Management of radiation induced xerostomia in head and neck cancer patients

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Abstract

Radiotherapy (RT) continues to play a key role in the management of head and neck cancer (HNC). Xerostomia remains a principal detriment to the quality of life (QoL) for 80% of surviving patients receiving head and neck radiation. Radiation-induced injury to the salivary glands is dose-dependent, and thus efforts have been focused on decreasing radiation to the salivary glands. Decreased saliva production reduces both short-term and long-term quality of life in head and neck survivors by altering taste and contributing to dysphagia. Several radioprotective agents to the salivary gland have been investigated. Surgical transfer of the submandibular gland prior to RT is the mainstay of surgical options in preventing xerostomia. This review focuses on the strategies to improve xerostomia following radiation therapy in head and neck cancers.

Keywords

Xerostomia; radiation therapy; head and neck cancers; salivary glands; submandibular glands

Introduction

Radiotherapy (RT) in combination with either surgery or chemotherapy plays a key role in the management of head and neck cancer (HNC). Up to 40% of patients with early-stage disease are amenable to curative intent treatment with surgery or RT, either in definitive or adjuvant settings.[1] The specialty of radiotherapy continues to evolve to provide patients with better outcomes and reduced complications. However, patients still experience radiation-induced sequelae, the most common of which is reduced saliva production, or xerostomia.

Some degree of xerostomia affects approximately 80% of patients who receive radiation therapy to the head and neck.[2] Subjective feelings of xerostomia are a result of reduced unstimulated saliva from the submandibular glands.[3,4] Further, the minor salivary glands produce up to 70% of the total mucin secreted.[2] During the first week of RT, a 50% to 60% decrease in salivary flow occurs. After 7 weeks of conventional RT, the salivary flow of affected glands diminishes to approximately 20%.[5] Salivary function continues to decline for up to several months after RT.[1] Although some regeneration occurs following therapy, a degree of chronic dry mouth remains a significant challenge for majority of HNC survivors. Decreased saliva production may also further worsen the quality of life of survivors by reducing the sensation of taste and making mastication of food uncomfortable or even painful.[6] The reduction in salivary flow in HNC survivors further increases the risk of dental caries and mucosal fissures.[1] In addition to decreased QoL, patients with radiation-induced xerostomia may also experience significant economic burdens due to the need for oral and dental treatments and possibly dentures or implants, which are out-of-pocket expenses in most countries.[7] Therefore, given the significance of the problem, there has been considerable clinical research in to strategies to reduce xerostomia in HNC patients. Several measures have been investigated for their role in prevention and treatment of xerostomia. These include pharmacologics like pilocarpine, amifostine, non-pharmacologic strategies like acupuncture, neural stimulation, hyperbaric oxygen and surgical options namely salivary gland transfer. This review will focus on current strategies for the reduction of xerostomia in HNC

survivors, including preventative surgical and non-surgical techniques, clinical management of xerostomia and future directions.

Minimizing radiation dose to the salivary glands

The development of intensity modulated radiation therapy (IMRT) has been a major advance in the practice of radiation oncology. IMRT became fairly common practice in most high-income countries in the early 2000s. Prior to this, patients were frequently treated with parallel opposed photon fields with no ability to separate radiation dose from the tumour and the normal tissues within that radiation field. IMRT allows for the radiation dose to conform more precisely to the three-dimensional shape of the tumor by modulating—or controlling—the intensity of the radiation beam in multiple small volumes. Consequently, there is now the ability to conform the radiation dose around the tumor and avoid nearby structures such as the parotid and submandibular salivary glands, minimizing the dose to uninvolved local tissue.[8,9] The precise design of treatment fields to incorporate the target volume while avoiding organs at risk (OARs) can be achieved using modern imaging. Pioneers in this area include Eisbruch et al, who contoured the parotid and submandibular glands, and the oral cavity (a surrogate for lingual salivary tissue), to allow radiation dose avoidance to these structures.[2] They were able to demonstrate in small prospective studies a correlation with radiation dose and the severity of xerostomia using both objective (measuring salivary flow) and subjective (patient reported xerostomia questionnaires) measures. There have also been 3 randomized controlled trials in HNC comparing IMRT and 2D radiotherapy (parallel opposed photon fields) showing a significant reduction in xerostomia in patients treated with IMRT**.** These studies and the work by Bentzen et al on the quantitative analyses of normal tissue effects in the clinic (QUANTEC), have resulted in standard dose constraints commonly used for HNC IMRT, namely a mean dose of less than 26Gy for a parotid gland and a mean dose of less than 39Gy for a submandibular gland.[10] Delivering adequate radiation dose to the tumor volumes always take priority over the dose to salivary tissues in radiotherapy planning. Clinically it can be difficult to spare parotid glands when in close

