

## Acupuncture for the prevention of radiation-induced xerostomia in patients with head and neck cancer

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**Abstract:** The aim of this study was to evaluate the effectiveness of acupuncture in minimizing the severity of radiation-induced xerostomia in patients with head and neck cancer. A total of 24 consecutive patients receiving > 5000 cGy radiotherapy (RT) involving the major salivary glands bilaterally were assigned to either the preventive acupuncture group (PA, n = 12), treated with acupuncture before and during RT, or the control group (CT, n = 12), treated with RT and not receiving acupuncture. After RT completion, clinical response was assessed in all patients by sialometry, measuring the resting (RSFR) and stimulated (SSFR) salivary flow rates, and by the visual analogue scale (VAS) regarding dry mouth-related symptoms. Statistical analyses were performed with repeated-measures using a mixed-effect modeling procedure and analysis of variance. An alpha level of 0.05 was accepted for statistical significance. Although all patients exhibited some degree of impairment in salivary gland functioning after RT, significant differences were found between the groups. Patients in the PA group showed improved salivary flow rates (RSFR, SSFR;  $p < 0.001$ ) and decreased xerostomia-related symptoms (VAS,  $p < 0.05$ ) compared with patients in the CT group. Although PA treatment did not prevent the oral sequelae of RT completely, it significantly minimized the severity of radiation-induced xerostomia. The results suggest that acupuncture focused in a preventive approach can be a useful therapy in the management of patients with head and neck cancer undergoing RT.

**Descriptors:** Acupuncture; Radiotherapy; Xerostomia.

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### Introduction

Xerostomia (dry mouth) is the most frequent and potentially debilitating side-effect of radiotherapy (RT) for head and neck cancer. Xerostomia can result in long-term or even permanent oral function impairment and usually is associated with morbidity that profoundly affects the quality of life.<sup>1-4</sup> Several potential methods for preventing radiation-induced xerostomia have been described; however, xerostomia management is complex and often is refractory to most interventions.<sup>5</sup>

Studies using systemic sialogogues (e.g., pilocarpine) concomitant with RT have failed to show significant maintenance of saliva production. Moreover, these therapies have the potential to induce a wide range of unfavorable side effects.<sup>6</sup> Surgical submandibular salivary gland transfer to the submental space outside of the radiation field appears to be

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promising; however, there are specific restrictions on its indication and the technique is not available readily in oncology centers.<sup>7</sup> The cytoprotective agent amifostine combined with careful treatment planning, including intensity-modulated radiation therapy (IMRT), can minimize radiation-induced xerostomia; however, this drug is associated with unfavorable side effects and IMRT is not available in many oncology centers.<sup>8-10</sup>

Despite the benefits of the above methods, all treatments have met with limited success. For many patients, only palliative care remains, in the form of a wide variety of salivary substitutes or simple water consumption, providing merely dry mouth symptomatic relief. These considerations lead many patients to search for alternative or complementary treatment methods, including acupuncture. As a therapeutic method, acupuncture involves the insertion of tiny needles at specific points, with the intent to prevent or cure diseases and symptoms and thereby to reestablish health.<sup>11</sup> The use of acupuncture for xerostomia first appeared in the Western medical literature in 1981.<sup>12</sup> Acupuncture administered after RT in the management of patients with xerostomia was investigated in early studies, demonstrating the benefits of this therapy for improving salivary flow rates and reducing xerostomia-related symptoms.<sup>13-18</sup>

However, studies of acupuncture use in xerostomia have focused mainly on a curative approach when the salivary gland tissues are already damaged and xerostomia is present. To our knowledge, no study has addressed the use of acupuncture for the prevention of irradiation-induced xerostomia. Accordingly, the aim of this study was to investigate the effectiveness of preventive acupuncture (PA) treatment in minimizing irradiation side effects on salivary flow rates and xerostomia-related symptoms in patients with head and neck cancer undergoing RT.

## Materials and methods

### Patients

A total of 24 eligible patients (8 females, 16 males; age range 44-82 years; mean age 63 years) with head and neck cancer (squamous cell carcinoma) were included. Patients were receiving either primary or

postoperative external beam RT (> 5000 cGy) whose irradiation fields involved  $\geq 50\%$  of the major salivary gland volume. Patients who received concomitant chemotherapy were not excluded. This study was approved by the Research Ethics Committees of the School of Dentistry, University of São Paulo and the Brazilian Institute for Cancer Control, Brazil.

