

**Prevention and Treatment of Radiation Induced Xerostomia in  
Head and Neck Cancer Patients:  
An Evidence Based Report**

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Tables: 3 Figures: 3

## **ABSTRACT**

Xerostomia is a common debilitating condition effecting up to 100% of head and neck cancer patients who undergo radiation therapy. This evidence based study examines four approaches to treating xerostomia in this population, submandibular salivary gland transfer, pilocarpine, acupuncture and salivary substitutes in hopes of determining the best available treatment. A thorough search of electronic databases yielded 91 potential studies, 35 of which were retrieved and eight of which were deemed relevant for inclusion in this study. Each study was evaluated using an “efficacy checklist” involving 17 items. Studies on pilocarpine for treatment of xerostomia achieved the best scores and were also assigned the highest design strength and level of evidence. Studies on submandibular gland transfer for prevention before radiation therapy commences, and acupuncture for treatment of xerostomia after radiation were both promising but require further investigation. Studies on salivary substitutes were of poor quality and statistically insignificant results correlate with lack of use in this population. Only pilocarpine 5mg t.i.d. had sufficient evidence to be recommended as treatment for xerostomia. Clinical evidence and review results suggest a team centred approach with a strong impetus for improved research to advance patient care in the population of radiation induced xerostomia.

## Introduction

Xerostomia is defined as the subjective sensation of dryness of the mouth [1]. It is a common condition with a prevalence of 35% in people over the age of 65 [2]. Adequate salivary flow is essential in the maintenance of oral health and function. A decrease in or lack of saliva secretion can result in numerous complications including rampant dental caries, candidiasis, mucosal atrophy and burning, difficulty in denture retention and use, compromised speech and swallowing, and reduced or altered taste sensation [3]. There are many causes of xerostomia including Sjogrens' Syndrome, medication and radiation therapy. Radiation-induced xerostomia is very common among patients with head and neck cancer as the radiation irreversibly damages the salivary glands in the exposed region. Salivary flow reduction depends on the radiation dose and fractional size as well as the volume of salivary glands irradiated [4-6]. Changes in the serous secretory cells, result in a reduction of salivary production and increased viscosity. A dose that exceeds 5,200 cGy can reduce salivary flow and cause the above symptoms mentioned [7]. Up to 100% of patients receiving radical radiotherapy develop some degree of xerostomia [4, 5]. The current paper focuses on the population of radiation-induced xerostomia in head-and-neck cancer patients.

Four treatment options have been identified in this population. The first is surgery aimed at preventing xerostomia by transferring the submandibular salivary gland to the submental region where it can be shielded from the radiation. Blood vessels and nerves supplying the submandibular gland are preserved during the transfer surgery and thus function is maintained [8]. After radiation therapy,

management of xerostomia is dependant on the degree of residual salivary gland function. It may be possible to stimulate remaining exocrine gland function to increase salivary flow by means of a cholinergic parasympathomimetic agent such as pilocarpine [7]. However, the generalized parasympathetic stimulation leads to many undesirable side effects including sweating, headache, urinary frequency, and vasodilation [9, 10]. Due to these adverse cholinergic effects, use of pilocarpine has been limited [11]. This has led some patients to explore alternative interventions such as acupuncture to stimulate remaining gland function. This is postulated to work by increasing the blood flow to the buccal area affecting salivary gland metabolism, increasing salivary production in turn [11]. Finally, for the patient with no residual salivary gland function remaining, only palliative care remains. This comes in the form of a wide variety of salivary substitutes which only provide symptomatic relief.

The aim of this review is to examine the above four approaches to treating xerostomia in head and neck cancer patients who have undergone radiation therapy. Upon evaluation of the evidence, we hope to determine the best treatment for xerostomia in this specific population.

