

A Review on Alternative Therapies Available for Cancer Chemotherapy**Kajal Sonker, Pilli Govindaiah***School of Pharmaceutical sciences, Lovely Professional University, Phagwara, Panjab,
144411*Corresponding Author: Pilli Govindaiah
Assistant Professor, School of Pharmaceutical Sciences
Lovely Professional University
govindaiah.25372@lpu.co.in**1. Introduction:**

Nowadays cancer is one of the serious disease and causing more deaths in humans worldwide. Chemotherapy is the effective therapy used to treat cancer, but cancer cells become resistant towards chemotherapy which leads to produce multidrug resistance (MDR). Due to low bioavailability as well as drug resistance chemotherapy causing many adverse effects. Some alternative therapies were available for the treatment of cancer. These therapies are becoming crucial nowadays in the treatment of cancer without causing side effects.

2. Alternative Therapies for Cancer Chemotherapy

The major alternative therapies of cancer chemotherapy are immunotherapy, stem cell therapy, target therapy, hormonal therapy, radio therapy and surgery. These are the alternative therapies have become useful in the treatment of cancer. Here the side effects which are occurring from the cancer chemotherapy that can be reduced efficiently. Scientists are working on these therapies to produce best results in the cancer treatment with low side effects.

2.1 Immunotherapy

Immunotherapy is the treat given in the cancer which helps to fight with cancer in this type of treatment white blood cells organs and tissues of the lymph system. Immunotherapy is the type of biological therapy as biological therapies the treatment where living organisms are used. Generally immunotherapy can be administered to the patient in different ways such as intravenous intravesical topical, oral.

2.1.1 Mechanism of immunotherapy

Immunotherapy helps to detect and destroy the cancer cells. Immunotherapy most likely resist the growth of cancer. In some cases, immune cells are found around the tumor

cell which are called as tumor infiltrating lymphocytes (TIL). The patients having TIL more likely to better than patients whose cancer do not contain TIL. Although immunotherapy prevents the growth of cancer cells. But cells avoid its destruction by several ways. As cancer cells can have genetic mutations that make them difficult to recognise by the immune cells. Protein on the surface which deactivates the immune cells.

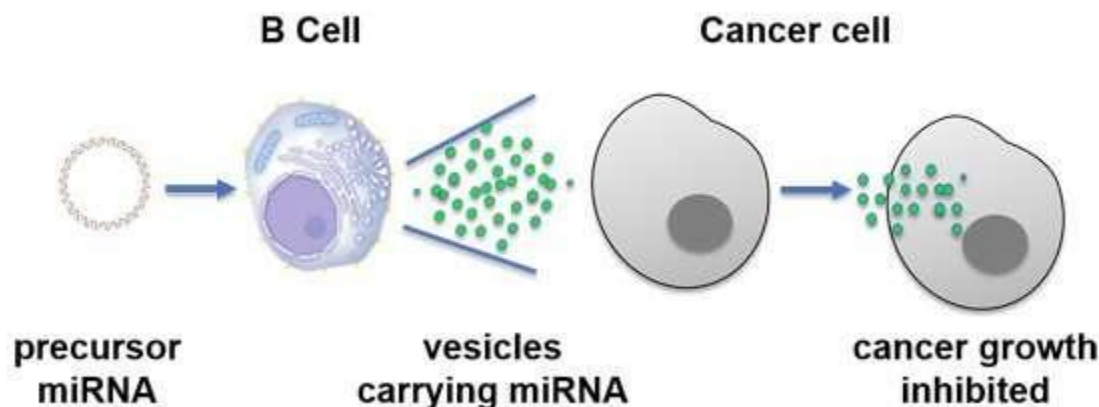


Figure 1: Mechanism of action of immunotherapy

2.1.2 Immune checkpoint inhibitor

Immune checkpoint inhibitor inhibits the immune checkpoint. Immune checkpoints prevent the immune responses to become stronger. These drugs help the immune response act against cancer. T-cell transfer therapy: In this type of therapy, immune cells are taken out of the body. the cells which have high response against cancer are selected and modified in the laboratories to make them more responsive against cancer. Monoclonal antibodies: these are synthesised in the labs which are made in the manner that binds to the specific target. Some antibodies mark cancer cells that they could be the easy target of the immune system. Immune system modulator: these improves the immune response against the cancer cells so that they can destroy the cancer cells [1].

