Abstract

Radiation therapy is therapy using ionizing radiation, generally as part of cancer treatment to control or kill malignant cells. Radiation therapy may be curative in a number of types of cancer if they are localized to one area of the body. It may also be used as part of adjuvant therapy, to prevent tumor recurrence after surgery to remove a primary malignant tumor (for example, early stages of breast cancer) and as synergistic with chemotherapy.

Most side effects from radiation are predictable and expected, they are divided into acute and late effects. They are usually limited to the area of the patient's body that is under treatment and are dose- dependent. Modern radiation therapy aims to reduce side effects to a minimum and to help the patient understand and deal with side effects that are unavoidable. The term radiation injury refers to the morphological and functional changes that occur in non-cancerous tissue as a direct result of ionizing radiation.

Radiation therapy causes significant side effects on skin. Pigmentary changes, erythema and epilation being the most common. Moist desquamation, Oral mucositis, xerosis and scalp alopecia are seen less often. Xerostomia, dry desquamation and ulceration are seen with further lower frequency. Atrophic changes like atrophy, fibrosis and telangiectasia are seen occasionally. Radiation-damaged tissue may cause serious wound-healing problems, either immediately or up to decades following radiotherapy treatment. Delayed Radiation ulcers are more common than acute ulcers; they heal slowly and may persist for several years. Some research has been carried out trying to minimize the effects of radiation on tissues to allow for normal healing.

Patients with radiation-induced ulcers are initially treated with narcotic analgesic agents, antibiotics, debridement, and local care. However, these conservative therapies are ineffective in most patients. The most crucial procedure is the complete resection of the radiation-affected area, followed by coverage with well-vascularized tissue. Many novel interventions are being investigated in animal models and in humans, e.g: Special dressings, injection of stem cells, topical administration of active substances and the use of growth factors and this is an exciting field of research that could have major benefits for the treatment of such wounds in the future.

Keywords: Management of Post Radiation Skin Ulcers

INTRODUCTION

Radiotherapy is the use of high energy ionizing electromagnetic or particular radiation to treat cancer ***(Khan, 2003)***. It makes a significant contribution to not only relief of physical symptoms, but also to improved psychological, emotional and spiritual wellbeing ***(Warnock and Lee, 2014)***.

Wound healing occurs in an ordered sequence of cellular interactions in the form of three phases: Hemostasis & inflammation (phase 1, day 0 to 4), are followed by proliferation (phase 2, day 3 to week 3) & maturation (phase 3, week 3 to 2 years) ***(Scheithauer and Riechelmann, 2003)***. Repetitive radiation injury disrupts this highly organized sequence of events, resulting in repetitive inflammatory responses and ongoing cellular regeneration ***(Dormand et al., 2005)***.

Complications after radiation therapy occur in up to 60 percent of surgical patients. Clinical sequelae include skin atrophy, soft tissue, fibrosis, desquamation, epithelial ulceration, fistula formation and major vessels rapture ***(Tang et al., 2011)***.

Radiation effects on normal tissue are divided into acute and chronic (late) effects. This depend on the radio sensitivity of the body sites being treated, the volume of the normal tissue irradiated, the total dose and the rate of dose accumulation ***(Stone et al., 2003)***. Acute effects can be quite uncomfortable

but they generally resolve, the chronic effects can be devastating, permanent and progressive ***(Schreiber, 2015)***.

Conservative treatment such as long-term dressing ***(Hom et al., 1999)***, topical negative pressure dressings ***(Banwell and Teot, 2003)***, hyperbaric oxygen and antibiotic treatment are first in line of consideration ***(Schimp et al., 2004).*** Also there are new therapeutic approaches to treat radiogenic ulcers includes: Special dressing, injection of multipotent cells, topical administration of active substances and the use of growth factors ***(Haubner et al., 2012).***

Surgical treatment is required for resistant non healing radiation ulcers, within the simplest, we can mention direct re-approximation of the wound edge, skin grafts and flaps coverage. Musculocutaneous or vascularized free flap coverage has shown a number of advantages: they allow more motion in kinetic areas, cover laid open structures (large vessels, nerves, tendons, bones, pleura, etc.) and provide a cover through which future reconstructive surgeries can be performed ***(Olascoaga et al., 2008).***

Aim of the Work

Is to review different modalities of management of post radiation skin ulcers.

RADIOTHERAPY WITH ITS ACUTE & CHRONIC (LATE) EFFECTS

History of radiation therapy

The history of radiation therapy or radiotherapy can be traced back to experiments made soon after the discovery of x-rays (1895), when it was shown that exposure to radiation produced cutaneous burns. Influenced by electrotherapy and escharotics — the medical application of caustic substances — doctors began using radiation to treat growths and lesions produced by diseases such as lupus, rodent ulcer, and epithelioma ***(Pusey, 1900)***. Radiation was generally believed to have bactericidal properties, so when radium was discovered, in addition to treatments similar to those used with x-rays, it was also used as an additive to medical treatments for diseases such as tuberculosis where there were resistant bacilli ***(Kassabian, 1907)***.

