



## Late Side Effects of Radiotherapy

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### Abstract

*The study carried on 40 women with breast cancer treated by radiotherapy at Atomic medical center(Bagdad/Iraq) and Gülhane hospital (Ankara –Turkey) during 2007 . The data was collected by direct interview with the patients whose age range was (48-75) years . The research done after ( 2-11) years of treatment. Mild to severe type of mouth dryness was noticed in almost all the cases with variety of teeth and gum problems.80% of the patients developed diabetes mellitus, 30% of them were with no family history of disease.Edema of the arm (lymphoedema) in the same side of the affected breast occurred in 25% of the patients. Cardiac manifestations recorded in 15% including dyspnea due to congestion and pericardial effusion (diagnosed by Echocardiography) , cardiacmyopathy due to radiotherapy may cause such manifestations . Fibrosis of the lung causing shortness of breath on exertion and liability to chest infection and allergy diagnosed by chest tomography in 10% of the patients. 10% of the patients developed cataract in one eye (in the same side of the tumor).The ionizing radiation which is used in treatment of malignancy may cause cell damage in healthy tissues exposed to it because of its high energy capable to remove electron from the atoms in the biological molecules of the cells leading to their damage and appearance of some clinical problems in the treated patients.Modern sophisticated methods are designed such as radio-immunotherapy, conformal radiotherapy that match the case precisely, using radio-sensitizer drugs and accurate dosing in order to reduce the unwanted clinical effects of radiotherapy and the doctors have to balance the likelihood of cure with the risk of side effects.*

**Keywords:** Cancer, Radiotherapy, lung fibrosis, cardiomyopathy.

## التأثيرات الجانبية المتأخرة للعلاج الإشعاعي

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### المخلص

أجريت الدراسة على 40 امرأة مصابة بسرطان الثدي عولجن بواسطة الاشعة . تم جمع المعلومات في مستشفى الطب الذري ( بغدا - العراق) ومستشفى كولمانا في (انقرة - تركيا) سنة 2007 ، عن طريق المحاورة المباشرة معهن واللاتي تتراوح أعمارهن بين 48-75 سنة وقد تم تسجيل نتائج الفحوصات والتحليل التي أجريت لهن للمتابعة. اجري البحث بعد 2-11 سنة من العلاج الإشعاعي. لوحظ وجود حالة جفاف الفم في كل الحالات تقريباً بدرجات متفاوتة مع حالات مختلفة من مشاكل اللثة والاسنان. ظهرت أعراض وعلامات داء السكر في 80% من الحالات ، 30% منهن ليس لديهن تاريخ عائلي للمرض. وذمة الذراع ( نتيجة تجمع السائل اللمفي) في نفس جهة الاصابة ظهرت في 25% من المرضى.

سجلت حالات وظواهر متعلقة بالقلب في 15% منها ضيق التنفس الناتج عن الاحتقان وتجمع السائل حول القلب ( تم تشخيصه بواسطة فحص القلب بالامواج فوق الصوتية وأشعة الصدر)، تأثر العضلة القلبية بالاشعة العلاجية بامكانه احداث هذه الظواهر. تليف الرئة وتسببه في الاصابة بضيق في التنفس اثناء الاجهاد والعدوى الجرثومية وزيادة التحسس للجسميات الغريبة ، تم تشخيصه بواسطة المفراس في 10% من الحالات . 10% من المرضى أصبن بتعمم عدسة العين في نفس جهة الاصابة بالمرض. ان الاشعة المتأينة التي تستخدم في علاج الاورام السرطانية قد تؤدي الى تأثر الخلايا في الانسجة الطبيعية نتيجة تعرضها لها لكونها تمتلك طاقة عالية تستطيع ازالة الالكترونات من الذرات الموجودة في الجزيئات الحية للخلايا مما تسبب في اتلافها وظهور مشاكل وحالات سريرية في المرضى المعالجين بها. الطرق والتقنيات الطبية الحديثة في اعطاء العلاج الإشعاعي مثل العلاج الإشعاعي المناعي والاشعة الانتقائية التي تخص منطقة الورم دون غيرها واستخدام الادوية المحسنة للاشعة وتحديد الجرعات بشكل دقيق واستخدام طريقة الابعاد الثلاثية في التقنيات الحديثة خففت من التأثيرات الغير المرغوب فيها لهذا النوع من العلاج وعلى الطبيب أن يوازن بين الهدف الرئيسي وهو علاج الورم ومخاطر الاضرار الجانبية.

