

Solid Tumors: Facts, Challenges and Solutions

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ABSTRACT

In 2005, 7.6 million people died of cancer out of 58 million deaths worldwide. Based on projections, cancer deaths will continue to rise with an estimated 9 million people dying from cancer in 2015, and 11.4 million dying in 2030. The increasing trend of cancer incidence has forced the humanity to work more on the cancer prevention and treatments. It is important for the public health professionals to understand the dynamics and kinetics of tumor incidence for future strategies.

Over here we have reviewed solid tumor modeling, their detail classification, treatment strategies available along with their merits and demerits. To overcome these limitations, design focus for future studies is suggested.

Keywords:

Solid tumor, Types of solid tumor, treatment strategies, solid tumor modeling

INTRODUCTION

SOLID TUMORS^{1,2,3}

Solid tumors are abnormal mass of tissue that usually does not contain cysts or liquid areas. Solid tumors may be benign (not cancerous), or malignant (cancerous). Different types of solid tumors are named for the type of cells that form them. Examples of solid tumors are sarcomas, carcinomas, and lymphomas.

The word tumor does not always imply cancer. In discussing tumors that are malignant (cancerous), however, the term solid tumor is used to distinguish between a localized mass of tissue and leukemia. Leukemia is a type of tumor that takes on the fluid properties of the organ it affects – e.g. the blood.

QUICK TUMOR FACTS

In 2005, 7.6 million people died of cancer out of 58 million deaths worldwide. More than 70% of all cancer deaths occur in low and middle-income countries, where resources available for prevention, diagnosis and treatment of cancer are limited or nonexistent. Based on projections, cancer deaths will continue to rise with an estimated 9 million people dying from cancer in 2015, and 11.4 million dying in 2030.

Incidence of Cancer in India:

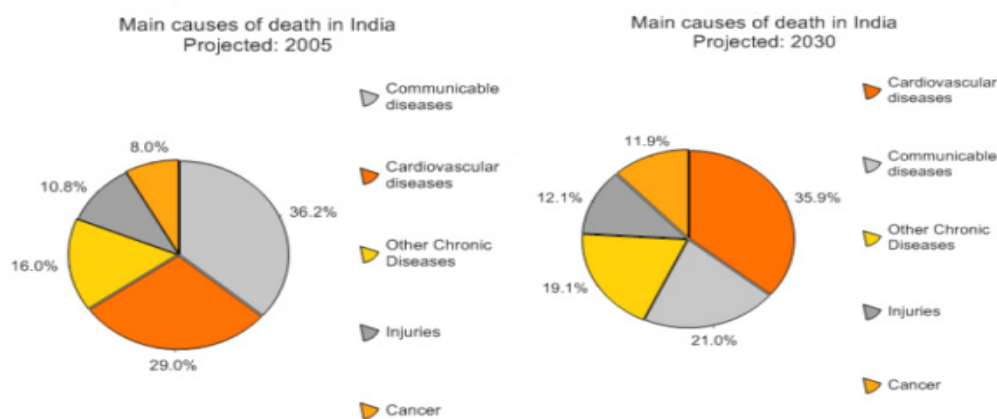


Figure No.1: Incidence of Cancer in India in 2005

Among this cancer prevalence, maximum is due to solid tumors. The increasing trend of cancer incidence has forced the humanity to work more on the cancer prevention and treatments. It is important for the public health professionals to understand the dynamics and kinetics of tumor incidence for future strategies.

Over here we have reviewed solid tumor modeling, their detail classification, treatment strategies available along with their merits and demerits. To overcome these limitations, design focus for future studies is suggested.

Modeling of Solid Tumor Growth

The biology of cancer is a complex interplay of many underlying processes, taking place at different scales both in space and time. A variety of theoretical models have been developed, which enable one to study certain components of the cancerous growth process. However, most previous approaches only focus on specific aspects of tumor development, largely ignoring the influence of the evolving tumor environment. An integrative framework to simulate tumor growth, including those model components that are considered to be of major importance. Lloyd et al developed by addressing issues at the tissue level, where the phenomena is modeled as continuum partial differential equations. They extended this model with relevant components at the cellular or even sub-cellular level in a vertical fashion. Implementation of this framework covers the major processes and treat the mechanical deformation due to growth, the biochemical response to hypoxia, blood flow, oxygenation and the explicit development of a vascular system in a coupled way⁴.