Additionally, because radiation was found to exist in hot spring waters which were reputed for their curative powers, it was marketed as a wonder cure for all sorts of ailments in patent medicine and quack cures. It was believed by medical science that small doses of radiation would cause no harm and the harmful effects of large doses were temporary ***(Singer and Heinrich, 1914)***.

The widespread use of radium in medicine ended when it was discovered that physical tolerance was lower than expected and exposure caused long term cell damage that could appear in carcinoma up to 40 years after treatment. The use of radiation continues today as a treatment for cancer in radiation therapy ***(Tange, 2014)***.

Radiotherapy has been utilized for over 100 years ***(del Regato, 1996).*** It is used to cure certain cancers, such as cancer of the retina, central nervous system, skin, oropharynx and larynx, oesophagus, cervix, vagina, prostate and lymphoma. Radiotherapy is also used as an adjuvant treatment, in addition to surgical resection (and chemotherapy, when appropriate) for cancers of the lung, breast, uterus, bladder, rectum, testis (seminoma) and soft tissues (sarcoma). In some patients, radiotherapy has a palliative role for pain relief and preservation of the skeleton following bone metastases, reduction of headaches and vomiting caused by raised intracranial pressure due to CNS metastases and for relief of obstruction due to compression of the bronchus, oesophagus, ureter or lymphatics ***(Ferris et al., 2001)***.

The response of a cancer to radiation is described by its radio-sensitivity. Highly radiosensitive cancer cells are rapidly killed by modest doses of radiation. These include leukemias, most lymphomas and germ cell tumors. The majority of epithelial cancers are only moderately radiosensitive, and require a significantly higher dose of radiation (60-70 Gy) to

achieve a radical cure. Some types of cancer are notably radio-resistant, that is, much higher doses are required to produce a radical cure than may be safe in clinical practice. Renal cell cancer and melanoma are generally considered to be radio-resistant but radiation therapy is still a palliative option for many patients with metastatic melanoma. Combining radiation therapy with immunotherapy is an active area of investigation and has shown some promise for melanoma and other cancers ***(Maverakis et al., 2015)***.

Table (1): Examples of cancers treated with radiation therapy ***(Baskar et al., 2012).***

Early cancers curable with radiation therapy alone	Cancers curable with radiation therapy in combination with other modalities
Skin cancers (Squamous and Basel cell)	Breast carcinomas
Prostate carcinomas	Rectal and anal carcinomas
Lung carcinomas (non-small cell)	Local advanced cervix carcinomas
Cervix carcinomas	Locally advanced head and neck carcinomas
Lymphomas (Hodgkin's and low grade Non-Hodgkin's)	Locally advanced lung carcinomas
Head and neck carcinomas	Advanced lymphomas
	Bladder carcinomas
	Endometrial carcinomas
	CNS tumors
	Soft tissue sarcomas
	Pediatric tumors

Before treatment, a CT scan is often performed to identify the tumor and surrounding normal structures. The patient receives small skin marks to guide the placement of treatment fields. Patient positioning is crucial at this stage as the patient will have to be set-up in the identical position during treatment. Many patient positioning devices have been developed for this purpose, including masks and cushions which can be molded to the patient ***(Camphausen, 2008)***.

The response of a tumor to radiation therapy is also related to its size. Due to complex radiobiology, very large tumors respond less well to radiation than smaller tumors or microscopic disease. Various strategies are used to overcome this effect. The most common technique is surgical resection prior to radiation therapy. This is most commonly seen in the treatment of breast cancer with wide local excision or mastectomy followed by adjuvant radiation therapy. Another method is to shrink the tumor with neoadjuvant chemotherapy prior to radical radiation therapy. A third technique is to enhance the radio-sensitivity of the cancer by giving certain drugs during a course of radiation therapy. Examples of radio-sensitizing drugs include: Cisplatin, Nimorazole, and Cetuximab ***(Messersmith and Ahnen, 2008).***

The effect of radiotherapy on control of cancer has been shown to be limited to the first five years after surgery, particularly for breast cancer. The difference between breast cancer recurrence in patients who receive radiotherapy vs. those

who don't is seen mostly in the first 2–3 years and no difference is seen after 5 years ***(Wickberg et al., 2014)***.