كلمات دالة: السرطان ، العلاج الإشعاعي، تليف الرئة ،تأثر العضلة القلبية.



## 1. INTRODUCTION

Radiotherapy is the use of a certain type of energy (called ionizing radiation) to kill cancer cells and shrink tumors. Radiation therapy injures or destroys cells in the area being treated (the target tissue) by damaging their genetic material, making it impossible for these cells to continue to grow and divide. Although radiation damages both cancer cells and normal cells, most normal cells can recover from the effects of radiation and function properly. The goal of radiation therapy is to damage as many cancer cells as possible while limiting harm to nearby healthy tissues [1]. Radiation is energy that moves through space or matter at a very high speed. This energy can be in the form of particles, such as alpha or beta particles, which are emitted from radiation materials, or waves such as light, heat, radio-waves, microwaves, x-ray and gamma rays. Radioactive materials, also known as radionuclide or radioisotopes, are atoms that are unstable in nature, there is a tendency for unstable atoms to change into a stable form, as they form, they release radiation [2]. Ionizing radiation is the energetic particles or waves that have the potential to ionize an atom or molecule through atomic interactions. It is a function of the energy of the individual particles or waves present, and not a function of the number of particles or waves present. A large flood of particles or waves will not cause ionization if the individual particles or waves are not energetic enough. This ionization if enough can be destructive to biological organisms, and can cause DNA damage in individual cells. Ionizing radiation are energetic Beta particles, alpha particles which are emitted from radioactive materials or waves (photons) e.g., x-ray and gamma ray. [3].

About half of all cancer patients receive some type of radiotherapy; R.T may be used alone or in combination with other cancer treatment, such as surgery and or chemotherapy. R.T may be used to treat almost every type of solid tumors including the brain, breast, cervix, larynx, lung, pancreas, prostate, skin, spine, stomach, uterus or soft tissue sarcoma. Radiation can also be used to treat leukemia and lymphoma.

Radiation dose to each site depends on a number of factors, including the type of cancer and whether there are tissues and organs nearby that may be damaged by radiation. For some types of cancer,



radiation may be given to areas that do not have evidence of cancer this is done to prevent cancer cells from growing in the area receiving the radiation. This technique is called prophylactic radiation therapy. Radiation therapy also can be given to reduce symptoms such as pain from cancer that has spread to the bones or other parts of the body. This is called palliative radiation therapy [1]. R.T may be the only treatment used to cure the cancer; this is known as radical R.T. It may be used to reduce the size of the tumor before surgery, this is called neo adjuvant treatment and it is used after surgery also to make sure that all the cancer cells are destroyed. There are two types of R.T: -

1-External R.T is where a machine is used to give a dose of energy, such as X - rays to attack the cancer cells.

2- Internal R.T is where the source of radioactivity is put inside the body so it can get closer to the cancer. This can be done in two ways: -

A- Brachytherapy: - This is when a solid source of radioactivity is put next to a tumor to give a high dose of R.T. This means the effect on body tissue around the cancer is as little as possible. Brachytherapy can be used to treat the cancers of the cervix, head and neck, uterus, prostatic gland, and skin. A minor operation is needed to put the source of R.T and the patient needs to stay in the hospital for a few days while it is in the place .When the treatment is over the radioactive source will be removed and the patient will be able to go home .

B- Radioisotope therapy: this is when a radioactive liquid (usually radioactive iodine) is given either as an injection in to a vein or as liquid to be drunk. Radioisotopes treatment can be used for thyroid, adrenal and bone cancers. [4].

