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Review Article

# THERAPIES IN CANCER TREATMENT: AN OVERVIEW

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**ABSTRACT**

Cancer is one of the most frequent and distressing diseases. The mortality caused by cancer and its prevalence has increased during the last 50 years. Cancer is still one of the most destructive disease of human beings due to its complexity and progressive nature and the clinical management of this deadly disease continue to be a challenge for the 21st century. Various types of cancer are reported in literature such as Carcinoma, Sarcoma, Lymphoma, leukemia, Blastoma and Germ cell tumor. There is a continuous need for new and better cancer therapies. A few years ago, surgery and radiotherapy were the only effective way to fight tumor growth. Now various therapies for the treatment of cancer have been developed including chemotherapy, radiation therapy, proton therapy, thermotherapy, Photodynamic therapy, laser therapy, sentinel lymph node biopsy, cryotherapy and differentiation therapy. These therapies have dramatically changed the scenario of cancer treatment. Further research is also needed to discriminate the various genes and signaling pathways in the process of the carcinogenesis of cancer stem cells for the development of novel therapies, with the ultimate goal of eliminating the residual disease and recurrence. This review aims to present the various types, stages of cancer and also focus on various therapies used for the treatment of cancer.

**Keywords:** Cryotherapy, Gene therapy, Laser therapy, Proton therapy, Thermo therapy.

## INTRODUCTION

The latest world cancer report provides clear evidence that global cancer rates could increase to 15 million by 2020 and is expected to grow to 21.4 million new cancer cases and 13.2 million cancer deaths by 2030 [1-2]. New and more effective drug therapies are being developed due to the progress in the field of tumor biology and molecular genetics [3, 4]. A lot of challenges lie ahead for all those that are involved in cancer research and patient management. In cancer, abnormal cells divide in an uncontrolled manner and invade to other parts of the body through the blood and lymph system. A single tumor cell surrounded by normal cells will replicate at a higher rate than the other cells. Once a small cancerous mass has formed, the normal cells will not be able to compete with the tumor cells for the supply of nutrients from the blood stream. The tumor cells will start displacing normal cells until the tumor reaches a diffusion-limited maximal size [4, 5]. Nutrients are easily available at the outer side of a mass, while cells on the inner side create a necrotic core within the tumor that is dependent on diffusion to receive nutrients and eliminate waste products. Thus a steady state tumor size, forms, until a better connection with the circulatory system is achieved. The tumor will remain at this size and the process take years until the tumor can gain that access to the circulation [5]. There are more than 100 different types of cancer. The commonly occurring cancers are bladder cancer, breast cancer, colorectal cancer, lung cancer, prostate cancer, etc. Alterations to normal cell physiology defines the progression of most human malignancies but six essential alterations are as:

### Self-sufficiency in growth signals

Tumor cells may proliferate either by internal production of growth factors or by high levels of external growth factors which usually not produce proliferation if present in normal level [6].

### Insensitivity to antigrowth signals

In normal tissues, the stability of the cell population is maintained by a host of signals and factors inhibiting cell proliferation and differentiation. For cancer cells to survive and replicate, these antigrowth signals are inhibited by cancer cells to survive and replicate [7].

**Tissue Invasion and Metastasis:** Once cancer cells leave the primary tumor and travel through the body, the ability to invade and colonize distant sites to form metastases are dependent on acquiring the ability to overcome the normal suppressors of invasion [7].

### Limitless potential for replication

Tumor cells develop unlimited replicative potential, effectively gaining "immortality" for expanding their population [6].

### Sustained angiogenesis

Angiogenesis, the process by which new blood vessels are formed, is not an inherent property of most of cells in small, localized neoplasms. Cancer cells acquire the angiogenic ability to develop into larger and potentially metastatic state.

### Evading apoptosis

In normal tissue, the stability of cell population is maintained through a process of programmed cell death or apoptosis. Acquiring resistance to apoptosis is one of the key mechanisms by which cancer cells maintain proliferation and is thought to be a critical survival factor for the majority of tumors [7]. The present review aims to discuss various therapies used to treat the cancer. Various types and stages of cancer have also been discussed in this review article.

### Types of cancer

On the basis of resemblance of the tumor with the type of cell, cancer can be classified as below:

### Carcinoma

Carcinoma is defined as the cancer that generally arises in a tissue lining the outer or inner surfaces of the body. It originates in cells developed in the endodermis or ectodermic germ layer during embryogenesis. Damage in the genome of putative epithelial cells may cause cells to exhibit abnormal, malignant properties resulting in carcinoma [8]. Small and localized carcinoma that has not yet permeated through the epithelial basement membrane is known as Carcinoma in situ (or CIS). It is not a pre-malignant type, but a pre-invasive type of cancer[9]. The carcinoma can further be classified as:

### Adenocarcinoma

This type of carcinoma resembles gland-related molecular products or microscopic glandular-related tissue cytology and tissue architecture [8].

**Squamous cell carcinoma**

This type of carcinoma includes features and characteristics like intercellular bridges, keratinization, squamous pearls which are indicative of squamous differentiation [10].

**Adenosquamous carcinoma**

This type of tumor contains both adenocarcinoma and squamous cell carcinoma, so known as mixed tumor, wherein a minimum of 10% of the tumor volume is comprised of each of these cell types [10].

**Anaplastic carcinoma**

It belongs to the heterogeneous group of high-grade carcinoma cells lacking any evidence of highly specific differentiated neoplasms histologically or cytologically. This type of carcinoma is also known as undifferentiated carcinomas [11].

**Large cell carcinoma**

Large cell carcinomas are also called large cell lung cancers as these often occur in the outer regions of the lungs. When examined under the microscope, these appear like large round cells and tend to be large as well when diagnosed. This type of carcinoma tends to grow and disseminate more rapidly than some other forms of non-small cell lung cancer [11].

