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CASE STUDY

RADIOTHERAPY: AN UPDATE

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ABSTRACT

Radiotherapy is defined as the treatment of malignant (occasionally non malignant) diseases by ionizing radiation. Radiation oncology is the science that deals with the study of tumor biology and application of ionizing radiation in the management of cancers. It is based on the principle that rapidly proliferating cells are more sensitive to ionizing radiation compared to normal cells. This differential cell kill is used for the treatment of tumors. A dose of radiation that is sufficient to kill cancer cells will produce considerable if not permanent damage to the normal tissues. The malignant cells which have a high rate of mitosis are highly susceptible to the action of radiation. However, the normal cells recover but not the malignant tissues. Thus the aim of radiotherapy is to deliver a homogenous dose of radiation to an accurately localized tissue target volume in order to produce tumor control with minimal effect on the surrounding normal structures

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INTRODUCTION

Cancer has been known to mankind since ancient times. It has been so called because it adheres to any part of the body in an obstinate manner like a "crab". It is one of the most fatal health problems faced by mankind today. Worldwide, oral carcinoma is one of the most prevalent cancers and is one of the 10 most common causes of death. Each year it accounts for more than 3, 00,000 cases worldwide. The 5-year survival rate for oral cancer has remained approximately 50% for the past several decades. A key factor in the lack of improvement in prognosis over the years is the fact that a significant proportion of oral cancers are not diagnosed or treated until they reach an advanced stage. *Great* therapeutic *strides* in the oncology have been made in the past decades.

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The basic treatment modalities for cancer are surgery, chemotherapy and radiotherapy. Surgery is indicated for tumors involving bone, when the side effects of surgery are expected to be less significant than those associated with radiation, for tumors that lack sensitivity for radiation and for recurrent tumors in areas that have previously received radiotherapy. Surgery also may be used in palliative cases to reduce the bulk of the tumor and to promote drainage from a blocked cavity. Surgery results in a sacrifice of structure, which may have important aesthetic and functional considerations and is associated with high postoperative morbidity (Greenberg *et al*., 2006; Rhodus, 2005; Zini *et al*., 2010). The prospects of cure with surgery, radiation, combined chemotherapy, or a combination of any of these modalities are on the rise. Radiotherapy plays an important role in the treatment of oral cancer in more than 80% cases. Radiotherapy is superior in preserving the structural integrity and functions of organs over surgery.

Surgery and radiotherapy are complimentary to each other and radiotherapy has found a definite role for itself in the management of several forms of cancer, for almost all stages of the disease (Mohanty *et al*., 2000; Shah *et al*., 1995). Radiotherapy is defined as the treatment of malignant (occasionally non malignant) diseases by ionizing radiation. Radiation oncology is the science that deals with the study of tumor biology and application of ionizing radiation in the management of cancers. It is based on the principle that rapidly proliferating cells are more sensitive to ionizing radiation compared to normal cells. This differential cell kill is used for the treatment of tumors. A dose of radiation that is sufficient to kill cancer cells will produce considerable if not permanent damage to the normal tissues. The malignant cells which have a high rate of mitosis are highly susceptible to the action of radiation. However, the normal cells recover but not the malignant tissues. Thus the aim of radiotherapy is to deliver a homogenous dose of radiation to an accurately localized tissue target volume in order to produce tumor control with minimal effect on the surrounding normal structures (Bailoor *et al*., 2005).

The superficial and deep x-ray therapies (in the range of 40-300 keV x-rays) were used in the early period of radiotherapy for the treatment of cancers. The initial period although recorded success in the treatment of superficial cancer, it was not found to be satisfactory in the management of deep seated tumors. The pioneering supervoltage radiotherapy machines began to be installed just before World War II. The objective was to generate more penetrating radiation to give a better depth dose to deep seated tumors. The first **Cobalt 6o machine** was installed in the Saskatchewan cancer centre in Canada in August 1951 (Mohanty *et al*., 2000).

Fractionation

Fractionation is a therapeutic modality that may be manipulated to attempt to improve control of malignant tumors or to decrease effects on the normal tissue.

