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REVIEW ARTICLE

Radiation-Induced Xerostomia

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ABSTRACT

Xerostomia is a common complication following radiotherapy for head and neck cancers. This has long-term implications on the quality of life of these patients. The better understanding of salivary function and the interaction of radiotherapy dose-volume and fractionation with salivary function has allowed us to intervene with various modalities to prevent or treat this common complication. Thus we present a review of published literature describing the factors affecting xerostomia, its prevention and treatment.

Keywords: Xerostomia, Head and neck cancer, Late effects of radiotherapy.

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INTRODUCTION

Head and neck cancers are a common problem worldwide with about 5,00,000 cases annually of which two-thirds are locally advanced.[1] Radiation therapy forms an integral component of the multimodal management of the disease. Radiotherapeutic management is a challenge in head and neck due to the close proximity of the tumor and avoidance structures (organs at risk).

Xerostomia, defined as dry mouth (reduced or absent salivary flow) due to damage of salivary glands, is a common complication. Its incidence varied in the range of 60 to 90% in the era of conventional radiotherapy.[2] Xerostomia has late effects on oral health, specifically dry mouth, sore throat, altered taste, dental decay, changes in voice quality and impaired chewing and swallowing function leading to nutritional depletion and weight loss.[3-5] Thus, maximal sparing of the salivary apparatus during a course of radiotherapy may have therapeutic implications on the quality of life postradiotherapy in a patient with an otherwise controlled cancer.

The Salivary Apparatus

The parotid and the submandibular glands are the main contributors to salivary flow, whereas several minor salivary glands present in the oral cavity and the pharynx are minor contributors, secreting less than 10% of the saliva. The parotid gland is a purely serous-secreting gland, whereas the submandibular is predominantly serous. In the unstimulated state, the submandibular gland produces most of the saliva, whereas in the stimulated state the parotid gland is responsible for most of the saliva produced. Total salivary flow can be up to 1.5 liter a day in healthy individuals.[6,7]

Effects of Radiation Therapy on Salivary Glands

Xerostomia is the most prominent late effect of radiation in head and neck cancers. Radiation leads to change in volume, pH, consistency making the secretions thick and tenacious with acidic pH thus, having serious implications not only on the oral flora and health but also on the nutritional well-being of the patient. Animal studies led us to believe that radiation damage occurs in four distinct phases. Phase I (0-10 days) in which there is depletion of the water component but no effect on the acinar cells or on amylase secretion. Phase II (10-120 days) in which the acini suffer membranous degradation and loose the ability to secrete amylase. Phase III (120-240 days) this marks the phase of late toxicity which is characterized by loss of functional acinar cells due to loss of progenitor stem cells. Phase IV marks the regenerative phase but the functional deterioration continues due to the damage to ducts nerves and vessels.[8] Similar findings have been documented in humans by Leslie and Dische.[9] They showed that salivary amylase became undetectable by 10th day of radiation due to acinar damage.

Factors Affecting Salivary Gland Function

Dose Volume Relationship

It has also been shown that minimal gland function reduction occurs at <10 to 15 Gy mean dose. Gland function reduction gradually increases at radiation doses of 20 to 40 Gy, with a strong reduction (usually by >75%) at >40 Gy mean dose.[10,11] Some recovery of function occurs with time, with the tissue dose required for a 50% response (TD50) increasing (i.e. more dose needed for the same level of injury) at longer follow-up times. It has also been demonstrated that salivary flow measurements have a lower TD50 than those measured by imaging techniques like scintigraphy.[11,12]

Fractionation

The effects of fraction size on xerostomia are limited and conflicting. The α/β ratio for parotid has been estimated to be close to 20 in rats.[13] Contrary to this it is believed from the continuous hyperfractionated accelerated radiotherapy

(CHART) experience that hyperfractionation is protective for late effects.[14,15] This may lead us to believe that the α/β ratio should infact be much smaller. Once again adding to the confusion a study done on Rhesus monkeys showed acini cell number reduction at 16 weeks after radiation therapy was worse for CHART hyperfractionation than for conventional fractionation.[16] Thus, it is believed that fractionation may have an impact on xerostomia with the salivary gland having a differential α/β ratio.

Radiation Technique

The impact of radiation technique has been discussed elsewhere in this article.

Use of Concomitant Chemotherapy

It has been reported that the addition of concomitant chemotherapy is associated with an increased incidence of acute toxicity, in particular mucositis, and there is some evidence to suggest an increased incidence of salivary gland dysfunction (about 70%) when compared with radiation alone.[17] Early data with concomitant cetuximab have suggested no increase in the incidence of long-term xerostomia.[18]

PREVENTING RADIATION-INDUCED XEROSTOMIA

Pharmacologic Methods

Amifostine

Amifostine works on the principle of radioprotection. This widely studied molecule (WR 1065) is preferentially taken up by tissues, such as salivary glands due to increased levels of alkaline phosphatase in normal tissues compared to tumor cells. Once inside these cells it prevents damage by acting as a free radical scavenger.