**Small cell carcinoma**

It refers to the carcinoma in which cells are approximately 3 times smaller than the diameter of a resting lymphocyte, little evident cytoplasm and usually round in shape. Occasionally, small cell malignancies may be of slightly polygonal or spindle-shaped cells. Small cell carcinoma (SCC) occurs in multiple sites throughout the head and neck and has become recognized as a relatively infrequent clinical pathology [12].

Other forms of carcinoma include the lesions of pseudo-sarcomatous origin like spindle cell carcinoma (encompassing elongated cells resembling connective tissue cancers), giant cell carcinoma (comprising of huge, bizarre, multinucleated cancer cells), and sarcomatoid carcinoma (encompassing mixtures of both spindle and giant cell carcinoma). Pleomorphic carcinoma contains spindle cell and giant cell components, with at least 10% tumor mass of highly differentiated characteristics (i. e. Adenocarcinoma or squamous cell carcinoma). Carcinosarcoma and pulmonary blastoma occur rarely ever and may contain tumor mass resembling both carcinoma and true sarcoma [13].

**Sarcoma**

Sarcomas are malignant tumors of mesenchymatous origin. This category of cancer includes malignant tumors of cancerous bone, cartilage, fat, muscle, vascular, or hematopoietic tissues [14]. Based on the type of tissue from which they arise, sarcomas are classified differently e. .g. osteosarcoma arises from bone, chondrosarcoma originating from cartilage, liposarcomaoriginating from fat, and leiomyosarcoma originating from smooth muscles. Sarcomas, such as leiomyosarcoma, chondrosarcoma and gastrointestinal stromal tumour (GIST) are more frequent in adults than in children. Most high-grade bone sarcomas, including Ewing's sarcoma and osteosarcoma, are more common in children and young adults [15]. Based on the presence and abundance of certain cellular and subcellular characteristics associated with malignant biological expression, sarcomas are classified into different grades i.e. Low grade sarcomas, Intermediate grade sarcomas and high grade sarcomas [14]. Higher grade tumors are treated more aggressively as they are more likely to undergo invasion and spread to locoregional and distant sites. The sensitivity of various types of sarcoma towards chemotherapy has dramatically improved the survival of patients to 60-70% with localized osteosarcoma as compared to pre-chemotherapy era where long term survival for patients was approximately 20% only [16].

**Lymphoma**

Lymphoma is a type of blood cancer in which white blood cells that help in protecting the body from infection and disease i.e. lymphocytes start behaving abnormally. Abnormal lymphocytes may divide faster or live longer than normal cells. Lymphoma may develop in several parts of the body, including the bone marrow, lymph nodes, blood, spleen, etc. The lymphomas refer to a heterogeneous group of tumors and also among the first type of cancer to respond to chemotherapy or radiotherapy [17].

There are more than 50 distinct lymphomas in the current World Health Organization (WHO) classification system, existing along a broad spectrum with regards to pathophysiology, natural history, prognosis, and optimal management [18]. Two broad types of lymphoma are:

**Hodgkin's Lymphoma (HL)**

Hodgkin's lymphoma was first described by Dr. Thomas Hodgkin in 1832. Hodgkin's disease involves the Reed–Sternberg cells. It has a bimodal distribution, occurring most frequently in human beings at 15–34 years and above 50 years of age and is generally asymptomatic with painless lymphadenopathy, usually in the cervical region [19]. The classification and diagnosis of Hodgkin's lymphoma may be compromised if the biopsy is crushed or unsatisfactory in size, as it is based on proper cellular and tissue architectural conclusions [20]. There are four main histological sub-types of Hodgkin's lymphoma. These include lymphocyte predominant, mixed cellularity, nodular sclerotic and lymphocyte depleted.

Nodular sclerotic Hodgkin's lymphoma occurs most commonly in young adult patients. Staging of Hodgkin's lymphoma is defined by Ann Arbor classification and is based on the involvement of lymph node above and below the diaphragm and the presence of B symptoms (fever, night sweat or weight loss). It is one of the most familiar non-AIDS defining neoplasm in the HIV+population and is treated with highly active anti-retroviral Therapy (HAART) [21-23].

**Non-hodgkin lymphoma (NHL)**

It does not involve Reed-Sternberg cells. There are more than 61 different types of NHL, some of which are more frequent than others [24].

**Leukemia**

Leukemia is characterized by an abnormal increase of immature white blood cells called "*blasts*". Leukemia is a broad term covering a spectrum of diseases. It is part of the even wider group of diseases known as hematological neoplasms and affects the blood, bone marrow, and lymphoid system. A characteristic quality of leukemia cells is an obstruction of differentiation at a specific stage in cellular maturation [25]. Leukaemia is mainly divided into two broad groups which are further subdivided into various groups clinically and pathologically.

**Acute leukemia**

It refers to a rapid increase in the number of immature blood cells. The bone marrow becomes unable to produce healthy blood cells due to crowding of such cells. These malignant cells grow rapidly and then spill over into the bloodstream and invade other organs of the body [25]. Acute forms of leukemia are the most frequent forms of leukemia in children [26].

**Chronic leukemia**

It refers to an excessive build up of relatively mature and abnormal, white blood cells. Many abnormal white blood cells are produced at a much greater rate than normal typically taking months or years to progress. Patients suffering from chronic forms are supervised some time before treatment to ensure maximum effectiveness of therapy, whereas acute leukemia need to be treated immediately. Chronic leukemia most frequently occurs in older people but can probably occur in any age group [26].

