Tumors of the oral and maxillofacial region constitute more than 5% of all tumors worldwide with an increasing rate of incidence[1.] Treatments of these tumors include surgery, radiotherapy, chemotherapy or a combination[2]. Despite aiming the radiation beam towards the diseased area during radiotherapy treatment, inevitable exposure of the healthy tissue to radiation occurs[3]. As a result, tissue changes are induced including; mucositis, hyposalivation, radiation caries, taste loss, trismus, soft-tissue necrosis and osteoradionecrosis with accompanying difficulties in speaking, eating and swallowing[4].

With decreased salivary flow, oral hygiene measures and patient immunity, increased prominence of cariogenic microorganisms follow leading to the rapid progression of carious lesions[5]. The restoration of such lesions can be extremely difficult, since the dental structures and restorative materials are subjected to the chemical and thermal variations during radiation therapy.

Glass ionomer cements are considered advantageous in restoring carious lesions in patients receiving radiation therapy due to their antimicrobial property and chemical adhesion to tooth structure. One useful property of glass ionomer is its ability to release of fluoride and other trace elements such as zinc. It is established, that the continuous release of low levels of these ions causes their accumulation in dental plaque, results in modulating the population of mutants streptococci and inhibits their growth around restorative margins[6].

Studying the effect of ionizing radiation therapy on glass ionomer restoration's antibacterial property became of prime importance for the service and future welfare of patients. Also studying the amount of fluoride release in relation to radiation dose & time of radiation become of major importance.

I- Introduction to ionizing radiation

Ionizing radiation is one of the treatment modalities for cancer treatment[7]. When cancer cells are exposed to ionizing irradiation, damage of their cellular deoxyribonucleic acid (DNA) occurred, this slows down or hinders their replication [8]. Ionizing radiation can be classified into photon radiation and particle radiation. Photon radiation includes x-ray and gamma rays. Particle radiation includes electrons, protons, neutrons, carbon ions, alpha particles and beta particles. In the medical field, ionizing radiation (x-ray and gamma rays) are used in x-ray machines and CT scans as diagnostic aids in treatment. However, radiation therapy using higher doses than in diagnostic aids is used as treatment in some cases of cancer [8].

Management of oral or head and neck cancers may include tumor radiation with different radiation doses, according to type and location of the tumor. Radiation dose exposure can be expressed by Gray or Sieverts, Gray defines it as a unit used to measure the total of radiation that a patient is exposed to. Radiation can also be recorded as centigray (CGY). A milligry (mGy), which is 1/1000 is of a Gy and millisieverts (msv), which is 1/1000 of asv, can also be used as units of radiation measurement [9].

Radiation therapy leads to tumor cell killing, primarily via apotosis and necrosis due to the DNA damage evoked within the tumor microenvironment [10]. Radiation-induced reoxygenation of tumor cell leads to improving tumor control, where low oxygen levels (hypoxia) within the tumor microenviroment leads to a malignant type. Moreover, radiation therapy inhibits the epithelial-mesenchymal transition which characterizes the tumor cell. Furthermore, radiation therapy induces vascular damage in

tumors, which can induce tumor cell death in addition to the direct action of radiation in producing DNA damage [11].

Upon exposing tissue to radiation, the ionizing radiation causes tissue changes through direct and indirect damages. Direct damage occurs when the displaced electron strikes and breaks a DNA strand. Indirect damage occurs when the electron reacts with a water molecule of the cells, creating a powerful hydroxyl radical which then damages the cell-DNA. Damage to a cell-DNA may occur as a single-strand DNA break, which can be repaired by the cell itself with no additional damaging sequelae. However, a break affecting both strands of DNA allows the effort for abnormal reconnection of the strands, which causes the adverse biological effects. A DNA strand may rejoin itself incorrectly to the other strand; then cell death may follow, or it may rejoin as a symmetrical translocation with the potential expression of an oncogene during division and development of malignancy [12].

