Oral adverse effects of head and neck cancer radiotherapy

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Abstract—Many head and neck cancers are treated with radiotherapy, either by itself or in combination with surgery or chemotherapy. However, exposure to high radiation doses may cause a number of undesirable side effects that may appear during or after treatment. These adverse effects present tough challenges to the patients and their physicians and require life-long strategies to alleviate their detrimental effect on basic life functions and on the quality of life. This article reviews the literature to delineate such side effects and the possible management or treatment options available for each.

Keywords—Radiotherapy, Radiation, Side effects of radiation, Head and neck cancer

I. INTRODUCTION
Head and neck cancer is defined as a heterogeneous group of malignancies that occur in the head and neck region, skin, oral cavity, oropharynx, nasopharynx, hypopharynx, larynx, paranasal sinuses, and salivary glands. A staggering majority of head and neck cancers, (90%) are of epithelial tissue origin, namely squamous cell carcinoma [1].

Recently, it was estimated that the Global Burden of Disease worldwide of head and neck cancer was 890,000 new cases. Head and neck cancer comprising of lip and oral cavity, nasopharynx, pharynx, and larynx cumulates to 5.3% of all cancers (excluding non-melanoma skin cancers). Moreover, head and neck cancer was ranked as the seventh most common cancer worldwide [2],[3].

II. TYPES OF CANCER TREATMENT
The journey to try to cure head and neck cancer has started centuries ago as it is not a novel disease. Treatment using one or more of the following modalities: surgery, chemotherapy, and radiotherapy was established many years ago. The most popular treatment modalities for head and neck cancer are radiotherapy and surgery. The choice to use one or both depends on many factors [4],[5].

According to the United Kingdom national guidelines for head and neck cancer management, in preliminary stages, surgery or radiotherapy have similar healing rates but radiotherapy has an added advantage of allowing preservation of organ functions such as speaking and swallowing in tongue and larynx cancers [6].

In other cases of cancer occurring elsewhere in the oral cavity, treatment may be surgery alone. Advanced cases of squamous cell carcinoma are best managed using a multidisciplinary treatment approach of surgery and postoperative radiotherapy or combined radio chemotheraphy [4].

III. RADIOThERAPy
Radiotherapy plays a crucial role in the treatment of head and neck cancer patients. About 80% (range 73.9 – 84.4%) of all head and neck cancer patients will be subjected to radiotherapy at least one time during the course of their disease [7],[8]

In addition to surgery, radiotherapy is regarded as one of the main curative-intent treatment options in both early and advanced cancer stages with its doses ranging from 54 to 70 Gy, given with a standard fractionation schedule of 2 Gy/fraction, one fraction/day, five fractions/week. Radiotherapy can also be used in combination with concurrent chemotherapy as a nonsurgical in high-risk settings or to promote organ preservation. Thus, radiotherapy is considered a crucial and cost-effective treatment option for patients with a diagnosis of head and neck cancer [9].

The main idea behind the effect of radiotherapy is that it inhibits the tumor cell’s ability to reproduce leading to cell death via apoptosis, necrosis, mitotic catastrophe, senescence, and autophagy [10].

However, the problem lies in the fact that not only tumor cells are irradiated during the course of treatment. A certain degree of unavoidable changes occurs in neighboring normal cells and tissues leading to a myriad of side effects. [8],[10],[11].
IV. ADVERSE EFFECTS OF RADIOTHERAPY

Adverse outcomes of radiotherapy can be divided into acute or late side effects. Acute side effects can usually disappear within weeks or months after the completion of radiotherapy, nonetheless they can negatively impact the course of treatment. Late complications of radiation usually occur at least 3 months after the completion of radiotherapy. All of these detrimental effects can significantly affect the patients’ quality of life [8],[12]. A link was established between the duration and severity of acute and late side effects. One classical explanation states that late side effects are adverse consequences of severe unresolved acute side effects. Such an example of this is acute mucositis in relation to late dysphagia [13].

The acute adverse effects of head and neck cancer radiotherapy include mucositis, thickened secretions, mucosal infections, pain, and sensory disturbances. As for the long term or chronic effects, these include tissue fibrosis, salivary gland dysfunction, increased susceptibility to mucosal infections, neuropathic pain, sensory disorders and an increased susceptibility to dental caries and periodontal disease [14].

The reported acute and late side effects of radiotherapy according to the literature also include cerebral radiation necrosis which is a dire consequence of radiotherapy occurring in head and neck cancer patients [15]. For symptomatic patients the preferred line of treatment is corticosteroids. Other treatment options include the use of hyperbaric oxygen. Surgery is nonetheless reserved for the minority of patients who suffer from refractory symptoms [16].

In addition, salivary gland deterioration and shrinkage of multiple salivary glands such as the parotid and submandibular salivary glands were reported leading to a decrease in the quality and or quantity of saliva. This is clinically manifested in many patients as Xerostomia. Maintaining proper oral hygiene, stimulate salivary glands with saliva substitutes, use chlorhexidine, antifungal therapy, sufficient hydration, and acupuncture to treat the salivary gland [17].

Teeth are also adversely affected rendering them more susceptible to dental caries, plaque, gingival and periodontal infections this is why it is crucial to maintain good oral health, control xerostomia, use topical fluorides and/or remineralizing compounds to protect against such problems [18],[19].