### Study design

The 24 subjects enrolled in this study were divided into 2 groups. The preventive acupuncture group (PA group) was comprised of 12 consecutive patients (3 females, 9 males; age range 47-82 years; mean age 64.5 years) who received acupuncture before and during the entire period of RT. The control group (CT group) was comprised of 12 consecutive patients (5 females, 7 males; age range 44-72 years; mean age 58 years) who were treated with RT and did not receive acupuncture or any other therapeutic modality to minimize the irradiation side effects.

After providing written informed consent, all patients were submitted to a clinical examination. Data regarding their treatment profiles, including RT, chemotherapy, and surgical planning, were gathered by a chart review. Data are summarized in Tables 1 and 2.

The RT planning for all patients included 33-35 sessions administered in fractional daily doses of 180-200 cGy, 5 days a week, with a linear accelerator (6-MV photons) or a TeleCobalt 60 unit. The mean total dose administered was 6,770 cGy (range 6,040-7,500 cGy) in the PA group and 6,810 cGy (range 6,040-7,580 cGy) in the CT group. The PA protocol was administered in the PA group before and during RT, twice a week, for 16-20 sessions. The protocol was conducted by the same clinician (FPFB), who was certified in acupuncture.

### Acupuncture protocol

Acupuncture points (acupoints) were selected according to the principles of traditional Chinese and orthodox Western medicine. Local (ST-3, ST-4, ST-5, ST-6, ST-7, GB-2, SI-19, TB-21), distal (LI-4, LI-11, LR-3, ST-36, KI-3, KI-5, GV-20), and auricular (*Shen-Men*, Central Nervous System, Neurovegetative System, Kidney, Spleen, Pancreas, and Mouth)

**Table 1** - Patient characteristics and treatment profiles in the PA group.

Patients	Gender	Age	Tumor site	Dose (cGy)	Salivary glands						CT	SG
					Right side			Left side				
					Parotid	Sub-mand.	Sub-ling.	Parotid	Sub-mand.	Sub-ling.		
1	F	50	Unknown primary	6,040	+	+	+	+	+	+	-	+
2	M	59	Hypopharynx	7,040	+	+	+	+	+	+	+	-
3	M	82	Hypopharynx	7,000	±	+	+	±	+	+	+	-
4	F	69	Larynx	7,000	-	+	+	-	+	+	-	-
5	M	54	Oral cavity	6,040	+	+	+	+	+	+	-	+
6	M	67	Hypopharynx	7,040	±	+	+	±	+	+	-	-
7	M	47	Larynx	6,040	±	+	+	±	+	+	-	+
8	M	53	Larynx	7,500	+	+	+	+	+	+	+	-
9	M	51	Oropharynx	6,040	+	+	+	+	+	+	-	+
10	M	76	Larynx	7,000	+	+	+	+	+	+	-	-
11	M	56	Larynx	6,040	±	+	+	±	+	+	+	-
12	F	73	Oral cavity	6,040	+	+	+	+	+	+	-	+

(+) salivary gland within the irradiation area; (-) salivary gland not irradiated; (±) salivary gland partially irradiated; cGy = centiGray; CT = chemotherapy; SG = surgery.

**Table 2** - Patient characteristics and treatment profiles in the CT group.

Patients	Gender	Age	Tumor Site	Dose (cGy)	Salivary glands						CT	SG
					Right side			Left side				
					Parotid	Sub-mand.	Sub-ling.	Parotid	Sub-mand.	Sub-ling.		
1	F	44	Unknown primary	7,000	+	+	+	+	+	+	-	-
2	M	46	Larynx	7,580	+	+	+	+	+	+	+	-
3	F	59	Oral cavity	6,600	+	+	+	+	+	+	+	+
4	M	60	Oropharynx	6,040	+	+	+	+	+	+	-	+
5	M	54	Oropharynx	7,000	±	+	+	±	+	+	+	-
6	M	59	Nasopharynx	7,000	±	+	+	±	+	+	-	-
7	M	61	Hypopharynx	6,040	+	+	+	+	+	+	+	+
8	F	52	Oral cavity	6,440	+	+	+	+	+	+	-	+
9	M	72	Larynx	7,100	±	+	+	±	+	+	-	-
10	F	64	Unknown primary	7,040	+	+	+	+	+	+	+	+
11	M	68	Oral cavity	7,000	+	+	+	+	+	+	+	-
12	F	46	Unknown primary	7,040	+	+	+	+	+	+	+	+

(+) salivary gland within the irradiation area; (-) salivary gland not irradiated; (±) salivary gland partially irradiated; cGy = centiGray; CT = chemotherapy; SG = surgery.

acupoints, named in accordance with the WHO Standard Acupuncture Nomenclature,<sup>19</sup> were included. For each patient, every acupoint was used in all treatment sessions for a total of 29 punctures (14 bilaterally plus one, GV-20).