Intra operative R.T (I O R T) is a form of external radiation that is given during surgery. (I O R T) is used to treat localized cancers that cannot be completely removed or that have a high risk of recurring in nearby tissues. After almost of the cancer is removed, one large, high energy dose of radiation is aimed directly at the tumor site during surgery (nearby healthy tissues are protected with special shields) I O R T may be used in treatment of thyroid, colorectal, gynecological, small intestine, and cancer of the pancreas . It is also being studied in clinical trials (research studies) to treat some types of brain tumors and pelvic sarcomas in adults.



Prophylactic cranial irradiation (P C I) is external radiation given to the brain when the primary cancer (for example small cell lung cancer) has a high risk of spreading to the brain. [1].

**Duration of treatment:** - The length of radiotherapy treatment varies. It depends on the type of cancer, if it has spread to other areas of the body, the type of R.T used, the patient's side effects and how successful the treatment is. A course of R.T can last up to eight weeks but usually it will be shorter than this. After the course of treatment, follow up will be done for the patient by oncologist to check the recovery from side effect, response to treatment and any long-term side effects that the patient might expect to have after treatment. A course of radiotherapy is usually given over a number of days or weeks. Each treatment is known as a " fraction". Fractions are usually given once a day from Monday to Friday with interval at the weekend to help normal cells recover. Healthy cells that are damaged can often be replaced. This depends on the type of cell and the dose of radiotherapy. But if cells cannot be replaced side effects can sometimes be permanent. [5] .

**Dosage of R.T:-** The dose of the R.T depends on the type and stage of cancer, in x-ray and gamma (high energy photons) the dose is usually measured in roentgens, What are the risks, gray or sieverts . The roentgen (R or rad) is the amount of x or gamma ionizing radiation in the air. The gray (GY) is the amount of energy absorbed by a substance or tissue. The roentgen and the centigray (1/100 of a gray abbreviation(CG) are essentially equivalent. The sievert (sv) equals the gray adjusted by a quality factor for the biologic effect. For x and gamma radiation the sv equals GY.

$$1 \text{ GY}=100\text{rad}$$

$$1 \text{ SV}=100\text{rem}$$

$$1 \text{ centigray(cGy)}=1 \text{ rad} . [6]$$

If a patient is to receive 3500 cGy it means 35 gray or 3500 rads.

**Side effects:-** There are unwanted effects of a successful treatment depending on which part of the body is being treated, possible side effects immediately after R.T include:- tiredness, loss of appetite, feeling sick, vomiting, diarrhea, skin may become red itchy, and sometimes burns. Coughing and shortness of breath may occur. Dry mouth causing difficulty in swallowing, losing weight, hair loss usually temporary but it can be permanent only happens in the area of the body being treated.



Emotional symptoms, feeling depressed or anxious after treatment may occur. Stiffness of joints and muscles sometimes happens. [4].

R.T can also cause some long term side effects such as tiredness, scarring of the skin in the area that has been treated this called fibrosis, other tissues can also become scarred and less stretchy because of fibrosis (e.g. the bladder may hold less urine and lung that affect breathing), darkening of the skin, hair may grow back in a different texture and color, hair loss is sometimes permanent, red marks on the skin which are result from broken blood vessels, swelling of the arms and legs due to the blockage of lymph vessels (this is called lymph edema ) shortness of breath on exertion due to lung fibrosis and other long term effects on the organs may result from R.T. [7].

R.T can affect salivary glands so less saliva is produced the, glands may recover over time but for some people the dry mouth may be permanent specially during talking for a time. Any gland in the body may be affected, its function disturbed or lost and this may be the reason for unwanted clinical effects which appear after R.T. [8] .

#### **The aims of study: -**

In our study we attempt to find and record the most serious clinical complications or side effects of R.T which occur later after treatment, in order to balance the likelihood of cure with the risks of side effects. In this research we try to reach to the possible measurements used recently in the centers of cancer treatment to reduce the risks of R.T.[8].