The second division is based on which kind of blood cell is affected. This leukemia is divided into lymphocytic or lymphoblastic leukemia and myelogenous or myeloid leukemia

**Lymphocytic leukemia**

It is characterized by the cancerous change occurring in a type of marrow cell that form lymphocytes (infection-fighting immune

system cells) in a normal manner. Lymphocytic leukemia affects a specific subtype of lymphocyte mostly, the B-cell [25].

**Myeloid leukemia**

It is characterized by the cancerous change occurring in a type of marrow cell that normally forms red blood cells, some other types of white cells, and platelets [25]. A total of four main categories result by combining these two classifications. There are typically several sub-categories within each of these four main categories. Some infrequent types also exist, which are considered to be outside of this classification scheme.

**Acute lymphoblastic leukemia**

It is the most common type of leukemia in young children. This disease also affects adults, especially above age 60. Sub-types include precursor B acute lymphoblastic leukemia, precursor T acute lymphoblastic leukemia, Burkett's leukemia and acute bi phenotypic leukemia [26]. It originates from recurrent genetic insults that obstruct differentiation of precursor B and T-cells, resulting in aberrant cell proliferation and survival [27]. Standard treatments involve chemotherapy and radiotherapy. The survival rate is 50% in adults and 85% in children.

**Chronic lymphocytic leukemia**

This type of leukemia is commonly found in adults over the age of 55, occurring rarely in younger adults, but it almost never affects children. Two-thirds of affected people are men. The five-year survival rate was found to be 75%. It is incurable, but there are many effective treatments. One subtype is B-cell prolymphocytic leukemia, a more aggressive disease [28].

**Acute myelogenous leukemia (AML)**

It is defined as a clonal disorder of haemopoietic progenitor cells, characterized by an increase in the number of myeloid cells in the marrow and seize in their maturation, resulting in a hematopoietic scarcity [29]. It occurs more commonly in adult men than in children and women. AML is treated with chemotherapy. Subtypes of acute myelogenous leukemia involve acute promyelocytic leukemia, acute myeloblastic leukemia, and acute megakaryoblastic leukemia. The five-year survival rate is 40%, except for acute promyelocytic leukemia, which is over 90% [30]. It is the most common malignant myeloid disorder in adults [31].

**Chronic myelogenous leukemia (CML)**

Chronic myeloid leukemia has led the way in developing rational drug development in cancer. It occurs mainly in adults. It has been reported in a very small number of children. Treatment is with chemotherapy. The five-year survival rate is 90%. One subtype is chronic monocytic leukemia [32].

**Hairy cell leukemia (HCL)**

Hairy cell leukemia was first recognized as distinctive clinical-pathologic entity approximately 50 years ago [33]. It is a unique chronic lymphoproliferative disorder [34]. It is sometimes considered a subset of chronic lymphocytic leukemia, however, does not fit neatly into this pattern. About 80% of affected people are adult men. No cases in children have been reported. It is incurable, but easily treatable. The ten years survival rate is 96% to 100%. The use of interferon alpha (IFN-α) in the treatment of Hairy cell leukemia was first recommended in 1984 [33].

**T-Cell prolymphocytic leukemia**

T-cell prolymphocytic leukemia is a very rare, highly aggressive leukemia. It affects adult men more than women [34]. It is also the most usual type of mature T cell leukemia in spite of its overall rarity [35]. It is too complicated type of leukemia that median survival is measured in months with treatment. The principal characteristics of the disease are organomegaly, skin lesions and raised lymphocyte count [36].

**Large granular lymphocytic leukemia**

It is a rare and indolent leukemia involving either T-cells or NK cells[37]. T-cell large granular lymphocyte leukemia is a clonal proliferation of cytotoxic T cells, which causes neutropenia, anemia, and thrombocytopenia [38].

**Adult T-cell leukemia**

It is caused by human T-lymphotropic virus (HTLV), a virus similar to HIV. Like HIV, HTLV infects CD4+T-cells and replicates within them. However, unlike HIV, it does not destroy them. Instead, HTLV immortalizes the infected T-cells, resulting in their abnormal growth rapidly. Human T cell lymphotropic virus types I and II are endemic in certain areas of the world [39].

**Germ cell tumor**

Germ cell tumors originate due to the abnormal growth and development of cells producing eggs or sperm in the reproductive organs [40]. These can be cancerous or benign. Germ cells are normally found inside the ovary and testis. Germ cell tumors developing outside the gonads may be due to birth defects resulting from abnormal development of the embryo. Patients having disorders of sex development (DSD) show more risk for the development of germ cell tumors [41]. Germ cell tumors are broadly divided into two classes based on their histology regardless of location in the body:

**The Germinomatous or Seminomatous Germ Cell Tumors (GGCT, SGCT)**

These include only germinoma and its synonyms dysgerminoma and seminoma.

**The Non-Germinomatous or Non-Seminomatous Germ Cell Tumors (NGGCT, NSGCT)**

These include all other germ cell tumors, pure and mixed.

The two classes reflect an important clinical difference. Compared to germinomatous tumors, non-germinomatous tumors tend to grow faster. As germinomatous tumors respond well to chemotherapy and radiation, the survival rate for these tumors is higher as compared to non-germinomatous tumor. However, the use of platinum-based chemotherapy regimens has dramatically improved the prognosis for nongerminomatous tumors [42]. Mixed Germ Cell Tumors exist in many forms, e.g. teratoma with endodermal sinus tumor. Teratocarcinoma refers to a mixed germ cell tumor that is a combination of teratoma with embryonal carcinoma, or with choriocarcinoma, or with both. This kind of mixed germ cell tumor may also be known simply due to its malignant components: embryonal carcinoma and choriocarcinoma ignoring the teratoma component. They can be present in the anterior mediastinum [43].