Hard tissue injuries such as osteoradionecrosis in which tissue dehiscence, chronic bone devitalization, hypocellularity and osteolysis can also occur as a result of radiotherapy. Hyperbaric oxygen, antibiotic prophylaxis therapy, and debridement have been proposed as a line of treatment for osteoradionecrosis [20].

Several soft tissue injuries are also common such as stiffness of cervicofacial muscles, limited mouth opening (trismus), swelling and discoloration of the skin, appearance of fistulas with persistent suppuration, muscle fibrosis and blood vessel fibrosis [21]. Some studies have demonstrated that about 94% of irradiated patients exhibit some degree of radiation induced subcutaneous fibrosis. Most of these changes occur as a result of an imbalance between tissue destruction and regeneration. Management of the resulting fibrosis can be done through physiotherapy, myofascial release, external laser, as for the trismus, the use of oral appliances, diet modification, pharyngeal strengthening, and swallow retraining can be beneficial [22],[23].

Nerves also suffer from acute and chronic alterations that may lead to multiple signs and symptoms such as sensory dysfunction, reduced hearing ability or total loss, changes in smell and taste sensation, neuropathies of the brachial plexus and cranial nerves. This may appear clinically as visual impairment, swallowing and speech difficulties attributed to nerve damage as well as neuropathic pain. Analgesics, antidepressant and anticonvulsant medication, physical and occupational therapy, acupuncture, and topical treatment can be employed to manage nerve related symptoms [24].

Changes in taste sensation ranging from hypogeusia, dysgeusia and ageusia were also evident in relation to head and neck cancer radiotherapy. A decline in overall taste perception was clear along with specific reduction in sweet and salt taste [25].

Another frequently encountered side effect of head and neck cancer radiotherapy is radiodermatitis, or inflammation of the skin caused irradiation. Radiodermatitis is characterized by erythema, dry desquamation, moist desquamation, skin folds, and pitting, even to the extent of painful ulceration or necrosis. One of the most effective ways to mitigate the effects of radiodermatitis is the use of topical olive oil [26].
In a recent study comparing different cancer patients, the majority of head and neck cancer patients suffered from fungal, bacterial and/or viral infections after treatment. At staggering levels, 88% of head and neck cancer patients treated with radiotherapy alone and 93% of patients treated with radio chemotherapy exhibited some kind of infection, rendering them more susceptible to infections even after 12 months. The use of prophylactic antibiotics, antivirals and antifungals as well as maintaining proper oral hygiene and treating xerostomia are the main treatment protocols for oral infections [27]. Examples of such infections include candida as seen in the photos below.

One less frequent adverse effect of radiotherapy is melanotic hyperpigmentation. Though commonly associated with concomitant use of radiotherapy and chemotherapy, it has been encountered on rare occasions with radiotherapy alone. This phenomena may be attributed to radiation-induced inflammation which stimulates melanocytes, resulting in hyperpigmentation and can regress spontaneously after cessation of the treatment [28]. Examples of hyperpigmentation are seen below.

The concomitant use of radiotherapy with chemotherapy can also cause an acute inflammatory response in mucosal body tissues leading to mucositis, pharyngitis, and esophagitis. Late toxicities such as voice hoarseness and sore throat may also occur [29]. One of the most popular adverse effects of head and neck cancer treatments is oral mucositis, in which detrimental inflammatory changes occur in the oral mucosa rendering it more susceptible to partial damage or total loss of the epithelial layer. This is often the result of cytotoxic local effects of radiotherapy and/or chemotherapy [14],[30].

Radiation induced oral mucositis is a major debilitating adverse effect to the treatment of head and neck cancer using radiotherapy. It can occur in up to 80% of irradiated patients and up to 100% of patients treated with altered fractionation. Almost
half of the patients receiving radiotherapy will even suffer from advanced stages of mucositis. As a consequence, oral pain is experienced by about 70% of these patients leading to an increased opioid consumption [31],[32],[33].

Oral Mucositis starts as erythema of the oral mucosa, usually followed by clear ulcerations which may be covered by a white pseudo membrane. Early signs of mucositis may appear after the patient receives approximately 30 Gy (at the end of week 3). The severity of oral lesions is also directly proportional to the dose of RT. Thus, almost all head and neck cancer patients subjected to doses greater than 50 Gy are at a high risk of developing ulcerative oral mucositis. Patients may however recover from these lesions 2 to 4 weeks after the last dose of therapy [34],[35].

Oral mucositis is commonly associated with dysphagia resulting in eating disturbances, malnutrition, albumin deficiency and subsequent significant weight loss. A staggering 70% of patients suffering from severe mucositis may also require gastric feeding tubes. Patients are also more liable to increased risk of systemic infections due to the compromised oral mucosal barrier [36],[37].

As a result, increased financial cost, unexpected interruption or cessation of treatment was found in about 35% of these patients. Moreover, 62% of them become severely ill that they require hospitalization. Needless to say, oral mucositis significantly and adversely affects the quality of life of cancer patients [38],[39]. Examples of severe oral mucositis can be seen in the photos below.

![Figure 3- Oral mucositis presented as severe extensive ulcerations and erythema on the tongue in photo A, and on the labial mucosa and sulcus in photos B and C, as well as in the floor of the mouth and lingual frenum in photo D.](image_url)

V. CONCLUSION

Most patients who receive radiotherapy as head and neck cancer treatment experience substantial acute and chronic adverse effects which may greatly influence the patients’ treatment plan and quality of life. This is why it is crucial for caregivers to recognize these adverse effects and to have the basic knowledge of how to manage or treat them.

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