Rationale of fractionation (Pant, 2000)

The aim of any radiotherapy treatment must be to sterilize all the clonogenic cells of the tumor and spare the normal tissue from the damage which is beyond repair. The dose of 1.8 to 2 Gy per fraction is normally given in a radical radiotherapy regime. The main factors contributing to dose fraction response to normal & malignant cells are considered in terms of 4 Rs in radiotherapy. They are;

Repair of sublethal injury

Redistribution of cells within the cell cycle

Repopulation of cells following a treatment

Reoxygenation.

Fractionation in Radiotherapy

Standard---- 5 Fractions/Week [FR]

2 Gy × 5 FR × 7 Weeks = 70 Gy

Hyperfractionation---------10Fractions/Week

1.2 Gy × 10 FR × 6 Weeks = 72 Gy

CHART (continuous hyperfractionated accelerated radiotherapy treatment) ---------- 1.5 Gy × 18 FR (12 days) = 54 Gy

Hypofractionation-------- 3 GY × 10 FR (22 days) = 30 Gy

Accelerated treatment

The aim of this modality is to deliver the dose in as short overall time as is consistent with tolerable acute toxicity. Three ways of accelerated treatment

1. To treat twice or thrice per day for some or the entire treatment course.
2. Booster dose is delivered to reduce volume after traditional completion of the treatment

To reduce the total dose to a level which is tolerated when given in a very short overall time (Cox, 1985; Krstev, 2006; Saunders, 1999; Wang *et al*., 1985).

Low dose rate irradiation

The low dose rate continuous irradiation may be treated as small dose fraction of infinite numbers. The repair of sublethal injury will balance infliction of that injury and the cell survival will follow non repairable damage. The reoxygenation process with low dose rate irradiation probably occurs adequately.

High LET radiation

Use of high LET radiation is also good alternative theoretically to treat anoxic cells in the tumor core. The use of high LET radiation could not solve the problem of radioresistance due to hypoxia. X-rays, gamma rays, beta rays, and electron beam are low LET radiation (Zaider, 1995).

Principles for Radiotherapy of Head And Neck Cancers Curative radiotherapy procedures are usually physically taxing with painful reaction in the oropharyngeal mucosa resulting into dysphagia and impairment of nutrition. Thus radical radiotherapy with intent to cure is not free from its morbid side effects and must be used judiciously. Palliative radiotherapy with the aim of providing symptomatic relief is indicated for massive primary tumor with multiple node metastases. Although the symptoms of pain, obstruction or ulceration are alleviated, the radiation dose required to achieve it is very high, about 500 rads or more in 6 weeks. Such a high radiation dose may produce radiation reaction. Hence it is recommended that for advanced cancers that are incurable and relatively asymptomatic in their terminal stages, the best treatment can perhaps be human kindness, morphine and a good nursing care (Fonseca *et al*., 2008; Ko, 2009).

Indications of Radiotherapy

1. T1-T2 lesions.
2. T3-T4 locally advanced lesions.

- -Post surgical treatment

- Radiotherapy with or without chemotherapy especially for organ preservation.

3. Lymph nodes

- Elective lymph nodes when no palpable lymph nodes present.
- Only treatment for clinically positive lymph nodes.
- Presurgical and postsurgical in combination with neck dissection for clinically positive lymph nodes.

Contraindications of Radiotherapy

1. Operable resistant growths

a. Osteogenic Sarcoma.
b. Fibrosarcoma.
c. Myosarcoma and liposarcoma.
d. Melanoma

2. Carcinoma of stomach, intestine, colon or rectum.

3. Fibrous dysplasia and Paget's disease (increased chances of sarcomatous changes)

Techniques for Radiotherapy (Mohanty *et al*., 2000)

Radiotherapy can be administered by two methods, i.e.