Classification of localized solid tumors⁵:

Different kinds of solid tumors are named for the type of cells of which they are composed:

- **Sarcomas** -- Cancers arising from connective or supporting tissues, such as bone or muscle.
- **Carcinomas** -- Cancers arising from the body's glandular cells and epithelial cells, which line body tissues.
- **Lymphomas** -- Cancers of the lymphoid organs such as the lymph nodes, spleen, and thymus, which produce and store infection-fighting cells. These cells also occur in almost all tissues of the body, and lymphomas therefore may develop in a wide variety of organs.

Various types of solid tumors are graphically shown in figure no.2^{5,6}:

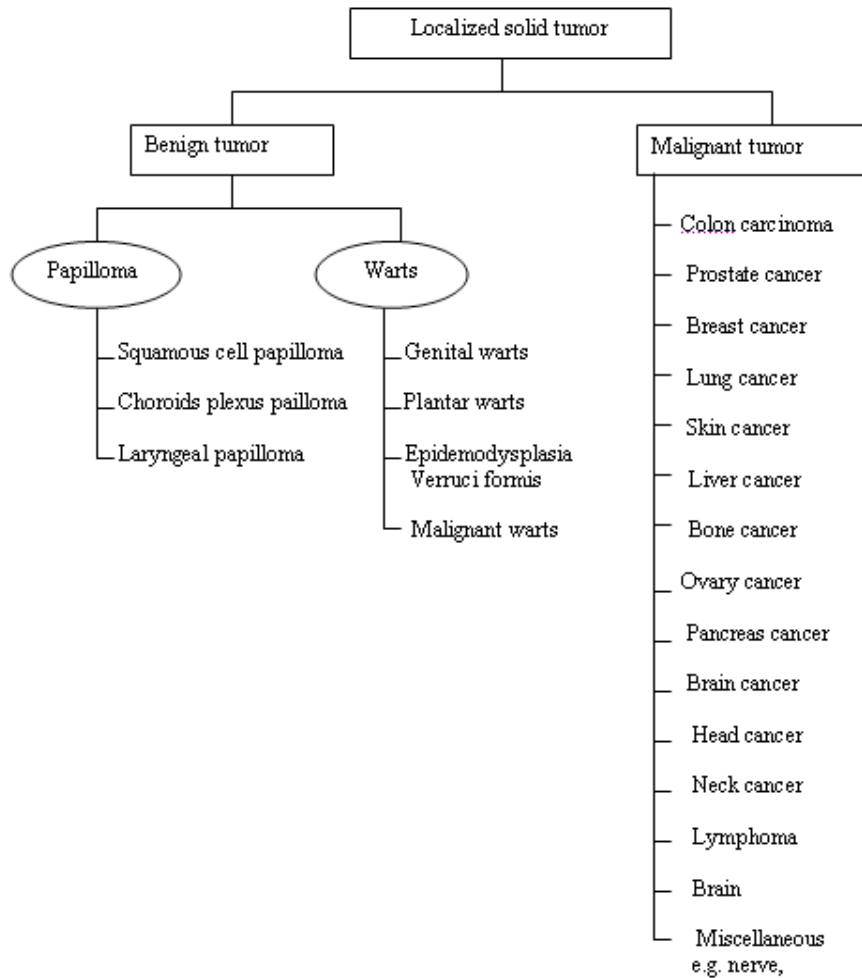


Figure no.2 Various types of solid tumors

Kinds of Solid Tumors^{5,6}:

Lymphomas Lymphomas are cancers of the lymphatic tissues, which make up the body's lymphatic system.

Lymphomas have been broadly divided into Hodgkin's disease and non-Hodgkin's lymphomas, which include a number of diseases.

a) Hodgkin's disease-

It tends to involve peripheral lymph nodes (those near the surface of the body), where the first sign of disease may be a painless swelling in the neck, armpit, or groin. Hodgkin's disease occurs most commonly in patients in their twenties and thirties and occasionally in adolescents; it is rare in younger children.

b) Non-Hodgkin's lymphomas -

In children, non-Hodgkin's lymphomas most frequently occur in the bowel, particularly in the region adjacent to the appendix, and in the upper midsection of the chest. An initial sign of disease in non-Hodgkin's lymphoma may be abdominal pain or swelling, breathing difficulties and sometimes difficulty in swallowing, or swelling of the face and neck. Non-Hodgkin's lymphomas may also occur in other organs, including the liver, spleen, bone marrow, lymph nodes, central nervous system, and bones.