After skin antisepsis, sterile acupuncture needles

(0.25 mm × 25 mm) were inserted to depths of 0.5-2.0 cm. The needles were stimulated manually until the appearance of *De Qi*, which is a needle sensation characterized by a subjective nonpainful symptom, tingling or distention around the acupoint, or a radiating sensation originating from the needled

point. The needles were maintained in position for 20 min and then removed. For auricular points, semipermanent needles (0.20 mm × 1.5 mm) were inserted and maintained in position for 7 days with the aid of adhesive tape. After the auricular needles were removed, a new set was inserted, alternating each side weekly until the completion of RT.

### Main outcome measures

The patient clinical response was assessed using objective (saliva collection) and subjective (xerostomia questionnaire) methods to evaluate the salivary gland functions and xerostomia-related symptoms. In both the PA and CT groups, measurements for each patient were performed at the same time of day (2 to 4 pm) after RT completion.

### Saliva collection

Saliva sampling was performed according to a standardized technique.<sup>20</sup> For the resting salivary flow rate (RSFR), all saliva produced over 10 min was collected by spitting. For the stimulated salivary flow rate (SSFR), all saliva collected over 2 min with paraffin chewing was collected. RSFR and SSFR were determined volumetrically in mL/min. The reference values considered respectively for RSFR and SSFR were:

- normal flow (0.25-0.35; 1.0-3.0 mL/min),
- low flow (0.10-0.25; 0.70-1.0 mL/min), and
- hyposalivation (< 0.1; < 0.7 mL/min).

### Xerostomia questionnaire

A modified visual analog scale (VAS; 0-100 mm) xerostomia questionnaire was administered to quantify the self-report of dry mouth symptoms.

The questions addressed were:

- Q1, rate the difficulty you experience in speaking due to dryness;
- Q2, rate the difficulty you experience in swallowing due to dryness;
- Q3, rate how much saliva is in your mouth;
- Q4, rate the dryness of your mouth.

For Q1, Q2, and Q4, higher scores represent a greater subjective degree of xerostomia; for Q3, higher scores represent greater saliva production.

### Statistical analysis

Statistical analyses with a mixed model procedure using random and fixed factors and analysis of variance (ANOVA) were performed to compare differences between the PA and CT groups. An alpha level of 0.05 was accepted for a statistical significance. Data obtained from these analyses were used to estimate the effectiveness of PA.

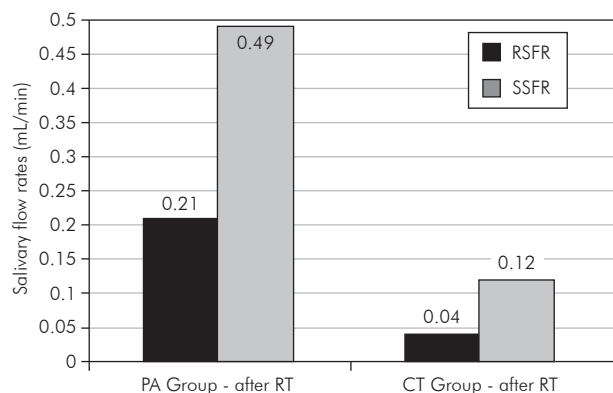
### Results

Previous analyses were performed to investigate similarities between the PA and CT groups regarding related factors that could influence acupuncture analysis. No significant differences were found among the variables age, gender, RT planning, chemotherapy, surgery, and their associations. Subsequently, data from the main outcomes measured in both groups after RT were compared.