To achieve a successful treatment, the maximum radiation dose to the tumor mass is needed with minimum exposure to the surrounding tissue. Prognosis of treatment depends on radiosensitivity of the tumor mass and radiosensitivity of the surrounding normal tissue, dose rate and total dose [8]. The majority of patients with head and neck tumors need a total irradiation dose from 50-70 Gy [13]. The dose must be given at dose rate of 2Gy/minute, since high dose rate (e.g. 5Gy/ minute) produces high damage to the biological tissues. Fractionation of the total dose into multiple small doses has the advantage of greater tumor destruction and gives a chance for cellular repair of normal tissue, compared to single dose radiation [14].

Radiation is delivered to tissue through two ways; teletherapy or brachytherapy. Teletherapy is based on delivering ionizing radiation through external source. Brachytherapy is a radioactive source implanted internally near the tumor [15]. Recently, a new method for radiation delivery is 360^{o}-rotation radiation therapy (conformal radiation therapy technologies). The most commonly used devices are the 3D-conformal radiotherapy (3D-CRT), or the intensity-modulated radiotherapy (IMRT). Their advantage over older delivering devices is that it allows the primary target to receive the total amount of radiation necessary for the treatment[5,16].

I-1 Effect of ionizing radiation on the oral cavity:-

Radiotherapy in the head and neck region may lead to many complications; including gland dysfunction, mucositis, taste loss, osteoradionecrosis and trismus. The complications depend on the location of the tumor and its proximity to different vital organs. Adverse effects from radiation are divided into acute and late reactions. Acute reaction includes mucositis and skin reactions; as redness, irritation and edema. Acute side effects occur during the course of treatment. These are generally reversible and patients normally recover from these adverse effects within 3 months after radiotherapy. Late adverse effects occur within 3 months after treatment. Reactions are characterized by gradual progression and they are irreversible, such as subcutaneous and sub mucosal fibrosis, xerostomia and osteoradionecrosis [17, 18].

Radiation of the salivary gland leads to gland dysfunction, due to cell death and fibrosis. The dysfunction often includes reduction in both quantity (hyposalivation) and quality (viscosity) of saliva. These changes

negatively affect the speech, taste and swallowing. Furthermore, saliva reduction may lead to development of oral infections, and may increase the risk of development of dental caries.

The incidence of xerostomia depends on many factors, such as type of salivary gland, the radiotherapy technique, radiation dose, as well as the tumor location. Various studies have shown that the serous salivary cells are more radiosensitive than mucous cells and that acinar cell are more sensitive to irradiation than duct cells. Parotid glands are more radiosensitive than submandibular gland [19]. The sensitivity of acinar cell is on account of its heavy metal granule content which would increase the lipid per oxidation [20]. When exposed to irradiation, more time leads to acinar cell's loss of progenitor stem cells [21].

Reduction of xerostomia can be achieved by using intensity modulated radiotherapy (IMRT) techniques, which are better than 3D conformal radiation therapy (3D CRT). Using IMRT, the radiation beams can be controlled to deliver a higher dose to particular target volumes, while reducing the dose to adjacent organs at risk [22]. The radiation dose, a lower mean dose, gives the irradiated gland time-related recovery; whereas with a higher dose, the flow rate is too low [23].

Xerostomia must be carefully managed to avoid its complications. Management should include dietary control of sugars, effective oral hygiene, fluoride supplements, salivary substitutes, as sorbitol-containing gum and recently suggested future therapies, as Gene therapy, stem cell transfer, as well as neuroelectrostimulation.

Before irradiation, the head and neck cancer patient must be introduced in preventive program to limit the incidence of radiation caries.

However, the restorative procedure prefers using an adhesive fluoride releasing restorative material [24]. Preventive measures must be performed in the form of fluoride application and strict oral hygiene [19]. In the post-radiotherapy phase, head and neck cancer patients suffer from chemical and microbial changes in their oral cavity resulting in a cariogenic environment. Since most of these changes are permanent, this places the patient in the high caries risk category for life. Dentition breakdown following radiotherapy tends to start within the first year, and becomes more severe with time with an incidence risk of 6% per month. Therefore, the prevention protocol assigned for the patient in the pre-radiotherapy phase must be continued throughout the post-radiotherapy phase [25].