Brain Tumors

Brain tumors are the second most common cancers of childhood.

Symptoms include seizures, morning headaches, vomiting, irritability, behavior problems, and changes in eating or sleeping habits, lethargy, or clumsiness. Diagnosis is often difficult, because these symptoms can and frequently do indicate any number of other problems, either physical or emotional.

Neuroblastoma

Neuroblastoma arises from very young nerve cells that develop abnormally. More than half of these tumors occur in the adrenal glands, which are located in the abdominal area near the kidneys.

Symptoms include a mass, listlessness, persistent diarrhea, and pain in the abdomen or elsewhere.

Wilms' Tumor

Wilms' tumor is a cancer that originates in the cells of the kidney. It occurs in children from infancy to age 15. It is very different from adult kidney cancers. It may rarely be hereditary, and about 5 percent of the cases involve both kidneys.

Imaging plays a crucial role in the evaluation of the primary tumor and regional and metastatic disease⁷.

Slight swelling or a lump in abdomen is its first most detectable symptom. Symptoms such as blood in the urine, weakness, fever, loss of appetite, or abdominal pain may or may not be present.

Retinoblastoma

Retinoblastoma is cancer of the eye. It may be hereditary, and one-third of the cases involve both eyes.

If diagnosed early, it is possible to destroy the tumor with radiation therapy and preserve normal vision. If the tumor is so large that there is no hope of maintaining useful vision using radiation, the eye is removed. In cases where both eyes are involved, an attempt is made to preserve vision in both eyes through treatment with radiation. When advanced disease is found in both eyes, an attempt is made to preserve vision in at least one eye. Whenever there is any possibility of useful vision, all efforts are made to preserve it. Chemotherapy, radiation, or both may also be used to treat metastases.

Rhabdomyo Sarcoma

Rhabdomyosarcoma, also called rhabdosarcoma, is a type of soft tissue sarcoma arising from muscle cells. It occurs slightly more frequently in males. Although it can occur in any muscle tissue, it is generally found in the head and neck area, the pelvis, or in the extremities.

A noticeable lump or swelling is present in almost all cases. Other symptoms depend on the location; if the growth is near the eyes, for example, a vision problem may develop. If the neck is involved, there may be hoarseness or difficulty in swallowing.

Osteogenic Sarcoma

It arises in the ends of the bones. The bones most frequently involved are the large bones of the upper arm (humerus) and the leg (femur and tibia). Osteogenic sarcoma usually occurs between the ages of 10 and 25 and is more common among males than females.

Young people with this type of cancer generally complain of pain and swelling.

Ewing's Sarcoma

Ewing's sarcoma differs from osteosarcoma in that it affects a different part of the bone. It tends to be found in bones other than the long bones of the arm and leg, such as the ribs. Like osteogenic sarcoma, it usually occurs between the ages of 10 and 25, is seen more often in males, and frequently spreads to other bones and the lungs.

Young people with this type of cancer usually have more general signs- fever, chills, and weakness- than is present in osteogenic sarcoma.

TREATMENT STRATEGIES FOR SOLID TUMOR^{8,9,10}-

Overview

The best strategy for fighting cancer is prevention - i.e., making changes in life-styles to reduce cancer risk. Nevertheless, even if we were to apply all that we know about preventing cancer, one out of four cancers would still occur. Because of this, therapies that target malignancies after they have developed will continue to be important for some time to come. The most commonly used treatment modalities for cancer include some combination of surgery, radiation therapy, and chemotherapy. Newer forms of treatment continue to emerge.

1. Goals of Cancer Therapy –

Treatment decision-making for cancer takes into account the stage and biological of the tumor, the risks vs. benefits of planned therapy, the wishes of the characteristics patient regarding treatment, and the economic costs associated with therapy. The best approach to treating cancer provides a balance between therapeutic effectiveness and minimization of treatment-associated side effects.