## **2. PATIENTS AND METHODS**

The study carried on 40 patients with breast cancer who were treated by R.T, after undergoing radical surgery (Radical Mastectomy).The data was collected by direct interview with the patients. From each patient full medical history was taken and their most important investigations were recorded which were done for follow up (2-11 years) after treatment with R.T. , we concentrated on the followings :-



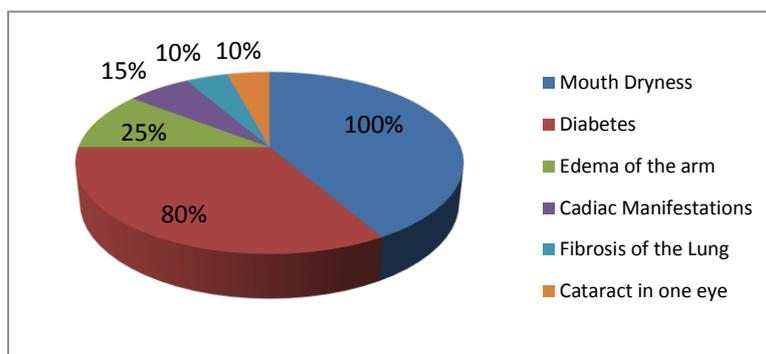
- 1 Chest X- ray.
- 2 E.C.G.
- 3 F.B.S.
- 4 C.T scans.
- 5 Echocardiography.

Thorough physical examination done for the patients and the reports from specialists, their opinions and managements are recorded.

A special form used in collecting the data, during the period 2004-2008, which included, name, age, duration of the disease, the breast affected, the date of treatment with R.T, the clinical complications occurred, the time of appearance of complications(how many years after receiving R.T) and the patients complaints.

### **3. RESULTS**

- 1) The age range was (48-75) years; the patients were treated by R.T (2-11) years before.
- 2) Mild to severe type of mouth dryness was noticed in almost all the cases with variety of teeth and gum problems.
- 3) 80% of the cases developed diabetes mellitus, 30% of them were with no family History of the disease.
- 4) Edema of the arm (lymph edema) in the same side of the affected breast occurred in 25% of the patients.
- 5) Cardiac manifestations recorded in 15% including dyspnea due to congestion and pericardial effusion.
- 6) Fibrosis of the lung causing shortness of breath on exertion and liability to chest problems including infection and allergy diagnosed by chest tomography in 10% of the patients.
- 7) 10% of the women developed cataract in one eye (in the same side of the tumor).



**Fig.1:** The percentages of late side effects of radiotherapy in this study.

#### 4. DISCUSSION

Most patients with cancer are treated with R.T, either alone or in combination with other types of treatment such as surgery and chemotherapy. The ionizing radiation which is used in the treatment of the tumors may cause cell damage in healthy tissue exposed to it because of its high energy capable to remove electron from the atoms in the biological molecules of the cells leading to their damage and appearance of some clinical problems in the treated patient[1].

Mild to severe type of mouth dryness with variety of teeth and gum problems was noticed in almost all the cases. The ionizing radiation may damage the secretory cells and tissues of the salivary glands and affect their function. Patients with mild mouth dryness complain of the condition during talking for a long period of time but in case of severe mouth dryness the patient complains of the condition in case of talking for a short time or even with out talking. Radiation therapy which kills cancer cells may also damage healthy cells such as those in the soft tissues of the mouth and glands e.g. those which make and secrete saliva which moist the lining of the mouth so it will predispose to dry mouth , inflammation and infection of the gum and problems in the teeth , also poor immunological status of the patient may cause such problems . [3,9, 10]

Diabetes mellitus (high level of blood sugar) noticed in 80% of the patients. Radio therapy may affect the cells of the pancreas and cause decrease insulin secretion leading to D.M. Although the age range of the women (48-51 years) who developed the disease suggest that there may be no relation



between the R.T they received and their condition and the stress about the disease may precipitate diabetes mellitus in patients with family history of the disease, but 30% of the patient were with no family history of D.M and 5% of them got improvement by time i.e. some cells may return their function and this improves the possibility of cell damage temporarily or permanently due to effect of R.T on pancreatic tissues and this depends on the amount of the exposure of the tissues to the radiation during treatment.

