The Gulf Journal of Oncology

Indexed By PubMed and Medline Database

Issue 43, September 2023
ISSN No. 2078-2101

The Official Journal of the Gulf Federation For Cancer Control

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Review Article

Early Development of Cancer Treatments

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Abstract:

The treatment of cancer has evolved as our understanding of the underlying biological processes has improved. Yet, the efficient delivery of cancer therapeutics remains a major challenge in the filed necessitating a multidisciplinary approach that integrates knowledge obtained from diverse fields, such as chemistry, biology, engineering, and medicine.

Cancer treatment aims to remove all or most of the tumor as possible and to prevent the recurrence or spread of the primary tumor. Cancer treatment involves a careful examination of the available options, which may include a combination of the major treatment methods, such as surgery with chemotherapy and/or radiation therapy. The type of therapy chosen depends on several factors, such as the location, grade, and stage of the tumor, as well as the patient's performance status. As new knowledge about cancer biology becomes available, treatments will be developed and modified in the pursuit of cancer cures to improve efficacy, precision, survivability, and quality of life.

The main objective of this review is to expand our understanding of the early development of commonly applied cancer treatment strategies: surgery, chemotherapy, and radiotherapy.

Keywords: Chemotherapy; Radiotherapy; Surgery; Therapy; Tumor.

1. Introduction

The historical development of cancer therapy started in 2600 BC and has gradually progressed. Imhotep, an Egyptian physician, suggested creating a localized infection to promote tumor regression and spread. This was accomplished by applying a poultice to the tumor, followed by performing a local incision to introduce the infection. Regional and whole–body hyperthermia was also used to treat masses by the Greeks, Romans, and Egyptians, whereas the first description of surgical cancer treatment by the Greeks was in 2 AD. During the 1500s, heavy metals were systemically used to treat cancer, but their efficacy is limited and their toxicity is high [(1)].

William Bradley Coley, The Father of Cancer Immunotherapy, was best known for his early contributions to the study of cancer immunotherapy. The first immunostimulants used to treat cancer, known as Coley's toxins, were developed and studied by William Coley in the early 1890s. Years later, the medical use of X–rays began in 1896 to treat skin malignancies through caustic burns [(2)]. The diminution of pain and reduction in the size of the tumor was also observed during attempted X–ray treatment on a patient with an epigastric tumor. Shortly after the discovery of radium in 1898, there was speculation about whether radium radiation can be used for therapy in the same way as X–rays [(3)]. Radium was soon recognized as a method to treat disorders that were not adequately treated by X–ray since it could be applied externally and into the substance of a tumor via incisions in manners that X–rays could not. X–rays were discovered to produce worse cosmetic effects than lasers; therefore, when a localized reaction was desired, radium was favored, while X–rays were used when a large area required treatment [(4)].

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The era of cancer chemotherapy began in the 1940s with the introduction of chemical warfare during World War I. Servicemen who were exposed to sulfur–

mustard gas experienced bone marrow and lymphoid suppressions; hence, it was hypothesized that because mustard gas effectively stopped the division of several types of somatic cells that had a proclivity to divide rapidly, it potentially helps to suppress the division of various types of cancerous cells as an effective treatment for cancer. By the time of World War II, the first antitumor antibiotics had been discovered by the use of folic acid antagonists that have been shown to be effective in the treatment of childhood acute leukemia [5]. In 1955, the National Cancer Chemotherapy Service Centre (NCCSC) was founded and dedicated to develop and test new chemotherapy drugs.

The 1960s witnessed an improvement in remission rates and minim toxicity of multidrug therapy. A combination of chemotherapy began to be used in conjunction with surgery and radiation to treat cancer. Cancers that were previously known to be fatal became highly curable using this approach. Adjuvant chemotherapy has begun to be used in the treatment of patients with advanced cancer following radiotherapy or surgery, and the use of this adjuvant chemotherapy in the late 1960s altered the concept of localized treatment [6].

After the 1970s, there was a rapid advancement in the understanding of the molecular biology of cancer cells with the use of the modern microscope. Cell culture systems also became more sophisticated; thus, adjustments had been made for drugs metabolized to their active form in vivo.

The area of medical oncology was formally founded as a subspecialty of internal medicine. Numerous treatments with various mechanisms of action were introduced throughout the 1980s. Several new chemotherapeutic agents became available with the increased use of multimodal therapies taking into consideration symptom management to alleviate dose–limiting toxicities. Another advance in the area of cancer treatment was the beginning of monoclonal antibody and cytokine trials in the late 1980s, as well as the foundational evaluation of recombinant DNA technology to cure cancer [7].