The irradiation damage to the dental tooth structure leads to unfortunate radiation caries progression. In this case, restorative intervention is mandatory. Restoration must have ideal properties, as resistance to recurrent caries, fluoride releasing material, good adhesion to tooth structure, good durability, acceptable aesthetics and ease of handling. Therefore, it is preferable to use glass ionomer cements, where recurrent caries reduction for glass ionomer and resin modified glass ionomer relative to other restoration were greater than 80% in xerostomic patients[26]. In addition, fluoride releasing materials may reduce caries surrounding restorations in high risk patients who didn't use topical fluoride routinely [27].

I-2 Effect of ionizing radiation on the tooth forming hard tissues:-

Irradiation has several oral complications, that may include an effect on the hard dental structure[28, 29] . Within three months of exposure to ionizing radiation in the head and neck region, the first signs of deterioration of hard tissue start to occur [30]. Changes of the organic

composition of dental hard tissues were noted for both high and low radiation doses [31].

After irradiation, enamel shows extensive destruction of the prismatic structure, and is more vulnerable to acid attacks than sound enamel [32]. On the other hand, dentin is severely affected by irradiation. Studies have shown that alterations occurring in irradiated dentin included damage for collagen fibrils. The collagen fibers of irradiated samples, when compared with non-irradiated, showed a loose organization. Well-defined dentinal tubules with a well-organized collagen network were observed in the nonirradiated teeth by using morphological analysis of the dentin. The electron micrographs of the irradiated dentin revealed a progressive change in the surface, in contrast to the nonirradiated dentin in all of the assessed regions. Changes in the intertubular and peritubular dentin and degradation of the collagen network occurred upon increasing the doses of irradiation. Upon exposure, the surface became amorphous, impairing identification of the dentinal tubules, collagen fiber network and hydroxyapatite crystals[28]. Moreover, water inside dentin structure, when exposed to ionizing radiation, releases free radicals which denature collagen fibers [33].

The changes in DEJ of irradiated teeth showed loss of the DEJ sharp contour resulting in reduction of the anchoring between dentin and enamel. Upon examining the junction between cementum and enamel, a narrow gap formation was revealed [30]. There was a great significant effect of radiotherapy on the stability of teeth at DEJ region in irradiated teeth [34]. Simulated radiotherapy leads to increase in the stiffness of enamel and dentin near the DEJ. Increased stiffness was predicted to be the result of the radiation-induced decrease in the protein content, with more reduction in enamel sites. Such changes in mechanical properties and chemical

composition could contribute to DEJ biomechanical failure. The disturbance at the region of the DEJ could result in the formation of a gap, loss of prismatic structure and bacterial colonization associated with the obliteration of the dentinal tubules and odontoblastic process atrophy[34].

Reduction in the ultimate tensile strength of enamel due to alterations in the protein component was reported [35]. Other authors have reported that enamel micro hardness was not affected by ionizing radiation, and proposed that any changes in the mineral structure caused by radiotherapy were due to chemical interactions rather than physical changes[36-38]. Some studies showed decrease of the micro hardness with small dose of radiation. With higher doses, dentin was severely weakened with obliteration of the dentin tubules, preceded by a degeneration of the odontoblast processes in irradiated dentin. This leads to obvious fall in hardness, wear resistance, dentoenamel junction stability and tensile strength[30,35,39]. The ionizing radiation exhibited alteration in nano-mechanical properties (elastic modulus, nano hardness and friction coefficient) of enamel and dentin, with deterioration in their mechanical properties. This deterioration increases the susceptibility of enamel and dentin to caries [40].

The damage of dental tissues is dose-dependent and mostly occurs beyond 60Gy irradiation dose. At dose higher than 60GY, more changes in dentin and enamel properties occur; including decreased hardness, elastic modulus, tensile strength, as well as increased susceptibility of enamel fracture. These changes in dentin and enamel are dose related. Radiation caries are highly destructive, from investigating the effect of gamma irradiation on hardness of hard dental tissue. Hardness of enamel and dentin was evaluated using nanoindentation, coupled with atomic

force microscope (AFM) technique. Resulting hardness decreased for both enamel and dentin, when comparing no irradiated with irradiated teeth [41].