Surgery

Excision of tumor is the most frequently employed form of tumor therapy. More patients are cured of cancer with surgery than any other treatment method. In recent years, combining it with other treatment modalities such as chemotherapy and radiation therapy has enhanced the effectiveness of surgery.

1. Goals of Surgical Therapy:

a. Cure - Tumor excision is most successful when disease is identified early, the tumor is small, and it is confined to a limited area or regional lymph nodes.

(1) A margin of normal tissue surrounding the tumor is almost always removed to help to reduce the risk of local recurrence due to infiltration of malignant cells beyond the visible margins of the tumor.

(2) Most solid malignancies spread by way of lymphatic. Removal of regional lymph nodes is often performed along with tumor resection to increase the chance of cure.

b. Palliation - Even when cure is not a reasonable expectation, tumors may be resected to relieve pain, life threatening hemorrhage, or compression of vital structures such as the spinal cord, vena cava, or trachea. Surgical bypass of obstructing lesions in the gastrointestinal, urinary, or biliary tracts can improve organ function and relieve distressing symptoms.

2. Limitations of Surgery -

a. Large invasive tumors, most metastatic disease, and hematological malignancies are essentially unresectable. However, solitary metastases in the liver and lung are sometimes successfully resected.

b. Patients with co-existing systemic disease (diabetes, cardiovascular disease, COPD, etc.), or those

with a poor performance status, may be unable to tolerate surgery.

c. Extensive surgery may affect surrounding normal tissues leading to significant deformity or organ dysfunction.

Radiation Therapy

Used for the treatment of localized solid tumors when surgery is not appropriate or feasible (e.g., inoperable lung cancer).

1. How Radiation Kills Cancer Cells - Ionizing radiation transfers energy to tissues, dislodging electrons from complex, biologically important molecules such as DNA. This produces breaks in DNA strands so that they cannot replicate during the cell cycle. Additionally, ionizing radiation, in the presence of water molecules, generates hydroxyl free radicals that can further damage DNA. Extensive DNA damage triggers apoptosis and cell death.

2. Types of Radiation Therapy:

a. **External beam radiation therapy** - Ionizing radiation that is delivered from a distance of 80-100 cm from the body. Several methods of delivering external beam RT are available including:

(1). **Electromagnetic x-ray and gamma rays.** This involves delivering electromagnetic energy in the form of **photons** generated by devices called linear accelerators or Cobalt-60 units. This provides good deep tissue penetration with very little energy deposited in skin. Used mainly for deep tumors.

(2). **Particle beam radiation.** (Electrons, protons, alpha particles.)

Electron beam radiation is produced by accelerating negatively charged electrons moving with high speed. Used mainly for certain skin cancers. Proton beam therapy offers pinpoint control over the delivery of radiation.

b. Brachytherapy-

This involves the temporary or permanent implantation of radioactive isotopes (e.g., ¹³⁷Cesium, ¹⁹²Iridium, radioactive iodine) directly into a tumor via catheter or large bore needle. Most of these isotopes emit alpha or beta particles, or low energy electrons. Has advantage of delivering high dose of energy to localized area with minimum dose to surrounding normal tissues. Mainly used for cervical and prostate cancer.

c. Radio pharmaceuticals-

Radioisotope preparations administered intravenously that target specific tissues:

(1) Radioactive iodine (¹³¹I) - Thyroid malignancies.

(2) Strontium (⁸⁹Sr) and

(3) Samarium (¹⁵³Sm) - Metastatic bone tumors.

4. Limitations of Radiotherapy:

Ionizing radiation injures normal tissues as well as malignant tumors. Potential toxic effects of ionizing radiation include:

Bone marrow suppression

Dryness of mouth (xerostomia) if salivary glands are irradiated.

Inflammation of the esophagus may cause painful dysphasia.

Inflammation of the mucosal lining of the gastrointestinal tract can cause diarrhea, nausea, or vomiting. Painful mouth sores may also occur.

Radiation injury to the lung may produce pneumonitis and pulmonary fibrosis causing

hypoxia and dyspnea.

Cataracts (if eyes are irradiated)

Infertility (if gonads are irradiated)

In case of radiation treated rectal cancer problems are bowel obstructions; bowel dysfunction presented as fecal incontinence to gas, loose or solid stools, evacuation problems or urgency; and sexual dysfunction¹¹.

