Agents:** Tumor cells need blood vessel for their expansion. Antiangiogenic agents are an exclusive class of drugs which is used for the treatment of cancer by inhibiting the growth of blood vessels rather than tumor cells. These drugs can be used either alone or in combination with other chemotherapeutic agents. A number of excellent reviews on anti-angiogenic therapy have appeared in the recent times [28,29].

## Outlook and Future Directions

Cancer has become one of the deadly and serious diseases of the present era. This is one of the leading causes of the death all over the world. Survival rate depends upon the diagnosis at the early stage of the disease. Over the past many years, researchers have made efforts to explore the various factors responsible for the development of cancerous cells and it has become clear from their studies that there is a complicated network of multiple causes and any individual factor cannot be held responsible for it. There are various techniques with which cancer can be diagnosed. In this review we have briefly summarized the factors which are responsible for this noxious disease along with the approaches. Experts have uncovered many small ways for the prevention from this disease and estimated that 4 in 10 cancer cases can be prevented by changing the life style, like saying no to tobacco, smoking, alcohol, following healthy diet, using mobiles for short duration and avoiding unnecessary exposure to radiations. Although in last few years, advancement in techniques and treatment have gained a new height in this field, still future research is needed in this direction to explore the efficient strategies to combat this disease.

## Acknowledgements

Authors would like to thank Prof. Shrikant Kukreti, Professor, Department of Chemistry, University of Delhi for his immense support and encouragement.

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