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Cancer Biology And Therapeutics: A Contemporary Review

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Abstract

Our understanding of the biology of cancer has advanced significantly during the latter part of the 20th century. Now that we have a better understanding of cancer at the genomic and epigenomic levels, we can identify the cell that initiates neoplastic transformation and understand the processes by which it invades other organs. With the use of this understanding, new medications that target certain molecules have been created, the immune system has been educated and tweaked to function more effectively, and ever-more potent treatment approaches have been created. However, the fight against cancer is still far from over, thus biomedical research in this field has to remain a top priority on a worldwide scale. Similarly, there is a need to enhance preventative initiatives and lessen disparate access to healthcare, particularly in nations with poor human development indices. Modern medical research continues to face significant challenges in the development of effective cancer therapy because of the intricate mechanisms behind carcinogenesis and tumor spread, as well as the drawbacks of the available cancer therapeutic choices. The application of nanotechnology in cancer therapies has great promise for enhancing cancer treatment outcomes. We could fully comprehend the pharmacological effects and investigate the mechanisms of the interaction between the nanomaterials with the help of information about the latest developments regarding cancer hallmarks. This could present opportunities for the development of mechanism-based Nano medicine to treat human cancers.

Keywords: cancer, cell therapy, epigenomics, genomics, immunotherapy, metastasis, stem cells, targeted therapy

INTRODUCTION

The World Health Organization (WHO) reports that, after heart disease, cancer is the leading cause of mortality worldwide. In most industrialized nations, cancer is a serious public health issue; nevertheless, during the past three decades, patient survival rates have significantly improved as a result of early identification and advancements in medical care [1][2]. Anticancer drugs and chemotherapy or radiation therapy are beneficial forms of treatment for many cancer patients. However, because anticancer drugs are toxic to healthy cells and tissues, they can cause a wide range of side effects, such as numbness, diarrhea, nausea, vomiting, anorexia, and oral mucositis. Patients' quality of life (QOL) is commonly reduced by these side effects, and they may be unable to continue getting radiation therapy or chemotherapy [3][4]. These negative impacts may be addressed or avoided using a number of useful strategies, yet they are still insufficient. Rare, aberrant growths known as neuroendocrine neoplasms (NENs) originate from widely dispersed cells in the neuroendocrine system. They produce peptide hormones, and the hormones they produce cause them to exhibit a range of symptoms. There are large differences in the extent of their metastatic pattern amongst them [5][6]. A growingly significant part of the worldwide cancer control strategy is early cancer diagnosis, in addition to primary preventive measures and screening programs [7][8].

Prior to 1970, when talking about oncology health outcomes, it was considered that the very limited end-points of survival and treatment toxicity were being discussed [9][10][11][12][13]. For diseases like cancer, the time scales for chemical reactions and protein interaction can vary from milliseconds to years. Size scales are applied to anything from molecules to cells to organs to whole organisms [19].