There was significant progress in the 1990s to treat cancer. New classifications of drugs were developed and approved by the U.S. Food and Drug Administration (FDA). One of the most exciting applications of biologic therapy has come from identifying the genetic basis of cancers as an important factor in cancer risk research. Moreover, a step forward for hormonal therapy occurred during the 1990s by the approval of aromatase inhibitors for breast cancer treatment [8].

As of the year 2000 and later, numerous oncogenes, suppressor oncogenes, and signaling pathways essential for developmental biology were identified. This ultimately contributed to the discovery of the majority of the novel drug targets that are the focus of cancer drug production, at present.

Biotherapy is approved to target and improve defense against certain antigens on malignant cells. Vaccines, monoclonal antibodies, cytokines, and adjuvants are examples of biological response modifiers (BRMs) used in biotherapy. BRMs may be used individually or in conjunction with one another. Several BRMs are commonly used in the treatment of specific forms of cancer, while others are being tested in clinical trials [9]. Radioimmunotherapy (RIT) is another promising method of delivering radioactivity directly to tumor cells while preventing exposure to healthy tissue. Radioimmunotherapy aims to selectively distribute radionuclides emitting alpha– particles, beta– particles, or Auger electrons to tumors through conjugation to monoclonal antibodies (mAbs) that recognize tumor–associated antigens/receptors. The technique has been more effective for cancer diagnosis and treatments, but there have been difficulties in translating these positive findings to the treatment of solid malignancies. The investigation of RIT radiolabeled agents is underway, at present. Principles regulating radionuclide selection, labeling protocols, antibody suitability, and the optimization of "tumor to normal tissue ratios" are presently under investigation [10].

The data obtained from genome sequences revealed that many of the mutations associated with cancer are caused by defective protein kinase activity, and one of the recent drug discovery era's main thrusts has been to produce a set of kinase inhibitors [11]. Several of these small molecules have been presently licensed by the United States Food and Drug Administration for the treatment of renal cell cancer, hepatocellular cancer, and gastrointestinal stromal tumors, all of which were previously resistant to conventional chemotherapy. These compounds carry a great deal of promise for treating a wide variety of solid tumors and hematologic malignancies.

Chemotherapy is also being used to treat a broader range of solid tumors. While treatments of these cancers are not always curative, there has been a notable increase in the overall survival rate. Furthermore, some of the most active chemotherapy regimens were paired with new selective treatments to be used in the neoadjuvant environment to reduce the size of the primary tumor and to protect essential organs [11].

Starting from the year 1990, the national incidence and mortality of cancer began to decline. Whereas half of this decrease is due to screening and early diagnosis, the other half is mostly due to advances in cancer treatment, which is mainly due to the use of chemotherapy in the majority of treatment planes [11].