A. Internal therapy/Brachytherapy
B. External therapy/ Teletherapy

Internal therapy/Brachytherapy

The term Brachytherapy was coined by Forsell in 1931. "Brachy" is a Greek word meaning short range. Here the source of radiation is placed in contact with the tissues. The radiation source may be placed,

1. Interstitially (inside the tissue)
2. Intra cavitary (in a suitable container placed in the natural body cavities like the maxillary sinuses)
3. As surface moulds on the skin, scalp, cornea or the conjunctiva.

One of the main advantages of brachytherapy is that large doses of radiation can be delivered to the tumor with minimum dose to the surrounding tissue. Radiation sources for brachytherapy used are Radium 226 (Ra226), Radon seeds and Cobalt 60 (Co60).

Pulsed Brachytherapy (Redding, 1990)

A single high activity source is programmed to pass through all the catheters of the implant/applicator system during each pulse. Computer controlled dwell time is decided for each position so that the source can deliver the desired dose distribution. For the patient it offers the practical advantage of receiving the treatment without being continually hooked to the brachytherapy unit. The linear quadratic model and repair times of sub lethal damage suggest that a 10 minutes pulse repeated at one hour intervals would produce a biological effect essentially similar to continuous irradiation at 50 cGy per hour.

External beam therapy / Teletherapy (Paterson, 1963; Souza *et al*., 2005)

The term teletherapy has been derived from a Greek word "tele" which means distant. Teletherapy or external beam therapy consists of using a radiation beam coming from a source located at a distance from the patient and is directed towards the tumor mass. Thus a large patient to source distance is employed usually in the range of 30 to 150 cm. Teletherapy may be broadly divided into two categories based upon the beam quality and their use.

1. The kilovoltage therapy
2. The mega voltage therapy

The kilovoltage therapy

The kilovoltage therapy is further divided into:

For Contact therapy a very short source to surface distance (SSD <2 cm) with a suitable aluminum filter of 0.5 to 1mm is used to remove the unwanted soft rays. The skin receives the maximum radiation dose while the underlying structures are spared. Contact therapy is restricted for small size tumors with thickness of 1-2mm.

For the superficial therapy, a short SSD of 10 to 25 cm is used with an aluminum filter of the thickness 1-3mm. These machines operate at a voltage of 50 to 150 kV to obtain an output of the order of 200 rads. Though superficial therapy is used for the treatment of non malignant dermatologic conditions, small superficial skin growths can also be treated by this modality.

The orthovoltage therapy has been gradually replaced by the megavoltage therapy. A SSD of 5 cm is used and x rays are produced at a variable voltage between 150 to 500 kV. Filters are used to achieve a beam of half value layer equivalent to 1-4 mm of copper. Using the orthovoltage therapy, 90% of the radiation is delivered at the depth of 2 cm below the skin surface.

The megavoltage therapy

X ray beams of the energy 1MV or more are classified as megavoltage beam. The gamma rays are also included if their energy is greater than 1MeV. Advantages of megavoltage therapy:

- Increased penetration power
- Reduced patient exposure
- Skin sparing effect
- Bone sparing effect
- Bone shielding effect

Newer Radiation Delivery Techniques (Bourhis *et al*., 2005; Harari, 2005)

3D Conformal Radiotherapy

In this the treatment volume conforms to the shape of tumor using 3D planning technique, minimizing the dose to the normal structures.

Intensity Modulated Radiotherapy (IMRT)

IMRT refers to a specific technique of linear accelerator based radiotherapy by which radiation beams are modulated in such a manner as to produce highly. Conformal dose distribution within the tumor while reducing the dose to the normal structures (Bailoor, 2005).

Advantages

1. Greater reduction of dose to surrounding tissues.
2. Complete flexibility in treating difficult lesions surrounding critical structures.
3. More conformal dose distributions around the target volume.
4. The entire treatment can be delivered remotely without the need to enter the treatment room to change fields and shaping devices.
5. Treatment time: 5 – 10 minutes

Conformal Radiotherapy, 3D Conformal Radiotherapy (3DCRT)

Conformal radiotherapy uses a different way of planning and giving radiotherapy. X rays give images of tumors in two dimensions (2D) – width and height. With computer technology it is now possible to see the tumor in three dimensions (3D) – width, height and depth using CT scan or MRI scan. The information from these scans feeds directly into the radiotherapy planning computer and the treatment area can be visualized in 3 dimensions. Following this, the computer programme designs radiation beams that 'conform' more closely to the shape of the tumor and avoid healthy tissue as far as possible. This is called '3D conformal radiotherapy' (3DCRT) (Cancer research, 2003). 3DCRT is used to treat tumors close to vital organs minimizing exposure to the spinal cord, optic nerve, salivary glands and other important structures.