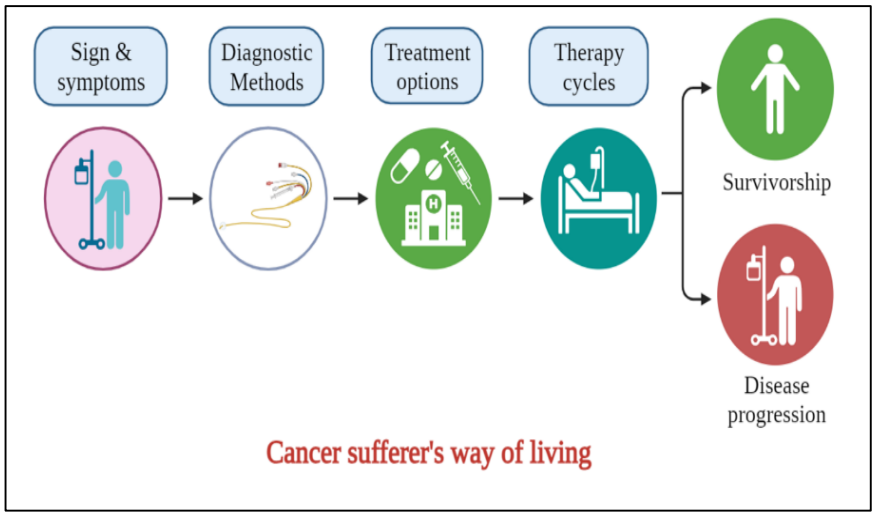

Figure 1: Cancer sufferers' way of living

According to the age category, there were 190 cases of cancer overall, with a greater incidence in males than in women. It is becoming more and more difficult to prevent cancer, a problem for public health in practically every nation. When cancer-related risks and variables are managed to increase the survival rate of cancer patients, over 40% of malignancies might be avoided in all circumstances. These elements have to do with things like nutrition, food, and exercise. All things considered, the global burden of cancer incidence and mortality is rising [20][21]. DNA damage in a normal cell is the first step towards the formation of cancer. This is followed by the precancerous stage, which ultimately results in genomic instability and the loss of anti-oncogenes, among other things. Although a lot of resources and time have been spent trying to find a cure for cancer up to now, many tumors' etiology and pathophysiology remain poorly understood [22]. Because of this, cancer still kills people even after a lot of effort has been directed towards other goals? Furthermore, a multitude of computational frameworks have been created thus far to investigate and comprehend the biology of cancer. The biology of the organism is complex and includes relationships between many different elements, including chemicals, proteins, and nucleic acids. The study of cancer biology frequently makes use of network-based techniques. Proteins that are involved in disease-related pathways and processes and interact with one another are commonly used to support the operation of biological systems [23][24].

With an estimated 14 million new cases and 8 million deaths from the disease in 2012 alone, cancer is one of the main sources of illness burden in the world. limited developed nations with limited access to cancer treatment resources saw about 57% of new cancer diagnoses and 65% of cancer-related fatalities. All cancer patients have difficulties connected to their treatment, although many of these problems are more severe in low- and middle-income nations. These issues include the need for qualified medical professionals, late-stage diagnosis, when treatment is usually less effective, geographic access issues to cancer care facilities, concerns about the cost of care, the stigma attached to the disease, and the scarcity of palliative care [25][26]. Combining allopathic and conventional therapy may provide a way to address some of the problems with cancer prevention. Allopathic medicine and traditional medicine are too frequently seen as two distinct fields. We fail to recognize that over the course of their illness, cancer sufferers move through both worlds simultaneously. Complementary and alternative medicine has been used more often throughout the years, according to a systematic analysis of research from Australia, New Zealand, North America, and Europe; about half of cancer patients reported using it in the last year. It is conceivable that some regions of the world have substantially greater prevalence rates [27][28].

CANCER BIOLOGY

The study of cancer biology focuses on the aberrant growth, behavior, and traits of cancer cells as well as the mechanisms that underlie the onset and spread of the disease. To comprehend the intricate mechanisms behind cancer, this multidisciplinary subject integrates aspects of cell biology, genetics, molecular biology, biochemistry, and pathology [29].

Cancer biology study starts with the most basic issues in an effort to define normalcy and abnormality. Scientists need to investigate the basic distinctions between malignant and healthy cells in order to comprehend how cancer starts and spreads. This work primarily focuses on the mechanisms that underlie basic processes such as cell proliferation, the conversion of healthy cells into malignant cells, and the metastasis (spread) of cancerous cells [29][30].

A number of genetic and environmental variables come together to cause complex illnesses like cancer. Investigating the mechanisms by which malignant tumors and cells change a phenotypic is challenging, and in the case of illnesses like cancer, this difficulty is compounded by the possibility of individual genetic variations. Network-based, or system-based, biology techniques have garnered a great deal of attention in recent years and have shown to be a valuable tool in the study of complex illnesses such as cancer. System biology techniques construct the so-called interconnections, or networks, by using data regarding the functional or physical interactions between medications, targets, or pathways [32][33]. Nodes and edges comprise a simple network. Genes, proteins, medications, and other relevant items might be considered interaction nodes, and binding affinities, connection orientations, and connection strengths could be considered node nomenclature. Connectivity between nodes is provided by network edges, which are recognized by their functional relationships—such as those involving proteins, physical interactions, and gene regulation—or by associations with diseases, which are followed by the identification of mechanisms of activation and inhibition. Larger networks are more complicated, thus to minimize their complexity, they are generally separated into quantifiable sub-networks of functionally linked nodes [34][35].