## **Methods**

### ***Search Strategy***

Three consecutive searches were used to identify eligible published studies. Two electronic databases were used in the original search: PubMed and Ovid (1966 to present). The searches were both limited to randomized controlled trials (RCTs) of human subjects printed in the English language. Using “xerostomia” as the first search

term, a group of studies were identified from both databases. These studies were evaluated for relevance to the study based on title alone. Abstracts of those deemed to be appropriate for inclusion were examined and all papers with potential relevance were retrieved. A second search was employed using the same databases and limits but using the keywords “xerostomia, treatment, head and neck cancer and radiation” to limit the search to the population of radiation induced xerostomia. This approach was used for four different treatments: submandibular salivary gland transfer surgery, pilocarpine, acupuncture and salivary substitutes as identified in the original search. Finally, reference lists from relevant articles were reviewed for more possible sources.

### ***Study Selection***

A study was deemed eligible for inclusion when classification as an RCT was confirmed. RCTs were chosen for having the best design strength and thus allowing for the strongest level of evidence. Exceptions to this were permitted in a case where ethical issues prevented randomization in an otherwise valuable study. Other inclusion criteria include human studies with subjects having xerostomia as confirmed by study investigators. Originally, all populations of xerostomic patients were accepted, but upon review of these search results, the greatest number and quality of studies were found in the specific group of radiation induced xerostomia. This became part of the inclusion criteria for the second and third searches. A study was excluded if it was a duplicate article selected by both databases. Titles and abstracts were reviewed by two independent groups of three reviewers with disagreement resolved by consensus.

### ***Validity Instrument***

All articles examined at full text level were scored using the “Checklist to assess evidence of efficacy of therapy or prevention” developed by Leake [12] (Figure 1). The maximum possible score was 17.

### ***Data Extraction***

Data extraction sheet (Figure 2) was piloted on a sample of 20 papers prior to the start of the formal review. Two independent observers then extracted general information about each relevant study including study characteristics, intervention and control participant traits and outcomes, design strength, classification of recommendation and study conclusions.

### ***Study Analysis***

Results from randomized control trials were used to determine Relative Risk (RR), Relative Risk Reduction (RRR) and Number Needed to Treat (NNT).

## **Results**

### ***Study Search and Selection*** (Figure 3)

The initial search identified 91 potential studies: 35 by PubMed and 56 by Ovid. Upon review of titles for subject relevance and duplicate studies, the article pool was narrowed to 59. Another 24 articles were eliminated at the abstract stage, leaving 35 full text articles to review. At this stage, the decision was made to focus the review on

the population of radiation induced xerostomia patients for reasons stated previously. Also, four main treatments were identified: submandibular gland transfer surgery, pilocarpine, acupuncture and salivary substitutes and stimulants. From the original search two papers were kept for each of salivary gland surgery, pilocarpine and acupuncture and four papers were kept for salivary substitutes. The second data base search was limited to radiation induced xerostomia and was completed four times, one for each treatment. Eleven, 14, two and three additional articles were identified respectively for each treatment followed by elimination of five, ten, zero and two studies by title and abstract. Upon critical appraisal of full text, three studies on submandibular gland transfer, four on pilocarpine and one on the subject of acupuncture were selected for inclusion in this study. None were selected for salivary substitutes due to poor quality of the studies and lack of statistically significant results. Review of relevant articles references list did not produce any articles for inclusion in the study.

### ***Submandibular Gland Transfer Surgery***

The three studies examining the gland transfer method provided the best evidence for the prevention of post-irradiation xerostomia in head and neck cancer patients (Table 1). None of the studies were randomized, thus strong evidence was not provided to support this prevention. Due to ethical concerns, randomizing patients into control and treatment groups was not possible as irradiating the submandibular gland causes irreversible damage. Therefore, level B evidence was the highest achieved. Non-randomization also accounts for the lower checklist scores in combination with the marks deducted because the studies could not be blinded. Two of the studies had

control groups that did not receive the gland transfer [8, 13], and one study compared function between a transferred and non-transferred gland in the same patient [14].