The children who were treated with R.T for leukemia or lymphoma developed juvenile diabetes mellitus whose families were free of the disease and this confirm the idea of cell damaging of the glands by the effect of radiation therapy. [10] Edema of the arm (lymph edema) in the same side of the diseased breast occurred in 25% of the patients and this is mostly due to the blockage of lymphatic vessels (drainage channels) which drain the lymph from the affected arm. Radical surgery and removing lymph nodes and tissues may aggravate the degree of the edema and increase the possibility of the occurrence of the condition. [4, 8] Cardiac manifestations recorded in 15% of the cases, including dyspnea due to congestion and pericardial effusion. Cardiomyopathy due to R.T may cause such manifestations. Although these problems can occur also because of other causes such as diabetes mellitus, inflammations of heart muscles and other cardiac diseases specially in older age groups. [11, 12, 13]

Fibrosis of the lung causing shortness of breath on exertion and liability to chest problems including infection and allergy diagnosed by chest tomography in 10 % of the patients the lung tissue is very sensitive to radiation. Lung fibrosis and fibrosis of other tissues of the body which occurs as late effects of the radio therapy results from local endarteritis which produces ischemia and proliferative fibrosis which is similar to inflammation, wound healing and fibrosis of any origin. [6, 11]

Cataract of the eye (in the same side of the tumor) occurred in 10% of the patients. Radiation of any origin even direct looking to the sun may cause clouding of the lens and blurred vision. Cataracts may also occur due to aging processes but mainly in older persons. [13, 14, 2]



When we balance the benefit of the R.T with the mentioned unwanted clinical effects our opinion will be as follow: the cure from cancer is the most important aim of the doctors and researchers, so they are working hard to do that in one hand and trying to minimize the unwanted side effects of any procedure used for that in the other.

There are many measurements used nowadays to improve the technique of R.T and reduce its risks and side effects or introduce other treatment technique for cancers such as immunotherapy. Radio sensitizers and radio protectors are chemicals that modify a cells response to radiation. Radio sensitizers are drugs that make cancer cells more sensitive to effects of the radiotherapy. Several compounds are under study as radio sensitizers. In addition anti cancer drugs, such as 5-flurouracil and cisplatin, make cancer cells more sensitive to radiotherapy. Radio protectors (also called radio protectant are drugs that protect normal (non cancerous) cells from the damage caused by radiation therapy. These agents promote the repair of normal cells that are exposed to radiation. Amifostine (trade name Ethyol R) is the only drug approved by the U.S Food and Drug Administration (PDA.) as radio protectors, it helps to reduce the dry mouth that can occur if parotid glands(which to produce saliva and located near the ear). Additional studies are under way to determine whether amifastine is effective when used with radio therapy to treat other types of cancer. Other compounds are under study as radio protectors. Researchers are also studying the use of radio labeled antibodies to deliver doses of radiation directly to the cancer site (radio immunotherapy) . Hyperthermia, the use of heat, is also being studied for its effectiveness in sensitizing diseased tissue to radiotherapy. [1, 10]

Doctors are trying to improve cancer treatment all the time. They are now trying to shape radiotherapy beams to fit the cancer more precisely this is called (conformal radiotherapy or intensity modulated radiotherapy). Conformal R. T is used for several different types of cancer. It means that less normal tissues will be in R.T treatment area so the risk is lower.

A number of refinements and techniques are in use or under study to improve the effectiveness of external radiation therapy.



**Three - dimensional (3-D) conformal radiation therapy.** Traditionally, the planning of radiation treatment has been done in tow dimensions (with and height). Three- dimensional (3-DO conformal radiation therapy uses computer technology to allow doctors to more precisely target a tumor with radiation beams (using width, height, and depth). Three-dimensional (3-D) conformal radiation therapy uses computer technology to allow doctors to more precisely target a tumor with radiation beams (using width, height and depth). [1, 2, 10].

## 5. CONCLUSION

1. Radiotherapy which is used in treatment of cancer may cause damage to the healthy tissues also because of its high energy, precipitating many unwanted late clinical effects.
2. The clinical manifestations recorded during the study were , dryness of the mouth (the result of effect of R.T on the tissues of salivary glands ) , lymph edema of the arm , dyspnea due to cardiomyopathy and pericardial effusion , shortness of breath on exertion because of lung fibrosis , hyperglycemia ( effect of R.T on pancreatic tissues ) and cataract.
3. There are many measurements used recently in the centers of cancer treatment to reduce the risks of radio therapy .

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