proximity to tonsillar cancers and/or nodal disease. Similarly, submandibular glands are more difficult to spare in base of tongue cancers or where there is level 1 nodal disease.

IMRT using Protons, or IMPT

In comparison to photon therapy, proton beam therapy (PBT) is another form of external beam radiotherapy that creates a limited high-dose volume to the target site with steeper dose gradients. Protons, positively charged particles, deposit energy in tissue at a certain depth by virtue of a phenomenon called the Bragg peak (Figure 1). This means that protons deposit radiation dose mainly at depth, with a very rapid fall off in dose compared to photons. Thus, proton therapy (PT) offers the possibility of delivering high dose to the target volume with much less dose to adjacent OARs compared to photons.[11] Preclinical and dosimetric studies comparing IMPT to IMRT have consistently demonstrated significant reductions of OAR dose, suggesting IMPT has the potential to decrease acute and long-term toxicities.[12] PBT has grown tremendously in the past few years for the treatment of HNC. However, its utilization has been limited due to cost and its limited availability.[13] Further, lack of randomized controlled trials (RCT) comparing the improved efficacy of PBT over IMRT has precluded the use of PBT as standard of care. Despite these advancements, however, complications like xerostomia remain a principal detriment to the quality of life (QoL) in HNC survivors.[2]

Pharmacologic Strategies

Pharmacologic agents that reduce the severity of radiation-induced xerostomia have been described. Traditional use of mucosal lubricants, sialagogues, and salivary substitutes for short-term improvement of xerostomia are commonly recommended to HNC patients undergoing RT. Theoretically, the ease of accessibility and low-risk profile are attractive features of these agents as first-line treatment and are used both during and after completion of therapy. Oral pilocarpine, a muscarinic agonist, has been used as treatment for xerostomia after radiotherapy. In a prospective study, oral pilocarpine significantly improved the QoL of 77% of HNC patients, with 67% reporting significant relief of symptoms at 12 weeks .[14] Controversy exists regarding whether

pilocarpine is beneficial when administered during radiotherapy by providing a protective effect on salivary gland function. One study demonstrated that the use of 5 mg oral pilocarpine four times daily, beginning on the first day of RT and continuing for 3 months after completion, was associated with significantly less xerostomia in patients who received at least 45 Gy to both parotid glands.[15] However, several randomized controlled trials (RCT) have found no statistically significant difference in xerostomia between patients treated with oral pilocarpine or placebo given during radiotherapy.[16-18] Further, most of these RCTs reported relatively higher rates of adverse effects in patients receiving pilocarpine. These included reactions secondary to cholinergic stimulation leading to varying degrees of vasodilation, bradycardia, and bronchospasm.[9,19] 9% of patients prematurely withdrew from these RCTs due to adverse effects.[14] A Cochrane review published in 2015 concluded that the efficacy of pilocarpine was limited. [20]

Pharmacologic preventive strategies

Several preventative agents have been investigated as radioprotectors of salivary gland tissue. Amifostine, a radical scavenger resides in high concentrations within salivary glands. When given during and after radiotherapy amifostine has been reported to reduce xerostomia. In an RCT, Jellema et al demonstrated decreased severity of xerostomia in patients treated with amifostine during RT 6 months after radiotherapy**.** Patients were divided into 3 groups – 30 patients did not receive amifostine, 31 received 200 mg/m^2 3 times a week and 30 received 200 mg/m^2 5 times a week. There was a significant difference in Grade 2 or greater late xerostomia at 6 months between the three groups (74%, 67%, 52% respectively, P = 0.03). However, this difference was not significant after 6 months.[21] A more recent randomized controlled trial (RCT) on 44 patients who received amifostine or placebo before standard radiotherapy demonstrated no significant difference in acute or late xerostomia.[22] A review of eleven studies involving amifostine determine that, although there seemed to be an overall benefit in reducing the risk of xerostomia, toxicity was noted in close to half of the patients treated.[23] With its challenging side-effect profile, the debate on Amifostine and its overall benefit in HNC patients continues.[7,24] A