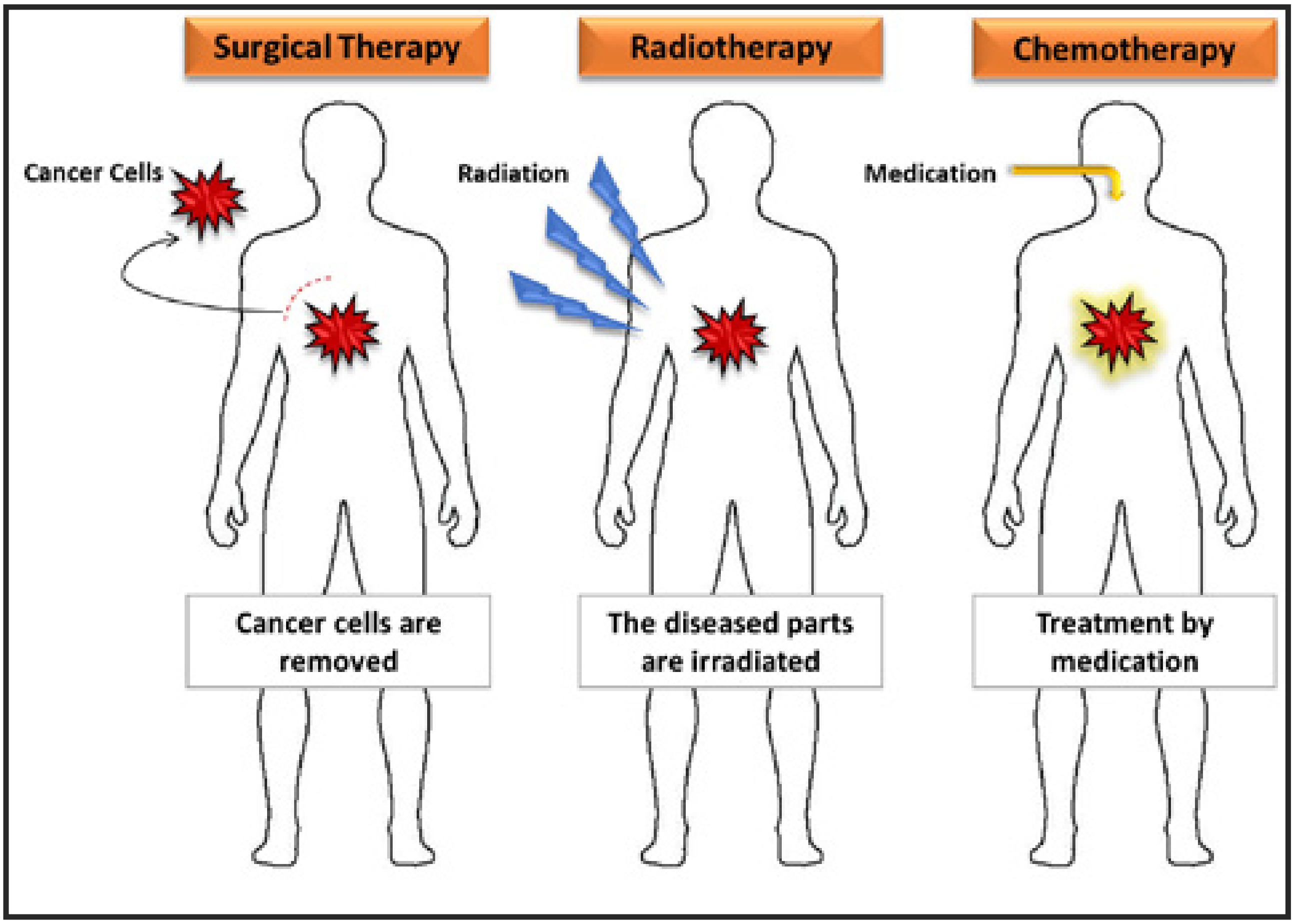

Figure 1: Traditional treatment modalities for cancer [39].

Cancer therapy is a treatment plan that aims to cure cancer using one or a combination of intervention strategies, such as surgery, radiation, chemical agents, immunotherapy, targeted therapy, gene therapy, hormone therapy, stem cell transplants, and the nanoparticle drug delivery system. The following sections of the review shed light on the traditional treatment modalities: surgery, radiotherapy, and chemotherapy (Figure 1).

2. Sequential approach of cancer treatments

Several trials are being conducted to evaluate potential cancer therapy methods. Sequential treatment is one of the most promising concepts, with effectiveness that has been shown in various experiments.

When cancer demonstrates resistance to therapy, experimental treatments are less likely to succeed, and the cancer can worsen, fatally wounding the patient. Changing therapies before it progresses could avoid the growth of resistance and increase medical conditions. Acute lymphoblastic leukemia, for instance, was originally fatal, but is 80–90% curable at present using a similar mechanism of sequential chemotherapy regimens delivered one after the other before the emergence of chemotherapy resistance [12].

In addition to improving survival rates, sequential treatment seems to provide a benefit in terms of concurrent toxicities, which are common in patients undergoing combined chemotherapy regimens. As a result, sequential administration enables non–cross–resistant agents to escalate to an appropriate dose.

This treatment approach is different from combination therapy. In sequential therapy, treatment is administered in phases, while in combination therapy multiple treatments are provided simultaneously.

Sequential therapy can be particularly beneficial in vulnerable or elderly patients who may be unable to handle the toxicity associated with combined therapy, or in patients with slow–growing tumors.

2.1 Primary treatment

Primary treatment is also referred to as induction therapy or first–line therapy. A primary treatment that aims to either eliminate cancer from the body or to destroy all cancer cells. Surgery is the most effective primary therapy for the most common forms of cancer. If the cancer is especially vulnerable to radiation therapy or chemotherapy, then the patient could be treated with one of these treatments as their main cure. Primary therapy is considered the safest course of action. However, if it fails to heal the condition or induces serious side effects, additional or alternative treatments can be applied [13].

2.2 Adjuvant treatment

Adjuvant therapy aims to eliminate all cancer cells that might survive the primary treatment procedure to minimize the potential of recurrence of cancer cell growth. Any cancer treatment can be used as adjuvant therapy. Chemotherapy, radiation therapy, hormone therapy, and targeted and biological therapy are examples of common adjuvant therapies [14].

2.3 Palliative treatment

Palliative treatment can be combined with other treatments directed at curing cancer. It can help alleviate treatment–related side effects as well as cancer–related symptoms to improve the quality of life in cancerous patients [15].

With the advances in the medical field, many treatment options for cancer have been discovered and briefly mentioned below.

3. Surgery and its advances

Surgery is the most ancient form of oncology treatments, dating back thousands of years. This approach has increased the long–term survival rate of patients [16]. At present, different surgical procedures are being performed. These include laser surgery, electrosurgery, cryosurgery, curative, palliative, and other surgeries. All these procedures have proved to be effective in enhancing the survival rate of patients and in improving their quality of life.