To improve comprehension of the systems biology techniques discussed in this work, specific examples of node, link, and graph prediction would be beneficial. The method of predicting the behavior of specific molecules, such genes or proteins, inside a biological network is known as node prediction. While graph prediction aims to forecast the network's overall behavior, link prediction concentrates on predicting the interactions between pairs of molecules inside the network. Using machine learning algorithms to predict drug-target interactions, network-based clustering to identify disease subtypes, and pathway analysis to discover important biochemical processes linked to illness are a few examples of these technologies in action [36][37][38].

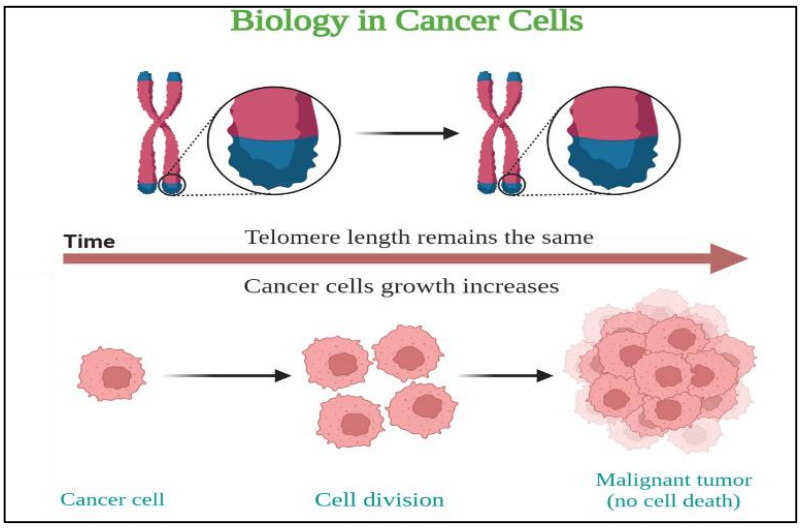

Figure 2: Biology in cancer cells

Key Concepts and Areas of Study in Cancer Biology Include:

Cell Proliferation and Differentiation

The link between cell differentiation and proliferation is obviously negative. Protocells divide several times before attaining complete differentiation, even though final differentiation usually coexists with a permanent break from the division cycle and a proliferation arrest. Cell division cycle choices about proliferation vs differentiation can be influenced by developmental changes in the way cells respond to environmental stimuli during the G1 phase. According to preliminary research, differentiation may be quickly induced in the G1 phase but not in the S phase in embryonic cancer cells. Since then, it has been proposed that developmental regulation throughout the length of the G1 phase is a mechanism directing differentiation [39][40]. Numerous animal species, including zebra fish, flies, and frogs, contain rapidly dividing undifferentiated cells that lack G1 and G2 phases in their early stages. Mammal cell division cycles shorten dramatically as pre-implantation embryos reach the blastocyst stage; certain cells can complete the division cycle in three hours or less. This is comparable to the unique cell cycles of embryonic stem cells isolated from the inner cell mass of pre-implantation embryos, which include a brief G1 phase lasting around two hours [41][42].

Changes in Genes and Epigenetics

Gene mutations that regulate cell division and proliferation are linked to cancer. Cancer is also impacted by epigenetic modifications, which are variations in gene expression without changing the DNA sequence. The study of heritable and persistent changes in gene expression brought on by chromosomal rather than DNA sequence differences is known as epigenetics. Although epigenetic processes cannot directly change the sequence of DNA, they can control the expression of genes by modifying the chemical components of DNA and the chromosomal superstructure that houses DNA [45][46].

An octamer of positively charged histone proteins, comprising two copies of each histone protein H2A, H2B, H3, and H4, surrounds negatively charged DNA. A nucleosome, the fundamental building block of chromatin, is this combination of nucleoproteins. While linker DNA joins the nucleosomes of a continuous DNA polymer, the histone protein H1 stabilizes the complex. A chromosome is created when chromatin aggregation occurs. A chromosome's chromatin can be either densely packed, transcriptionally inactive heterochromatin or loose, transcriptionally active chromatin. Heterochromatin states can be produced chemically by modifying histone proteins. Open chromatin permits transcription factors and enzymes to interact with DNA to promote gene expression, whereas closed heterochromatin inhibits gene expression [47][48].

Apart from modifications to histones, DNA methylation in the CpG islands of promoter regions is another epigenetic process linked to the silencing of genes. Moreover, it has been demonstrated that non-coding RNA sequences are essential for controlling the expression of some genes. A number of variables, including age, nutrition, smoking, stress, and health status, may be involved in these epigenetic modifications. Even while epigenetic changes are reversible, in humans, they seldom last for generations, even in cases when they can withstand many rounds of cell division [49][50].