**Blastoma**

It refers to a type of cancer that is caused by uncontrolled growth in precursor cells usually known as blasts. It is more frequent in children. The blastoma can be of various types: Hepatoblastoma, Medulloblastoma, Nephroblastoma, Neuroblastoma, Pancreato blastoma, Pleuropulmonary blastoma, Retinoblastoma, Glioblastoma Multiforme. Mutations in tumor suppressor genes result in various types of blastoma e.g. pleuropulmonary blastomas occur due to a mutation of the coding for p53. However, the mutation which allows propagation of precursor cells can differ from patient to patient and thus the prognosis of the tumor get altered. There is loss of function mutation on a specific band of chromosome XIII and patients carry an abnormal karyotype in the case of retinoblastoma. Various other types of cancer are also associated with this recessive deletion of the retinoblastoma gene. Thus, a practitioner may go directly into treatment in the case of common blastomas such as retinoblastomas, but in the case of rarer and more-genetically-linked blastomas, the appearance of the chromosomal makeup of a somatic cell of the patient, including the size, structure, the number and arrangement of the chromosomes must be studied before proceeding with treatment [13].

**Stages of cancer**

Most of the cancers have four stages, numbered from I to IV [44]. These stages are

**Stage I**: usually means a cancer is moderately small and limited within the organ it started in.

**Stage II:** usually means the cancer has not disseminated into the surrounding tissue, but the size of the tumor is larger than in stage I. Sometimes stage II means that cancer cells have spread into the lymph nodes near the tumor. This depends on the particular type of cancer.

**Stage III:** generally means the cancer is larger. It may have started to disseminate into the encompassing tissues and there are cancer cells in the lymph nodes in the area.

**Stage IV**: means the cancer has disseminated to other body organs. This is also called secondary or metastatic cancer.

**Therapies used in treatment of cancer**

Cancer is one of the most common disease causing nearly 7 million deaths each year worldwide. The scenario of cancer treatment has dramatically changed over the last few decades. New trends of therapy are now emerging in cancer treatments that are mainly based on the molecular features of tumor. The treatment of cancer has been made more tumor specific and less toxic with the help of novel cancer targeted therapies based on therapeutic antibodies or small molecules [45-46]. A team of oncologists generally design the treatment for cancer and is based on the type of cancer and the stage of the cancer [47]. Most treatments are premedicated specifically for each individual. Patients may obtain a unique tumor treatment protocol for their cancer. Various treatments used for the treatment of cancer include chemotherapy, surgery, radiation, or a combination of these treatments. The various advanced therapies included in cancer treatment are discussed below:

**Chemotherapy**

The use of chemotherapy to treat cancer commenced at the beginning of the 20th century with an effort to narrow the list of chemicals by developing methods to screen them using transplantable tumors in rodents. Chemotherapy has been used since the late 1940's. Now a days, important molecular abnormalities are being used to screen for the new promising anticancer drugs and targeted therapies resulting in more advancements in chemotherapy [48]. Various drugs are used in chemotherapy, such as Gemcitabine, Gefitinib, Azacitidine, Pemetrexed, Paclitaxel, Carboplatin, Docetaxel *etc*. The various routes of administration of anticancer drugs are oral (tablets, capsules) and parenteral (intramuscular, intravenous). Currently, chemotherapy is used as part of a multimodal approach to the initial treatment of different types of tumors, including locally advanced stages of esophageal, lung, head and neck cancer, pediatric solid tumors and soft tissue sarcomas [49]. The actions of anticancer drugs relate to the cell cycle in the body. Chemotherapy is the choice of initial treatment. The main side effect of chemotherapy includes nausea, vomiting, hair loss, anemia, diarrhoea, constipation, low blood count, and fertility changes etc. Chemotherapy has made significant improvement in both early and advanced stage breast cancer with several notable studies identifying clear survival benefits for newer therapies in the last 10 years. The Risk to benefit ratio of current therapies used in the treatment of breast cancer could be improved by using personalized therapies based on the molecular characteristics of the tumor [50]. Chemotherapy has made successful management of various types of cancer, enhancing survival rates. However, it is generally not very specific and thus puts normal tissues and organs at threat [51]. Many chemotherapeutic agents affect brain function by direct/indirect mechanisms even if the brain is provided with safeguards for systemic treatment by the blood-brain barrier. Chemotherapy adversely affects cognitive function both intensely and chronically, but the mechanism is still unknown [52]. Patients acquiring chemotherapy for cancer are at high risk for venous thromboembolism. Semuloparin is a drug of choice which reduces the development of thromboembolic events, with no apparent increase in major bleeding in patients receiving chemotherapy for cancer [53, 54]. Superior clinical outcomes may be produced by a dose-dense (DD) regimens of combination chemotherapy [55].