All three studies demonstrated that gland transfer is effective in decreasing xerostomia after bilateral radiation treatment. All of the studies used baseline salivary flow as a measure of efficacy and all showed a significantly higher salivary flow rate in transferred glands compared to controls [8, 13, 14]. In two studies [8, 13] the stimulated salivary flow was also measured. In both studies the stimulated flow rate was significantly higher in transferred glands. The Seikaly (2004) study reported 83% of submandibular transfer group preserved function versus none in the control. This allowed calculation of RR of 0.167, an RRR of 0.833 and a NNT of 1.3. These calculations could not be performed for the other studies as only average salivary flows were reported. This evidence supports the conclusion that gland transfer is effective in conserving significant gland function.

### ***Pilocarpine***

The four included studies (Table 2) demonstrated the efficacy of pilocarpine in prevention or treatment of radiation-induced xerostomia in head and neck cancer patients. All of the studies included were randomized controlled trials and scored above 14 out of 17 on the checklist to assess efficacy.

Three studies established clinically significant benefits of pilocarpine for symptomatic relief of xerostomia when administered four months after radiation therapy was completed [9, 10, 15]. Clinical examination showed that all patients had at least one parotid gland and some indication of residual salivary function as shown by visual

evidence of moisture in the oral cavity. All of these studies recorded each patient's subjective assessment of improvement in overall condition of xerostomia by using the Visual Analog Scale (VAS) or Linear Analog Scale (LASA). Improvement in overall condition of xerostomia assessed the patient's condition based on his/her recollection of the severity of symptoms. The studies by Leveque et al (1993), Johnson et al (1993) and Rieke et al (1995) also measured salivary flow as an objective measure of treatment efficacy. The studies showed that saliva production was improved which however did not correlate with improvement in symptoms. In all three studies, a patient with an increase of at least 25 mm from baseline in the VAS score was considered a responder. The findings of the three suggest that the use of 5mg pilocarpine three times a day (t.i.d.) administered four months after completion of radiation therapy is most clinically beneficial in terms of maximizing efficacy and minimizing the cholinergic side effects described earlier. 2.5mg pilocarpine did not produce any clinically significant effects and 10mg produced maximal side effects, namely severe sweating.

The fourth study examined the preventative potential of pilocarpine when administered concomitantly with radiation treatment [16]. Repeated measures analyses were used to test the differences between treatment groups overtime for the LASA xerostomia score. The paper reported that there was no difference between the improvement of overall condition of xerostomia between pilocarpine and placebo groups ( $p=0.92$ ). The results remained the same when gender was controlled for in the analysis.

Study analysis calculations for pilocarpine as a xerostomic treatment after radiation provided an RR of 2.07, RRR of 1.07 and an NNT of 3-5. These findings

suggest that pilocarpine is an effective treatment for reducing symptoms caused by radiation induced xerostomia.

### ***Acupuncture***

The potential effectiveness of acupuncture in stimulating salivary flow rate has been demonstrated in a few studies; however, only one was selected for inclusion in this study (Table 3). In this randomized controlled trial, 38 patients with radiation-induced xerostomia underwent two series of 12 acupuncture treatments and were observed for one year after the treatment. Subjects showed significantly increased salivary flow rates after the treatment and the effects persisted during the observation year [17]. RR was calculated as 1.36, RRR was 0.36 and NNT was 6. The other reviewed studies were excluded due to poor study design or a lack of control group.

### ***Salivary Substitutes***

No RCTs were found for this treatment and studies were of poor quality. Few results were statistically significant and most studies concluded that patient individual preference was the more important determinant of use versus product efficacy [18-20]. These products are used as a last option when there is no residual salivary gland function remaining and thus pilocarpine is ineffective. For these reasons, studies on salivary substitutes were not included in this report on the best treatment for xerostomia.

