Head and Neck Cancer

Chapter 1

Complications of Head and Neck Radiotherapy: Prevention and Management

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Abstract

Radiotherapy plays an essential role in the treatment of head and neck cancer patients either definitive or adjuvant radiotherapy after surgery. Radiotherapy given to head and neck region has caused problems to several normal organs. In this chapter, consideration will be given to the complications of radiotherapy on skin, salivary glands, oral mucosa tissue, taste buds, jaw bones, teeth, larynx, pharynx, and temporomandibular joint (TMJ) as well as the prevention and the management of symptoms from theses complications.

1. Skin

After undergoing the first radiotherapy (RT) session, basal cell layer is destroyed to some extent [1]. The rest of basal cells will become horny layer which it is sometimes called keratinization or cornification. These cells will flake off more quickly. Furthermore, the loss of balance between the production of normal cells in basal layer and the cell destruction in the skin layer will occur. Then, the skin will be swollen and become red which results from the expansion of small blood vessels in dermis and the blockade in blood vessels [2]. The change of the skin colour occurs when there is the migration of melanin to the top layer of epidermis. The growth of hair is restrained while hair follicles are changed to a resting phase in cell cycle. With respect to hair loss, it results from high sensitivity to RT of hair follicles. Only 3 Gy of RT can cause alopecia irredeemable. With regard to permanent alopecia, it will occur when the RT dose is at least 30 Gy [3,4]. After that, the repairing process of normal tissues will create the balance by stimulating the re-epithelialization. There is a proliferation and cell division from

basal membrane level including the migration of epithelial cells from outer areas of radiation beam within 10 days [5].

The changes of the skin at the first stage are erythema and dry desquamation and it will become moist desquamation for more severe symptoms (**Figure 1-3**). Hyperpigmentation or hypopigmentation are found for a long-term change and new telangiectasias are also detected. Furthermore, lost hair occurs on the affected area(s) and the skin atrophies or is webbed. For a severe case, chronic wounds might occur [6,7].

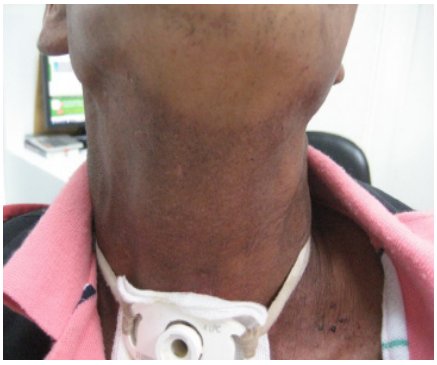

Figure 1: Shows dry desquamation in a patient with advanced laryngeal cancer who was exposed to RT dose of 3000 cGy concurrent with cisplatin.

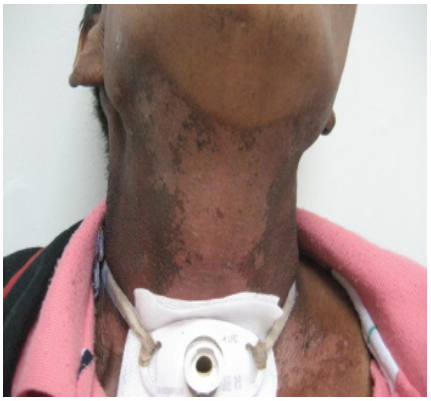

Figure 2: Shows dry desquamation in a patient with advanced laryngeal cancer who was exposed to RT dose of 5000 cGy with concurrent cisplatin.

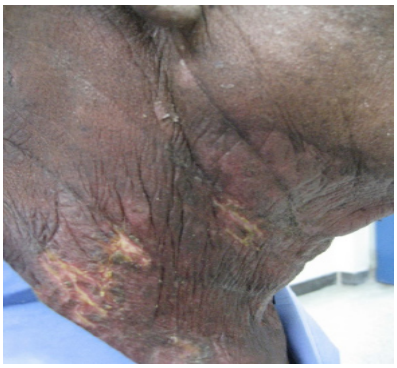

Figure 3: Shows hyperpigmentation skin and moist desquamation in a patient with advanced laryngeal cancer who was exposed to RT dose of 5000 cGy with concurrent cisplatin.

These changes take place within 1-6 weeks of irradiation and they will last 2-4 weeks after the treatment. During the first two weeks of irradiation, patients will have no abnormal symptoms. However, transient erythema might be detected within 24 hours and it will occur on the irradiated area(s). The skin will be red with temperature higher than normal. Patients frequently explain that the irradiated area is warm. Moreover, it might be itchy in some cases. Hyperpigmentation will appear after 2-4 weeks of the treatment to the dose of 20 Gy [8]. Sweat glands and sebaceous gland will be damaged permanently after radiation exposure to the dose of 30 Gy. This damage results in dry and itchy skin. With the dose of 30-40 Gy, the skin will be hyperemia and swollen. In a severe case, hair loss and moist desquamation will occur to the dose of 45-60 Gy. For the dose of 55 Gy or more, complete hair loss will happen. Hair will grow again approximately two months after the last dose of irradiation. The risks of skin reaction from irradiation can be divided into 2 factors:

1. Factors from patients

They include medical history for diabetes, kidney failure, smoking, autoimmune disorder or environmental factors of patients [9,10]. Besides, having had skin lesion, burns, and previous surgery can be the cause of risks [11,12].

2. Factors from the treatment

Factors can be large volume irradiation, dose per fraction that higher than conventional RT, prolonged overall treatment time, the use of the low energy photon, use of electron, or use of bolus which increase radiation dose on the skin [13].

The most important things in the prevention of skin reaction from RT are skin care on irradiated area(s), the use of skin lotion or cream and wound care in the moist desquamation area if occur. There is an old belief that the radiated skin has to be taken care of strictly and be kept dry and clean. It is not allowed for patients to take a shower and to apply cream or lotion on the skin. However, the belief has been changed. Nowadays, patients are advised to take a shower at the appropriate temperatures. However, they have to avoid rubbing on the area(s) where the radiation beam has passed through. After that, the radiated skin should be dabbed until it dries [12]. Frosch et al. [14] have evaluated the skin of patients who had a shower. It showed that patients having a shower had skin reactions at less severe level than the group of patients who did not. In any case, patients should avoid swimming in chlorine water pools. With regard to clothing, it is advisable to wear loose clothing with cotton or soft fabrics to prevent friction. Furthermore, patients should stop using cosmetics and perfumes to prevent irritation and reactions that might occur with RT. As for men with beard, they should avoid shaving on radiated area(s) with a razor. Alternatively, they should use a shaver.