**Radiation therapy**

Radiation therapy continues to be a crucial component of cancer treatment with the majority of all cancer patients acquiring radiation therapy during their course of illness and it contributes towards 40% of curative treatment for cancer. The radiation therapy deprives cancer cells of their multiplication potential [56]. In order to achieve this goal various techniques of radiation therapy are urbanized as Fractionation, 3D conformal radiotherapy (3DCRT), Intensity modulated radiation therapy (IMRT), Image-guided radiotherapy (IGRT) and stereotactic body radiation therapy (SBRT). Efforts towards designing new radiation treatment modalities and techniques are going on, which perk up the survival and quality of life of cancer patients [57]. High-energy radiation is used to shrink tumors and kill cancer cells in radiation therapy. Various types of radiation used for cancer treatment are X-rays, gamma rays, and charged particles. The radiation therapy may be done by various means, including external-beam radiation therapy in which a machine outside the body delivers radiations, or internal radiation therapy in which irradiation from radioactive material placed in the body delivers radiation near tumor cells. Radiation therapy kills cancer cells by damaging the molecules known as DNA, which are present in cells and carry genetic information from one generation to the next for killing cancer cells [58]. DNA can be damaged directly or free radicals may be generated within the cells that can in turn damage the DNA by radiation therapy. Radiation therapy may be used in combination with other therapies like surgery and chemotherapy. Depending on the type of cancer being treated, a patient may receive radiation therapy before, during, or after surgery [58]. Year 2011 has been designated as the Year of Radiation therapy in the UK to celebrate the 100th anniversary since Marie Curie won a second Nobel Prize for her research into radium. Over the last 100 years, enduring advances in the radiation therapy treatment and progress made in cancer cell responses to radiation enterprise to reduce treatment side effects for cancer patients. Intensity modulated radiotherapy represents a noteworthy advancement in conformal radiotherapy [59] IMRT is highly beneficial for patients with tumor targets that are concave and where normal tissue forestalling is clinically important [60].

**Proton therapy**

The use of high-energy protons in radiotherapy was first proposed in 1946. In the last decade, there has been a significant escalation in the number of centers using protons in the treatment of malignant and non-malignant disease [61]. Treatment of patients is being done in various proton therapy centers in the United States and numerous others are under construction or in the planning phase. Proton therapy has wonderful potential as a treatment for various tumors. Public interest in proton therapy has grown to a large extent since the FDA approved it in 2001. Enthusiasm for the proton therapy is getting ahead of the research due to the concern among members of the medical and research communities. Proton therapy is allied with considerable benefit in terms of normal tissue sparing and potential radiation dose amplification for many patients with malignant diseases. This beneficial technology is provided to a larger number of patients as a result of such expansion. However, the importance of careful treatment planning, precise scientific investigation, including comparison to other technologies, ethical issues and cost effectiveness must not be forgotten [62]. Proton therapy is being used more commonly in children suffering from various types of cancer, and adults having tumors in organs such as the prostate, bladder, brain, spine, lungs, head and neck. Proton therapy centers are further pursuing in research to test its use for additional cancers [63]. X-rays have no charge. On firing the X-rays at a tumor in radiation therapy, their energy is transferred at an evenly decreasing rate to the normal tissues between the surface of the body and the target as well as to the tissues beyond the tumor until they exit the body. On the other hand, as proton beams have a positive charge, they transfer their energy at a defined distance within a region called the Bragg peak, *i. e.* Charge is delivered to its calculated destination. When the target is hit, there is greater damage to the tumor sparing healthy tissues of the side effects from the treatment [64].

**Thermotherapy**

Thermotherapy has been used with the purpose to cure tumors for at least 4000 years, and as a tool to destroy tumor masses well before that period [65]. Thermotherapy is a type of therapy for the

cancer treatment in which body tissues are exposed to elevated temperatures up to 113°F. High temperatures can damage and kill cancer cells, causing nominal injury to healthy tissues [66]. Hyperthermia may shrink tumors by killing tumor cells and damaging proteins and structures within the cancer cells [67]. Finally, the target of thermo therapy is to capitalize on the difference in thermotolerance between normal and cancer cells. Hyperthermia is commonly used with radiation therapy and chemotherapy for cancer treatment. In numerous clinical trials, hyperthermia was used in combination with radiation therapy and chemotherapy for the treatment of various types of cancer, including cancers of the rectum, cervix, breast, brain, esophagus, appendix, bladder, lung, liver, head, neck and peritoneal lining (mesothelioma) resulting in the improvement of the effect of various anticancer drugs [68]. Several methods of hyperthermia, including regional, local and whole-body hyperthermia, are currently under study [69].

*Local hyperthermia:* In local hyperthermia, various types of energy, including microwave, radiofrequency, and ultrasound may be used to apply heat to the tumor with the help of different techniques. Depending on the location of the tumor in the body, there are several approaches to local hyperthermia, such as External, Intraluminal or endocavitary and Interstitial.

*Regional hyperthermia:* In regional hyperthermia, heat is applied to large areas of tissue, like a body cavity, organ, or limb using various approaches.

*Whole-body hyperthermia:* In whole-body hyperthermia, the various techniques that elevate the body temperature to 107–108°F are used to apply heat to the tumor. These techniques include the use of thermal chambers similar to large incubators or hot water blankets. It helps in the treatment of metastatic cancer, disseminated throughout the body [70].

Now a day, the concept of intracellular hyperthermia has emerged as a novel approach in which magnetic particles are made to accumulate at the cancer site and a magnetic field is applied to remotely heat them to accomplish hyperthermic temperatures (42-45°C) [71].