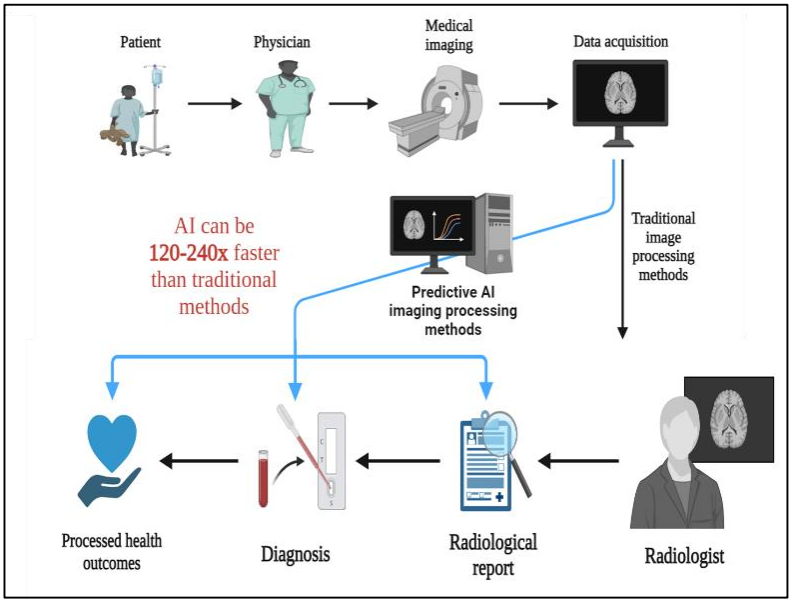

Figure 3: Different techniques for cancer analysis

Translocation

Metastasis is the process by which cancer cells move to different areas of the body. Understanding the mechanisms of metastasis is essential to developing effective therapies. Metastatic cancer is defined as cancer that has spread to an area of the body from its original site. It is also referred to as stage IV cancer for many forms of cancer. Metastasis is the process by which cancer cells move to other areas of the body [51]. Under a microscope and in other tests, the characteristics of the initial malignancy are what distinguish metastatic cancer cells from those at the site of the sickness. Medical practitioners can identify cancer that has spread from another area of the body by using this procedure. Both primary and metastatic cancer are included in the definition of "primary cancer". For instance, metastatic breast cancer, not lung cancer, is the term used to characterize breast cancer that spreads to the lung. Lung cancer treatment is substituted with stage IV breast cancer treatment [52][53].

The origin of cancer cells that metastasize

A. Mesenchymal to Epithelial Transition (EMT)

Based on studies demonstrating aberrant cell-matrix and cell-cell interactions during tumor growth in epithelial tissues—the site of genesis for many malignancies—this notion is put forth [54]. Neoplastic cells eventually arise from Mesenchymal cells that have dysmorphic forms, no cell-cell adhesion, and the capacity to move to distant organs. What is the actual mechanism underlying this extraordinarily complex phenomenon? EMT might have a part in metastasis. Even though the process is quite complex, new research indicates that in some gliomas, ectopic (misplaced) co-expression of just two genes may be enough to cause EMT. Since EMT is seldom observed during tumor pathological preparation, the EMT theory of metastasis is, however, very controversial [55][56].

B. Metastatic Tumor Cells Derived from Stem Cells

According to some studies, populations of tissue stem cells give rise to metastatic cancer cells. Semi-differentiated cells can replace damaged or dead cells resulting from natural wear and tear in most tissues. It is a widely held assumption that undifferentiated or semi-differentiated tissue stem cells are the source of metastatic malignancies. Cancer cells and stem cells frequently have biological traits and gene expression similarities [57]. Since both tumor cells and embryonic stem cells have the ability to use anaerobic energy (fermentation) for metabolism, it has been observed that tumor cells have traits of undifferentiated stem cells. Similar to fermentation energy, telomerase activity is also often elevated in tumor cells relative to normal ones. It is therefore not unexpected that tumor cells and stem cells have many genetic and metabolic characteristics, as the majority of tumor cells also require fermentation energy for growth and survival [58][59].