2.1.3 The major advantages of immunotherapy

Some specific cancers like skin cancer cannot be treated well with radiation and chemotherapy but respond well to immunotherapy and able to be treated. Chemotherapy can work better in combination with immunotherapy. Low chances of cancer again as immunotherapy is given immune system memorise to recognise and destroy cells which is called immunotherapy [2].

2.2 Stem cell transplant

Stem cell transplant is used in treatment in which stem cells are restores who have been destructed by the high dose of chemotherapy and radiation used in cancer treatment. Blood forming stem cells are required for a healthy body as stem cells differentiate into blood cells. White blood cells which helps to fight with any type if infection. Red blood cells which carries oxygen. Platelet for blood coagulation [3].

2.2.1 Types of transplant:

There are different types of transplants were available in the market for the treatment of cancer which includes autologous, allogenic, synergenic. Autologous transplant stem cells will be obtained from the patient, allogenic transplant stem cells can be obtained from the donor and in syngeneic transplants the stem cells were obtained from the identical twin.

2.2.2 Mechanism of stem cell transplant

In this blood forming stem cells are given through intravenous route. The time they reach to the blood, they start to go into the bone marrow and start to take place of the older cells which were destructed by the high potency of chemotherapy and radiation. Stem cells do not directly treat the cancer but they enhance the ability to make stem cells after the treatment of high potential of chemotherapy and radiation. Some types of cancer can be treated directly by stem cell transplant like in myeloma and in some type of leukemia works by an effect called graft-versus-tumor occurs by allogenic transplant in which stem cells are taken by the donor. In this stem cells destroy the cancer cells left behind even after chemotherapy or radiotherapy. This improves the result of the treatment [4].

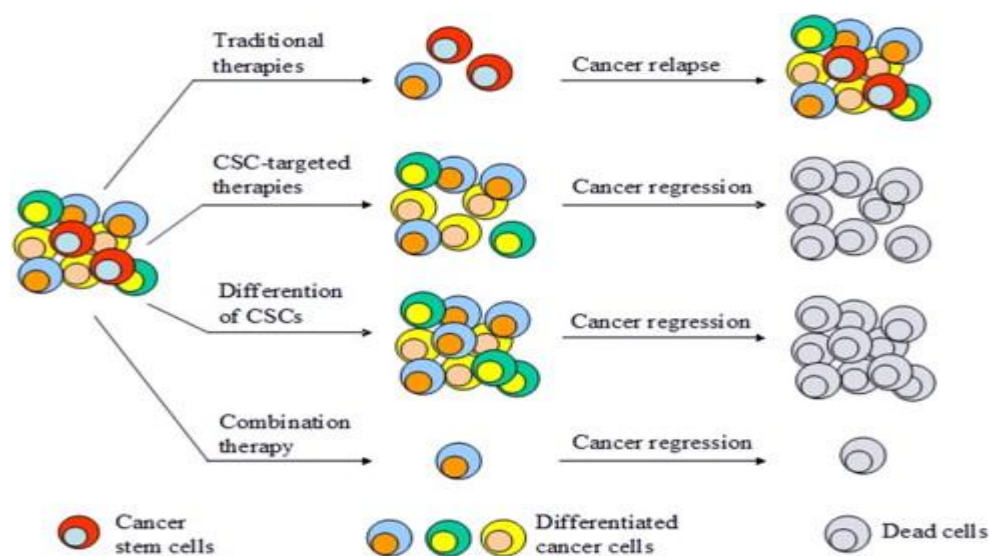


Figure 2: Mechanism involved in the treatment of stem cell therapy

2.2.3 Advantages of stem cell transplant

Used for the patients whose stem cells are damaged. Stem cells transplant found to improve the function and structure of kidney which have damaged from pyelonephritis. Use to treat neuroblastoma [5].

2.3 Target therapy

Targeted drug delivery system works by targeting the proteins, or tissues that contribute to the cancer growth. This therapy is given in the form of drugs but different from the conventional chemotherapy as it targets only the affected area. It is used in combination with chemotherapy to make the chemotherapy specified to the site [6].

2.3.1 Types of Target Therapies

Monoclonal antibodies: Monoclonal antibodies are the drugs which works by targeting the specific site on the surface of cancer cell. These helps radiation therapy and chemotherapy to reach to the cancer cell and shoe their action better. These drugs are usually given through intravenous route [7].

Small molecule drugs: These drugs work by inhibiting the function which multiplies and spread the cancer cells. As cancer cells requires nutrients and take from the blood vessels around them. So, anti-angiogenesis drugs are used which resist the formation of blood vessels and helps to ultimately reduce the proliferation and spread the cancer cells [8].