1.1. Treatments for dry desquamation

Patients with dry desquamation will feel itchy. Their skin will dry and flaky. Therefore, the main treatment is to soothe itchy skin and prevent wounds, bursts, and skin infections. It is suggested that unscented lotion or cream with lonalin-free hydrophilic be used in order to keep moisture and have skin elasticity. In addition, there have been experiments on emollient cream or ointment with trolamine, hyaluronic acid, almond, or chamomile as an ingredient. Trolamine or Biafine cream is the mixture consisting of oil and water. It is a compound with properties similar to non-steroidal anti-inflammatory. It is frequently used in radiation-induced dermatitis. One of the non-blinded randomized trials showed that Trolamine or Biafine cream was effective in healing dry desquamation. Another single-blind trial was conducted to compare Biafine cream to calendula ointment [15]. Concerning chamomile and almond cream, it is found that there is no difference in skin reactions [16] although less skin reaction higher than grade 2 is later detected compared to the groups using chamomile cream. Our recent study reported the addition of an emulsion of olive oil and calcium hydroxide for patients undergoing hypofractionation RT yielded more preventive results over a general skin care regimen alone, in terms of delaying skin toxicity, reducing the severity of acute radiation dermatitis, and a better quality of life [17]. Regarding to steroid cream, the study showed that the use of 0.1% mometasone furoate cream could cause red skin at non severe level [18]. Additionally, the randomized study of Schmuth et el. between 0.1% methyl prednisolone aceponate (MPA) cream and 0.5% dexpanthenol cream [19] revealed that there was no statistically significance difference in severity of skin reactions in two groups. As for the evaluation of burning sensation from patients, it illustrated that patient's preferred corticosteroid cream (MPA) to dexpanthenol. However, physicians have concerned about allergy to topical corticosteroid because it could happen in some patients. Hyaluronic acid is polymer whose properties are to repair the skin and build granulation. There was only one study in humans [20] which evaluated the use of 0.2% prophylactic hyaluronic (HA) cream in irradiated patients for head and neck cancer. They applied the cream in the morning and in the evening from the beginning of the treatment. This could delay the skin reaction occurrence with statistical significance. The reactions often occurred in the third week of the treatment. Furthermore, the cream could help reduce the severity and the duration of the reactions of irradiation on the skin.

1.2. Treatments for moist desquamation

In case of moist desquamation, it involves cracked skin, wounds, and burns. The skin on that area will be open and risk being infected. Erythema. The use of antimicrobial ointments, for example, silver sulfadiazine which is preferred to heal burns, is not recommended due to the concern about antimicrobial drug resistance. Another concern is the reactions to irradiation which can have more side effects on the skin. Concerning moist desquamation treatment from irradiation, physicians have to realize that it also has an effect on wound healing process.

It will accelerate the existence of re-epithelialization more quickly. The study of the result of hydrocolloids which is a wound treatment in semi-permeable dressings was a combination of polymers, for instance, polysaccharicles, sodium car boxy methyl cellulose, pectin gelatin, and adhesive. When they were used to cover the wounds, polymers would cake with exudates and helped remove them or dead tissues from the wounds. In addition, it would balance the moisture in wounds with low to moderate levels of exudates, for example, moist desquamation from irradiation [21]. These gel products are used to help wounds not too dry and absorb exudates. When it is applied to a wound, a piece of sterile gauze is recommended to cover the wound for rapid healing. Salvage surgery after RT is sometimes held and it can cause a wound healing problem after the surgery among groups of patients. After RT, the skin will become atrophy. The soft tissues will become fibrosis. Desquamation and skin ulceration will occur. In some severe cases, patients can have a deep wound or a fistula.

1.3. Wound healing process after RT

Wound healing depends on the reactions among different types of cells, such as keratinocytes, fibroblasts, and endothelial cells. Epithelial wound closure is the most essential and this process is needed to stimulate the functions of keratinocytes and dermal fibroblasts [22]. Wound healing process has three stages. The first phase is the occurrence of hemostasis and inflammation which will occur on 0-4 days. The second phase is the process of proliferation which will arise on the third day to the third week. Maturation will occur in the third phase which takes place from the third week to two years. All three stages are controlled by the complicated network of cytokines, the grow factors, and cellular receptors. These cytokines are produced in a very large quantity after injuries from the irradiation. This results in accumulation of cytokines without control and it will later become fibrosis [23]. The current clinical practice guidelines on radiogenic ulcer are to keep wound healing to standard of care, to alleviate malnutrition, and to have an effort to keep the patient's hemoglobin level. Hyperbaric oxygen (HBO) is one of the approaches to manage oxygen in tissues as it has positive responses to the treatment for osteoradionecrosis. It theoretically helps increase the concentration of oxygen in capillaries and create neovascularization [24-27]. HBO is currently used to heal chronic wounds from diabetes and wounds from irradiation. In any case, HBO should be used together with standardized wound healing protocols. There will be new medications and innovations in the future which help wound healing from irradiation. At present, there are a number of studies conducted including special wound healing using membranes to cover irradiated wounds, for example, hydrogel membrane or even human skin graft.