Skin changes such as alopecia, erythema, pruritis, increased pigmentation, or desquamation. Since radiation is itself capable of causing cancer, secondary malignancies (e.g., leukemia, thyroid cancer) may be induced by radiation therapy.

Less frequent complications of radiation therapy include: spinal cord dysfunction (myelopathy), pericardial or myocardial damage, bone necrosis, and necrosis of the bowel.

Chemotherapy

Chemotherapy may also be combined with surgery or radiation to increase the effectiveness of these treatment modalities.

1. How chemotherapy kills cancer cells - Like radiation, most chemotherapeutic agents target malignant cells that are actively replicating. Many chemotherapy drugs directly damage DNA - interfering with cell division and activating programmed cell death (apoptosis). Other antineoplastic agents act indirectly by interfering with mitosis or by blocking the utilization of nucleotides required for DNA synthesis by replicating tumor cells.

Even in cancer patients of ≥ 80 years old selected for chemotherapy, both single and multi-agent therapy appeared to be feasible¹².

In addition immune cells called macrophages can destroy tumor cells by producing inflammatory proteins that are toxic to the tumor. Hence, immune stimulators can be combined effectively along with chemotherapeutic agents¹³.

Over the past 2 decades chemotherapy for advanced prostate cancer has evolved from a frightful, toxic experience to one that frequently provides clinically meaningful palliation and a modest, but real survival benefit. With the establishment of docetaxel-based chemotherapy as initial therapy, efforts are underway to evaluate the role of second-line systemic therapy options¹⁴.

2. Limitations of Chemotherapy:

a. Toxicity - Like radiotherapy, chemotherapy can injure normal tissues especially tissues that contain cells that divide frequently such as bone marrow, GI tract, hair follicles, and gonads. Common toxicities include:

1. Nausea and vomiting - Usually occurs during the first few hours of treatment.
2. Hair loss (alopecia) - Usually occurs about two weeks after treatment is begun. Not all chemotherapy agents produce alopecia. Regrowth of hair almost always occurs. There are no reliable methods for preventing hair loss.
3. Myelosuppression⁵ - It leads to suppression of WBC and platelet production in the bone marrow associated with risk of infection and bleeding. Lowest WBC counts usually occur 10-14 days after treatment. Cell counts usually return to normal by 3-4 weeks.
4. Painful mouth sores (stomatitis) - Usually occur within a week of therapy and then resolve.
5. Diarrhoea - Some chemotherapy agents can cause diarrhoea which is occasionally profuse leading to dehydration.

6. Decreased spermatogenesis/ decreased ovarian follicle formation - It may lead to permanent infertility. For premenopausal women – premature menopause may be induced.
7. Carcinogenicity - One of the cruel ironies of cancer treatment is that chemotherapeutic drugs (especially the alkylating agents like cytoxan and nitrogen mustard) are themselves carcinogenic and may produce a secondary malignancy (usually leukemia).
8. Some chemotherapeutic agents have tissue specific toxicities including nerve, heart, kidney, liver, and lung injury.

b. Drug Resistance by Tumors - The tendency of malignant cells to acquire mutations that allow them to resist the effects of antineoplastic drugs is an important factor limiting the effectiveness of chemotherapy. Tumors that are heterogeneous mixtures of chemo sensitive and chemo resistant cells may initially appear to respond to treatment, but then relapse as the chemo sensitive cells are killed off and the drug resistant cells become predominant.

The most common mechanism for this is over-expression of specialized proteins embedded in the plasma membrane called p glycoprotein that actively “pump” drugs out of the cell before they can exert their pharmacological effect. Since this mechanism is not drug-specific (i.e., it works on any potentially toxic molecule) it can make a tumor resistant to many drugs - even drugs to which it has not been previously exposed. This important phenomenon is called “multiple drug resistance”.

c. Poor penetration of antineoplastic agent via solid tumor-

Successful pharmacotherapy of solid tumors remains an unfulfilled medical goal, despite increased understanding of the molecular biology of tumor cells, the identification of novel cellular targets, and the availability of increased numbers of potential therapeutic agents, chemotherapy often fails because adequate cytotoxic concentrations are not achieved. It is due to poor penetration and non-uniform distribution of the drug.