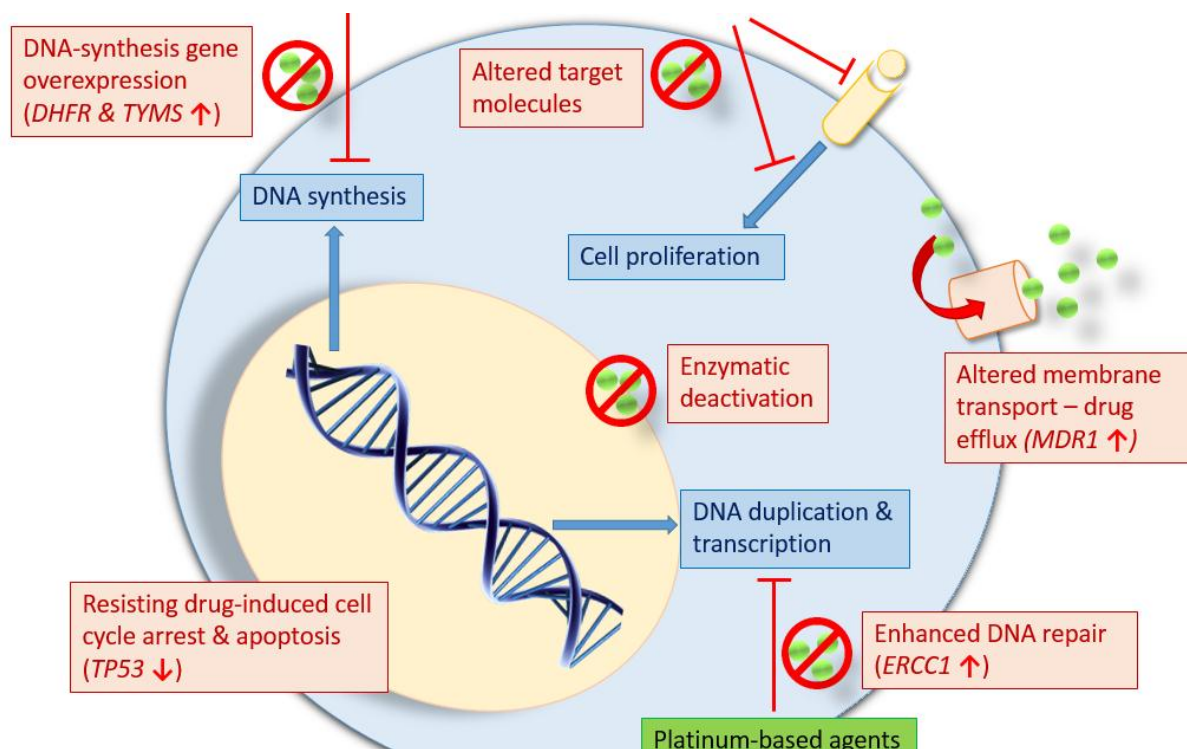


Figure 3: Mechanism involved in the target therapy

2.3.2 Advantages of target therapy

Inhibits the cell growth: Healthy cells divide when they get the signal to divide. The binds to the outside of the protein to divide the cell. But sometime there is a mutation in genes which also alters the protein and by binding the signal (not necessary) and cells start to divide in uncontrolled manner. Target therapy helps in inhibiting the function by interfering in the signal and stops the growth of cancer cells.

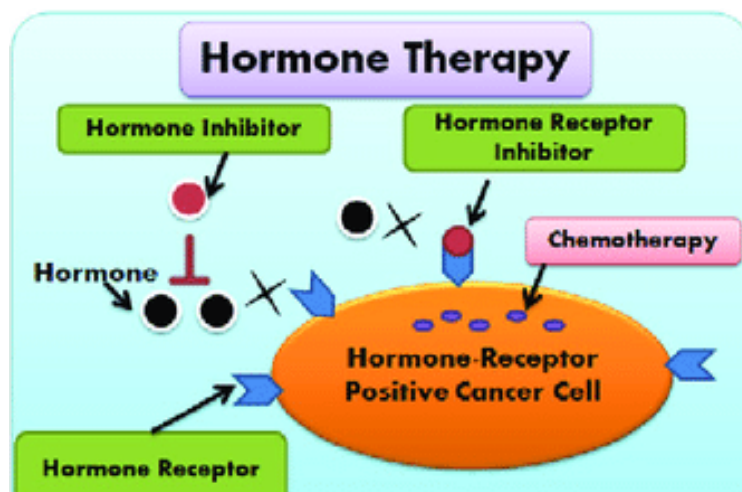
Keep signal from blood vessel formation: cancer cells need formation of blood cells for nutrition which is known as angiogenesis. In target therapy angiogenesis inhibitors are used which interferes in formation of blood vessels and stops the growth of cancer.