## Discussion

Upon review of the literature two main approaches to radiation induced xerostomia surfaced, prevention and treatment. For prevention, only submandibular salivary gland transfer surgery offers promise. Pilocarpine was found to be ineffective in this respect. For treatment however, pilocarpine was found to be most effective 5mg t.i.d., and acupuncture also showed potential for patients with residual salivary gland function. For those patients in which all the above has failed, personal choice prevails in the use of salivary substitutes, but due to their unreliable effectiveness and unfavorable characteristics, most patients will simply carry water [6, 21, 22].

Submandibular gland transfer is a fairly new option for the prevention of xerostomia in patients undergoing radiation therapy to the head and neck. The surgery allows patients to retain a significant amount of gland function following radiation therapy. Patients are likely to accept the submandibular gland transfer surgery due to its short duration and high success rate. Most general dentists and surgeons are not yet familiar with the surgery, since it is still early in development. Further studies are needed that involve larger populations in order to confirm the efficacy that submandibular gland transfer surgeries have reported to date.

Communication with clinicians whose patient population is largely or entirely based on those who have undergone radiation therapy to the head and neck, reveals a number of potential roadblocks to the acceptance of this surgery. Of great significance are long wait times for operating rooms (OR) in the Ontario health care system. A salivary gland surgery to prevent xerostomia would be lower priority than life saving procedures and thus would be less likely to get OR time. A delay in the commencement

of cancer treatment to wait for submandibular transfer is not a viable option. Also of note is that an additional surgery may be extremely undesirable in head and neck cancer patients who are already undergoing tremendous amounts of treatment [22].

Upon review of the pilocarpine studies, it was noted that the overall placebo effect was fairly high, 25% versus 48% in responders. This may be related to different levels of residual salivary gland function in study participants. In each of the included studies, only total radiation dose was disclosed. This means the reader does not know the number of treatments, referred to as fractional size, to reach this total dose. A dose over a larger number of treatments is less damaging to the gland and thus the patient would have higher residual salivary flow [6]. Since these details were not provided, the spectrum of radiation damage and thus resultant salivary flow is truly unknown.

Another concern in the pilocarpine studies was the significant number of dropouts. In the study done by Rieke et al (1995) 15.8% of patients in the placebo group and 21.7% of patients in the treatment group dropped out of the study due to intolerable adverse effects, mainly excessive sweating. This has also been noted clinically as a major barrier to use [22]. The higher dropout rate decreases the power of the study to detect a statistically significant difference.

The results of the acupuncture study suggest that this therapy may be valuable in stimulating salivary secretion. However, the mechanism of acupuncture in the treatment of disease has never been clarified. More studies should be conducted with a larger sample size in order to confirm the effectiveness and safety of acupuncture, as well as investigation into its mechanism of action. These deficiencies need to be

resolved before acupuncture can reliably be recommended as a treatment for radiation-induced xerostomia.

In discussion with clinicians it was also apparent that communication between radiation oncologists and dentists stands to be improved. In cancer care centers with attached dental clinics, for example Toronto's Princess Margaret Hospital and Sunnybrook and Women's Health Sciences Centre, the set up is such that a patient will see a dentist before undergoing radiation therapy so a patient's care can be planned in advance and monitored throughout [22]. However, in many places in Canada and North America this may not be the case. Many patients will see a private dentist who may not be in communication with the oncologist, or of greater concern, some patients will not be seeing a dentist at all [6]. The success of systems like those in Toronto, emphasize the importance of a team centered approach in maximizing patient care.

## **Conclusion**

There is insufficient evidence to conclusively evaluate each available treatment option for xerostomia in radiation-induced patients. Pilocarpine 5 mg t.i.d. demonstrates the greatest success in the literature and at present is the best available treatment. Both submandibular salivary gland transfer and acupuncture hold promise, but additional evidence is required to suggest these treatments with confidence. The support for salivary substitutes is weak and correlates with lack of patient use. At this point, a team centered approach involving researchers, oncologists and dentists is needed to further patient care in radiation induced xerostomia.