2017 Cochrane analysis by Riley et al., showed that amifostine, when compared to placebo, reduced the risk of moderate to severe xerostomia (Grade 2 or higher) at the end of radiotherapy (risk ratio (RR) 0.35, 95% confidence interval (CI) 0.19 to 0.67; P = 0.001, 119 participants), and up to 3 months after radiotherapy (RR 0.66, 95% CI 0.48 to 0.92; P = 0.01, 687 participants), but the effect was not statistically significant at 12 months after radiotherapy (RR 0.70, 95% CI 0.40 to 1.23; P = 0.21, 682 participants).[25]

A similar agent, stable-free radical Tempol (4-hydroxy-2,2,6,6-tetramethylpiperidine-N-oxyl) has demonstrated radioprotective benefits in animal models and may warrant further investigation in clinical trials. Acting as a stable nitroxide, it shows promise with the potential for fewer side effects than amifostine.[26,27] Several other agents have been studied in animal models, including insulin growth factor-1 (IGF-1), keratinocyte growth factor (KGF), and locally administered adenovirus vectors encoding growth factors, [7]

Pharmacologic Treatment Strategies

Interestingly, a study in rats using intraglandular application of botulinum toxin prior to RT demonstrated significant reduction in radiation-induced toxicity to the granular tissue.[28] Safety and efficacy of Botulinum toxin has been studied in a Phase 1 clinical trial to preserve gland function following radiotherapy.[29] Botulinum toxin was injected in the submandibular glands prior to radiotherapy in the treatment group. There was no significant difference in the treatment group compared to the placebo group. Other animal studies have supported the role of botulinum toxin injections in reducing hyposalivation.[30] However, these results need to be validated in clinical trials.

Additionally, products including xylitol are recommended to be used continuously as they have been shown to increase saliva production and thus help to prevent caries formation. They increase saliva pH and improve the buffer capacity of saliva.[31]

Salivary substitutes

Saliva substitutes have been studied with varying degree of benefit in xerostomia.[32] Several artificial saliva substitutes have been marketed including BioXtra (BX) and Biotene-Oralbalance (BO). BioXtra is a synthetic saliva containing the components lactoferrin, lysozyme and lactoperoxidase.[33] These substitutes are used as a moisturizing gel, mouth spray, toothpaste or mouthwash. Dirix et al., reported results of 3 questionnaires administered before and 4 weeks after treatment with BioXtra in patients with xerostomia. Patients reported significant benefit and reduction of symptoms of xerostomia. QoL scores improved significantly from a mean of 59.4 increasing to 70.5 ($p<0.001$).[34] In a recent systematic review, Assery et al. concluded that artificial saliva substitutes do reduce the symptoms of xerostomia. Unfortunately, the benefits are variable, and concluded that the type of substitute used should be based on the patient's needs and concerns.[32]

Surgical Preventive Strategies

Surgical transfer of the submandibular gland prior to radiation has been studied in the prevention of radiation-induced xerostomia. First described by Jha et al. in 2000, the procedure involves repositioning the submandibular gland to the submental space to protect the gland from the radiation field.[35] The procedure, also known as the Seikaly and Jha method, has been noted to have low risks, with the most common complications being ipsilateral facial edema (13.6%), cutaneous numbness (6.8%), and hypoglossal or lingual nerve injury (2.5%).[3] Successful transfer of the gland depends on proximal ligation and division of the facial artery, as the gland remains vascularized by retrograde flow from the facial artery which must be confirmed after clamping and before cutting the proximal facial artery. If there is no retrograde flow, the transfer is abandoned. The anterior belly of the digastric is released from the underlying structures and the mylohyoid is bisected. This allows the gland to be repositioned in the submental space under the anterior belly of the digastric and secured with absorbable sutures.[36] The transfer should be conducted on the contralateral side of the primary cancer as long as the contralateral side of the neck is without nodal disease.