3.1 Types of cancer surgery

3.1.1 Curative surgery

Surgery is an integral part of the cancer treatment plan. Curative or primary surgery is often performed where cancer is detected in just one area of the body. The operation is referred to as "curative" since the aim of the procedure is to eradicate cancer. It can be used with other procedures, such as chemotherapy or radiation therapy administered before or during the procedure [17].

The early ligation of blood vessels and lymphatics is conducted during the tumor resection process to reduce the possibility of expansion, and the tumor can be removed with minimal manipulation. Lymph nodes presenting next to the tumor are also cut. This surgery aims to reduce the risk of remaining cancer cells that lead to a recurrence of the disease [17].

Localized cancer responds best to curative surgery. Radiotherapy or chemotherapy can be used to shrink the tumor prior to surgery, and to remove any cancer cells that persist following surgery.

3.1.2 Palliative surgery

Palliative surgery is used to treat cancer–related problems, such as ulcerations, nerve block, obstructions, hemorrhage, nausea, and malignant effusions. It is a critical part of surgical oncology, accounting for 10–20 % of the procedures conducted on cancer patients.

The two most important aims of palliative surgery are pain relief and recovery from distressing symptoms. It is often considered when no alternative treatment is available.

Palliative surgical operations are divided into two categories:

- Procedures that specifically alleviate symptoms or that are conducted as part of an interdisciplinary symptom–reduction program.
- Non–surgical palliative care procedures that promote or direct a non–surgical palliative solution [18].

3.1.3 Diagnostic surgery

Diagnostic surgery is also known as a biopsy. The microscopic inspection of biopsy specimens is the optimal method for performing a positive diagnosis of cancer [19]. This technique entails physically removing any part of a potential tumor involving cells, fluid, or tissue, and inspecting it under a microscope. Then, this biopsy specimen is used to determine the histologic form of cancer and, probably, the stage of illness.

3.1.4 Preventive surgery

Preventive surgery involves the removal of tissue that does not yet produce cancer cells, but has a high risk of developing into cancer in the future. This type of surgery is also known as prophylactic surgery. Polyps, for instance, are considered precancerous tissues and are removed with the help of preventative surgery. Prophylactic surgery is further divided into different surgeries, such as colectomies, oophorectomies, and mastectomies [20] .

3.1.5 Debulking surgery

Debulking is the process of removing as much of the bulk of a tumor as possible without attempting a full eradication. The procedure is known as "debulking" because the tumor being treated is a large, dense mass that can be situated very close to vital organs or tissues. When used for curative purposes, it is referred to as the surgical debulking of tumors or cytoreductive surgery or "cytoreduction," which refers to the process of reducing the number of tumor cells. Debulking is used curatively in only a few forms of cancer since, in most cases, the partial resection of a malignant