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## Figure 1. Checklist to Assess Evidence of Efficacy of Therapy or Prevention [12]

### Checklist to Assess Evidence of Efficacy of Therapy or Prevention

Citation: \_\_\_\_\_

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1. Was the study ethical? \_\_\_
2. Was a strong design used to assess efficacy? \_\_\_
3. Were outcomes (benefits and harms) validly and reliably measured? \_\_\_
4. Were interventions validly and reliably measured? \_\_\_
5. What were the results?
  - Was the treatment effect large enough to be clinically important? \_\_\_
  - Was the estimate of the treatment effect beyond chance and relatively precise? \_\_\_
  - If the findings were “no difference” was the power of the study 80% or better? \_\_\_
6. Are the results of the study valid?
  - Was the assignment of patients to treatments randomized? \_\_\_
  - Were all the patients who entered the trial properly accounted for and attributed at its conclusion?
    - i) Was loss to follow-up less than 20% and balanced between test and controls? \_\_\_
    - ii) Were patients analysed in the groups to which they were randomized? \_\_\_
  - Was the study of sufficient duration? \_\_\_
  - Were patients, health workers, and study personnel “blind” to treatment? \_\_\_
  - Were the groups similar at the start of the trial? \_\_\_
  - Aside from the experimental intervention, were the groups treated equally? \_\_\_
  - Was care received outside the study identified and controlled for? \_\_\_
7. Will the results help in caring for your patients?
  - Were all clinically important outcomes considered? \_\_\_
  - Are the likely benefits of treatment worth the potential harms and costs? \_\_\_

## Figure 2. Data Extraction Sheet

### EVIDENCE BASED REPORT: WHAT IS THE BEST TREATMENT FOR XEROSTOMIA INDUCED BY RADIATION IN PATIENTS WITH HEAD AND NECK CANCER?

#### Data Extraction

Author: \_\_\_\_\_

Title: \_\_\_\_\_

Journal: \_\_\_\_\_

Date of Publication: \_\_\_\_\_

Critical Appraisal Score from Checklist: \_\_\_\_\_

INCLUDE?  Yes  No  
If no, please explain: \_\_\_\_\_

Study Location: \_\_\_\_\_

Study Setting:  University  Hospital  Nursing Home  
 Private Practice  Other: \_\_\_\_\_

Type of Trial:  Single Centre  Multi Centre

Population Status- Participant Ages: \_\_\_\_\_  
Number of Participants: \_\_\_\_\_ Sex (#):  M  F  
Disease Status: \_\_\_\_\_