2. Salivary Glands

Each salivary gland provides different types of saliva, for example, the parotid gland, which consists of serous acini and produces proteinaceous saliva which has the texture qual-

ity of water while the submandibular gland, which consists of mucous and serous acini, produces saliva which is moderately sticky, and a sublingual gland which consists of only mucous acini produces very sticky saliva [28-30]. These three saliva glands are the main glands which produce 70 to 80% of saliva whilst the remaining saliva is produced by other small salivary glands which are spread around the entire oral cavity [28-30]. When stimulated, most of the saliva is produced by the parotid gland. The main function of saliva is to lubricate to protect the oral cavity from bacteria, to maintain the balance of tooth minerals, to clean the oral cavity, to enhance the pH balance and assist in food digestion. When a salivary gland is radiated with a high dose of radiation, the tissue of each gland is damaged which results in cessation of saliva production. The structure of salivary gland tissue is replaced by thin fibrous connective tissue in between the lymphocytes and plasma cells. As a result, the salivary glands produce membrane atrophy [31,32]. Even though a salivary gland has a low division property, but it is very sensitive to radiation. The serous acini cells of a submandibular salivary gland are the most sensitive to radiation. The second most sensitive to radiation are the serous acini cells of the parotid glands. The mucous acinar cells of the submandibular glands and sublingual glands are the least sensitive to the radiation [33]. Therefore, mouth dryness is the first symptom experienced by a patient after a few days of radiotherapy. Reports indicate that, even a low dose of radiation of 2.25 Gy, can reduce up to 50% of saliva production within 24 hours of radiation therapy [33]. If every salivary gland is in the area affected by radiation, it can result in sticky saliva for one week (with a dose of approximately 10 Gy), saliva production will decrease beyond 50%. When the radiation is completed with approximately 60Gy, saliva production decreases more than 75% [34,35]. Some studies report that the amount of saliva production decreases after having the radiation beyond 40 Gy [36,37]. Driezen [34] report the reduction of saliva pH after six weeks of radiation (approximately 50 Gy), from the average of 7.01 to 6.83 and the production decreases from 83.3% to 44%. At the same time that the saliva pH changes, the intensity of minerals in the saliva increases respectively including sodium, chlorine, calcium, magnesium and protein, while bicarbonate decreases. Bicarbonate is the most important factor in creating pH balance in saliva. It fights acidity from tooth plaque. Bicarbonate increases the pH of saliva, therefore, if the intensity of bicarbonate decreases because of the reduction of saliva, it affects the pH balance and results in high acid-content saliva.

Treatment for radiation induced mouth dryness or xerostomia

Radiation induced xerostomia may be treated by alternative methods depending on the response to stimulation attempts.

2.1 Treatment for the patient group that responds positively to stimulation (Responders)

As mastication is a physical stimulation to salivary flow, irradiated patients are advised

to chew thoroughly to generate more saliva. Carrots or sugar-free chewing gum are suggested to encourage chewing. Studies have found that after about 1 – 2 weeks of gum chewing, saliva from the parotid glands is increased. Apart from that, the saliva pH level is also increased which results in a suitable pH balance within the oral cavity [38]. The best saliva stimulation is provided by acidic food. Therefore, sour fruit or candies with a citric acid component are used to stimulate saliva. However, these are not recommended in patients who still have teeth as it can ruin tooth surface. In the responders, the use of parasympathomimetic drug e.g. pilocarpine was recommended to manage the symptom of mouth dryness.

2.2. Treatment for the patient group that does not respond to stimulation at all (Non-responders)

This group of patients does not respond to any method of stimulation. Other methods to moisten the oral tissues are needed. The easiest method is drinking more frequently. The patients should carry a personal drinking water bottles to allow them to drink more often. Another method is using artificial saliva. There are several types of artificial saliva including aqueous ion solution or aqueous mixed with carboxymethyl cellulose (CMC) or mucin containing solution or glycoprotein containing solution or they may use enzyme containing gel. These saliva substitute options can decrease the symptom of mouth dryness and there is little difference in the results between each. Studies done by Visch [39], found that one third of the patients do not get any benefits from using these substances. Hatton [40], has found that substituting substances which contain mucin-base can better lubricate than those containing CMC.

2.3. How to prevent and manage radiation induced xerostomia

2.3.1. Using saliva substitutes

These substitutes consist of mucins and carboxymethyl cellulose or other substances which have similar qualities to saliva. However, there is no evidence that indicates the patients' satisfaction with the treatment result. Also, the results of the randomized studies do not show any benefit in the patient symptoms when using these substances comparing to the placebo [41-43].

2.3.2. Saliva stimulation after being irradiated

Saliva stimulation using pilocarpine which is a cholinergic Para sympathomimetic type, acts as a stimulator to muscarinic receptors. The usage was first studied in 1964 [44], and was confirmed by the randomized studies in the last few decades that it is one of the effective methods to cure the symptom of dry mouth [45,46]. The first studies were performed by adjusting the amount of medicine applied to be 2.5-10 mg, 3 times per day for a period of four months. The modification was based on the effectiveness as well as the side effects [45]. The later stud-

ies were performed by randomly choosing the patients and giving them 5 or 10 mg of placebo three times per day [46]. The evaluation of both studies was performed using questionnaires which asked about the adequacy of saliva including mouth dryness, discomfort within the oral cavity, speaking difficulty, chewing and swallowing, and the denture wearing. The necessity for the use of artificial saliva together with the patients' feeling regarding dry mouth are improved. The results of these studies have shown that the symptom of mouth dryness in the patients using pilocarpine have improved with statistical significance. The best result was found with the dosage of pilocarpine of 5mg three times per day. There is no evidence that using 10 mg of pilocarpine produces better results than 5 mg, however the higher dosage does not give more effective treatment, but produces side effects such as sweating, nasal tissue inflammation, and nausea. Therefore, the appropriate dose of pilocarpine suggested is 5 mg, three times per day. Interestingly, the permanent flow of saliva was not observed in any study.

A non-randomized study performed in France has found that two thirds of the patients who used the medication have significant differences in symptoms improvement. The study showed that the number of patients who could not swallow hard food before the treatment but who could, following the treatment, had doubled [47]. From these studies it can be concluded that at least one to two thirds of the patients benefit from using this medicine. However, it may take up to four weeks to see the effectiveness of the medicine usage. For the patients who do not respond to the 5 mg dose, the dosage can be increased up to 10mg but the side effects must also be concerned. Six to eight weeks after the application of this medicine, appointments should be made for follow-up medical treatment. A physician may continue to prescribe this medicine for patients even after the mouth dryness has been cured. However, the side effects and the patients' resistance to the medicine must be considered, especially in patients with high blood pressure, kidney disease, severe respiratory disease, arrhythmia or patients with hypersensitivity to this group of medicines. Also, before this medicine can be prescribed, the physician should have prior history about the patients' closed angle glaucoma. In the event that the physician is unsure about the significance of this history, the patients should consult with an ophthalmologist in order to check the patients' eye pressure as well as screening the closed angle glaucoma prior to the application of this medicine.