Radiotherapy is the use of high energy ionizing electromagnetic or particulate radiation to treat cancer ***(Khan, 2003).*** Ionizing radiation (IR) is used to treat _60% of cancer patients ***(Rubin et al., 1998)***. Although most patients tolerate treatment, 5–10% of patients suffer significant toxicity. Risk factors include age, concurrent chemotherapy, and anatomical variations from factors such as congenital malformations, postsurgical adhesions, fat content, and tissue oxygenation, ***(Rubin et al., 1998)*** or concurrent illnesses such as diabetes and autoimmune diseases such as lupus ***(Chon et al., 2002)***. These factors account for an unknown fraction of adverse radiation reactions. In rare cases, radiation sensitivity can be attributed to specific genetic mutations. Diseases of IR sensitivity include ataxia telangiectasia (AT) ***(Savitsky et al., 1995),*** AT-like disorder ***(Stewart et al., 1999),*** Nijmegen breakage syndrome ***(Varon et al., 1998)***, and radiosensitivity with severe combined immunodeficiency ***(Moshous et al., 2001),*** but these autosomal recessive diseases are uncommon. Heterozygosity for mutations in ATM, the gene mutated in AT, may occur in 1% of individuals and has been reported to confer moderate sensitivity to IR in tissue culture ***(West et al., 1995)***. However, relatively few adverse radiation reactions are associated with ATM mutations ***(Oppitz et al., 1999***).

Electromagnetic ionizing radiation includes artificially produced X-rays and naturally produced γ-rays, emitted as a result of disintegration of unstable atoms. Particulate radiation comprises subatomic particles such as α particles (helium nuclei), β particles (electrons) and neutrons. As radiation penetrates tissue, it physically interacts with electrons, either ejecting them from atoms (ionization) or exciting them to higher energy levels ***(McMillan et al., 2002)***. These electrons may ionize or excite other atoms, resulting in a cascade of ionization events. The most important effect of ionization and excitation is damage to DNA, resulting in either single strand breaks, cross-linking or double strand breaks which may be lethal to the cell when it tries to divide and cause apoptotic cell death ***(McMillan et al., 2002)***. Damage to DNA is repaired by enzymes, with either correction of the damage or fixation of the damage resulting in mutations which can lead to cell dysfunction, inability to proliferate or later carcinogenesis ***(McMillan et al., 2002).***

It has been postulated that differing patient susceptibility to radiation damage may be partly due to differences in their DNA repair mechanisms. Mutations affecting DNA-repairing enzymes lead to increased radio-sensitivity, for example, in patients with ataxia telangiectasia and Nijmegen breakage syndrome ***(McMillan et al., 2002)***. Ionizing radiation also leads to the generation of short-lived free radicals and cytotoxic peroxides which damage DNA, proteins and membranes. Cells are able to

scavenge and neutralize free-radical-induced reactive molecules; however, these mechanisms are likely to be saturated in the event of radiation injury ***(McMillan et al., 2002)***.

DNA damage due to radiotherapy (Figure1-1)

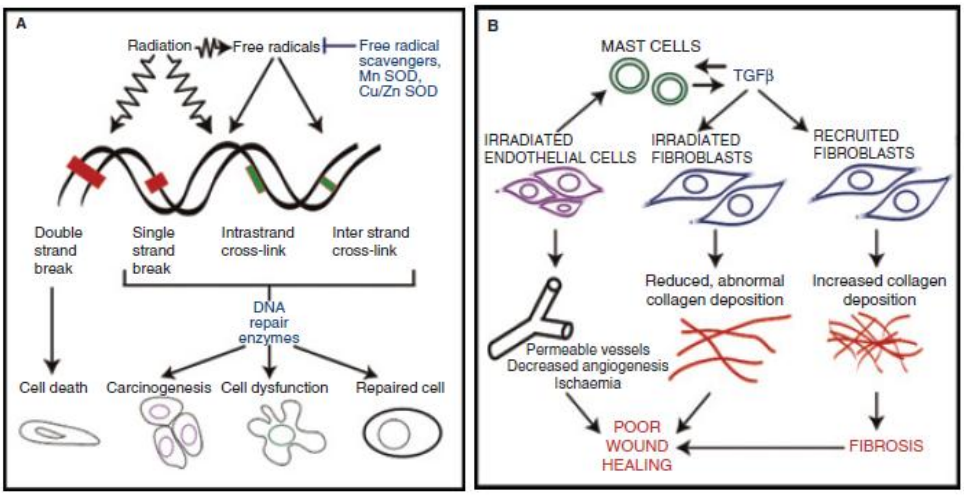

Figure (1): DNA damage due to radiotherapy. Radiation induces single and double stranded DNA breaks and DNA strand cross-linking. The cell may repair the damaged DNA or die by apoptosis ***(Dormand et al., 2005).***

Early radiotherapy involved huge radiation doses and was accompanied by severe radiation sickness, radio-epidermitis and other side effects. Fractionated radiotherapy was found to result in better tumor control with fewer side effects, allowing healthy tissue to recover between doses of radiation ***(Dormand et al., 2005)***.

