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Review

Salivary gland transfer to prevent radiation-induced xerostomia: A systematic review and meta-analysis

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SUMMARY

Salivary gland transfer (SGT) has the potential to prevent radiation-induced xerostomia. We attempt to analyze the efficacy of SGT in prevention of xerostomia and maintenance of salivary flow rates after radiation treatment (XRT). Systematic review and meta-analysis. Primary endpoint was efficacy of SGT in prevention of radiation-induced xerostomia. Secondary endpoint was change from baseline of *unstimulated* and *stimulated* salivary flow rates after XRT. Seven articles, accruing data from 12 institutions, met inclusion criteria. In a total of 177 patients at mean follow-up of 22.7 months, SGT prevented radiation-induced xerostomia in 82.7% (95% CI, 76.6–87.7%) of patients. Twelve months after XRT, *unstimulated* and *stimulated* salivary flow rates rose to 88% and 76% of baseline values, respectively. In comparison to control subjects twelve months after XRT, SGT subjects' *unstimulated* (75% vs. 11%) and *stimulated* (86% vs. 8%) salivary flow rates were drastically higher in SGT patients. Salivary gland transfer appears to be highly effective in preventing the incidence of xerostomia in patients receiving definitive head and neck radiation therapy.

Introduction

Head and neck cancer accounts for nearly 3% of all diagnosed malignancies, making it the sixth most commonly diagnosed cancer worldwide [1–3]. While early stage disease can be treated with either surgery or radiation, definitive treatment for advanced stage head and neck cancer typically mandates multi-modality therapy to include either concomitant chemotherapy and radiation, or surgery with adjuvant radiation [4,5]. It is generally accepted that radiation therapy in head and neck cancer patients causes salivary gland destruction, inevitably leading to radiation-induced xerostomia [6–14]. The exact incidence of xerostomia is unclear, as grading definition and radiation fields may vary [10,15–19]. However, reported percentages in the literature range from 60% to 100% of patients [3,10,20,21]. Regardless, an increasing body of evidence supports the notion that xerostomia appears to occur in a majority of patients receiving radiation for oropharyngeal, hypopharyngeal, laryngeal, and nasopharyngeal carcinomas [6,7,9,10,13,14,22–27].

Some studies suggest radiation therapy induces irreversible salivary gland damage, potentially with as low a dose as 6 Gy [7,28]. While the exact mechanism of radiation-induced gland destruction is unknown, it is hypothesized that radiation has direct cytotoxic effects on salivary tissue and causes indirect changes in vascular blood flow to the gland [29]. The result is predominant salivary gland dysfunction that manifests itself as reduced salivary flow rates, reduction in saliva pH, changes in electrolyte and immunoglobulin saliva composition, and increased cariogenic mouth flora [29,30]. In fact, investigations of fractionated radiation therapy demonstrate up to a 60% decrease in salivary flow during the first few weeks of radiation therapy, further decreasing by 20–30% after 6–7 weeks of conventional radiation therapy [7,9,13,14,28]. These changes have significant impacts on patients' quality of life and may be responsible for, but not limited to, oral discomfort, mucositis, dental caries, mastication difficulties, and deglutition dysfunction that may lead to nutritional deficits [8,31–36]. Further, the emotional impact xerostomia has on patients' psychosocial well-being is significant, with approximately 50% of patients reporting depression, worry, or feelings of tension related to this condition [3].

Despite a variety of therapeutic agents such as pilocarpine, lubricants, salivary substitutes, and acupuncture that are available for the treatment of radiation-induced xerostomia, medical management of this condition is rarely effective [12,20,37–39]. In fact, a recent review stated that *prevention is paramount* to avoid radiation-induced xerostomia [3]. For this reason, recent investigation

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has focused on strategies aimed at prevention of radiation-induced xerostomia. In the last decade, radiation oncologists have attempted parotid-sparing techniques such as intensity modulated radiation therapy (IMRT) and 3-D conformal radiation therapy to prevent the incidence of xerostomia after definitive radiation treatment [19,40–53]. Of these two modalities, multiple studies demonstrate that IMRT preserves salivary function and decreases incidences of xerostomia at higher rates compared to 3-D conformal radiotherapy [44,47,53,54]. As such, the international use of IMRT in head and neck cancer has drastically increased over the last decade but is limited by availability in many countries and regions of the world. Further, prevention of xerostomia with IMRT has had variable successes worldwide. Some studies demonstrate grade 2 or higher xerostomia (defined by the RTOG [15]) in 20–30% of patients after IMRT [41,44,48], whereas others reveal grade 2 or higher xerostomia in up to 65% of head and neck cancer patients receiving definitive IMRT treatment [55,56]. Thus, in addition to parotid-sparing radiation therapy techniques, alternative prevention strategies must be considered.