Chitapanarux et al. [48] have studied the results of the oral application of pilocarpine to manage the symptom of xerostomia in head and neck irradiated patients. The study has been conducted as a single blind type to compare the results of using a placebo and pilocarpine in the same patient. The study was done in head and neck cancer patients whose irradiated areas covered the parotid saliva glands at least 5000 cGy and had the symptoms of xerostomia. The procedure involved giving the patients the placebo three times per day for one month, together with the questionnaires (subjective assessment) and the objective assessment by the supervising physician. After that, pilocarpine is prescribed, 5 mg three times a day for three months to-

gether with subjective and objective assessments each month. The results of using the placebo and pilocarpine were compared. The results revealed that of the 33 patients, the symptom of mouth dryness was significantly better in all of them in the first month of using pilocarpine and this efficacy continued until the end of the study. The objective xerostomia assessment which was evaluated by a physician, as well as the subjective assessment found that the patients taking pilocarpine, had significantly different statistical clinical symptoms than those taking the placebo. The side-effects of using pilocarpine found in this study, is the same as that observed in other studies. These effects are sweating, nausea, arrhythmia and increased tearing. However, sweating is the most observed side-effect. If the patients cease using pilocarpine, the medical effect also stops. Therefore, the patients will have a life-long commitment to this medicine. Apart from the studies on using pilocarpine, some other studies include acupuncture and the use of hyperbaric oxygen, but there is no evidence to support their relevance therefore the method is not applicable.

2.3.3 Protection of saliva glands whilst being irradiated

It may be of interest to investigate if there is a method of prevention of oral cavity dryness other than drugs. One of the methods is the application of pilocarpine along with radiation. One theory proposes that if the serous cell is damaged during radiation, there is a leakage of granules within the cells which consists of proteolytic enzymes and it is believed that if pilocarpine is applied during radiotherapy can prevent this damage, reducing the number of inter-cellular granules [49]. However, the results obtained from this experiment does not support this theory [50]. There are controlled studies which make comparisons between patients who did and did not receive pilocarpine while being irradiated. The results show that the symptom of mouth dryness decreased [51,52], together with an increase in the amount of saliva. The Radiation Therapy Oncology Group (RTOG) [53], has randomly studied 249 patients and the Princess Margaret Hospital (PMH) [54] has studied 130 patients. Patients who received radiotherapy more than 50 Gy and covered more than 50% of the major saliva glands were randomly prescribed the placebo and 5 mg of pilocarpine 3 times per day during the period of radiation and up to 3 months after the radiation. The patients studied by the PMH were given the prescription one month after RT. In the study by RTOG, it was shown that the saliva flow level in patients using pilocarpine was higher with statistical significance at the time of the RT termination and after 3 months of the radiation. But no difference at 6 months after RT. Some further studies were made of the effects of using this medicine on the patients' quality of life but no relations between saliva flow rates and the mouth dryness was seen. The evaluation of the study performed by PMH was done through questionnaires. The results did not show any differences between the two groups of patients.

Another group of medicines which has proven to be able to prevent the salivary glands from being damaged by the radiation is the radiation protector group, which is called

amifostine (WR-2721). This medicine is organic thiophosphate which can be dephosphorylated by alkaline phosphate enzyme which is in plasma membrane to active metabolite (WR-1065). After that, effective substance WR-1065, will act as a scavenger of free radicals caused by radiation. Because Alkali phosphate enzyme is rarely found in cancer cells in comparison to normal cells, the enzyme chooses to protect the normal cells which results in an increase of therapeutic index in radiation [55,56]. Due to the very short half-life of this medicine, the application is to be injected into the vein, a short time before each session of RT, actually not more than 15 minutes. The side-effects frequently found are nausea, vomiting and low blood pressure. The study done by Brizel et al [56], a large random study which compared the patients' prescribed amifostine 200 mg/m^2 before each radiotherapy session with patients who were not prescribed any drugs. The evaluation of mouth dryness was done by subjective assessment using a questionnaire and the objective assessment, by the evaluation of the saliva flow rate. The findings show that the number of patients with prescribed medicine who had grade 2 xerostomia or more were lower than the control group with statistically significance. There is no difference between oral mucositis and the local control rate between these two groups of patients. Even though there is clinical evidence that supports the efficiency of salivary gland protection with no cancer prevention in this medicine, the application of this medicine is not popular or acceptable. This is because of the price and also the complicated usage of this medicine which must be applied in a very short time before the radiation. The side-effects caused by the medicine, primarily low blood pressure in patients, also concerns the physician. There are some studies about this medicine which suggest subcutaneous injection instead of intravenous both of which provide equal effectiveness. The different side effects are that subcutaneous does not cause low blood pressure and severe vomiting but does cause skin toxicity in the area injected [57].

Protect saliva glands by using sophisticated radiotherapy techniques

Limiting the volume of salivary glands from receiving a high volume of radiation can help decrease mouth dryness from radiation. There are several studies with statistical significance about three dimensions conformal radiotherapy (3D-CRT) as well as intensity modulated radiotherapy (IMRT) in the ability of partially maintaining the salivary gland and assistance in decreasing the amount of radiation to the salivary glands [58-63]. The latest systematic review and meta-analyses concluded that IMRT significantly reduces the risk of moderate to severe acute and late xerostomia compared to 2D/3DCRT in curative intent RT for head and neck cancer with moderate quality evidence [64]. A study from the University of Michigan which was done by providing questionnaires to IMRT bilateral neck irradiated patients in comparison with patients irradiated using normal techniques [65]. After the one year of follow-up, it was found that the level of mouth dryness in patients with IMRT technique was 3.1 ± 0.19 compared with 5.1 ±0.2. The higher level was the worst symptom of mouth

dryness. It can be concluded that IMRT technique had two scores more useful in decreasing the mouth dryness. In addition, Eisbruch et al [65], have found that two years after having IMRT radiation, the flow rate of saliva from protected parotid glands has been back to the same state as before being irradiated. The submandibular glands are also the important part for resting saliva production. However, it is very difficult to protect these glands from being ruined by the radiation, especially in the cases with bilateral neck radiation because they are very close to the cervical lymph nodes level II. There are some studies about using medicines along with the IMRT, for example Valdez et al [51], have found that the patients whose parotid glands in the area of radiation cannot get any benefits from using pilocarpine with the radiation.