I-3 Effect of ionizing radiation on bacterial activity:-

A major side effect of head and neck radiotherapy is radiation caries [1]. However, the etiology of caries results after radiation remains controversial. At first, the in vitro study approaches that direct radiogenic damage to hard dental tissue is responsible for the development of radiation-induced caries[8, 36]. Conversely, later studies have shown that the microscopic pattern of radiation caries progression is the same as in non-irradiated tooth structure [42]. Nowadays, radiation caries are a highly destructive form with multifactorial origin. The direct radiogenic damage to tooth structure is coupled with the indirect effects of head and neck radiotherapy, such as xerostomia, reduction of fluoride in oral flora and more cariogenic diet; these factors lead to caries [43]. One of the most important properties of irradiation is inactivation of microorganisms, especially pathogens. A decrease in the total number of bacteria up to 95.5-99.5%, especially when exposed to high dose of irradiation, was reported in previous study [44].

The direct mechanism of microbial inactivation is by gamma radiation due to damage of DNA chromosome and nucleic acids, which renders multiplication of microorganism impossible. The indirect action is by free radical production, radiolysis of water and alteration of the cell membrane of microorganisms [45]. Though a decrease in micro-organisms is usually present accompanying radiation, radiation caries is a fact affecting patients in the period of months after radiation. This effect was related to xerstomia in cancer patients. Once they occur, caries-promoting changes

in oral microflora, antibacterial properties, saliva electrolytes and serum proteins lead to reduction in the pH of saliva. The xerostomia-related redistribution of the oral micrflora forms imbalance between bacteria, saliva and caries relationship leading to increase of caries activity. The saliva is important in maintaining oral microbial equilibrium. The extremely viscous xerostomic saliva is mainly produced from cellular break down of products from the major salivary glands, minor salivary glands and sulcular fluids [41].

In a study conducted on irradiated patients with head and neck cancer, an increase in the occurrence of caries was referred to cariogenic micro-organisms predominating over the non cariogenic micro-organisms. Significant increase has been shown in the number of streptococcus mutuns and lactobacillus species at the expense of streptococcus Sangius, Neisseria and Fusobacterium. Moreover, Actinomyes species are also increased [47]. Another study has found no obvious relation between patient salivary microbiota and radiation caries after one year following intensity modulated radiotherapy techniques [46].

Microbial community shifts were recorded from one side of the cavity that had undergone radiation relative to the other side. The microbial shift occurred after three weeks of irradiation. Regarding the tongue, shifts could be noticed earlier, about 2 week of irradiation [46]. After radiation, an increase in the amount of plaque material on the tooth surface and the number of viable microorganisms per gram of plaque remained similar to that found in untreated patients [48]. The facultative streptococci that were considered the main facultative flora of saliva and plaque showed alteration after irradiation. After irradiation, increase in the number of strept. mutans in saliva, as well as dental plaque was observed.

This increase of strept. mutans was higher in plaque than in saliva. Large changes were noticed in the anaerobic flora after irradiation. Actinomyces showed marked increase in number after irradiation in saliva and plaque. The increase was more in plaque than saliva. These organisms probably play an important role in the development of human caries, where they contribute to lowering the pH of saliva and plaque. The anaerobic streptococci remained relatively constant before and after irradiation [48].

II- Historical introduction of glass ionomer cements

The glass ionomer cements (GICs) are clinically bioactive and attractive dental materials that have unique properties, and have a wide range of uses, such as luting, lining, or restoring a tooth. Glass ionomer material was introduced by **wilson and kent in 1972** as a "new translucent dental filling material ", recommended for the restoration of cervical lesions. It consists of a powdered fluoraluminosilicat glass, and a polyalkenoic acid. Polyacrylic acid is often incorporated into the powder in its dehydrate form, leaving the liquid to consist of water, or an aqueous solution of tartaric acid [49].

The main characteristic of GICs is adhesion to tooth structure and fluoride release. Some of the disadvantage of GI is early sensitivity to moisture, long-term wear, in addition to low flexural strength and high modulus of elasticity; as it is brittle and tends to bulk fracture. They have undergone remarkable changes in their composition, which contributed to improving their properties. The resin modified materials appear to have substantial benefits, while retaining the advantages of fluoride release and adhesion [50].