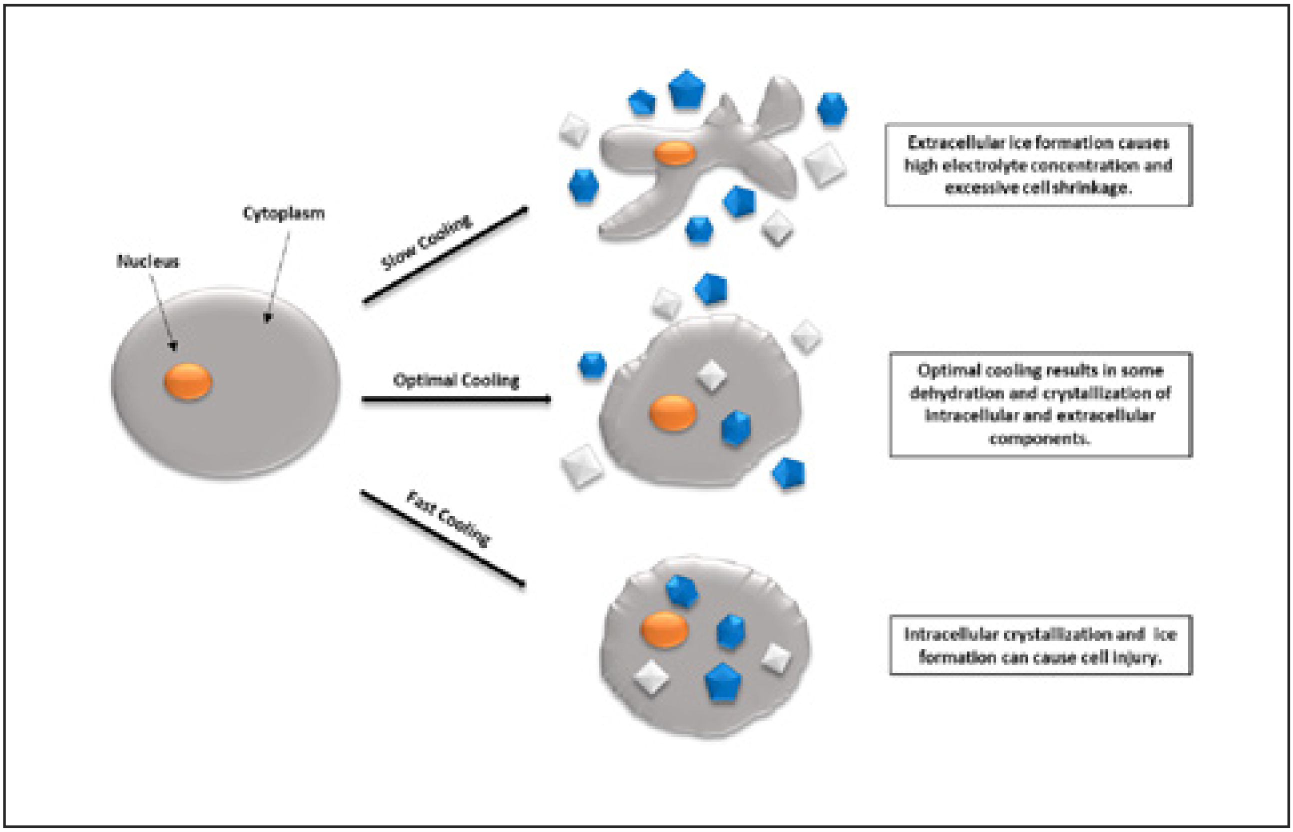

Figure 2: Mechanism of freezing injury [40].

tumor is not a curative intervention. When removing the whole tumor will considerably damage the surrounding organs or tissues, this form of surgery is used. It is used to remove a part of the tumor before treating the remainder of it with radiation, chemotherapy, or other therapies.

Debulking has been used for ovarian cancer, mucinous appendiceal cancers, and some forms of brain tumors prior to initiating radiotherapy or chemotherapy, which increases the efficacy of those treatments [21].

3.1.6 Cryosurgery

Cryosurgery is a particular minimally invasive procedure that is used in a variety of clinical settings. It is the surgical use of cryoablation, in which extreme coldness is used to remove diseased or abnormal tissue, particularly in different malignant and benign skin conditions [22].

At present, cryoablation treatments are used to treat benign breast cancers and the early stages of advanced breast cancer with a relatively high response rate.

Cryosurgery causes damage to cancerous tissues via its effect of freezing, thawing, and warming (Figure 2).

3.1.7 LASER surgery

Laser surgery is a procedure used for removing cancer cells by using light energy beams rather than devices. Their high–intensity light can shrink or eliminate tumors and precancerous growths. Laser surgery is an effective and direct method used for treating difficult–to–reach body areas, such as the rectum, cervix, scalp, and larynx, as well as superficial cancers (tumors lining the internal organ or presenting on the skin), such as basal–cell skin cancer, penile, vulvar, cervical, vaginal, and non–small–cell lung cancer. Additionally, since the 1980s, pre–malignant lesions have also been treated with LASER therapy [23].

Lasers chiefly focus on tiny regions, so they can be used for tissue cutting or extremely detailed surgical work. Therefore, it cannot be used in situations when tumors are larger than 6 mm depth invasive and grade T2 tumors.

Three kinds of lasers are used to treat cancer: argon, carbon dioxide, and neodymium lasers made of “yttrium–aluminum–garnet”.

3.1.8 Electrosurgery

Electrocoagulation, electrosection, and electrofulguration are all examples of high–frequency electrosurgery. These approaches are sometimes used to treat oral and skin cancers, as well as uterine tumors. They can be used for the treatment of basal–cell skin cancer and a variety of other skin conditions, including moles, warts, and actinic keratoses. Additionally, they may be used to eradicate abnormal cells from the cervix and to treat anus, vaginal, penis, and vulva tissue that may develop into cancer [24].

3.1.9 Microscopely controlled surgery

This cancer surgery is recommended for tumors in challenging locations that require a tissue–sparing surgical procedure or where rapid growth is present, and a local cure or complete remission is needed [25].

4. Radiotherapy and its advances

Radiotherapy is another treatment approach for cancer. External beam radiation, also known as "teletherapy," is the most often employed method, and it requires a radioactive source located outside of the patient, with the energy directed and shaped to the target. Brachytherapy, on the other hand, is the method of concentrating naturally occurring radioactive sources that degrade over time and deliver high doses of radiation in a specific region [26].