Harmful Effects of Radiation: Prevention and Management

Harmful effects become evident in the head and neck region, as it is a complex area composed of several dissimilar structures that respond differently to radiation: mucosal linings, skin coverings, subcutaneous connective tissue, salivary gland tissue, teeth, and bone/cartilage. The radiation-related changes in the oral mucosa, salivary glands, taste, dentition, periodontium, bone, muscles, and joints are discussed in the order that they appear. They can be divided into early (mucosa, taste, salivary glands), intermediate (taste, salivary glands), and late (salivary glands, dentition, periodontium, bone,muscles, joints) effects (Vissink *et al*., 2003).

Oral Mucosa

Mucositis induced by radiotherapy is defined as the reactive inflammation of the oral and oropharyngeal mucous membrane during radiotherapy in the head and neck region (80% of the patients develop pseudo membranous mucositis) It is characterized by atrophy of squamous epithelial tissue, absence of vascular damage, and an inflammatory infiltrate concentrated at the basement region. The first clinical signs of mucositis occur at the end of the first week of a conventional seven-week radiation protocol (daily dose of 2 Gy, five times a week).

For relief of pain and discomfort due to mucositis, anaesthetics, analgesics, and mucosal-coating agents have been recommended. Periodic rinses with topical anaesthetics such as viscous xylocaine (lidocaine) and benzydamine have been proposed. Cytoprotectants, antibacterial can been used to prevent or reduce radiation mucositis.

Taste Buds (Vissink *et al*., 2003)

Radiotherapy to the head and neck affects taste threshold and is characterized by partial or complete loss of taste acuity with a cumulative dose of about 30 Gy (3 weeks), 2 Gy *per* fraction, after which it becomes virtually absent. Perception of bitter and acid flavors is more susceptible to impairment than perception of salt and sweet flavours .Direct radiation damage to the taste buds or their innervating nerve fibers has been reported as the main cause of taste loss. In most instances, taste gradually returns to normal or near-normal levels within one year after radiotherapy, there is usually no need for treatment. Since taste loss can result in weight loss, the importance of dietary counseling should be stressed and should be continued until the complaint completely subsides. Zinc supplements are reported to be helpful in increasing taste acuity.

Salivary Glands (Vissink *et al*., 2003)

Four phases in the radiation- induced loss of salivary gland function

First phase (0-10 days): characterized by a rapid decline in flow rate without changes in amylase secretion or acinar cell number**.**

The second phase (10-60 days): characterized by decrease in amylase secretion and acinar cell loss.

Third phase (60-120 days): No change in the flow rate, amylase secretion, and acinar cell numbers.

The fourth phase (120-240 days): characterized by a further deterioration of gland function but an increase in acinar cell number, with poor tissue morphology.

The most effective intervention for reduced salivary gland function is its prevention, which is best accomplished by meticulous treatment planning, changing a conventional schedule of fractionated radiotherapy into a schedule of continuous, hyperfractionated, accelerated radiotherapy (CHART), gustatory and tactile Sialogogues acid-tasting substances: Vitamin C tablets, citric Acid crystals, sugar-free gums, lemon pastilles and lemon slices and Pharmacological Sialogogues: Pilocarpine hydrochloride, pilocarpine nitrate, Anetholetrithione, Carbachol, Cevimeline, Neostigmine and Betanechol chloride to stimulate any residual function of the salivary glands can be used. Moistening of the mouth with water, saline, solutions containing sodium bicarbonate and sodium chloride, or diluted milk of magnesia and salivary substitutes containing carboxymethylcellulose can be helpful.