The benefits of this drug were demonstrated in a large randomized trial by Brizel et al. In their study they demonstrated significant reduction in grade II acute and chronic xerostomia.[18] Inspite of this, the drug did not catch the eye of many in the market. This was due to the demonstration of a tumor protective effect by some and the lack of benefit in the setting of chemoradiation by others.[19] This led to the recommendations of the American Society of Clinical Oncology which advised against its use in the setting of chemoradiation (standard of care in head and neck tumor).[20] The dose-limiting side effects like hypotension, vomiting and Steven Johnson syndrome were a challenge in its administration. All these led to the nemesis of this approach.

Pilocarpine

Pilocarpine is a parasympathomimetic agent that functions primarily as a muscarinic agonist with mild β-adrenergic activity. This alkaloid causes pharmacological stimulation of exocrine glands in humans, resulting in diaphoresis (sweating), salivation, lacrimation, gastric and pancreatic secretion. Fisher et al and Warde et al put this agent to the litmus test of a trial. Even though Fisher et al demonstrated some improvements in salivary flow at 3 to 6 months, both Warde and Fisher failed to demonstrate any improvements in quality of life of patients.[21,22] Thus, currently this drug is a historical bullet in the armamentarium of radiation oncologists.

Radiation Treatment Techniques

Parotid Sparing Radiotherapy

Due to the close proximity of large treatment volumes and the parotids in most cases of head and neck malignancies and the requirements of dose in excess of the tolerance of parotids it is almost impossible to spare even a single parotid gland with the available conventional radiotherapy techniques. Three-dimensional (3D) techniques have been described but are cumbersome due to the use of multiple beams and cerrobend blocks in various directions.[23]

The advent of multileaf collimators and the use of intensity modulated radiotherapy (IMRT) has been a sort of revelation in the field of radiation oncology. Pow et al randomized 51 patients of nasopharyngeal carcinoma to conventional *vs* IMRT. They showed that at 12 months 83.3% patients in the IMRT arm had recovered 25% of their pre-radiation therapy salivary flow compared to 9.3% in the conventional arm. This also translated into better quality of life for the group receiving IMRT.[24] A similar trial, also on early stage nasopharyngeal cancer, assigned 60 patients to receive either conventional radiotherapy or parotid-sparing IMRT. At 1 year after treatment, patients in the IMRT group had a significantly lower incidence of observer-rated severe xerostomia than those in the conventional radiotherapy group (39.3 *vs* 82·1%; $p = 0.01$), as well as a significantly higher parotid salivary flow ($p < 0·0001$). However, there was no difference in patient-reported xerostomia between the two groups.[25]

In another landmark trial (PARSPORT) in United Kingdom, it was shown that the incidence of xerostomia at 1 year was 74 *vs* 39% in the conventional *vs* IMRT arms. At 18 months the gap widened with 71% having grade II xerostomia with conventional radiation while only 29% had it in the IMRT arm. There was no compromise in the locoregional control or overall survival. This study taught the natural history of xerostomia. It told us that initially both xerostomia and quality of life scores worsen with a gradual improvement overtime which continues for a long duration up to at least 18 to 24 months.[26]

These studies raise important questions with regard to the evaluation and prevention of xerostomia. They

emphasize that xerostomia is essentially a patient-related quality of life issue hence, patient-related end points are more indicative of the impact of any modality on its outcome.

These studies have raised important questions with regard to ideal dose and volume relations with regard to parotid sparing radiotherapy. In a recent publication Deasy et al have made the following recommendations for parotid sparing radiotherapy.[27]

1. Sparing at least one parotid gland appears to eliminate xerostomia.
2. Severe xerostomia (long-term salivary function <25% of baseline) can usually be avoided, if at least one parotid gland has been spared to a mean dose of less than 20 Gy or if both glands have been spared to a mean dose of less than 25 Gy.
3. A lower mean dose to the parotid gland usually results in better function, even for relatively low mean doses (<10 Gy).

Submandibular Gland Sparing

Submandibular gland secretions are important in the unstimulated state and essentially contribute to the subjective sensation of moisture in the mouth.[28] This infact maybe the reason for the difference in patient and observer related outcomes after radiotherapy. Thus, there was great interest in sparing the submandibular gland. Among the initial efforts to spare the submandibular gland was the use of glandulopexy (surgical transfer of the submandibular gland to the submental space). This was tested in a trial which showed that only 19% patients had xerostomia with this technique.[29] This technique had its limitations because they can not be used for oral cavity and oropharyngeal tumors. They involve the risks of an operative procedure and may lead to delay in radiation due to wound-healing problems.