Intervention (include n): \_\_\_\_\_

Control (include n): \_\_\_\_\_

Outcome: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

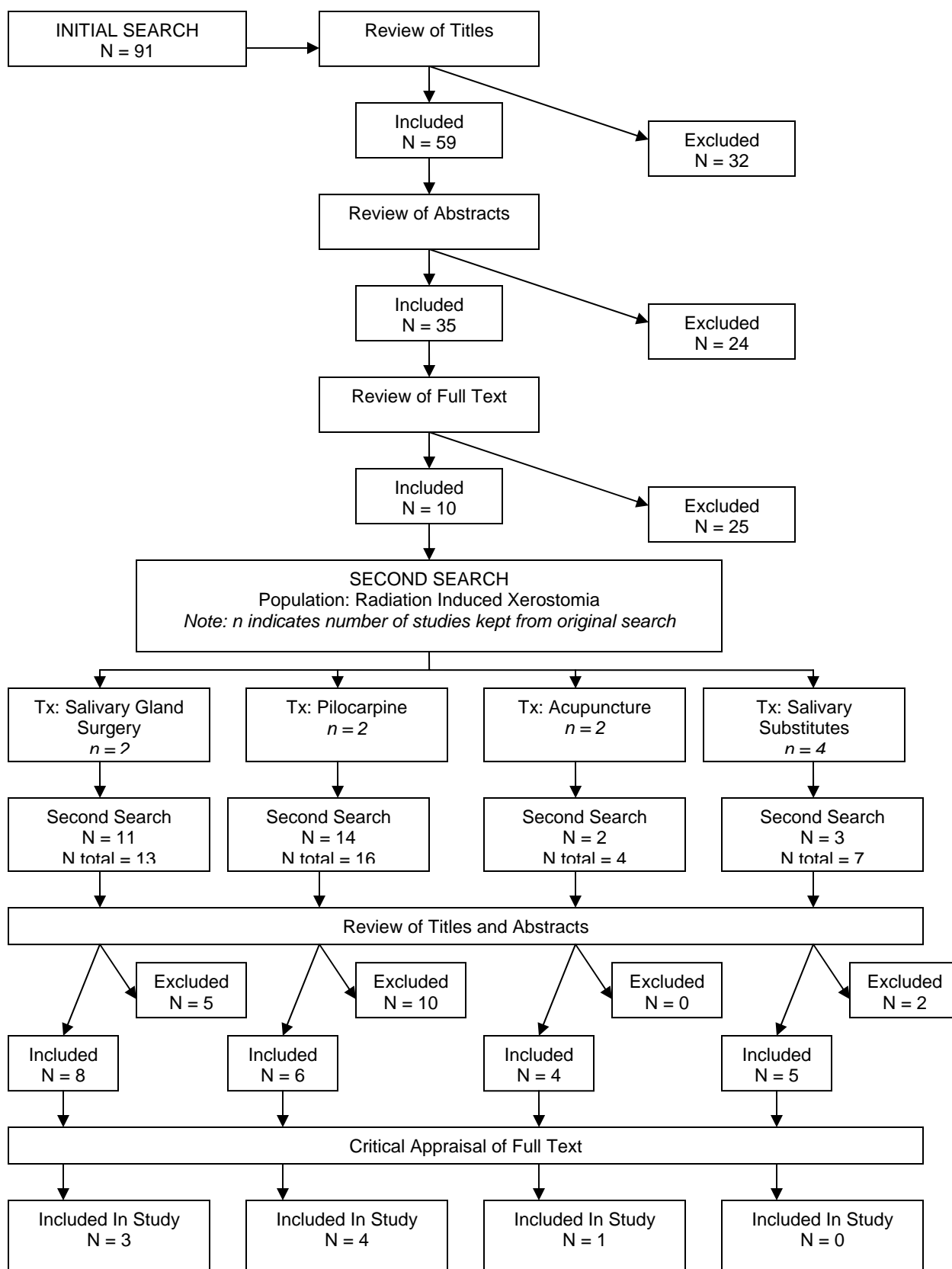
Design Strength: \_\_\_\_\_

Classification of Recommendation: \_\_\_\_\_

Critical Appraisal Comments: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Conclusion: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Figure 3. Flow of articles through the review



**Table 1. Evidence Table for Submandibular Gland Transfer Surgery**

Author, date	Population	Outcome	Critical appraisal comments	Conclusion, strength of evidence and classification
Rieger, Seikaly et al, 2005	Irradiated head and neck cancer patients Tx= 13 Cx= 11	<u>Salivary Flow Rate:</u> U=> Tx=0.07mL/min Cx=0mL/min p=0.002 S=>Tx=0.32 mL/min Cx=0mL/min p=0.05	Not randomized or blinded.	II-1, B CA Score 12/17
Seikaly, Jha et al, 2004	Irradiated head and neck cancer patients Tx= 26 Cx= 12	Statistically significant prevention of xerostomia in 83% of treated patients in 16 months U=>Tx=0.06mL/min Cx=0mL/min; p=0.001 S=>Tx= 0.4 mL/min Cx=0mL/min p=0.001 <u>Calculations</u> RR= 0.167 RRR= 0.833 NNT= 1.3	Not randomized or blinded.	II-1, B CA Score 11/17
Pathak, Bhalavat et al, 2004	Irradiated head and neck cancer patients Tx= 22 Cx= 22 (patients acted as own controls)	Following radiotherapy, 73% of the mean salivary output of transferred gland was preserved while only 27% was preserved for untransferred gland (p<0.001) U=0.08mL/min; Cx=0.03ml/min	Not randomized or blinded. Weaker study design.	II-1, B CA Score 10/17