- Radiation therapy is an option that can be applied at different times during cancer treatment and for different reasons, including:
- As the only (primary) cancer therapy;
- To reduce the size of a cancerous tumor prior to surgery (neoadjuvant therapy);
- To prevent the development of any residual cancer cells following surgery (adjuvant therapy);
- To destroy cancer cells in conjunction with other therapies, such as chemotherapy;
- In advanced cancer, to relieve cancer–related symptoms.

Radiation therapies can be used as an adjuvant treatment to reduce tumor recurrence following primary malignant tumor removal surgery (for example, the early stages of breast cancer). It may also be used as a palliative treatment (when a cure is not achievable and the aim is to manage the disease locally or provide symptomatic relief). Radiation treatment has a synergistic effect with chemotherapy and has been used before, during, and after chemotherapy in tumors that are vulnerable to it. Radiotherapy, at present, holds the promise of extinguishing cancer cells while sparing as many normal cells as possible.

4.1 Mechanism of action

Radiation therapy is the use of targeted X–rays or subatomic particles to treat cancer. Traditionally, treatment was provided with naturally occurring radioactive elements that emit photons during the decay process. Radiation causes various biochemical changes in cells during therapy; since natural cell toxicity reduces the doses required for successful treatment, methods are intended to achieve a balance between killing cancer cells and protecting normal tissues [27].

All cells have their methods to repair their DNA damage. However, when double–stranded DNA breaks down, it is far more difficult to restore and can result in significant genetic deletions and chromosomal defects. Cancer cells normally replicate more rapidly than most healthy differentiated cells and have a reduced capacity to sustain sub–lethal damage. DNA damage is passed on through cell division, resulting in damage occurring to other cancer cells allowing cells to die or replicate more slowly.

Charged particles, such as neon ions, carbon, boron, and protons, have the capability to damage cancer cell DNA directly via "high–linear–energy transfer", and they exert an antitumor effect regardless of the supply of oxygen to the tumor since these particles function primarily via the direct transfer of energy, often "triggering double–stranded DNA breaks". Since most of the charged particles and protons have a comparatively large mass, they have no lateral side spread. This treatment is provided in minor dosages so it cannot cause significant side effects in adjacent tissue.

Radiotherapy can also cause cell damage directly through disrupting cellular homeostasis by altering signal transduction pathways, the redox state, and apoptotic disposition. Ideally, in radiation therapy, cellular modifications increase tumor cell death while decreasing the likelihood of normal cell death [28].

4.2 Types of cancer radiation therapy

4.2.1 Conventional external beam radiation therapy (EBRT)

EBRT is an important palliative care option for certain patients with an incurable disease. It can also be used as adjuvant therapy for patients having residual tumors after insufficient or incomplete resection. EBRT is a technique used for targeting a patient's tumor with high–energy electron beams or X–ray. Typically, linear accelerators generate beams that are targeted to kill cancer cells while sparing normal tissues in the surrounding area. EBRT can also be used to treat complications in patients with terminal cancer or metastasized cancer [29].

4.2.2 Brachytherapy

Brachytherapy is a radiotherapy procedure in which radioactive instruments are placed adjacent to tumors to administer high doses of radiation in a controlled manner for the purpose of removing or shrinking tumors. Brachytherapy works by deploying sources that contain radioactive isotopes, and they emit radiation over a predetermined range.

Brachytherapy is being mainly used for prostate, cervical, and breast cancers. Although it allows the provision of higher doses of radiation, it does not cause significant damage to normal tissues. Brachytherapy can be delivered through multi–catheter interstitial delivery, intracavitary, and intraluminal [30].

4.2.3 Intensity–modulated radiation therapy (IMRT)

IMRT is next–generation, three–dimensional conformal radiation therapy (3DCRT) that is used in the treatment of both cancerous and non–cancerous tumors. IMRT is another kind of radiation therapy that utilizes advanced technology to shape proton beams of radiation and photons to correspond to the tumor shape. IMRT specifically irradiates a tumor by using several proton beams of different intensities or photons. As a result, tumors are more precisely targeted, side effects are minimized, and treatment outcomes are improved [31].

4.3 Side effects of radiation therapy

The most common side effects of radiation therapy start within a few weeks after the initiation of treatment, and they are known as early side effects. People can experience itching, blistering, peeling, soreness, and swelling. These symptoms depend upon the part that is being treated (Table 1).

Part of body being treated	Common side effects
Any part	Hair loss at the treatment site (sometimes permanent), skin irritation at the treatment site, fatigue
Head and neck	Dry mouth, thickened saliva, difficulty swallowing, sore throat, changes in the way food tastes, nausea, mouth sores, tooth decay
Chest	Difficulty swallowing, cough, shortness of breath
Abdomen	Nausea, vomiting, diarrhea
Pelvis	Diarrhea, bladder irritation, frequent urination, sexual dysfunction

Table 1: Common side effects of radiotherapy according to the body part being treated [13].