Dentition (Vissink *et al*., 2003)

The most common complication for the dentition is radiation-related caries. Radiation caries is a highly destructive form of dental caries which has a rapid onset and progression.

Dental caries may become evident as early as three months following the initiation of radiotherapy. Clinically, three types of caries lesions can be observed. The *first* type (circumferential) is observed on the labial surface at the cervical area of the incisors and canines. Initially, the lesion extends superficially around the entire cervical area of the tooth, and then progresses inward, often resulting in complete amputation of the crown The *second* type (superficial spreading) of lesion is a generalized superficial defect that first affects the buccal and later the lingual or palatal surfaces of the tooth crowns. This lesion often begins as a diffuse, punctuate defect and then progresses to generalized, irregular erosion of the tooth surfaces. The *third* type (pigmented) is characterized by heavy brown-black discoloration of the entire tooth crown, accompanied by wearing away of the incisal and occlusal surfaces. If exposure to irradiation occurs before calcification, the tooth bud may be destroyed. Radiation at a later stage of development may arrest further growth and result in irregularities in enamel and dentin together with shortened roots, tooth eruption is mostly delayed but not hindered.

In the early days of radiotherapy, extraction of the teeth prior to irradiation was proposed. Comprehensive preventive measures including rigorous oral hygiene, daily self-application of topical fluoride, and limitation of cariogenic foods, remineralizing mouth rinse solutions, and artificial saliva preparations, interdental techniques such as flossing assisted, if necessary, with plaque disclosing agents can be beneficial.

Periodontium (Vissink *et al*., 2003)

Radiation results in decreased vascularity and acellularity of the periodontal membrane with rupturing, thickening, and disorientation of Sharpey's fibers and widening of the periodontal space. The cementum appears completely acellular, and its capacity for repair and regeneration is severely compromised. These changes may predispose individuals to infection. The direct and indirect effects of high-dose radiotherapy on the periodontium result in an increased risk of periodontal attachment loss and tooth loss, and even in an increased risk for the development of osteoradionecrosis. This underscores the need for proper pre- and post-irradiation treatment planning. Mechanical oral hygiene procedures (calculus removal, root planing, soft tissue curettage, tooth surface polishing, and daily plaque removal) must be used to remove the local etiologic factors of inflammatory diseases of the periodontium (Sharma *et al*., 2009).

Muscles and Joints (Sharma *et al*., 2009)

Trismus, or limited jaw opening, may develop due to tumor invasion of the masticatory muscles and/or the Temporomandibular joint (TMJ), or be the result of radiotherapy if masticatory muscles and/or the TMJ is included in the field of radiation, or a combination of both. Trismus is attributed to muscle fibrosis and scarring in response to radiation injury as well as to fibrosis of the ligaments around the TMJ and scarring of the pterygomandibular raphes. Trismus develops three to six months after radiation treatment is completed and frequently becomes a lifelong problem Prevention of trismus, rather than its treatment, is the most desirable objective. Patients at risk of trismus should be put on home exercises to maintain maximum opening and jaw mobility as soon as radiotherapy begins.

Bone (Sharma *et al*., 2009)

The most severe potential complication of bone irradiation is osteoradionecrosis and can be defined as "bone death secondary to radiotherapy. It is characterized by clinical signs such as severe pain, non-healing (exposed) bone within the treatment area after completion of radiotherapy, and repeated infections which may progress to fistula or sequestrum formation and eventual spontaneous fracture. In the early literature, the pathogenesis of osteoradionecrosis of the jaws was regarded as the inevitable triad sequelae of radiation, trauma, and infection. The sources of trauma may be include denture irritation, sharp or hard food particles, sharp bony ridges an extraction. According to Marx, the sequence in the development of osteoradionecrosis is:

1. Radiation;
2. Hypoxic-hypovascular-hypocellular tissue: the ability of bone to replacenormal collagen loss or normal cellular loss is severely compromised or nonexistent;
3. Tissue breakdown: unrelated to micro-organisms but related to the degree of radiation damage and the rate of normal or induced cellular death (Collagen lysis and cell death exceed synthesis and cellular replication.); and
4. Chronic non-healing wounds: energy, oxygen, and metabolic demands exceed the supply.