**Abbreviations:**  
Tx= Number receiving Gland Transfer Therapy  
Cx= Control Group  
U= unstimulated flow  
S= stimulated flow

**Table 2. Evidence Table for Pilocarpine**

Author	Population	Intervention or Test treatment	Outcome	Critical appraisal	Strength of evidence
Johnson JT, Ferreti W. et al August 1993 (Pittsburgh,US)	- 207 px with > 40Gy radiation to head and neck completed more than 4 months before entry into study - 12 weeks - Tx pilo. = 75 - Cx placebo = 65	- 5mg or 10mg pilocarpine t.i.d	- 5mg group = 54 % improvement and placebo = 25% improvement (p=0.003) - saliva production improved but did not correlate with symptomatic relief - NNT=3-4 RR=2.22(95%CI=1.39→3.62) - RRR=1.22	- Met all criteria successfully	- I-A  -CA score 16/17
Leveque FG , Montgomery M et al 1993 (Michigan,US)	-162 px with > 50Gy radiation to head and neck completed more than 4 months before entry into study - 12 weeks - Tx pilo. = 75 - Cx placebo = 87	- 2.5mg pilocarpine t.i.d for 4 weeks followed by 5mg t.i.d for 4 weeks followed by 10mg t.i.d for 4 weeks	- 5mg = 46.4% improvement and placebo = 26% improvement after 8weeks - reduced need for oral comfort agents, salivary responses remained strong at dose levels greater than 2.5mg - NNT=5 - RR=1.79(95%CI=1.15→1.79) - RRR=0.79	- Care received outside the study was not controlled for	- I-A  - CA score 15/17
Warde P, Sullivan MB, Aslandis J 2002 (Toronto,Canada)	-130 patients received radiation >50Gy for head and neck cancer therapy - Tx= 65 - Cx= 65	- Pilocarpine 5mg three times daily from the start of RT and continuing for one month after tx.	- No statistically significant difference between symptoms were observed between the pilocarpine-treated px and the placebo group - Oral dryness as indicated by VAS increased similarly in both groups p=0.92	- Care received outside the study was not controlled for	- I-I  - CA score 15/17
Rieke JW, Hefferman MD et al 1995 (Minneapolis, US)	- 369 px with > 50 Gy radiation to head and neck completed more than 4 months before entry into study - 12 weeks - Tx pilo. = 73 - Cx placebo = 65(f.d), 87(d.t)	- fixed dose study- 5mg or 10mg pilocarpine t.i.d	- fixed dose 5mg pilocarpine = 44% improvement and placebo = 26% improvement - significant improvement in whole saliva (p=0.043) by week8 of treatment - NNT=3-4 -RR=2.22(95%CI=1.41→3.58) - RRR=1.22	-Total loss to follow up was 15.8% in placebo and 21.7% in Tx group	- I-A  - CA score 14/17

t.i.d= three times a day; Tx= patients receiving pilocarpine ; Cx= patients receiving placebo

**Table 3. Evidence Table for Acupuncture**

Author, date	Population	Intervention or Test treatment	Outcome	Critical appraisal	Strength of evidence
M. Blom, I. Dawidson et al 1996 (Stockholm, Sweden)	- 38 px with >50Gy radiation to head and neck 14 wks for treatment and 1 yr observation - Tx = 20 - Cx = 18	- classical acupuncture versus superficial acupuncture	- classical acupuncture 68% improvement in salivary flow and control had 50% improvement but not statistically significant - NNT=6 - RR=1.36(95%CI=1.08→1.71) - RRR=0.36	- Single blind study - Need a better placebo control	- I-A - CA score 14/17