For the effective treatment of solid tumors, anticancer drugs must gain access to all viable cells within the tumors in sufficient concentrations to cause lethality. However, many solid tumors have a poorly formed blood vascular system with variable rates of blood flow and much larger intercapillary distances than those found in normal tissues. The requirement for drugs to penetrate several layers of tissue might pose a barrier to the effective treatment of solid tumors.

Moreover, the imperfect nature of vasculature in solid tumors also leads to tumor regions with deficiencies in the supply of oxygen and other nutrients and to the accumulation of metabolic acids. According to research done at St. Jude Children’s Research Hospital on neuroblastoma patient, temporary improvement of tumor blood flow can improve chemotherapy^{15,16}.

(3) Combination Chemotherapy¹⁷ - Increasing the dosage of single agents in order to prevent drug resistance may not be possible because of the risk of unacceptable toxicity. To overcome this limitation, modern chemotherapy almost always employs combinations of multiple antineoplastic drugs that have different mechanisms of action and different, non-overlapping toxicities. Almost all aggressive malignancies that are sensitive to chemotherapy are best treated with drug combinations rather than single agents.

d. Other problems that may limit the effectiveness of chemotherapy include:

(1) Tumor Sanctuary - Tumors may be located in areas of the body that drugs cannot effectively reach (e.g., in the CNS or areas with poor blood supply).

(2) Inadequate Drug Dosing - Reducing the dose of a drug, or increasing the interval between treatments, in order to reduce toxicity may result in increased survival of malignant cells and reduce the chance for cure.

Other Treatment Modalities for Cancer

Combined Modality Treatment:

a. Surgery plus Chemotherapy

(1) Adjuvant chemotherapy^{18,19} - For many solid tumors, surgery followed by chemotherapy produces a better long-term survival rate than surgery alone. The rationale for adjuvant chemotherapy is that by the time many cancers are diagnosed, small numbers of malignant cells have already spread to distant sites. This makes it unlikely that surgery alone will achieve a cure²⁰.

(2) Neoadjuvant chemotherapy - For some advanced cancers that have extensively invaded surrounding tissues, chemotherapy can be given before surgery or gene therapy²¹ in order to reduce tumor size making later excision and therapeutics of the cancer easier.

b. Surgery plus Radiation - For early stage breast cancer, a “lumpectomy” (excision of the tumor without mastectomy) followed by irradiation of the operation site is just as effective as radical mastectomy in terms of long-term patient survival.

c. Chemotherapy plus Radiation - For example, chemotherapy for acute leukemia is occasionally followed by radiation to the spine and skull to prevent the recurrence of disease in the CNS. Some chemotherapy drugs can sensitize head and neck tumors to radiation therapy.

But chemotherapy and radiation make these tumors stronger since solid tumors adapt the body's machinery to bring themselves more oxygen²².

Future investigation will focus on optimizing the concomitant chemotherapy and radiotherapy schedules used, integrating targeted agents into these established treatment schedules, addressing the problem of distant metastases, minimizing both acute and late toxicities, and identifying the most appropriate patient populations for this kind of aggressive treatment²³.

Hormonal therapy²⁴

More accurately it is called anti-hormonal therapy. It is frequently effective in those cancers that are hormone dependent. Antiestrogen drugs Tamoxifen, Arimidex, and Letrozole can be used to treat some breast cancers. Orchiectomy or the anti-androgenic drugs Leuprolide and Flutamide are used in metastatic prostate cancer. Corticosteroids such as Prednisolone or Dexamethasone are useful for controlling some forms of leukemia and lymphoma²⁵.

Stem Cell transplantation

As noted above, one of the limitations of chemotherapy is its toxicity to hematopoietic stem cells in the bone marrow. The principle behind stem cell transplantation is that higher than normal doses of chemotherapy drugs can be given in order to achieve a higher rate of cancer cell killing.

A reevaluation of the published studies and related claims within awarded U.S. patents suggests that the mathematical support for the concept of therapeutically useful stem cells is weak and may even invalidate the foundations of these publications and patent claims. Mathematical arguments should be used more consistently, because they can serve as a guide for interpreting studies into cancer stem cells of solid tumors²⁶.