The objective and subjective outcomes measured in the PA and CT groups are detailed in Table 3 and illustrated in Figures 1 and 2. After RT, all patients exhibited some degree of impairment in their salivary gland functioning. Nevertheless, significant

**Table 3** - Salivary flow rates and VAS results in the PA and CT groups.

Main outcomes	PA Group - after RT mean (range)	CT Group - after RT mean (range)	p-value
RSFR (mL/min)	0.21 (0.01 - 0.56)	0.04 (0 - 0.16)	$p < 0.001$
SSFR (mL/min)	0.49 (0.05 - 0.98)	0.12 (0 - 0.48)	$p < 0.001$
VAS Q1 (0-100)	23.1 (0 - 53)	53.7 (7 - 96)	$p < 0.05$
VAS Q2 (0-100)	30.3 (0 - 74)	71.1 (0 - 100)	$p < 0.05$
VAS Q3 (0-100)	51.8 (9 - 75)	15.3 (0 - 66)	$p < 0.001$
VAS Q4 (0-100)	39.8 (0 - 90)	74.6 (1 - 100)	$p < 0.05$



**Figure 1** - Mean values of RSFR and SSFR after RT in the PA and CT groups.

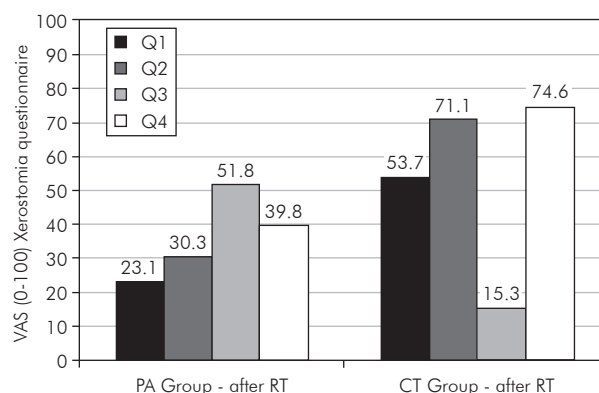
differences between the groups were demonstrated after RT completion for both objective (saliva collection) and subjective (xerostomia questionnaire) main outcomes.

Data from sialometry revealed that patients in the PA group obtained higher mean RSFR and SSFR values than individuals in the CT group ( $p < 0.001$ ). Similarly, the data obtained from the VAS questionnaires revealed that the means of the VAS scores were significantly lower for Q1, Q2, and Q4 ( $p < 0.05$ ) and higher for Q3 ( $p < 0.001$ ) in the PA group than in the CT group.

In addition to the results described above, other subjective findings related to the alleviation of oral and systemic symptoms, including a reduction in burning and painful sensations, dysgeusia, and sleeping, also were observed. Acupuncture treatment was well-tolerated by all patients. No severe adverse effects were evidenced, although somnolence and/or tiny hemorrhages at the puncture sites causing small hematomas were reported.

## Discussion

In this study, we report an innovative protocol for xerostomia prevention through PA treatment, and evaluated its clinical effectiveness in minimizing the severity of irradiation side effects on salivary flow rates and xerostomia-related symptoms. Based on objective and subjective analyses, our clinical findings showed a significant maintenance of salivary flow rates and oral functions (e.g., chewing, swallowing, and speech) for most patients who re-



**Figure 2** - Mean scores on the 4-item VAS xerostomia questionnaire after RT in the PA and CT groups.

ceived PA treatment as compared with those who did not receive acupuncture. The effective use of acupuncture is preferable to pharmacological agents (e.g., pilocarpine or amifostine) because acupuncture presents virtually no significant side-effects. In addition, patient dropout, which is common in studies using pharmacological agents,<sup>6-10</sup> was not seen in this study, showing the clinical feasibility of the therapy.

Among control groups employed in acupuncture clinical trials, superficial, placebo, or *sham* acupuncture methods are common. Studies have shown that even superficial needling is able to promote sensory stimulation, although with a lower intensity than the standard needling technique.<sup>13,14</sup> Therefore, we employed reference data measured after RT to compare differences between the PA and CT groups.

The specific mechanisms underlying the effects of acupuncture on salivary gland tissue are not well known. Further studies with a larger sample should be conducted to corroborate the effectiveness of PA treatment, as well as to investigate its mechanism of action.

## Conclusion

Patients receiving PA exhibited significantly improved salivary flow rates and decreased xerostomia-related symptoms compared to patients who did not receive acupuncture. Although PA treatment did not prevent the oral sequelae of RT completely, it significantly minimized the severity of radiation-induced xerostomia. These findings suggest that acupuncture

can be a useful therapy in the management of patients with head and neck cancer undergoing RT.

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