Saliva is an important factor in oral cleaning and it assists food digestion. Because of its characteristic of being 'water-like', saliva helps in cleaning and with enzymes such as amylase, protease, nuclease which make saliva sticky (mucin), it helps in bonding food particles, whilst watery saliva helps in dissolving food and promotes taste enhancement. A reduction of saliva makes a patient eat less which leads to malnutrition. Moreover, a decrease of saliva and a change of food taste acquisition may cause pain in an oral cavity and throat due to radiation mucositis in some patients. As a consequence, a patient has more serious malnutrition problems.

3. Oral Mucosa

Oral mucosal tissue reaction to radiation depends on many factors, such as the fraction of radiation used, the areas to which radiation is applied and patient's oral hygiene [34]. Mucous membrane is one of the very sensitive organs to radiation and also has quick cell replacement. These qualities cause a red and swollen area after one week of RT [66]. If a normal fractionation is applied, stem cell killing and repopulation of mucous is balanced. But if more than 2 Gy of radiation per fraction is applied, the greater volume causes more cell-killing than stem-cell division, which leads to a patient's confluent mucositis. This starts in the third week of radiation [66]. The swelling and redness of the mucous membrane is caused by epithelium getting thinner as well as the expansion of blood vessels and the inflammation of the submucosa layer [67,68]. If the radiation is continued, mucosa falls off and this will cause wounds and creates fibrinous exudate which covers the wound. As a result, a patient will suffer significant inflammation of the mouth especially when eating hard or spicy food. A patient will therefore have discomfort with food swallowing and speaking. These symptoms will remain for approximately two or three weeks after RT and they will subside eventually. There are several levels of severity of mucositis. The least severe level is slight redness and swelling, and the most severe is wounds. The problems that can follow include infection which can spread to the blood system as well as feelings of pain and uneasiness which can lead to delay or decrease RT dose or even termination of treatment. The patient may need to be admitted in a hospital due to the inability to eat which dictates that patients be fed intravenously.

The Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ ISOO) recommends the prevention and the treatment of radiation induced oral mucositis. Oral cavity care is a key role in the prevention of oral mucositis. They also have recommended utilizing benzydamine hydrochloride mouthwash, which is a non-steroidal anti-inflammatory agent, to prevent oral mucositis in head and neck cancer patients receiving moderate doses of radiation up to 50 Gy without concomitant chemotherapy with the level I of evidence [69]. Still, there has been no evidence to support using this mouth wash to prevent oral mucositis in patients who received high dose radiotherapy and concurrent with chemotherapy which is the standard of care for the curative intent of locally advanced squamous cell carcinoma of head and neck. Chitapanarux et al. [70] compared the efficacy of benzydamine HCl with sodium bicarbonate mouthwash in the prevention of high dose of radiotherapy concurrent with platinum-based chemo radiotherapy induced oral mucositis in head and neck cancer patients. They found that this mouthwash was superior to basic oral care using sodium bicarbonate mouthwash in terms of reducing the severity of oral mucositis and encouraging trend for the less need of oral anti-fungal drugs.

Apart from mouth dryness and inflammation of oral mucosa, radiotherapy has also change to oral microflora. Human saliva has many antibacterial systems to protect the host from infection. Normal saliva has mucin, electrolytes and poly-peptides which contain proline which control oral bacteria. Secretory immunoglobulin A helps in coating bacteria and fungi prior to combining them with white blood cells, after which they are destroyed. Negative poly-peptides damaged the bacteria cell wall and fungi which causes the cell walls to split which is the primary mechanism to prevent oral candidiasis. When the saliva glands are destroyed by radiation, it results in an imbalance of the body's immunization from bacteria. This leads to exposure to oral fungi and caries. Candidiasis is an oral and throat infection that is most often found in irradiated patients [71]. It has been found that irradiated patients have up to 100 times more oral fungi than non-irradiated people. In the first stage of fungi infection, a patient has redness and pain in their oral cavity which some physicians have misdiagnosed as radiation mucositis. However, a physician should observe that if there is symmetrical redness in tissues and this occurs on the non-irrradiated part, that is candidiasis. In the chronic stage of candidiasis, the redness can be found on the corner of the patient's mouth and beneath dentures. Irradiated patients have more bacteria that cause crises than that does not. Streptococcus mutans, Lactobacillus, S. Sanguis, Neisseria Fusobacterium, and Actinomyces are the most common types found. Getting rid of oral bacteria such as gram-negative bacilli by using lozenges which have a mixture of antibiotic such as polymyxin B, tobramycin and amphotericin B, can prevent the occurrence of the most severe mucositis [72]. Mucositis can escalate in severity if patient wears dentures which are ill-fitting. Therefore, it is suggested that the patient should leave their dentures in their mouths whilst being irradiated to prevent any mucosa wound. Patient should also keep the oral cavity clean and moist by drinking enough water. Chlorhexidine, which has

a characteristic of a broad-spectrum biocide effective against gram-positive bacteria, gram-negative bacteria, yeast and fungi, is recommended. However, chlorhexidine cannot kill virus, fungus spore or the acid-fast bacteria type [73].

For oral candidiasis, using hydrogen peroxide or normal saline mixed with nystatin (200,000-400,000 IU) to clean the mouth by retention in the mouth for three minutes before swallowing. This action must be repeated four times per day for two weeks. If the symptoms persist, the usage of systemic ketoconazole 200 mg once per day for at least two weeks is recommended [74]. A decision for oral candidiasis treatment is based on the patient's clinical symptoms. The treatment can be given before the laboratory confirmation. The risk factors for the treatment are cigarette smoking, alcohol drinking and dentures. The studies indicate that using lozenges is also effective. In cases where patients have a very dry mouth, lozenges cannot dissolve, therefore a solution mixture is recommended [74]. Apart from that, a patient who received radiotherapy and/or chemotherapy has more possibility of oral wounds from Herpes Simplex Virus (HSV) also [75]. HSV is the main virus that causes oral infection in head and neck radiated patients. An appropriate medication is the oral application of acyclovir 400 mg, every eight hours for 7-14 days.