Other side effects of radiation therapy include fatigue, mouth sores, dry mouth, gum sores, difficulty in swallowing, jaw stiffness, hair loss, nausea, tooth decay, lymphedema, nipple soreness, breast soreness, shortness of breath, stiffness in the shoulder, fever, cough, chest fullness, pneumonitis, lung fibrosis, vomiting, loss of appetite, abdominal cramping, diarrhea or loose stools, bleeding through the rectum, incontinence, irritation of the bladder, erectile dysfunction, sexual problems in men, such as diminished sperm activity and lower sperm counts, menstrual cramps, and symptoms of menopause, such as vaginal itching, dryness, and burning.

Late side effects may take months, if not years, to manifest. They can develop in any healthy tissue in the body that has been exposed to radiation. The probability of long–term side effects is determined by the area administered, as well as the radiation dosage used [32].

5. Chemotherapy and its advances

Chemotherapy is a type of cancer treatment that uses effective chemicals to destroy fast–growing cells while sparing normal cells. Chemotherapy operates by halting or delaying the development of cancer cells, which multiply and differentiate rapidly. It may, however, affect healthy cells that differentiate rapidly, such as those that line the mouth and intestines or cause the hair to grow [33].

Chemotherapy might be used to:

- Cure cancer: when it is used to eliminate cancer cells to the point that they are no longer detectible and they lose their ability to grow back.
- Control cancer: when it prevents cancer from growing, delays its progression, or kills cancer cells that have spread to other areas of the body.
- Ease cancer symptoms (also called palliative care): when it is used to shrink tumors that are causing pain or distress (33).

5.1 Mechanism of action

Chemotherapy drugs attack cells at various stages of the cell cycle. Cancer cells divide more rapidly than normal cells, making them a suitable choice for chemotherapy. Every time chemotherapy is administered, an attempt is made to achieve the correct balance between suppressing cancer cells and sparing normal cells [33].

The positive part is that most normal cells will recover from chemotherapy's associated impacts. Cancer cells, on the other hand, are mutant cells that usually do not recover from the consequences of chemotherapy.

5.2 Types of chemotherapy

5.2.1 Alkylating agents

The first type of chemotherapy to be successfully used in the treatment of cancer was alkylating agents. By disrupting the cell's DNA, alkylating agents prevent cancer cells from reproducing. Previous studies showed a drastic reduction in the tumor and relief of symptoms in lymphoma patients when using an alkylating agent. The chemotherapy performed through alkylating agents is effective at all stages of the cell cycle. They are used to treat a variety of cancers, including sarcomas, lymphoma, multiple myeloma, leukemia, and Hodgkin's disease. Several cancers of the lung, ovary, and breast are also treated with alkylating agents.

Alkylating agents	Antimetabolites	Cytotoxic antibiotics	Anti–microtubule agents	Topoisomerase inhibitors
Altretamine	Azacitidine	Daunorubicin	Taxanes include: Cabazitaxel Docetaxel Nab–paclitaxel Paclitaxel	Topoisomerase I inhibitors (also called camptothecins) include: Irinotecan Irinotecan liposomal Topotecan
Bendamustine	5–fluorouracil (5–FU)	Bleomycin		
Busulfan	6–mercaptopurine (6–MP)	Dactinomycin		
Carboplatin	Capecitabine (Xeloda)	Doxorubicin (Adriamycin)		
Carmustine	Cladribine			
Chlorambucil	Clofarabine	Doxorubicin liposomal	Vinca alkaloids include: Vinblastine Vincristine Vincristine liposomal Vinorelbine	Topoisomerase II inhibitors (also called epipodophyllotoxins) include: Etoposide (VP–16) Mitoxantrone (also acts as an *anti–tumor antibiotic*) Teniposide
Cisplatin	Cytarabine (Ara–C)			
Cyclophosphamide	Decitabine	Epirubicin		
Dacarbazine	Floxuridine			
Ifosfamide	Fludarabine	Idarubicin		
Lomustine	Gemcitabine (Gemzar)	Daunorubicin		
Mechlorethamine	Hydroxyurea	Valrubicin		
Melphalan	Methotrexate	Mitomycin–C		
Oxaliplatin	Nelarabine	Mitoxantrone (also acts as a topoisomerase II inhibitor)		
Temozolomide	Pemetrexed (Alimta)			
Thiotepa	Pentostatin			

Table 2: Examples of different types of chemotherapy [32].