In a meta-analysis of 177 patients spanning 7 studies, Sood et al. reported significantly higher unstimulated and stimulated salivary flow rates, 12 months after completion of RT in patients with submandibular gland transfer compared to the control. The mean salivary rates were as high as 73% versus 27% in preserved and unpreserved salivary glands, respectively ($p<0.0001$).[37] They concluded that salivary gland transfer appeared to be highly effective in preventing xerostomia. Wu et al. demonstrated similar findings in a meta-analysis of 369 patients.[38] Jha et al. reported results of RTOG 0244, a multi-center study where submandibular gland transfer technique was noted to be within acceptable variation in nearly 80% of patients, supporting reproducibility of the procedure between instiutions.[3] The authors successfully prevented 74% of patients from XRT-induced acute xerostomia, which is congruent with the established literature on submandibular salivary gland transfer.[39,40] However, submandibular transfer has not become standard of care despite these favorable results.

In 2020, Murray et al. reported outcomes of a modified technique of submandibular gland transfer that was first described by Marzouki et al. in 2016. [41,42] The University of Washington Quality-of-Life (UW-QOL) questionnaire was used, and the authors reported that 65% of patients rated their salivary flow as normal or mildly reduced compared to only 16% in the control group. ($p=0.01$).[41] Chang et al. reported a modification of the technique for submandibular gland transfer, wherein they preserved the ipsilateral facial vessels resulting in minimal post-operative swelling of the transferred area. At 24.5 months, the incidence of moderate to severe xerostomia was 16.7% as the transferred SMG received significantly lower radiation dose than the SMG on the involved neck (30.86 Gy versus 63.02 Gy, respectively, $p < 0.001$).[43]

Whether regional recurrence on the side of the transferred gland is higher due to occult cancer cells being left behind is controversial. However, a review of three studies assessing the rate of regional or local recurrences determined no significant difference between the transfer and the control groups, with no significant difference in survival rates.[38] In a meta-analysis by Wu et al., 31% of the patients in the salivary gland transfer group presented with acute post-radiation

xerostomia and 19% patients had late onset xerostomia, a marked improvement from over 60% of patients without SGT who develop xerostomia post-treatment.[38] Joshi and colleagues studied the oncologic feasibility of preserving the submandibular gland during neck dissections for oral cavity SCC.[44] The findings from 555 neck dissections determined that the submandibular gland itself was involved in only 2 (0.36%) cases, although 95 necks were positive for metastasis at Level 1B. Several studies have reported a similarly low incidence of submandibular gland involvement in different sub-sites of the oral cavity with the highest incidence being in the floor of mouth (2.6%-11.3%).[45-48] Markey et al compared the degree of xerostomia in patients who underwent submandibular gland preservation during level IB node dissection. They observed no differences between the control and experimental groups with regards to reduction of xerostomia. Overall, submandibular gland transfer remains a new technique that has not been widely adopted amongst the community. Its applicability remains limited, due to the fact that the gland transfer is only relevant when the planned post-operative radiotherapy volumes are largely unilateral. Additionally, there remains insufficient data in support of preservation of the submandibular gland in patients with positive lymph nodes, locally advanced cancers with high-risk features, patients who have received radiotherapy in the past, atrophic glands, or in patients with sialadenitis.[44]

Non-pharmacologic methods in treating xerostomia

Acupuncture

Non-pharmacological treatments exist with mixed results for radiation-induced xerostomia. Stimulation of the residual salivary gland tissue after RT through the practice of acupuncture has been shown to alleviate the symptoms of dry mouth in some patients.[7] Blom et al demonstrated a significant improvement in unstimulated and stimulated salivary flow rates in xerostomia of several etiologies including RT, after 24 acupuncture treatments. These effects lasted for 6 months and the authors demonstrated a sustained benefit for up to 3 years after additional treatment.[49] Despite no significant difference in whole salivary flow rates between acupuncture and placebo treatment, Cho et al reported significantly improved unstimulated flow rates along

with an improved subjective sensation of xerostomia in irradiated HNC patients.[50] In contrast, a Cochrane review demonstrated that, despite a small increase in salivary production, there was insufficient evidence supporting the use of acupuncture in significantly improving xerostomia.[51] A systematic review conducted subsequently also reported that there was insufficient evidence to support the use of acupuncture in xerostomia patients.[52]

