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Parotid Sparing Study in Head and Neck Cancer Patients Receiving Bilateral Radiation Therapy: One-year Results

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Abstract. Many patients with head and neck cancers receive radiation therapy as part of their treatment which frequently causes considerable morbidity, including various degrees of permanent salivary gland dysfunction. Three-dimensional treatment planning [3-DTP] and conformational dose delivery constitute a new therapeutic modality that conforms the high-dose radiation volume to the shape of the tumor volume while minimizing the dose to tissue that is not at risk of containing cancer. The treatment volumes for head and neck tumors as well as parotid glands can be well-defined on cross-sectional CT imaging techniques. The purpose of this investigation is to determine if 3-DTP and conformational dose-delivery could minimize radiation dose and salivary gland dysfunction to contralateral parotid glands in patients with head and neck cancers. Eleven patients with head and neck cancers who required bilateral radiation therapy were treated with 3-DTP. Unstimulated and stimulated bilateral parotid saliva was collected prior to radiotherapy, weekly during treatment, and 1, 3, 6, and 12 months after the completion of radiotherapy. Treated parotid glands received an average dose of 5745 cGy, while spared glands received only 1986 cGy ($p < 0.0001$). Unstimulated and stimulated parotid flow rates decreased dramatically in treated glands after the initiation of radiotherapy, remained at extremely low rates without any improvements, and were significantly lower at 1 year after radiotherapy compared with baseline. Conversely, parotid flow rates in spared glands underwent mild changes during radiotherapy and were approximately 50% of baseline values. The results of this study suggest that with the use of 3-DTP, contralateral parotid gland function can be partially preserved for at least 1 year in patients with head and neck cancers requiring bilateral radiation.

Key words: salivary gland function, three-dimensional treatment planning, parotid sparing, head and neck cancer.

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Introduction

In 1995, there were an estimated 28,150 newly reported cases of oral-pharyngeal cancer in the United States, resulting in over 8370 deaths from these cancers (Wingo *et al.*, 1995). Many of these patients receive radiation therapy as part of their treatment. The goal of radiation therapy is to eradicate the tumor without causing significant or permanent damage to the oral-pharyngeal tissues that are at low risk for cancer spread (Semba *et al.*, 1994). Currently, many of the radiation therapy techniques used in the treatment of head and neck cancer have serious side-effects detrimental to the oral cavity, including the loss of salivary gland function and a persistent complaint of a dry mouth (xerostomia) (Valdez *et al.*, 1993). Salivary secretions contain numerous proteins and electrolytes that provide dental remineralization, antimicrobial action, lubrication, buffering, and mucosal repair (Mandel, 1989). Patients with radiation-induced salivary dysfunction suffer from oral discomfort and mucositis, difficultly in chewing and swallowing, taste changes, dental caries, oral microbial changes, chronic esophagitis, and a diminished quality of life (Parsons, 1994; Whelton, 1996). Despite much research, there is still no effective treatment for radiation-induced salivary dysfunction (Greenspan, 1990).

Parotid glands consist entirely of serous acini, submandibular and sublingual glands contain mucous and serous acini, and minor salivary glands contain predominantly mucous acini (Young and Van Lennep, 1979). Serous acini are thought to be the most radiosensitive, followed by mucous cells and duct cells (Stephens *et al.*, 1986). Data from rhesus monkey salivary glands (Stephens *et al.*, 1991) suggest that irradiated serous cells undergo interphase cell death by a process of active cellular self-destruction (apoptosis).

Previous studies of head and neck radiotherapy patients have shown that there is a dose-response relationship in parotid flow rates (Valdez *et al.*, 1993; Mira *et al.*, 1981; Marks *et al.*, 1981). For most head and neck cancers, radiation dosages delivered to tumor regions are greater than 4500 cGy (Parsons, 1994). Doses of from 2100 to 4000 cGy have been shown to cause significant damage to salivary glands (Mira *et al.*, 1981).