**Photodynamic therapy**

In 1903, eosin was applied topically to basal cell carcinomas (BCCs) prior to illumination and thus found the first clinical application of Photodynamic therapy in the treatment of cancer [72]. A drug, known as a photo sensitizer or photosensitizing agent having a specific wavelength of light is used for the treatment in photodynamic therapy (PDT). On exposure to a specific wavelength of light, photosensitizing agent releases a form of oxygen that kills nearby cells [72, 73]. Each photo sensitizer is activated by light of a specific wavelength which determines the distance to be travelled by light into the body. Thus, Specific photo sensitizers and light of particular wavelength are used to treat tumors in various areas of the body with photodynamic therapy. In photodynamic therapy for cancer treatment, photo sensitizer on injection into the bloodstream is absorbed by cells throughout the body, but the duration of stay of photo sensitizer is longer in cancer cells than in healthy cells. The tumor is exposed to light approximately 24 to 72 hours after injection as most of the anticancer drugs are excreted by normal cells upto this time period but stay in the tumor. The photo sensitizer in the tumor absorbs the light and releases an active form of oxygen that destroys nearby tumor cells [74, 75]. The three main mechanisms involved in the antitumor effects of PDT include direct tumor cell death (also known as necrosis, apoptosis and autophagy) in which cancer cells are directly killed using PDT, vascular destruction in which the blood vessels in the tumor are damaged by the photosensitizing agent, thus depriving the tumor cells from receiving necessary nutrients, and immune system activation in which the immune system is activated by photo sensitizer to attack the cancer cells [76]. Photo sensitizers in Photodynamic therapy include various nontoxic drugs or dyes that are pharmacologically active only after exposure to light in the presence of oxygen. Due to its deep selectivity and specificity, PDT has been considered to be a feasible treatment for neoplasms, including cancers of the skin, head and neck, nasopharynx, esophagus, lung, pancreas, biliary duct, and bladder. Laser or other sources of light can be used for the activation of photo sensitizer. PDT may be used in combination with other therapies, such as chemotherapy, radiation or surgery. Numerous clinical trials are in progress to evaluate the use of PDT for various types of cancers [77]. The most promising approach as carriers of photo sensitizers is the use of nanoparticles as these can satisfy all the requirements for an ideal PDT agent [78]. Photodynamic therapy has been applied clinically to both early and advanced stages of lung cancer. It can preserve pulmonary function, well tolerated and cost-effective in comparison with other treatments [79].

**Laser therapy**

The term "laser" stands for light amplification by enthused emission of radiations. In comparison to ordinary light which has many wavelengths and spreads in all directions, laser light has a particular wavelength which is focused in a narrow beam and produce a very high-intensity light to treat cancer and other illnesses. Lasers are most often used to shrink or destroy tumors and precancerous growths. Laser therapy is most commonly used to treat peripheral cancers, including basal cell skin cancer and the very early stages of different types of cancer, such as non-small cell lung cancer, vulvar, vaginal, penile, cervical cancer. Various symptoms of cancer, such as bleeding or obstruction may also be relieved using laser therapy. Laser therapy can be used in combination with various other treatments, such as surgery, chemotherapy, or radiation therapy. In addition, Lymph vessels may be sealed with the help of laser therapy to reduce swelling and limit the tumor cells to metastasize. Laser therapy may also seal nerve endings to reduce pain after surgery. A thin, lighted tube known as a flexible endoscope (fitted with thin optical fibers that transmit light) is often used to look at tissues inside the body during laser therapy [80]. Laser light is particularly focused to destroy a tumor after being inserted through an opening in the body, such as the vagina, anus, mouth and nose. In laser-induced interstitial thermotherapy (LITT), or interstitial laser photocoagulation, lasers are used to treat some cancers. LITT is similar to a cancer treatment called hyperthermia in which heat is used to shrink tumors by damaging or killing tumor cells. Another type of cancer treatment that uses the laser is Photodynamic therapy (PDT). Three types of lasers are most often used to treat various types of tumor, including neodymium: yttrium-aluminum-garnet (Nd: YAG), argon lasers and carbon dioxide ($CO_2$) lasers. Each of these can be used with endoscopes to shrink or destroy tumors. Operations are usually shorter with laser therapy. Numerous clinical trials are under the way to find the use of lasers in the treatment of cancers of the brain and prostate [81].

**Sentinel lymph node biopsy (SLNB)**

Lymph nodes refer to small round organs that are part of the body's lymphatic system, are connected to one another by the lymph vessels and are found widely throughout the body. Lymph nodes are important parts of the body's immune system containing B lymphocytes, T lymphocytes, and other types of immune system cells, which monitor lymph for the presence of "foreign" substances, such as bacteria and viruses [82]. If a foreign substance is detected, an immune response will be triggered by the activation of some of the cells. Lymph nodes also help in determining whether cancer cells have developed the ability to disseminate to other parts of the body. A sentinel lymph node refers to the first lymph node to which tumor cells are more likely to disseminate from a primary tumor. Sometimes, there can be more than one sentinel lymph node. A positive SLNB result indicates that cancer has spread to the sentinel lymph node, nearby lymph nodes also known as regional lymph nodes and, possibly to other body organs. A negative SLNB means the cancer has not developed the ability to disseminate to sentinel lymph node, nearby lymph nodes or other body organs. If the sentinel lymph node is negative for cancer, it may not be necessary to remove additional nearby lymph nodes to look for cancer cells. SLNB is most commonly used to find the stage of breast cancer and melanoma. However, it is also being studied with various other cancer types, including gastric cancer, head and neck cancer, colorectal cancer, thyroid cancer, esophageal cancer and non-small cell lung cancer [83]. Currently, the sentinel lymph node biopsy procedure is recognized as the standard treatment for stages I and II.

SLNB is not contra indicated in pregnancy as the dose transferred to the fetus from this procedure is negligible [84].