A prospective nonrandomized trial has shown the feasibility of submandibular gland sparing. In a selected subset of patients, all treated with parotid-sparing IMRT, the contralateral submandibular gland was also spared (mean dose <25 Gy). One year after radiotherapy, these patients had substantially less observer-rated xerostomia, compared with patients in whom both submandibular glands received a high dose (>25 Gy) and had preserved total salivary flow.[30] Recently, a prospective evaluation has established a dose–response relation for the submandibular gland, on the basis of patients who underwent salivary flow measurements selectively from Wharton's duct before and after radiotherapy. The preservation of submandibular gland function was shown to depend on the mean radiation dose, with recovery over time up to a mean dose threshold of 39 Gy.[31]

Although intuitively appealing, the available evidence regarding the safety and efficacy of submandibular gland-sparing radiotherapy is extremely limited. Moreover, meaningful reduction of the mean dose to the submandibular gland is potentially hazardous owing to its close proximity to the lower level II nodes. With regard to the submandibular gland Deasy et al made the following recommendations.[27]

1. Sparing at least one submandibular gland also appears to reduce xerostomia risk and increase stimulated and unstimulated salivary function.
2. When it can be deemed oncologically safe, submandibular gland sparing to modest mean doses (<35 Gy to see any effect) might reduce xerostomia symptoms.

Treatment of Xerostomia

The general approach to treating patients with radiation-induced xerostomia is directed as palliative treatment for the relief of symptoms and prevention of oral complications. It is a difficult procedure. Symptomatic treatment includes increase in existing saliva flow, replacing last secretion, control of dental caries and infection treatment. Orodental hygiene, regular visit to a dentist, avoidance of smoking, use of dentures can reduce xerostomia. A number of over the counter products that can function as saliva substitutes have been developed specifically for patients with xerostomia. Variety of formulations like rinses, aerosols, chewing gums and dentifrices promote salivary gland functions. The main ingredients of commercial mouth rinses, like alcohol, may desiccate the oral mucosa and patients with xerostomia should avoid using them.

Salivary Substitutes

Artificial saliva or salivary substitute normally provide temporary relief of some patients. Though it is marketed under many names without any prescriptions as a name of biotene mouthwash, saliva orthana (a mucin-based artificial saliva) none of them proves to be superior among themselves. Most of the patients use water for their symptom relief.[32]

Salivary Stimulants

Pilocarpine has become the focus of most clinical trials investigating salivary stimulants for the treatment of radiation-induced xerostomia. The recommended dose of pilocarpine is 5 mg three times daily. There was a significant improvement of salivary flow rate and quality of life in pilocarpine.[33,34] Most common side effect of pilocarpine is sweating. It is contraindicated in bronchospasm, congestive heart failure, chronic obstructive pulmonary disease and

acute bronchial asthma and acute congestive glaucoma. Cevimeline is now being evaluated for radiation-induced xerostomia.[35] It has no cardiorespiratory side affect as that of pilocarpine. It acts on M1, M3 receptor.

ACUPUNCTURE

Blom et al reported that stimulated and unstimulated salivary flow rates were significantly better after 12 to 24 weeks of acupuncture.[36,37] Study by Wong et al used a transcutaneous acupuncture-like nerve stimulation method (Codetron) to avoid the needle use associated with acupuncture. There was a significant improvement in the reported xerostomia (using the visual analog scale) and stimulated and unstimulated salivary flow rates.[38] There was, however, no improvement in the patients' QoL. Phase III trials are required before widespread clinical implementation of this technique can be recommended.

Gene Therapy

The major glands are attractive target for gene therapy. Animal experiments have attempted to improve post-radiation salivary function by attempting to transfer genes coding for water channels in the acinar cells and genes coding for enzymes that mop up the free radicals produced during radiation.[39] All these experiments may give a clinically applicable solutions for this condition in future.

CONCLUSION

Xerostomia is an important acute and late sequelae of radiation therapy leading to lot of patient anxiety and morbidity. Important advances have been made in the understanding of the dose response of salivary glands and prevention and treatment of xerostomia. However, important questions remain: Whether partial sparing of the parotids with sparing of submandibular glands can affect patient related outcomes? Whether local or spatial effects exist with regard to radiation effects on salivary glands? Whether tumor shrinkage in close proximity to the parotid leads to worsening of patient-related outcomes? What is the role of adaptive radiotherapy in parotid sparing? The answer to these questions can only be answered by well-designed clinical trials. The authors urge all the readers of this review to indulge in such research to provide solutions for the betterment of radiation science and the quality of life of our patients.

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