Pain killers are recommended when the patient's quality of life is threatened by mucositis symptoms such as pain, inability to eat or weight loss. Pain killers must be applied according to the WHO recommendations pertaining to increasing strength from paracetamol, codeine and then to strong opioids. The initial dose should be short-acting and if this is not effective, may be changed to long-acting opioids. When the patient's pain subsides, the dose must be decreased. The usage of benzydamine hydrochloride can also reduce the patient's pain. The local anesthetic activity of this product has been shown to be useful in the treatment of painful oral mucositis. Many studies suggested that topical benzydamine was effective in reducing the severity of the pain from radiation-induced oral mucositis [76-79]. Other medicines which can reduce pain are benadryl mixed with kaopectate, or kaopectate mixed with milk of magnesia, or xylocaine viscous [74].

4. Taste Buds

There are several taste buds on a tongue's circumvallate papillae in front of the sulcus terminalis gland. On the front part of a tongue there are a moderate number of fungiform papillae. The rest of these are spread on the tonsil gland and the base of tongue, soft palate, laryngeal surface of the epiglottis and posterior pharyngeal wall down to the lower part of cricoid cartilage [80]. These taste buds shrink with time. Taste buds for sweetness are on the tip of the tongue while the buds for sourness are on either side of the tongue. The buds for bitterness are circumvallate papillae and the buds for saltiness are spread all over the tongue [81]. Saliva helps taste buds to perceive the tastes better and it also helps these buds adjust to different

tastes. Normally, saliva consists of bicarbonate, glucose, sodium and urea in low levels which result in the ability to acquire the taste of acid, sweetness, saltiness and bitterness respectively [82]. The state of mouth dryness after radiotherapy causes the loss of taste perception. It also causes faults in taste perception (Dysgeusia). This happens when receiving radiation dose beyond 30Gy where the perceptive ability of these taste buds is gradually lost. Apart from this, the radiation also destroys the taste bud microvilli which causes the taste perception to deteriorate further. Actually, the ability to acquire taste can be partially restored gradually up to approximately 20 to 60 days after the radiotherapy is completed. This ability can be completely restored within 2 to 4 months after the completion depending on the amount of radiation a patient has been treated with as well as the volume of tissue which has been irradiated [83].

5. Jaw Bones

The density of bones is 1.8 times of the density of soft tissue therefore bones can absorb more radiation than soft tissue. As it is the era in which most radiotherapies are of high energy radiation sources, the side effects of radiation on bones have been decreased [35]. Radiation causes the narrowing of the blood vessels in the area being irradiated which results in a decrease of blood to the bones and causes dead cells in the area. Because of the structure of sclerotic connective tissue in the bone marrow, it causes a construction of obliterative endarteritis and periarteritis. However, the severity depends on the dose of radiation received. As we have already known, radiation causes endothelial cells to die and causes hyalinization and blockage in the blood vessels, and this creates fibrosis of periosteum tissue. It also causes osteocytes and osteoblasts to decompose and die then fibrosis was formed in the bone marrow. The number of cells in these tissues decrease and not only that, but the blood vessels also decrease which leads to a lack of oxygen, according to the 3H Theory of osteoradionecrosis (ORN) creation; 3H including hypo cellular, hypo vascular and hypoxic [84]. Trauma or damage to the irradiated jaw bone caused by tooth extraction or denture irritation or oral cavity surgery can increase the risk of ORN. Symptoms can vary from ulcer, pain, swelling, truisms, exposed bone in the oral cavity, loss of sensation in the affected area, or infection. Jaw bones are the most common site of ORN in head and neck cancer. However, ORN of skull base can be found after radiotherapy for nasopharyngeal cancer with the different symptoms such as headache, epistaxis and foul smell.

ORN can prevented by using the sophisticated technology of radiotherapy to limit high dose radiation to the mandible and pre-radiotherapy oral care. The treatment options such as antibiotic, hyperbaric oxygen therapy, surgical intervention, and the combination drugs of pentoxifylline and tocopherol [85].

6. Teeth

We do know very little about the effects of radiation on teeth. Some studies have shown

that irradiated teeth have decreased amounts of calcium compared with non-irradiated teeth. However, other studies did not confirm this phenomenon [35]. But all studies shared the same conclusion that radiation results in less blood vessels in the dental pulp and it also causes connective tissue which eventually leads to shrinkage and atrophy. Dental pulp tissue is very sensitive to infection and wound as well as to other dental procedures [35]. A patient with problems concerning dental pulp arising from radiation usually has less dental pain even though they may have caries or some open wound to dental pulp tissue. Caries caused by radiation have different characteristics from normal caries. Teeth with a smooth surface (which actually have more resistance to caries) are the first sites for caries in irradiated patients. After caries have started it spreads very quickly within a few weeks.

Enamel of the teeth has peptides and water. When the free radicals H+, OH- were released from the indirect effect of radiotherapy, the interaction of these free radicals with other ions contribute the new compounds. And together with the changes of mineralization in the enamel tissue resulting the cracked teeth [86] (**Figure 4**).

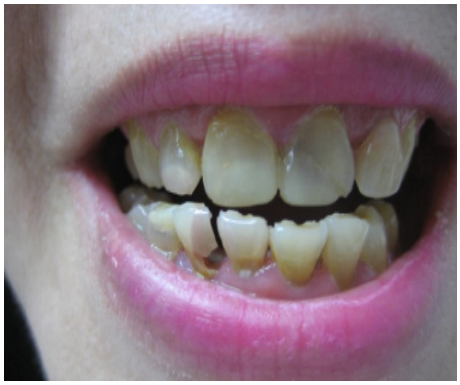

Figure 4: Shows the enamel delamination, cracked teeth, and carries after 5 years of radiotherapy

6.1 Dental Care in Order to prevent and reduce the Side-affects

As previously mentioned, prevention is the easiest route to reduce the side-effects from radiation therapy on these areas of the body. The following describes preventative dental care for reducing the side effects. The procedure is as follows:

1. Pre-treatment oral assessment

In this stage, if possible, the radiation oncologist and a dentist should work together either on the radiotherapy field and dose being used on a patient or some aspect that a dentist has found which may cause complications to the radiation plan. A dentist should examine both the teeth and the periodontium – which consists of gum (gingiva) and periodontal joints (periodontal ligament), tooth root enamel (cementum) and tooth bone (alveolar bone). After that a dentist should examine and remove anything that can cause problems before radiotherapy is applied, for example in a situation where a patient does not have good oral hygiene or broken teeth, or caries as well as any periodontal disease. In a case where a patient has gum infection

or cysts and needs an X-ray to confirm the spread of the infection on the alveolar bone.