Electrical nerve stimulation

Electrical nerve stimulation, either placed intra-orally or transcutaneously, has also been tested in palliation of xerostomia, with minimal risk.[7] Lakshman et al noted improved salivary flow rates in patients who received TENS therapy over their parotid glands while undergoing RT.[53] Though not focused on radiation-induced xerostomia, a study enrolling 114 xerostomia patients from 13 countries used an intra-oral device that electrically stimulated the oral mucosa in the proximity of the lingual nerve. There was some alleviation of xerostomia after 5 months of active use, though with mixed results and poor patient adherence.[54] Finally, Wong et al showed that electrical nerve stimulation was as effective as pilocarpine with fewer adverse events, along with a higher response rate after 15 months. Unfortunately, the study had low statistical power.[55]

Hyperbaric oxygen (HBO)

The role of Hyperbaric oxygen therapy (HBO) in xerostomia has been controversial. The benefits of improving salivary flow rates and reducing subjective symptoms of xerostomia are demonstrated in several studies of irradiated HNC patients who underwent multiple treatments of HBO. It is hypothesized that increased vascularity and stem cell mobilization improves salivary gland function.[56-58] Three studies, including one RCT, further reported significant improvement of QoL in patients undergoing HBO for xerostomia.[58,59] The benefit that patients appear to have needs to be supported with further studies aimed at long-term follow-up and especially with studies looking at locoregional control rates in these patients following HBO.

Role of Intraoral stents

Intraoral stents are personalized intraoral devices worn during radiation therapy to reduce irradiation to adjacent normal tissues. These stents keep the mouth open to maintain a stable and reproducible position of the mandible thus sparing normal surrounding organs at risk (OAR). Goel et al. (RTOG 045) reported a significantly lower incidence of xerostomia (p=0.06) in patients who wore the positioning stent compared to the control group at 60 days following radiation therapy. The authors hypothesized that the benefit of these stents was primarily from exclusion of the maxilla and parotid glands from the radiation field.[60] A recent systematic review by Chen et al in 2020 on 5 studies included in the analysis concluded that the evidence is weak regarding the efficacy of stents in preventing xerostomia and there is a need for more long-term prospective studies to recommend stents as standard of care.[61]

Future Directions

Stem cell transplant

Stem-cell based approaches for treating xerostomia have shown some encouraging results in preclinical studies. Differentiation of stem cells into functioning salivary gland cells have been studied.[62,63] Mesenchymal stem/stromal cells are a rich source of stem cells which are typically harvested from the bone marrow, adipose tissue or umbilical cord blood.[64,65] Until recently, most of the studies were limited to regeneration of salivary gland cells in animal models.[66] Lynggard et al. investigated the safety of autologous adipose tissue-derived mesenchymal stem/stromal cell (ASC) injections into the submandibular glands to reduce radiation-induced xerostomia at 2 years. Although the sample size was only 15 patients in each of the treatment and placebo groups, the unstimulated saliva flow rate increased in the treatment group. (p=0.051). Safety data reported no treatment related serious adverse effects (SAE). However, a larger RCT is warranted to confirm these results.[67] Pringle and colleagues successfully cultured human submandibular gland cells using a xenograft model thus underpinning the promise of its potential role in xerostomia patients.[68]

Gene therapy

Gene therapy using Human Aquaporin-1 (hAQP-1) gene transfer and human neurotrophic factor neurturin (CERE-120) have been studied to increase salivary flow following radiation therapy or in preventive settings.[69,70] These effects have persisted close to 5 years after completion of treatment and symptoms have improved for about 2-3 years.[69] No clinically significant adverse effects have been reported with the use of hAQP-1

Conclusion

Xerostomia is an important complication of radiation therapy for head and neck cancers. Some studies have demonstrated the benefit of pharmacologic agents like pilocarpine and amifostine. However, these treatments are not well tolerated by all patients. Salivary gland sparing using IMRT is the most practical approach to reduce salivary gland dysfunction and is now standard of care in all patients. Salivary gland transfer holds promise in preventing xerostomia without compromising oncologic outcomes or increasing local complication rates. However, all patients may not be eligible. Preventive approaches should be maximized for all patients undergoing radiation therapy for HNC.

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