Toxic substance sent to cancer cells: The monoclonal antibodies bind with toxic substances in combination with radiation are sent to the targeted cancer cells which cancer cells takes up and get destroyed. The cells which are not targeted do not get any harm.

Helps immune system to recognise cancer cells: In target therapy some markers are put on the cancer cells so the immune cells can recognise them and destroy them. Target therapy also help immune system to boost and show their action better [9].

2.4 Hormone therapy

Hormone therapy is used in cancer is a form of systemic therapy in which the drug passes throughout the body rather than giving to the affected area. Hormone therapy removes or block the hormone in the body which resists the growth of cancer cells as cancer cells needs hormones for their growth. Hormones are chemical found in the body which act as a messenger, found in endocrine gland such as thyroid gland, pancreas, testes and ovaries. In some types of cancer like breast and prostate cancer, cancer cells utilize hormones for their growth and in some cases hormones destroys 1or resists the growth of the cancer cells. Prostrate and breast cancers are found to be fatal in male and female. Anti-hormone therapy is given to abolish the hormone or the effect of certain hormone depending upon the type of the cancer. Although resistance is found in local and metastatic tumor. Glucocorticoids, such as prednisone and methylprednisolone, are commonly used hormonal drugs to treat some cancer. They suppress the lymphatic activity and enhance the chance of success in the treatment of leukaemia’s and lymphomas. These agents are also used in the some estrogen dependent cancers such as breast cancer, endometrial cancer, and metastatic cancer of the prostate These drugs acts on the steroidal receptors and inhibits the secretions of hormones [10,11].



2.4.1 Drugs used in hormone therapy:

The drugs used for the treatment of cancer by hormonal therapy are anastrozoler, letrozole, exemestane and tamoxifen used for treatment of breast cancer. Another drug leuprolide is used for the treatment of breast cancer, prostate cancer and uterine cancer. The drug

abiraterone is used for the treatment of prostate cancer. Hormone therapy is given prior surgery or radio therapy as it reduces the size of tumor and destroys the abnormal cells that have occurred again. This combination therapy is also reducing the chances of recurrence after the final treatment [12]. This hormonal therapy can be administered in three ways such as parenteral, Oral, surgery. The parenteral drugs can be administered through intramuscular route. The oral drugs can be administered orally which are available forms of pills [13].

2.4.2 Advantages of Hormone therapy

This hormonal therapy abolishes the testosterone instantly and successful in producing controlling at prostate and breast cancer. This hormonal therapy majorly used for the treatment of prostate cancer in men those patients are unable to have radiation therapy as well as surgery that patients can be used to treat with hormonal therapy [14].

3.3 Radiation therapy

Radiation therapy is the treatment given in cancer beam of high intensity of energy is used to destroy the cancer cells. In this treatment mostly X-rays are used but proton and other type of energy also can be used. Radiation is also one of the critical modalities for the modern cancer treatment. At high doses, radiation kills the tumor cells or damages the DNA of cells causing the cancer cells to die [15]. Radiation therapy can induce cell death through two different types of mechanisms are direct or indirect mechanisms. In direct mechanism, gamma radiation directly induces DNA damage by excitation of target atom. In indirect mechanism, the gamma radiation produces the free radicals by interacting with the nearby DNA molecules. The photoelectric effect of gamma radiation kills the higher amount of cancer cells [16].

3.3.1 Factors on which radiation therapy depends:

The major factors which are affecting radiation therapy that includes Size of tumor, type of cancer. location of the tumor in the body. distance of the tumor from normal cells that are sensitive to the radiation. age and medical conditions.

External beam radiation therapy: External beam radiation therapy is done via machine which throw the radiation beam on the specific part of the body where the cancer is present.

Types of radiation beam

Photon: Photon beams are used in most of the radiation machines. X rays also contains photon beams. Photon beams do not stop once it reaches to the target when it travels, it scatters its radiations a little. The radiation enters to the normal cells also.

Proton: protons are the particles which have positive charge on it. This beam do not scatters its radiation while passing through these beams stops once they meet to the target. It is seen that proton beams also destructs the normal cells.