Alkylating agents, on the other hand, have the potential to harm bone marrow by damaging DNA that can lead to acute leukemia. Alkylating agents and some platinum drugs, such as oxaliplatin, cisplatin, and carboplatin, are often grouped because of their common modes of action. These medications have a lower risk of causing post–treatment leukemia [34]. Examples of different types of chemotherapy are included in (Table 2)

5.2.2 Antimetabolites

Antimetabolites belong to the category of cytotoxic agents that have been developed and researched for over 50 years. Antimetabolites are described as substances that interfere with the production of DNA components. They are known as the structural analogs of pyrimidine and purine bases or folate cofactors. These drugs target the S phase of the cell cycle and are used to treat ovarian, intestinal, and breast cancers, leukemia, and pancreatic cancer. The most used antimetabolites for the treatment of cancers are 5–fluorouracil, gemcitabine, platinum, zebularine [35]. These antimetabolites target intracellular enzymes: ribonucleotide reductase, thymidylate synthetase, and DNA polymerases.

5.2.3 Anti–microtubule agents

Anti–microtubule agents or cell cycle inhibitors are plant–derived antimitotic chemicals that inhibit cell proliferation by interfering with the polymerization dynamics of spindles. Microtubules are a critical component of the intracellular cytoskeleton structure, possessing specific polymerization dynamics that are required for a variety of cellular functions, such as cell division. Taxanes and Vinca alkaloids are two distinct classes of anti–microtubule agents that can cause microtubule dysfunction.

These agents are used to treat a variety of cancers, including breast cancer, prostate cancer, myelomas, lymphomas, and leukemias. However, these medications can inflict nerve damage, limiting the amount that can be administered to patients [36].

5.2.4 Topoisomerase inhibitors

These anti–cancer drugs work by interfering with the function of topoisomerases that are typically required for maintaining DNA topology. They are critical for DNA organization and cellular reproduction since they catalyze the cleavage of single– and double–stranded DNA in eukaryotic cells to provide relaxation to condense chromosomes, supercoils, and untangle catenanes.

Topoisomerase inhibitors, such as camptothecin and Irinotecan; ellipticines; teniposide etoposide (VP–16); and amsacrine cause the irreversible breakage of double–stranded DNA, which ultimately leads to apoptosis.

Topoisomerase–inhibitor drugs are used to treat stomach, lung, and ovarian cancers, and leukemia (34).

5.3 Side effects of chemotherapy

Although chemotherapy is a life–savior–treatment approach for cancer, most patients who undergo chemotherapy experience a variety of psychological and physical symptoms that affect their quality of life. These include hair loss, poor appetite, change in taste, vomiting, mouth sores, nausea, pain, fatigue, abdominal cramps, anorexia, constipation, depressed mood, increased satiety, and anxiety. Certain patients may also experience chemotherapy–associated fluid–retention edema, which may result in substantial weight gain during chemotherapy.

All the chemotherapeutic drugs can depress the immune system. These agents decrease the number of red blood cells, platelets, and white blood cells in the body.

Chemotherapy can also result in the development of diseases, such as neutropenic enterocolitis. This condition is also called typhlitis, and it is a life–threatening gastrointestinal condition.

Chemotherapy may also have long–term side effects, including damage to the heart, lungs, muscles, kidneys, or reproductive organs. Some forms of chemotherapy may result in the development of a second cancer years later (33).

5.4 Advances in chemotherapy

5.4.1 Nanoparticles

Nanoparticles are composed of magnetic material, and with the help of an "externally applied magnetic field", these nanoparticles can be used to increase the concentration of drugs or other agents at various tumor sites. These nanoparticles include elements, such as chromium, cobalt, nickel–iron, and other magnetic elements, as well as their chemical compounds (37).

The disadvantage of nanoparticles is that they can be damaged by the body's immune system. For this reason, nanoparticles are being formed at present by red blood cell membranes (37).

5.4.2 Electrochemotherapy

Electrochemotherapy is a combination therapy in which a "chemotherapeutic drug" is injected into the tumor accompanied by the usage of high–voltage electric pulses. Electric fields are applied on local sites to briefly destabilize cell membranes in the presence of a drug, allowing for greater drug uptake into the cytosol. This therapy allows chemotherapeutic drugs, including bleomycin and cisplatin, to infiltrate cancer cells (38).

Conclusion

Cancer is a serious life–threatening disease that affects millions of people around the world. With medical advancements, several cancer cure methods have been identified, including toxic weapons, immunotherapy, precision therapy, gene therapy, hormonal therapy, stem cell transplant, and the nanoparticle drug delivery method. This review explored and illuminated the most common treatment modalities used in the field, which are surgery, radiotherapy, and chemotherapy.

Acknowledgement

The author gratefully acknowledges the Deanship of Scientific Research at King Faisal University, Saudi Arabia, for funding this work (Grant No. AN000157).

Funding and Conflict of Interest

This work was supported by the Deanship of Scientific Research, King Faisal University, Saudi Arabia, under Annual Track (Grant No. AN000157). The author declares no conflict of interest.

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