In 2000, salivary gland transfer (SGT) was introduced as a novel method for prevention of radiation-induced xerostomia [57]. The attractiveness of SGT lies in the fact that it attempts to maintain salivary function without altering definitive radiation therapy treatment and compromising oncologic intent. As described by the Seikaly–Jha Method [28], transfer of one submandibular gland (contralateral to location of tumor) to the submental region prior to radiation therapy greatly decreases the incidence of xerostomia [11,12,26,57]. Transfer from Level 1B to the submental region under the belly of the digastric muscle "shields" the transferred gland, where it would only receive approximately 5% of the total radiation dose [28]. Using this technique, blood flow is maintained with retrograde flow from the facial vessels [28]. This can be applied for patients with primary tumors located in the posterior oral cavity, oropharynx, nasopharynx, larynx, and hypopharynx, as they do not have lymphatic drainage into Level 1 region [28,58].

Since its introduction over a decade ago through the Seikaly–Jha Method [28], a number of institutions internationally have trained in this procedure and utilized it to prevent radiation-induced xerostomia. Currently, however, no combined analysis on salivary gland transfer exists in the literature. Salivary gland transfer has the potential to greatly improve quality of life in head and neck cancer patients receiving radiation treatment. Thus, we attempt to provide analysis on salivary gland transfer's ability to prevent radiation-induced xerostomia, with specific emphasis on incidence, maintenance of salivary flow rates, and patients' perception in maintaining normal saliva amount and consistency after radiation treatment.

Materials and methods

Design

Meta-analysis and systematic review.

Literature search

A comprehensive literature search was conducted using the PubMed-NCBI database. The following searches were conducted: (1) "Salivary gland transfer and xerostomia", (2) "submandibular gland transfer and xerostomia", (3) "Xerostomia/prevention and control" [Mesh] OR "Xerostomia/surgery" [MESH], (4) "radiation induced xerostomia", and (5) "xerostomia" AND "radiotherapy" [MESH]. Our search was then subject to inclusion and exclusion criteria.

Inclusion criteria

(1) Prospective studies (randomized and non-randomized studies).
(2) Biopsy-proven squamous cell carcinoma.
(3) Anatomic locations included were nasopharynx*, posterior oral cavity†, oropharynx, larynx, hypopharynx, and unknown primary with neck nodes.
(4) Patients underwent salivary gland transfer prior to radiation treatment, as described by the Seikaly–Jha Method [28].
(5) Patients received commonly accepted conventional radiotherapy for definitive head and neck cancer treatment with a similar fractionation schedule of the following: 2 Gy per fraction, 1 fraction per day, 5 days per week for 6–7 weeks, totaling up to 70 Gy [5].
(6) Complete obtainable manuscripts in English.

*: Patients included in our analysis are generally considered to have indications for salivary gland transfer [28,57,58]. Nasopharyngeal carcinomas were included as radiation fields are similar to oropharyngeal fields when using conventional radiation therapy (3-field technique) [58]. Further, the incidence of xerostomia after radiation for nasopharyngeal carcinomas is comparable to its oropharyngeal carcinoma counterpart [22–25,27].

†: Distinctions within oral cavity were made based upon lymphatic drainage patterns. Anterior oral cavity carcinomas were excluded since these tumors may drain into Level 1, whereas posterior oral cavity carcinomas parallel oropharyngeal carcinoma draining patterns to the cervical neck nodes and uncommonly metastasize to the Level 1 region [58–61].

Exclusion criteria

(1) Recurrent or metastatic disease.
(2) Bilateral neck nodes or Level 1 neck nodes.
(3) Co-morbid conditions associated with salivary gland disease, including rheumatoid arthritis, Sjögren's syndrome, diabetes, hypertension, and immune deficient states [29].

Endpoints

Primary endpoint

Prevention of xerostomia, defined as "moderate"/"severe" (Grade 2 or higher) as defined by the ROTG [15].

Secondary endpoint

Maintenance of salivary flow rates before, during, and after course of radiation therapy (XRT). Stimulated and unstimulated salivary flow rates were assessed in mL/min across time (months).

Tertiary endpoint

Patients' perception of maintaining normal/near normal saliva amount and consistency. This endpoint was assessed using the University of Washington Quality of Life Questionnaire [62].

Statistical analysis

Primary endpoint: incidence of xerostomia

Salivary gland transfer efficacy in preventing xerostomia was calculated through meta-analysis software. Data analysis was performed using MedCalc 12.6.1.0 (MedCalc Software bvba, Belgium). Each technique was weighted according to the number (n) of patients treated. Analysis of pooled proportions was performed when appropriate. To correct for probable variance, the pooled proportions were subject to a Freeman–Tukey transformation (arcsine square root transformation) [63] to calculate the weighted sum-