2. Extraction before radiotherapy

As the patients with osteoradionecrosis (ORN) usually are those who have teeth before the radiation and as extraction can destroy the irradiated alveolar bone, every tooth which is in the way of the radiation must be closely assessed. There are many factors related to which tooth a dentist should consider extracting before the radiation. However, there are still some controversies about an indication of extraction before radiation [35]. A patient's tooth condition is the best indicator for prognosis. Teeth with poor prognosis should be extracted, for example, a tooth with advanced caries or a tooth with periodontal disease. This is because they are not only difficult to take care of but also have the potential to cause many other side effects. A Patient's awareness of oral hygiene is also the key role to prevent late complications of jaw bone and teeth. A physician has to inform a head and neck irradiated patient about the side effects of radiation therapy and encourage a patient to take good care of oral hygiene. A patient with poor oral hygiene before treatment indicates that he or she may not take good care of personal oral hygiene after treatment. Therefore, this becomes another factor that a dentist must consider before deciding on an extraction prior to radiation treatment. The urgency of tooth extraction before radiotherapy is also concerned. Sometimes cancer of the head and neck needs the urgent treatment intervention. Delay between an operation to treat such conditions and commencement of radiotherapy may result in effects on disease control and survival rates of patients [87]. When the radiation oncologist has determined that cancer has a fast growth rate and the delay in treatment can affect the patient's treatment results, extraction before radiation is not essential. A multi-disciplinary team is needed for such a case and the patient must have this explained and accept the side effects resulting from failure to tooth extract before radiotherapy.

Methods of radiotherapy are also important factor in a decision to extract the tooth before radiation. Even though the radiation used these days involving high energy, external beam radiotherapy, destroys less of the alveolar bone than using the low energy external beam, it still damages the soft tissues, saliva glands and the alveolar bone which the radiation gets through. Therefore, the importance of radiation technique is not to be overlooked. The areas being irradiated are the most important factor that effects the seriousness of the side effects. If radiation is applied to the salivary glands and mandible as may occur in radiation on cancer of the oral cavity, tonsil, base of tongue and retro molar trigone, it causes serious mouth dryness and problems in blood vessels to the jawbones, resulting in caries and osteoradionecrosis. In this case, extraction before radiotherapy is recommended. Another important factor is the dose of radiation. Most cancers on the head and neck are squamous cell carcinoma which need a high dose of radiation, approximately 6,000 - 7,000 cGy. In this case extraction before radiotherapy is recommended. However, lymphoma which occur most commonly in younger

patients, require a lower dose of radiation. Therefore, extraction before radiotherapy is not recommended for this latter group of patients.

The disease prognosis and the intent of treatment are also important factors. If the aim of the treatment is merely to keep the patient alive, the possibility of controlling the disease is very low or the patient has very poor performance status. In order to not make the patient suffer, extraction before radiotherapy is not recommended. However, there are still some arguments about this.

6.2 Prevention of caries affected by radiation

Caries affected by radiation is an important issue because it reduces the patient's quality of life after being irradiated on the head and neck. There are many factors that cause caries such as some bacteria, food, tooth structure and the condition of mouth dryness. Therefore, it is necessary for the patients to have proper education about this, for example, they should be advised about consumption of a suitable portion of carbohydrate because high consumption of carbohydrate can lead to destruction of calcium beneath the tooth enamel, while the tooth surface is still intact. The calcium on a tooth surface has very low solubility while the calcium beneath the tooth enamel has not. A loss of calcium beneath the tooth enamel causes small holes which can allow acid to get to deeper layers of a tooth. As has been mentioned earlier, saliva has a significant role in creating pH balance within a tooth, patients have to be educated about how to protect their teeth from caries affected by mouth dryness caused by radiation as follows:

1. Food consumption adjustment

This adjustment can be done by reducing sugar and carbohydrate consumption. Sweetener substances such as sorbitol, xylitol or aspartame and saccharine can be used instead of sugar since these substances cannot be transferred into acid by bacteria inside the oral cavity. Additionally, patients should avoid eating foods which can cause oral irritation or mouth dryness such as frozen, spicy, sour and hot food as well as avoiding drinking alcohol and carbonated drinks or smoking cigarettes [88].

2. Fluoride usage

Fluoride can reduce caries. The effectiveness of fluoride usage depends on the intensity of the fluoride as well as the frequency of fluoride use and its types of compound substances. A low level of fluoride intensity protects tooth enamel mineral from oxidation as well as enhancing tooth enamel mineral embedment. The studies have found that a discontinuation of fluoride usage can diminish the level of fluoride to the patient's original fluoride level within 2 weeks [89-91]. Therefore, regular usage of fluoride is suggested for patients. Moreover,

patients should not use much water to clean the oral cavity after using fluoride as it can flush the fluoride. Though there are no solid suggestions to prevent caries resulted from radiation, fluoride treatment has resulted in much lower numbers of tooth extractions in irradiated patients. Thus, apart from having daily fluoride treatment at home, patients are advised to regularly consult their dentist every 3-6 months. Suggested fluoride formulas are: 0.4% stannous fluoride, 1.1% sodium fluoride, 1.23% sodium fluoride, 1.23% acidulated phosphate fluoride [89-91]. Patients have to use a brush to smear or spread fluoride on their oral cavity mold, then keep the fluoride covered mold in their mouth for 5-10 minutes. The positive and negative effects of different types of fluoride are: stannous fluoride (SnF2) can protect the tooth root from caries and kill bacteria which causes caries to the tooth root. However, it has a metal-like taste and can cause gum irritation as well as marks on the patients' gums and teeth. Sodium fluoride not only causes less allergy and irritation on gums and teeth, but also has a good taste and proper pH level as well as quality tooth mineral protection. However, it has lower resistance to bacteria than Stannous fluoride. While acidulate phosphate fluoride has good taste, it does not leave any mark on patients' teeth and gums, it is able to prevent caries as well as maintain tooth mineral. It is effective only with a low pH condition [89-91].