**Cryotherapy**

Cryotherapy helps in reducing the tissue temperature, tissue stiffness, muscle spasm, metabolism, circulation, inflammation, and symptoms of delayed-onset muscle soreness and thus can be used to control pain and edema [85]. Cold hypersensitivity and persons with vasospastic disorders are contraindicated for cold therapy. Cold sensitive patients may risk local burns or systemic complications with cold therapy [86]. Tumors are being eradicated safely and with significantly decreased morbidity by the introduction of the recent modifications in the technique of salvage cryosurgery and third-generation cryotechnology using 17-gauge Cryo Needles™. Cryosurgery is effective in destroying radio recurrent tumors [87-88]. In cryotherapy, extreme cold produced by liquid nitrogen or argon gas is used to destroy abnormal tissues. Cryosurgery helps in the treatment of external tumors, such as those on the skin as well as internal tumors, such as tumors in the bone and the body. Liquid nitrogen is applied directly to the tumor cells with a spraying device or a cotton swab for the treatment of external tumors. Liquid nitrogen or argon gas is circulated through a cryoprobe placed in contact with the tumor for the treatment of internal tumors. A lump of ice crystals forms around the probe, freezing nearby cells. Sometimes many probes are used to transfer the liquid nitrogen to different parts of the cancer and may be placed into the tumor percutaneously or through surgery. After cryosurgery, the frozen tissue deliquesces and after dissolving other forms a shell (for external tumors) or is either naturally absorbed by the body (for internal tumors). Cryotherapy has acquired significance as a locally ablative treatment option for patients with non-resectable liver tumors, especially metastases from colorectal cancer [89]. Cryosurgery can be an effective treatment for retinoblastoma, prostate and liver tumors. It has been found that cryosurgery is most effective in meagre tumors, early-stage cancer of the skin, including both basal cell and squamous cell carcinomas, cervical intraepithelial neoplasia and various parts of the retina. Cryosurgery endeavors various advantages over other therapies for cancer treatment. It involves only a small cut or inclusion of the cryoprobe through the skin and thus less invasive than surgery. Cryotherapy may be used in combination with surgery, chemotherapy, hormone therapy, and radiation therapy. It can be safely repeated. Furthermore, it can be used for patients who cannot tolerate surgery because of their age or other medical illness. The effectiveness of cryosurgery is unpredictable as the cells exhibit different thermal histories. Cryosurgery will likely have a more clinical usage with a better understanding of cell injury mechanisms [90].

**Heavy ion therapy**

Energetic heavy ions are the charged particles having high relative biological effectiveness and are heavier than helium ions [91]. Unlike conventional photons such as X-and γ-rays, heavy ions result in a remarkable rise in energy deposition of radiation during its travel through matter (represented by a sharp Bragg peak), with a steep dose falloff downstream. To enable Spread-out Bragg peaks (SOBP) have been devised to raise the dose to the targeted tumor site avoiding much exposure to normal tissue, which resulted in broad and uniform dose distribution [92], So the rationale for heavy-ion cancer therapy is the distinguished biological properties and dose conformity. So far, the heavy-ion therapy has accomplished good control in short cancer treatment sparing critical normal organs [93]. Heavy-ion therapy has become a world wide popularity as a number of new facilities are becoming functional worldwide in addition to the existing ones. The rate of energy loss along the trajectory of an ionizing particle, known as linear energy transfer (LET) affects the biological effectiveness of ionizing radiation. High-LET heavy ions produce dense ionization along their path, and cause clustered DNA damage that is complex and not repairable [94]. Heavy ions are generally more genotoxic and cytotoxic to cancerous cells than low-LET photons [91]. The biological effectiveness depends not merely on LET but also on ionic species or ion track structure [95]. Few minutes after heavy-ion exposure, changes in cellular ultrastructure at the electron-microscopic level occur like irregular swellings and invaginations of plasma membrane, distended sarcoplasmic reticula, and increased autophagic vacuoles might be involved in removal of such disruption [96]. The mechanism of action behind the heavy ion–induced cell death includes premature agedness, apoptosis, necrosis, autophagy, accelerated differentiation, delayed reproductive death in the descendants of irradiated cells, and spectator cell death [97-100]. Heavy ions are effective at killing cells by possessing high potential to suppress angiogenesis, metastasis and arrhythmia [101]. It has also been observed from the studies that heavy ions can also overcome tumor radioresistance caused by intratumor hypoxia, overexpression of the oncogene *BCL2* (also *Bcl-2*) and mutation of the tumor suppressor gene *TP53* (also known as *p53* [102-103]. Research is becoming more focused on combining heavy ion therapy with other modalities, especially molecularly targeted approaches. Despite the heavy-ion therapy has provided remarkable clinical outcome with irradiation alone, the combination with gene therapy, chemical agents (e. g., halogenated pyrimidine analogue 5-iodo-2′-deoxyuridine, Bcl-2 inhibitor HA14-1, anticancer drug docetaxel) and hyperthermia killed tumor cells more effectively [104-105]. There is need of understanding the mode of action of heavy ions more deeply which will help in designing of various biological approaches based on the mode of action that enhance the targeted killing of cancer cells, avoiding normal tissue complications and prediction of responsiveness of cancer and normal tissue complications prior to treatment by the heavy-ion. In this direction, recent studies have been conducted to find the heavy-ion response of tumor cells irradiated in vivo, [106-107] and further investigations are being done to clarify the genes responsible for susceptibility to heavy ions.