The primary goal towards prevention should be to optimize the condition of the patient's dentition, so that high-risk procedures, such as extraction of teeth, apicoectomies, etc., will not have to be performed in the post-irradiation period. It is now generally accepted that all teeth with a questionable prognosis must be extracted before radiotherapy. An interval of 21-days or greater interval between extraction and initiation of radiation therapy minimizes the risk of osteoradionecrosis. Also, antibiotic coverage is strongly recommended. Hyperbaric oxygen (HBO) treatment is more beneficial than conventional antibiotic prophylaxis in preventing osteoradionecrosis as it stimulates angiogenesis, increases neovascularization, optimizes cellular levels of oxygen for osteoblasts and fibroblast proliferation, stimulates collagen formation, and supports in growing blood vessels, all of which enhances the healing potential in irradiated compromised tissues.

There are two goals in the treatment of osteoradionecrosis, *viz*. Elimination of the necrotic bone and improvement in the vascularity of the remaining radiation-damaged tissues. The system of Marx (1983, 1984) focuses chiefly on the use of and response to HBO, and thus on the treatment of osteoradionecrosis. The first step in the treatment of osteoradionecrosis is débridement of all bone that is no longer vascularized. The removal of this dead bone eliminates any nidus for continued infection and inflammation, but does nothing to improve the vascularity of the adjacent tissue bed and the remaining vascularized bone. These tissues remain compromised by the previous radiation and are at continued risk for the development of osteoradionecrosis in the future. Therefore, based on clinical experience and empirical evidence, a protocol (Marx protocol) has been developed aimed not only to improve the healing of radiation injured tissue, but also to increase their vascularity permanently.

Stage I ORN/Extraction

Patients with exposed bone who have no serious manifestations of those in Stage III. Begin with 30 HBO_2 treatments with no debridement or only minor bony debridement. If patient progresses, give 10 additional HBO_2 treatments.

Stage II ORN

If not progressing, Stage II patients should receive surgical debridement and 30 HBO_2 treatments followed by 10 post-operative treatments. Surgery for Stage II patients must maintain mandibular continuity.

Stage III ORN

If mandibular continuity is not achieved, Stage III patients are entered into a reconstructive protocol where a mandibular resection if followed by a planned reconstruction. All necrotic bone must be surgically eradicated. Stage III patients receive 30 HBO2 treatments prior to resection followed by 10 post-resection treatments (Marx *et al*., 1985).

Drugs used to minimize the side effects of radiotherapy (Ko, 2009)

Amifostine: Amifostine formerly known as WR-2721 protects cell damage by scavenging free radicals. A dose of Amifostine 200mg/m2 is given as rapid infusion 30 minutes before each fraction of radiation.

Pilocarpine: This drug is used against dryness of mouth to increase the salivary flow.

Erythropoietin: 10,000 units given as subcutaneous injection 3 times a week is used to correct anemia before radiotherapy.

Colony-stimulating factor (CSF): G-CSF and GM-CSF are used to diminish myelosuppression associated with chemoradiotherapy. These agents also provide mucosal protection in patients treated with chemoradiotherapy.

Conclusion

Radiotherapy should be the treatment of choice in all patients with early head and neck cancer where the use of surgery may result in significant alteration of anatomy and/or function. Radiotherapy can give nearly 100% tumor control in early-stage lesions (T1 NO). Advanced tumors (T4 N3) will have low tumor control so for this reason, combined therapy may be indicated. Combined therapy is usually irradiation and surgery, but definitive radiotherapy reserving surgery for salvage of failures can be a valid alternative. The latter is particularly so in terms of oral cavity and the oropharynx and for the neck metastatic lymph node problem. Improved cancer control activities aimed at prevention and early diagnosis should present a better future for these patients. Dental health care providers are a necessary part of the team and must be involved in the care of the head and neck cancer patient. Continuing research is needed in the field of radiotherapy.

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