II-1 Conventional Glass Ionomer Cement:-

II-1-1 Composition of conventional glass ionomer cement:-

There are three essential components of glass-ionomer cement; namely polyalkanoic water-soluble acid, basic (ino-leachable) glass and water. The aqueous solution of polymeric acid dissolves glass powder, which is mixed by an appropriate method to form a viscous past that sets rapidly [51]. The main components of the powder are alumina ($AL2O_3$), silica (SiO_2), calcium fluoride (CaF_2) as flux, sodium fluoride (NaF), cryolite ($NaAIF_{6)}$ and aluminum phosphate ($AIPO_4$).

The structure of the glass is mainly the alumina and silica, which form the skeletal backbone of the glass. Their structure is a tetrahedron with a three-dimensional silicate glass structure. The alumina acts as the intermediate oxide that takes part in glass structure, but cannot form glass on its own. Addition of alumina gives the network negative charge and renders it susceptible to acid attack. This negative charge must be balanced by the inclusion of positively charged network modifying cations, such as calcium and sodium to sustain electro-neutrality. Phosphate and fluoride ions are present in the basic glass to modify the setting characteristics, where their influence lies in the degree of cross-linking of the polysalt matrix [52].

The aqueous solution of polycarboxylic acid is where the polyacid at a concentration of 45wt% reacts with the ionomer glass. A variety of acids are used, as acrylic acid, maleic acid, itaconic acid, butene dicarboxylic acid and vinyl phosphonic acid. Their reactivity depends on the ingredients of the acids of copolymeric acids, and on their molecular weights and concentrations. The acid dissolves the glass structure by

hydrolyses of the bonds of the glass network and cations as aluminum and calcium are released. The cations are then chelated by the carboxylate groups, and serve to crosslink the polyacrylic chains to have final set cement, formed of hard, cross-linked cement [52]. This cement takes gradual hardening or setting and maturing process, where ratio of bound to unbound water increases and mechanical properties; especially compressive strength increases, gradually with time, to a maximum value [53].

High-viscosity GIC was developed to overcome some of the drawbacks of conventional GIC, such as moisture sensitivity and low mechanical properties. It is provided as encapsulation that gives uniform proportioning and mixing under a standard mixing technique with less porosities. Where setting reaction is rapid, early moisture sensitivity is minimized and solubility in oral fluids is very low. Furthermore, it improved mechanical properties compared to conventional GICs expressed by high wear resistance, sufficient tensile and compressive strength that resists masticatory force [54].

II-1-2 Setting reactions of conventional GIC:-

The setting reaction is an acid base reaction with the ion leachable glass. The setting process occurs in three overlapping stages: Decomposition of the glass powder, gelation-precipitation of cations and anions, as well as hardening and maturation stages. Decomposition of the glass powder, this phase described as the ion leaching or migration phase. When the powder and liquid are mixed together, the surface layer of the glass particles is attacked by the polyacide, resulting in limited degradation of the glass surface with the release of calcium, aluminium and fluoride ions. The metal ions are depleted from outer layer of glass

particles and the cement matrix [52]. As pH of aqueous phase increases, polyacrylic acid will ionize and create electrostatic field that will aid the migration of liberated cations into the aqueous phase [55].

Migration of ions into the aqueous phase of the cement forms complexes, but they remain as an insoluble form. The calcium ions concentrations of the cement solution grow more rapidly than the aluminium ion concentration, and initially form mainly calcium complexes. This is probably due to two factors: Firstly, the ionic radius of aluminium and its high trivalent charge, resulting in a lower rate of diffusion of the ionic species through the cement solution when compared with calcium, and secondly; both calcium and aluminium will easily and quickly form complexes with fluoride ions. Aluminium fluoride complexes are subjected to less decomposition than calcium fluoride complexes. As the ionization reaction continues, the molecule becomes more polar in nature [55]. Sodium and fluorine ions are leached into the aqueous medium upon acid attack, but they do not participate in the cross linking of the cement. They remain scattered uniformly within set cement[52].

Gelation-precipitation of cations and anions: At critical pH, precipitation of insoluble polyacrylates takes place. The initial set (Cross linking the available calcium ions), increases the viscosity of the freshly mixed cement. This reaction is rapid, forming a hard cement within 10 minutes from the start of mixing. Calcium acrylate is more vulnerable to water. When cement is not fully hardened Al, Ca, and F polyacrylate ions may leach out leading to irretrievable loss of cement matrix. The divalent linkages are not as stable as they might be, and the setting reaction