C. The Facilitation of Metastasis by Macrophages

It is well known that many malignant tumors contain sizable numbers of macrophages and other stromal cells. The macrophages that are present inside tumors are referred to as tumor associated macrophages or TAMs for

short. TAM may create the pre-metastatic milieu and encourage angiogenesis and tumor inflammation. Put another way, TAM encourages the metastatic chain reaction [60]. According to this view, stromal macrophages functioning as cellular chaperones are in charge of tumor formation, metastatic seeding, and progression, while gene mutations remain the source of neoplastic changes. Even while stromal TAM is known to be crucial to every stage of metastasis, they are not regarded as malignant in and of themselves. However, recent studies have shown that a significant proportion of patient-derived metastatic tumor's also contain neoplastic cells that resemble macrophages [61][62].

D. The Metastasis Origin of Myeloid Cells

Our hypothesis states that respiratory insufficiency in myeloid cells or in their lineage offspring, such as lymphocytes, dendritic cells, or macrophages, is the main cause of metastatic malignancies. Mitochondrial respiration may be hampered by persistent inflammation around macrophages that are actively functioning. PET scans can identify aerobic glycolysis, often known as the Warburg effect, which is expressed in a large number of metastatic tumors. The main reason tumor cells engage in aerobic glycolysis is inadequate respiration. The distinction between the nuclear and cytoplasmic contributions to the metastatic phenotype is further muddied by fusion hybridization between macrophages and non-metastatic cancer stem cells. It would be wise to first take into account the data that myeloid cells can give birth to metastatic cancer cells before addressing these difficulties [63][64].

CANCER THERAPIES:

Cancer-Specific Treatments:

The US Food and Drug Administration (FDA) defines targeted therapy as a prescription drug with an authorized label that makes it clear that the patient must first pass a concurrent or previously approved diagnostic test in order to be eligible to receive the medicine [65].

Table 2: Therapeutics Using Targeted Anticancer Antibodies

Drug Name	Brand Name	Type	Target	Indication	References
Alemtuzumab	Campath	Monoclonal antibody, humanized; anticancer, immunologic; multiple sclerosis treatment; immunosuppressant	CD52	CLL	[66]
Rituximab	Rituxan	Monoclonal IgG1; chimeric; anti- cancer, immunologic; antiarthritic, immunologic; immunosuppressant	CD20	NHL	[67]
Trastuzumab	Herceptin	Monoclonal IgG1 humanized; anticancer, immunologic	p185neu	Breast cancer	[68]
Gemtuzumab	Mylotarg	Monoclonal IgG4 humanized	CD33/calicheamicin	AML (patients >60 y)	[69]
Edrecolomab	Panorex	Monoclonal IgG2A murine; anticancer	EpCAM	Colorectal cancer	[70]

Gene editing and gene therapy

Recently, companies and their spinoffs have demonstrated a remarkable interest in gene therapy. This reflects the industry's increasing confidence, which is supported by an increase in treatment success stories and the EMA's 2012 approval of the first gene therapy medications. In August 2017, the FDA authorized Novartis's Kamiah, also referred to as tisagenlecleucel-T and CTL019. This medication is the first to be used in CAR T cell therapy. Among the most recent developments is this. The FDA quickly approved the use of axicabtagene ciloleucel, also sold by Spark Therapeutics and Kite Pharma under the brand name Luxturna, in combination with another CAR T cell treatment [71][72]. The focus on approaches other than gene insertion, including as

gene editing, RNA interference, targeted recombination, and antisense oligonucleotide-induced exon skipping, has undergone a dramatic paradigm shift since our 2012 study. Each of these tactics has been used in a therapeutic context before. These strategies will be particularly crucial when it comes to dominant disease processes, as adding a functionally normal gene on its own is inadequate [73][74].

Advances in Clinical Radiation Therapy

Tumor-derived antigens need to be absorbed by DCs and cross-presented to T cells in order to trigger endogenous anticancer T-cell responses. Type I interferon (IFN-I), which is required for DC activation and recruitment to tumors, is a crucial component of this process. Preclinical research demonstrates that when DCs come into contact with DNA from cancer cells that activates the STING pathway, they release more IFN-I. It's crucial to remember that radiation encourages the transfer of tumor DNA to DCs, which boosts IFN-I production through the STING-mediated pathway and helps prime T cells that combat cancer. Furthermore, it has been demonstrated that three important chemical signals produced by radiation-induced apoptosis promote tumor-derived antigen expression and DC absorption. The endoplasmic reticulum transports calcreticulin to the cell surface, instructing DCs to gather cancer cells that are about to die. 14 To facilitate antigen cross-presentation on DCs. By activating the Inflammasomes via the P2XR7 receptor, adenosine triphosphate (ATP) ultimately results in the downstream production of interleukin (IL)-1 [75][76][77].