Three-dimensional treatment planning [3-DTP] and conformational dose delivery constitute a new therapeutic modality that conforms the high-dose radiation volume to the shape of the tumor volume while minimizing the dose to tissue that is not at risk of containing cancer. Treatment volumes for head and neck tumors as well as parotid glands can be well-defined on cross-sectional CT imaging techniques. Beam's-eye-view displays are used to ensure adequate target volume coverage while excluding the opposite (contralateral) parotid gland from the primary beam. Recent results from our laboratory demonstrate that, by means of 3-DTP and dose delivery techniques, contralateral parotid gland function can be spared in patients with unilateral head and neck cancers 1 yr after radiation therapy (Jones *et al.*, 1996). However, many patients with head and neck cancers require bilateral head and neck radiation due to extension of the cancer into the ipsilateral or bilateral lymph nodes. Usually these patients receive high-dose bilateral radiation, causing complete destruction of salivary gland function due to irradiation of both parotid glands (Franzen *et al.*, 1992; Marks *et al.*, 1981; Dreizen *et al.*, 1977).

The purpose of this investigation was to determine if 3-DTP and dose delivery could minimize radiation dose and salivary gland dysfunction to contralateral parotid glands in patients with head and neck cancers requiring bilateral radiation treatment without leading to an increase in locoregional failure (cancer recurrence). It was hypothesized that objective measurements of parotid salivary flow rates would be greater in spared glands compared with irradiated glands due to the use of 3-DTP and conformational dose-delivery techniques.

Materials and methods

Subjects

Entrance criteria for patients included an histologically confirmed invasive cancer of the head and neck region. Patients had to demonstrate a need for irradiation to both sides of the neck due to: (1) a central tumor; (2) a lateralized tumor and ipsilateral neck node metastases where the contralateral node involvement was high; or (3) the condition where the contralateral neck was clinically negative but contained microscopic disease which was surgically resected. A Southwestern Oncology Group (SWOG) performance status of 0-2 (Karnofsky > 40) was required for entrance into the study (Mor *et al.*, 1984). Patients who had previous surgery on the contralateral parotid were ineligible, but those who had cancer surgery on the ipsilateral gland prior to radiotherapy were eligible. A signed informed consent form was also required. The experimental protocol and the consent form were approved by the University of Michigan IRB.

3-D radiation treatment planning

All patients underwent immobilization and full 3-DTP through the University of Michigan Radiation-Oncology planning system (Hazuka *et al.*, 1993). The target volume included the primary tumor mass and lymph node areas which contained metastases along with adjacent areas that were at low risk for microscopic extension. Lymph node areas which were at risk for subclinical disease were defined and included in the target volume. For planning, the target volume was expanded by approximately 1 cm to account for uncertainties of the target location and set-up error. Both parotid glands were contoured into the planning system.

The goal of treatment planning was full exclusion of the contralateral parotid gland (in the case of a lateralized tumor) or the gland at the side of the neck least involved with the tumor (in the case of bilateral neck involvement) from the primary beam, with adequate volume coverage provided to the tumor area. If this was not possible, the treatment planning permitted the lowest dose possible to be administered to the contralateral gland or the side of the neck least involved. Frequently, the tail of the contralateral parotid gland was irradiated to provide complete coverage to contralateral subdigastric and jugular neck nodes. All patients were treated with continuous conventional fractionation, and received 1.8 Gy to 2.0 Gy fractions, 1 fraction *per* day, 5 fractions *per* week. All treatment was delivered with megavoltage energies by the linear acceleration or racetrack microtron.

Parotid salivary flow measurements

Bilateral parotid saliva was collected prior to radiation treatment (baseline), weekly during treatment, and at 1, 3, 6, and 12 months after completion of radiotherapy. Subjects were instructed to refrain from eating, drinking, smoking, and oral hygiene for a minimum of 90 min prior to salivary collection. All patients were seen between 8 a.m. and Noon to control for circadian variations in salivary gland function (Dawes, 1974). Unstimulated parotid saliva was collected from both parotid gland orifices (Stenson's duct) with the use of a Carlson-Crittenden cup as described previously (Baum, 1981; Heft and Baum, 1984). Salivary flow was stimulated by 2% citric acid swabbed onto the dorso-lateral surfaces of the tongue at 30-second intervals for 2 min for equilibration. This was followed by a two-minute collection period during which gustatory stimulation was maintained (Tylenda *et al.*, 1988). Following salivary collection, the volumes of all salivas were determined gravimetrically by means of an analytical balance, assuming a specific gravity of 1.0.