Fractionation allows normal cells time to recover, while tumor cells are generally less efficient in repair between fractions. Fractionation also allows tumor cells that were in a

relatively radio-resistant phase of the cell cycle during one treatment to cycle into a sensitive phase of the cycle before the next fraction is given. Similarly, tumor cells that were chronically or acutely hypoxic (and therefore more radio-resistant) may re-oxygenate between fractions, improving the tumor cell kill ***(Smirnov, 2012)***.

Conventional fractionation is considered to be 1.82 Gy/day, administered 5 days each week for 5-7 weeks, depending on the particular clinical situation. Alteration to this scheme have been considered for various reasons, including time constraints, staff constraints, machine availability, and patient convenience ***(Schreiber, 2015)***.

There are two ways to deliver radiation to the location of the cancer. External beam radiation is delivered from outside the body by aiming high-energy rays (photons, protons or particle radiation) to the location of the tumor. This is the most common approach in the clinical setting. Internal radiation or brachytherapy is delivered from inside the body by radioactive sources, sealed in catheters or seeds directly into the tumor site. This is used particularly in the routine treatment of gynecological and prostate malignancies as well as in situations where retreatment is indicated, based on its short range effects ***(Baskar et al., 2012)***.

Radiation therapy (RT) is in itself painless. Many low-dose palliative treatments (for example, radiation therapy to

bony metastases) cause minimal or no side effects, although short-term pain flare-up can be experienced in the days following treatment due to oedema compressing nerves in the treated area. Higher doses can cause varying side effects during treatment (acute side effects), in the months or years following treatment (long-term side effects), or after re-treatment (cumulative side effects). The nature, severity, and longevity of side effects depends on the organs that receive the radiation, the treatment itself (type of radiation, dose, fractionation, concurrent chemotherapy), and the patient.

The term radiation injury (RI) refers to the morphologic and functional changes that can occur in noncancerous tissue as a direct result of ionizing radiation. These complications can range from mild to extremely debilitating or life-threatening ***(Vuilleumier and Reis, 1998)***. The nature of tissue injury from ionizing radiation is thought to be caused by:

- DNA and cell division disruption.
- Generation of oxygen free radicals which has a direct toxic effect of the cell.
- Destruction of stem cells necessary for both revascularization and fibroplasias ***(Arnold et al., 1994).***

Morphological changes when using low doses of radiation occur mainly in the nucleus and are probably because of an apoptotic mechanism. In contrast, when using higher doses, the cell nucleus becomes dense and disfigured, and there may be loss

of the nuclear membrane. These changes are probably caused by direct cellular necrosis. The cytoplasm may show distension, the mitochondria may be deformed and the endoplasmic reticulum may degenerate ***(Mendelsohn et al., 2002).***

The success of the clinical application of RT rests on its lethal effects on cancer cells at sub-lethal levels for normal tissue ***(Luce, 1984).***

Side effects may be because of cell death within irradiated organs and ischemia because of the effects of radiation on small blood vessels or because of perturbed inflammatory and repair responses. Radiotherapy protocols should balance the expected outcome of the radiotherapy with the expected side effects. More severe side effects may be tolerated following curative radiotherapy but are not acceptable for palliative radiotherapy. The skin is particularly affected by radiation damage, as it is in the path of all external radiotherapy (Table 2) ***(Dormand et al., 2005)***.

Table (2): Complications of radiotherapy ***(Dormand et al., 2005)***.

	Complication
Acute	
General	Anorexia, nausea, malaise and pain
Skin	Erythema, dry desquamation, pigmentation and hair loss
Mucosa	Oesophagitis and diarrhoea
Bone	Myelosuppression
Long-term	
Skin	Ischaemia, ulceration and telangiectasia
Bone	Necrosis and fracture
Cardiovascular	Atherosclerosis Pericardial fibrosis and cardiomyopathy
Respiratory	Radiation pneumonitis and lung fibrosis
Gastrointestinal	Xerostomia, sialitis, mouth ulceration, bowel stenosis, fistula and diarrhoea
Genitourinary	Cystitis, nephropathy, sexual dysfunction, dyspareunia, vaginal stenosis, infertility and menopause
Nervous system	Myelopathy, brain lesions, brainstem encephalopathy, sensorineural hearing loss and otitis media

CLINICAL MANIFESTATIONS

Acute effects:

The most sensitive cells to RT are those that divide rapidly, such as skin, bone marrow and gastrointestinal tract cells. Acute effects result from necrosis of the rapidly proliferating cell lines ***(Herndon, 1996).***

- **Nausea and vomiting:** This is not a general side effect of RT, and mechanistically is associated only with treatment of the stomach or abdomen, or with radiation therapy to certain nausea producing structures in the head during treatment of certain head and neck tumors, most commonly the vestibules of the inner ears ***(Lee et al., 2012).***