The lack of ability of effector T cells to UN homing to tumors significantly impairs tumor rejection. T-cell migration is regulated by chemokine's. By inducing the creation and release of chemokine's like CXCL16 and CXCL10 by cancer cells and/or immune cells that have infiltrated the body, radiation can enhance effector T cell homing to tumors. The tumor's endothelial abnormalities and cancer-aberrant vasculature significantly hinder T cell penetration. Radiation has been shown to rewire tumor macrophages in a mouse model of pancreatic cancer, enhancing T-cell infiltration and vascular normalization. One of the main factors influencing angiogenesis is macrophages. It's noteworthy to note that this impact happened following a single low-dose radiation part and that it needed macrophages to create inducible nitric oxide synthase [78][79].

In 1993, the American Cancer Society projected that 1,170,000 new instances of aggressive cancer would be found in the country. For individuals who were first diagnosed with local or regional illness, new technologies have made it possible to examine and diagnose cancer with greater precision. Research indicates that more successful tactics to support regional and local control would significantly increase the likelihood of long-term life free from recurrent illness. Numerous drugs have been investigated to increase the possibility of local control [80][81]. They've also been linked to higher rates of survival. All of these efforts are built upon significant scientific advances in dosimeters, physics, clinical treatment planning, equipment, and skilled radiation oncologists. The concepts of tumor cell healing, oxygenation, repopulation, and redistribution may now be included into radiation therapy in novel ways thanks to advancements in radiation oncology treatment and a better knowledge of fundamental biological concepts. Better local and regional control would not have been achievable without these significant developments in the use of radio biologic concepts in clinical radiation oncology [82].

SBRT (stereotactic body radiotherapy):

For men with locally advanced prostate cancer, fractionated radiation therapy with daily doses of 1.8–2.0 Gy is the typical course of dose-escalated external beam radiation therapy (EBRT) administered for eight–nine weeks. Moreover, clinical evidence suggests that hypo fractionated radiation therapy may be radio biologically preferable to lower fraction sizes in the treatment of prostate cancer as prostate cancer may be more sensitive to larger daily radiation fractions [83]. In order to capitalize on this theoretical radiobiological advantage, daily radiation percentages used in stereotactic body radiation therapy (SBRT) are progressively higher. The radiation delivery systems used in the early SBRT experiments did not offer continuous prostate location tracking with intra-fractional beam targeting correction in the event that movement was noted [84].

Proton treatment:

Proton therapy is a tempting treatment option for non-small cell lung cancer (NSCLC) because of the physical feature known as the Bragg peak, which happens when the majority of the proton dosage is deposited inside a relatively limited region with little to no "exit dose" to normal tissues in the thorax. Active scanning proton therapy (sometimes referred to as pencil beam scanning proton therapy, or PBS) and passively scattered proton therapy (PS) are the two main categories into which proton treatment planning and execution may be broadly

separated [85]. The two main elements of this challenging process are the dispersion of particles in a plane orthogonal to the beam entry and the dispersion of particles in a plane parallel to the beam entry [86][87].

Utilizing MR guidance during radiation therapy:

Scan guided radiotherapy uses cone-beam CT to scan the patient before to radiation therapy. The improved soft-tissue contrast of MRI may be used to scan the patient both before and during radiation therapy using integrated MRI accelerator systems. The following challenges have to be overcome in order to integrate an accelerator with an MRI: The improved active shielding of the magnet allows critical accelerator components to be positioned close to the scanner in a magnetically non-conductive region [88][89][90]

Radiation therapy has advanced significantly in the last several decades. The advent of precision dose calculation algorithms, intensity modulated radiation therapy (IMRT), image-guided radiotherapy (IGRT), and stereotactic body radiotherapy (SBRT) has altered our therapeutic practices. For example, even though surgery used to be the recommended course of therapy, our clinic routinely uses definitive SBRT to treat patients with early-stage lung cancer [91][92][93][94].

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