Anti cancer-stem cell therapy

Finlan et al have compared epidermal stem cells and cancer stem cells in order to develop potential therapeutic strategies²⁷. To study ways to develop drugs that target cancer Stem cells (SC), Boman et al investigated changes in cellular mechanisms and kinetics that occur in SC populations during colorectal cancer (CRC) development. They used computer modeling to determine which changes could give rise to exponential increases in both SC and non-SC populations in CRC. Results show that the only mechanism that can explain how these subpopulations

increase exponentially in CRC development involves an increase in symmetric SC cell division. This findings suggested that any systemic therapies designed to effectively treat CRC and other cancers must act to control or eliminate symmetrical cancer SC division in tumors, while minimally affecting normal SC division in non-tumor tissues^{28,29}.

Monoclonal antibody³⁰

The recent clinical and commercial successes of monoclonal antibodies (MAbs) have made them the most rapidly expanding class of therapeutics being developed for many disease indications, including cancer. PCa is well suited for antibody-based therapy due to the size and location of recurrent and metastatic tumors, and the lack of necessity to avoid targeting the normal prostate, a nonessential organ. These properties have fostered interest in the development and clinical evaluation of therapeutic MAbs directed to both well established and newly discovered targets in PCa.

Genomics efforts have yielded a large number of novels, clinically relevant targets in PCa with the desirable expression profiling in tumor and normal tissues, and with an implicated role in tumor growth and spread. Growing efforts are directed to the development of naked or payload-conjugated therapeutic antibodies to these targets, and a variety of MAb products are currently progressing through preclinical and various stages of clinical development. The clinical experience with some of the commercialized MAb products points out specific challenges in conducting clinical trials with targeted therapy in PCa.

Application of Electric Field

The transmission of electric fields using insulated electrodes has demonstrated that very low-intensity, properly tuned, intermediate-frequency electric fields, termed tumor-treating fields (TTFields), selectively stunts tumor cell growth and is accompanied by a decrease in tumor angiogenesis.

Open, prospective pilot study was designed to evaluate the safety, tolerability, and efficacy profile of TTFields treatment in patients with locally advanced and/or metastatic solid tumors using the NovoTTF100A(TM) device. No related serious adverse events occurred. Outcomes showed 1 partial response of a treated skin metastasis from a primary breast cancer³¹.

Thus the lack of therapy toxicity and the efficacy observed in data gathered to date indicate the potential of TTFields as a new treatment modality for solid tumors, definitely warranting further investigation. Nowadays the research of mostly used chemotherapeutic approach is mainly focused -

- 1) To improve efficacy.
- 2) To eliminate toxicity.
- 3) To eliminate premedications.

Various DDS and the problems encountered in their application as a successful therapeutics³² is mentioned in table no.3.

Table No. 1: DDS and The Problems Encountered In Tumor Therapy.

Drug Delivery System	Problems encountered
Emulsification	- Stable emulsions are hard to achieve
	- Limited drug loading
	- Entrapment in tumor is problematic
Nanoparticles ³³	- Entrapment in tumor is problematic
	- High dose administration is difficult.
Liposomes	- Entrapment in tumor is problematic
	- High dose administration is difficult
Micro spheres	- Entry of large volume microspheres I tumor nodules is difficult.
Micelles	- Disassemble on injection and hence show "Burst release"

The mostly used approach for treatment of solid tumors is surgery in combination with localized chemotherapy. Nowadays localized chemotherapy involves two drug delivery techniques¹⁷ viz.-

Administration of systemic IV infusion.

Administration of localized implant.

Systemic IV infusions need the professional observation and care throughout administration period and thereby raise the cost of treatment. Also implant needs creation of an opening with dimensions at least their size, which is source of potential risks and patient discomfort.

To overcome these limitations, design focus is being placed on injectable materials with the ability to form three dimensional elastic matrices or gel structure under physiological conditions or by environmental / external stimuli (pH, light, temperature, solvent exchange, etc.). Such materials are called as "smart polymers" and formulation as "Environment-responsive Formulations"^{34,35}.

Ultrasonication

It has long been shown that therapeutic ultrasound can be used effectively to ablate solid tumors, and a variety of cancers are presently being treated in the clinic using these types of ultrasound exposures.

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