3. Saliva stimulating and pH level increasing

Stimulated saliva contains high level of bicarbonate. Therefore, chewing gum can increase a level of bicarbonate as well as of pH in saliva and enhance mineral absorption inside an oral cavity [92,93]. Some studies introduce chewing hard cheese which contains nitrogen as a process of pH level increasing. While hard cheese is being chewed, casein protein is digested by a proteolysis procedure. As a consequence, pH, calcium and phosphorus levels in plaque increase, leads to a result in stronger tooth enamel [94,95].

4. Oral care after being irradiated

Following discussion about care of the oral cavity prior to radiation which included plaque removal and care of remaining teeth, patients have to know how to maintain the hygiene of their oral cavity. There are 4 actions things patients have to do to maintain their oral hygiene which are: regular inspection of the oral cavity, regular brushing and flossing of teeth, regular flushing of the mouth. All of these are recommended for patients to apply before and after the radiotherapy. A small size head with soft bristles is recommended because this toothbrush can access the entire mouth, teeth, gum and spaces between the gum and teeth with fluoride toothpaste [96]. Some studies suggested toothpaste with salt and baking powder [97], because most toothpastes have bleach and effervescent agents such as sodium lauryl sulfate (SLS), which cause irritation and wounds to oral cavity tissue. The patients, especially those with mouth dryness, should not use the latter of these types. The patients should brush their teeth at least twice per day up to four times per day, which means after each meal and before bed, and

also every four hours during the day before bed time [98].

Oral cavity rinse with clean water after a meal can get rid of food scraps between teeth. However, it does not help with reducing the acid level within a mouth. Because sugar takes less than one minute to spread to teeth plaque, while saliva takes approximately 2-3 minutes to chemically deteriorate sugar, these natural processes disturb in the patients with radiation induced xerostomia. Washing the mouth with sodium bicarbonate instead of water can increase the pH level of saliva and maintain a pH balance. After each brushing, the patients should gargle so that their mouth and throat are properly cleaned. The recommended mouthwash is hydrogen peroxide or normal saline or a mixture of hydrogen peroxide and water in the ratio of 1:2 or 1:4 [99]. Alternatively, the patient may use one tablespoon of sodium bicarbonate mixed with a glass of water [40] which can increase the pH level of the saliva. The patient may also use half a teaspoon of salt plus one teaspoon of yeast mixed in one liter of water. However, the mouthwash that has strong alcohol content is not recommended as it can cause irritation and dryness in oral tissues. In addition, sodium bicarbonate, which may be found in a form of sticky cream can be used on the gum and tooth-base to decrease bacteria. The last step is to use unwaxed dental floss. These are the regular procedures following radiation.

7. Larynx, Pharynx, and Temporomandibular Joint (TMJ)

A swelling of the larynx is one of the radiation side effects frequently found in head and neck irradiated patients. A swollen larynx causes the swelling of connective tissues over the swollen area which results in the patients' long-term problems of pronouncing and food swallowing [100]. Preserving of a larynx for pronunciation and food swallowing is one of the main objectives of the head and neck cancer treatment. If there are problems which may be caused by radiotherapy, laryngeal preservation can be of less interesting. A fatal and long-term side effect of radiotherapy which is not frequently found is chondroradionecrosis **(Figure 5)**. The CT scan of patients with chondroradionecrosis shows an anterior dislocation of arytenoids, gas bubbles, fragmentation and collapse of cartilage which is sometimes difficult to differentiate from a recurrent tumor. In that case, an inspection by a physician and regular X-ray and endoscopy examinations are recommended. PET-CT scan or diffusion-weighted MRI are also recommended for patients whose symptoms worsen, as they are useful for the diagnosis of illness. Bilateral vocal cord paralysis can happen to patients with nasopharyngeal carcinoma or patients with radiated skull base. The symptom is caused by a neuropathy of the cranial nerve on the patients' skull base. Bilateral vocal cord paralysis can also happen to patients with severe neck fibrosis. In these cases, the most frequent finding is with the hypoglossal nerve and with a latency period of 1-20 years.

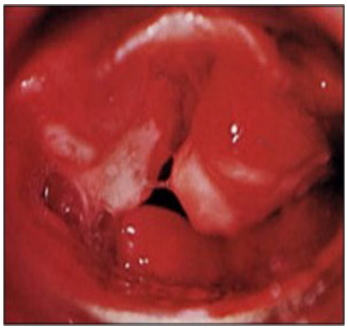

Figure 5: shows chondroradionecrosis which affected to patient's pronunciation, swallowing and breathing

Difficult swallowing is another side effect frequently found in patients after receiving radiotherapy plus chemotherapy for head and neck cancer. In the studies of RTOG 91-11 [101] with comparisons between radiotherapy and chemotherapy, the findings indicate that cancer cells could be more effectively controlled in patients who had radiotherapy together with chemotherapy. However, after 1 year of treatment, 23% of the patients who received two modalities of treatment not able to eat hard food while 9% of the patients who had only radiotherapy alone had the same problem. Aspiration pneumonia is another consequence of swallowing difficulty [102].

Sophisticated high technology of radiotherapy can reduce the delivered dose to the swallowing organs such as constrictor muscle, and larynx. Must also be attention to reduce the dose to major salivary glands and pharyngeal uninvolved mucosa [103].

Radiation on some parts of the head and neck can make temporomandibular joint (TMJ) and chewing muscles overexposed to radiation which causes limitation of jaw mobility or trismus. The degree and frequency of trismus is unpredictable therefore prevention is the easiest solution. However, currently there is no any evidence proven the effective prevention and treatment for trismus. The systematic review by MASCC/ISOO concluded that IMRT may be associated with decreasing prevalence of trismus and jaw exercise appear to be useful in the management of trismus [104].

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