Electrons: electrons have negative charge on it. Electrons do not much longer as photon and proton do. So, electrons are used for the cancer which are over the surface and are used less.

Internal radiation therapy: In internal radiation therapy a carrier of radiation is put inside the body of the patient the carrier could be solid or liquid. When solid source is used then internal radiation therapy is called brachytherapy. Ribbons, capsules, seeds are kept near the tumor. This therapy is also specific and treat the affected part.

Types of brachytherapy

Low dose implants: In this radiation carrier or source stays in body for 1-7 days, once the treatment is done the radiation source is removed.

High dose rate implants: In this type the radiation source is kept for 10-20 mins and taken out post to that. Treatment schedule may be twice a day for 2 to 5 days or once a week for 2 to 5 weeks. The schedule depends upon the type of the cancer. During treatment catheter is placed but after finishing the treatment catheter is removed.

Permanent implant: Once the radiation source is kept inside the catheter is removed and the radiation is kept for the whole of the patient. Radiation goes on decreasing day by day but initially radiation is too strong that it can harm the people surrounding. Pregnant women should be away from the patient.

3.3.2 Radiation therapy can treat:

Radiation therapy is majorly used to treat Bradycardia can treat neck, eye, prostate, cervix cancer. External beam radiation therapy treats many types of cancer. Systemic radiation therapy treats thyroid cancer.

3.3.3 Advantages of radiotherapy

The major advantages of radiation therapy include that Have minimal effect on daily life. Radiation Treatment is given in outpatient basis; patient do not need to stay at hospital. Time for the treatment is less than other type of therapy [17].

3.2 Surgery

Surgery is used to remove the tumor and cancer cells completely out of the body.it is most efficacious when the tumor is at a specific place and at the early stage. Surgery could be used for the cancer that has spread from one place to another as site where cancer is started is called primary site and the place where the cancer has spread is called as secondary site. In surgery knives called scalpels are used to cut the part where cancer has happened. Surgery often requires cut through skin muscles or bones sometimes. During surgery while removing the cancer some normal cells around the cancer also removed so as to ensure that the cancer is removed properly this is called surgical margins. The removal of the normal cells depends on the type and location of cancer. Surgeons detect the removal by vision or by microscope to ensure that all cancer affected cells are removed within safety margin [18].

Based on the type of cancer sometimes lymph nodes near to the tumor can be removed. Lymph node are sent to the labs to determine if there are cancer cells in lymph nodes. If there is cancer in lymph nodes there are chances of recurrence [19].

3.2.1 Types of surgery do not include cut with scalpels

Cryosurgery: In this type of treatment liquid nitrogen or argon is used which cause extreme cold and destroys abnormal cells. This surgery is used to treat the cancer at early stage skin cancer, retinoblastoma and precancerous growth on the skin and cervix. Cryosurgery is also known as cryotherapy.

Laser: In this type of treatment a beam of light is thrown on the affected area. Laser light cut through the tissues. Laser light falls on specific area which makes the surgery precise. Laser is useful in shrinking, destroying the tumor or stops the growth of cells that can turn into

cancer. Laser is used to remove the cancer over the skin or in an internal organ which includes vaginal cancer, cervix cancer etc.

Hyperthermia: In this type of treatment high temperature of heat is produced which destroys the abnormal cells. This heat makes the cells sensitive to certain chemotherapy and radiation. Radio frequency is used to remove cancer cells by high energy radio waves which generates heat and responsible for the destruction of the cells.

Photodynamic Therapy: In this type of therapy drugs are given to the patients which respond to some specific lights. When such lights are fallen on the affected area drugs becomes active and destroys the abnormal cells. This therapy is used treat the symptoms caused by skin cancer, mycosis fungoides, and non-small cell lung cancer.

3.2.2 Advantages of surgery

Depending upon the type of the cancer, surgery used to remove the complete tumor, surgery removes the tumor from a specific area.

Debulk of tumor: in some types of cancer surgery cannot remove the complete tumor or when removal of cancer damage other organs. Removing part of tumor can help other therapies to work well. Surgery is used to remove the cancer that causes pain. Most effective in removal of pancreatic cancer. Symptoms such as jaundice, problem with digestion can be improves after surgery [20].