**Gene therapy**

Gene therapy involves the transfer of genetic material to alleviate a disease or at least to refine the clinical status of a patient. Transformation of viruses into genetic shuttles, which deliver the gene of interest into the target cells, is one of the basic concepts of gene therapy [108]. Gene transfer is a novel treatment option for the cancer that introduces new genes into a tumor cell or the surrounding tissue to cause apoptosis or slow the growth of the tumor. Genes are the biological units of heredity. Genes determine the ability of the blood to carry oxygen and individual characteristics like eye and hair color. Genes are made of deoxyribonucleic acid (DNA), a type of biological molecule and are located on chromosomes in cells. They have been identified in lung, brain, ovarian, prostate, colon, melanoma, pancreatic, breast and blood cancers [109]. Gene therapy has been found to be one of the most promising novel therapeutic approaches for the treatment of various cases of cancer, not responding to traditional therapies [110]. It has gained importance in the treatment of chemo-resistant and radio-resistant cases of cancer that lead to the failure of traditional therapies. Most therapies used in the treatment of cancer are focused on the rapidly growing tumor mass, but not the slow dividing cancer stem cells (the root of cancer origin and recurrence. Cancer stem cells possess the capability to self-renew and to cause the heterogeneous succession of tumor cells and are found within the tumor. Eradicating cancer stem cells has proved to be an assuring approach to improve cancer survival or even to cure patients suffering from cancer [109]. There are different approaches for the treatment of cancer, which involves targeting either to healthy cells to enhance their ability to fight cancer or to tumor cells, to destroy them or prevent their growth. Some gene therapy techniques involve replacement of missing or altered genes with healthy genes [110]. Now days, research is mainly focused on studying ways to improve a patient's immune response to cancer. In gene therapy, body's natural ability to attack cancer cells is stimulated. In general, a gene is delivered to the cell using a carrier, or "vector". The vectors most commonly used in gene therapy are viruses. The unique ability of viruses is to identify certain cells and insert genetic material into them. In most clinical trials of gene therapy, researchers remove cells from the blood or bone marrow of the patients and grow them in the laboratory. The cells are exposed to the virus carrying the desired gene and thus the desired gene is inserted into the cells' DNA of the virus. After the growth of cells in the laboratory, the cells are then injected into a vein of the patient. This type of gene therapy is called ex vivo as the cells are grown outside the body. The type of gene therapy in which viruses or fatty

particles are used to deliver the desired gene to cells in the patient's body is called in vivo, as the gene is transferred to the cells inside the body of the patient [111]. Antiangiogenic therapy designed to arrest the growth or spread of tumor (tumor angiogenesis), has emerged as a safe and non-invasive option for tumor treatment. As there is over expression of integrin receptors on the surface of angiogenic endothelial cells, various targeted delivery systems for gene utilizing integrin-targeting peptides with an exposed arginine–glycine–aspartate (RGD) sequence have been developed [112]. In various clinical trials of gene therapy, a wide range of genes and viruses are being used with successful outcomes. On treatment with Gendicine™ (a replication-incompetent adenovirus encoding for the *TP53* gene in place of the viral E1 gene) of 12 laryngeal cancer patients in a phase I clinical trial, none of the patients suffered from tumor relapse during the five-year follow-up after the treatment and thus Gendicine™ demonstrated therapeutic potential [114]. In a phase II/III trials with Gendicine™, 132 head and neck squamous cell carcinoma patients were treated. It was observed that 32% patients showed fever as the only side-effect of the treatment showing good safety profile of Gendicine™. [115]. When Gendicine™ was combined with radiotherapy for the treatment of cancer, complete regression was observed in 64% of the patients and partial regression was observed in 29% of the patients while when treated with radiotherapy alone, complete regression was observed in 19% of the patients and partial regression was observed in 60% of the patients, suggesting a synergistic effect of the combination treatment [115]. Thus Gendicine™ became the first gene therapy product that has been approved for clinical use [113].

Oncorine™ (a conditionally replicative adenovirus produced by deleting the adenoviral *E1B 55K* gene) was a second gene therapy product developed by Chinese Shanghai Sunway Biotech and received market approval by the Chinese SFDA. The deletion of adenoviral *E1B 55K* gene avoids the virus to attach and inactivate the wild-type p53 protein, which is a vital self-protection mechanism of the host against virus infection [116]. The removal of the E1B 55K activity allows the replication in p53-deficient cells only, blocking the replication in normal cells. The viral proliferation in malignant cells leads to oncolysis and thus treating the solid tumors. Now a days,, additional therapeutic proteins are added to the viruses to improve efficacy of oncolytic viruses, e. .g., Onco VEXGM-CSF, a second-generation oncolytic herpes simplex virus (HSV), additionally coding for the therapeutic protein granulocyte macrophage Biomedicines 2014, 2154 colony-stimulating factor. In a phase I safety study, Onco VEXGM-CSF was administered by intratumoral injection in patients with malignant melanoma, gastrointestinal, head and neck cancers who had failed prior therapy. The study showed that Onco VEXGM-CSF was well tolerated and safe [117]. In a Phase I/II study, antitumor effect was seen in which Onco VEXGM-CSF was given in combination with cisplatin and radiotherapy to patients with untreated squamous cell cancer of the head and neck at stage III/IV [118]. As this therapy will grow, it may be used alone or in combination with other therapies as a promising approach for the treatment of cancer [119].

## CONCLUSION

Tumors represent a very heterogeneous group of cells having different receptivity to cancer therapy. At present, the cancer treatments are mainly focused on rapidly dividing cells and molecular targets that represent the bulk of the tumor. Various current concepts in tumor therapy and tumor biology are continuously evolving due to better understanding of therapeutic and pathophysiological concepts. Research is more focused on finding the specific genetic and molecular abnormalities in different types of cancer, and then to find the appropriate therapy that targets those abnormalities. Treatment should be designed to identify novel techniques of surgical and radiation therapy, pathologic evaluation, diagnostic imaging and symptom management. New concepts are needed to be investigated in order to achieve a further increase in survival for this deadly disease. To identify new targeting drug delivery systems for cancer, cancer cell biology as well as cancer stem cell biology needs to be deeply understood. A major challenge for the development of new therapeutic agents is the necessity to discriminate between cancerous stem cells and normal stem cells. The therapeutic options for cancer therapy have been significantly broadened with the introduction of targeted therapies. Further research is also needed to discriminate the various genes and signalling pathways in the process of the carcinogenesis of cancer stem cells for the development of novel therapies, with the ultimate goal of eliminating the residual disease and recurrence.

## CONFLICT OF INTERESTS

The authors do not have any conflict of interest to declare

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