4. Conclusion: Chemotherapy have become resistant towards cancer cells due to its toxicity and low metabolic rates. That's why scientists are searching for alternative therapies for chemotherapy. Here we are reporting different types of alternative therapies to treat cancer. It has been concluded that different alternatives available other than chemotherapy which are efficient in the treatment of cancer as target therapy acts only on specific target and do not harm the other parts and normal cells. Immunotherapy useful for the treatment of cancer those cancer cells are not responding for chemotherapy as well as radiation therapy that cancer cells can be treated by using immunotherapy. Radiation therapy useful for the removal of large tumors. Hormone therapy suppresses the hormone to stop the growth of cancer cells abolishes the hormone instantly mostly used in prostate and breast cancer. Stem cell transplant are found useful which restores the damage cells and found to be most beneficial in treatment of cancer. So here we are summarizing the these all other therapies also treat the cancer effectively than chemotherapy without causing side effects.

References:

1. Couzin-Frankel, Jennifer. "Cancer immunotherapy." (2013): 1432-1433.
2. Rosenberg, Steven A., James C. Yang, and Nicholas P. Restifo. "Cancer immunotherapy: moving beyond current vaccines." *Nature medicine* 10.9 (2004): 909.
3. Centers for Disease Control and Prevention. "Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients." *MMWR. Recommendations and reports: Morbidity and mortality weekly report. Recommendations and reports* 49.RR-10 (2000): 1.
4. Imhof, Alexander, et al. "Breakthrough fungal infections in stem cell transplant recipients receiving voriconazole." *Clinical infectious diseases* 39.5 (2004): 743-746.
5. Giebel, Sebastian, et al. "Survival advantage with KIR ligand incompatibility in hematopoietic stem cell transplantation from unrelated donors." *Blood* 102.3 (2003): 814-819.
6. Santinelli, Alfredo, et al. "HER- 2 status discrepancy between primary breast cancer and metastatic sites. Impact on target therapy." *International journal of cancer* 122.5 (2008): 999-1004.
7. Kennett, Roger H., and Thomas J. MacKearn, eds. *Monoclonal antibodies*. Plenum Press, 1982.
8. Giordano, Silvia, and Alessio Petrelli. "From single-to multi-target drugs in cancer therapy: when aspecificity becomes an advantage." *Current medicinal chemistry* 15.5 (2008): 422-432.
9. Dine, Jennifer, et al. "Immune checkpoint inhibitors: an innovation in immunotherapy for the treatment and management of patients with cancer." *Asia-Pacific journal of oncology nursing* 4.2 (2017): 127.
10. Gupta, A.; Kumar, B. S.; Negi, A. S. Journal of Steroid Biochemistry and Molecular Biology Current Status on Development of Steroids as Anticancer Agents. *Journal of Steroid Biochemistry and Molecular Biology* **2013**, 137, 242–270.

11. Jordan, V. C.; Lewis, J. S.; Osipo, C.; Cheng, D. The Apoptotic Action of Estrogen Following Exhaustive Antihormonal Therapy: A New Clinical Treatment Strategy. *The Breast* **2005**, 14 (6) 624–630.
12. WEST, CLARK D. "Use of combined hormone and mechlorethamine (nitrogen mustard) therapy in lipid nephrosis." *AMA journal of diseases of children* 95.5 (1958): 498-515.
13. Straczek, Céline, et al. "Prothrombotic mutations, hormone therapy, and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration." *Circulation* 112.22 (2005): 3495-3500.
14. Whitmore Jr, Willet F. "Hormone therapy in prostatic cancer." *The American journal of medicine* 21.5 (1956): 697-713.
15. Plgf, T.; Park, I.; Yang, H.; Park, J.; Koh, G. Y.; Choi, E. K. VEGF-Grab Enhances the Efficacy of Radiation Therapy by Blocking VEGF-A And. *Radiation Oncology Biology* **2018**, 102 (3), 609–618.
16. Yan, Di, et al. "Adaptive radiation therapy." *Physics in Medicine & Biology* 42.1 (1997): 123.
17. Dawson, Laura A., and David A. Jaffray. "Advances in image-guided radiation therapy." *Journal of clinical oncology* 25.8 (2007): 938-946.
18. Hüser, Norbert, et al. "Systematic review and meta-analysis of the role of defunctioning stoma in low rectal cancer surgery." *Annals of surgery* 248.1 (2008): 52-60.
19. Lowery, Aoife J., et al. "Locoregional recurrence after breast cancer surgery: a systematic review by receptor phenotype." *Breast cancer research and treatment* 133.3 (2012): 831-841.
20. Lange, Marilyn M., et al. "Level of arterial ligation in rectal cancer surgery: low tie preferred over high tie. A review." *Diseases of the colon & rectum* 51.7 (2008): 1139-1145.