Saliva was collected by two investigators (JAS and REJ) who were calibrated for unstimulated and stimulated parotid salivary flow rates. Unstimulated and 2% citrate-stimulated parotid salivas were collected from eight unmedicated and healthy subjects by both investigators. Inter-examiner correlation coefficients were 0.924 for unstimulated parotid and 0.925 for stimulated parotid flow rates.

Statistical analysis

To control for inter-individual differences in flow rates (Ship *et al.*, 1991), we converted each subject's flow rates at each visit into the percentage of unstimulated or stimulated flow rate at baseline. Paired tests were used for comparisons between unstimulated and stimulated flow rates and percentages of baseline flow rates between untreated and spared glands for each collection period. Comparisons were also performed for unstimulated and stimulated parotid flow rates and the percentages of baseline flow rates between baseline and one-year post-completion of radiation therapy for the treated and spared glands. A paired *t* test was used where mean values were assumed to have normal distribution, and a two-sample robust analysis was used where normality was not a plausible assumption (DuMouchel, 1987). Direct comparisons (paired *t* tests) were used for the evaluation of differences in the amount of radiation delivered to the spared and treated glands. All data were analyzed with the RS/1 software package (BBN Software Products Corp., Cambridge, MA). A criterion of $p < 0.05$ was accepted for significance in all statistical tests.

Table 1. Cancer diagnosis

Subject	Cancer	Location	TMN Staging[a]
1	Squamous cell carcinoma	Tongue	T1N0M0
2	Squamous cell carcinoma	Pyriform sinus	T2N1M0
3	Squamous cell carcinoma	Tonsil	T2N2aM0
4	Squamous cell carcinoma	Tonsil	T1N3M0
5	Squamous cell carcinoma	Tonsil	T2N1M0
6	Squamous cell carcinoma	Larynx	T3N2bM0
7	Squamous cell carcinoma	Larynx	T4N2cM0
8	Squamous cell carcinoma	Tonsil	T3N0M0
9	Squamous cell carcinoma	Tongue	T2N2bM0
10	Squamous cell carcinoma	Submandibular region	TxN3M0[b]
11	Squamous cell carcinoma	Tonsil	T1N2bM0,Tis[c]

a American Joint Committee for Cancer Staging and End Results Reporting, 1988.
b Tx = primary tumor could not be assessed.
c Tis = carcinoma *in situ*.

Results

This paper describes the results from 11 patients treated to date with the use of 3-DTP over the course of a 66-week period up to 1 yr post-radiation. The subjects consisted of nine males and two females, aged 60.4 ± 9.9 years (mean ± sd; range, 45 to 75 years). Each patient was diagnosed with a head and neck cancer (Table 1) and met all of the entrance criteria of the investigation. With the use of 3-DTP, patients received significantly ($p = 0.0001$) greater radiation to the treated parotid gland compared with the spared gland (Table 2). On average, radiation exposure to spared glands was less than one-third of the total amount of radiation delivered to treated glands. During the one-year period in all 11 patients following radiation therapy, there were no cases of cancer recurrence in the regions spared of radiotherapy.

Statistical tests on flow rate values and on the percentages of baseline flow rates revealed similar results with identical trends. For example, unstimulated flow rates from the treated glands were lower at 12 months after radiotherapy compared with baseline flow rates ($p = 0.002$), and percentages of unstimulated baseline flow rates from treated glands were also lower at 12 months after radiotherapy compared with baseline ($p = 0.000$). Therefore, only statistical results from salivary flow rates will be provided.

Unstimulated parotid salivary flow rates in both treated and spared glands throughout the period of radiotherapy and up to 1 yr after the completion of treatment are illustrated in Fig. 1. Salivary flow rates decreased dramatically in treated glands after the initiation of radiotherapy, and were significantly lower at 1 yr after radiotherapy compared with baseline ($p = 0.002$). Alternatively, flow rates in spared glands underwent milder changes during radiation therapy compared with treated glands, and were approximately 50% of baseline values at 1 yr after radiotherapy compared with baseline ($p = 0.004$). There were no significant differences in unstimulated salivary flow rates between treated and spared glands at baseline; however, at the completion of radiotherapy and at 1, 3, 6, and 12 months after the completion of radiotherapy, these differences were highly significant (Table 3). Unstimulated flow rates from treated glands were undetectable (0.000 mL/min) 1 yr after the completion of radiotherapy, compared with output from spared glands (Fig. 1, Table 3).

Stimulated parotid salivary flow rates for treated and spared glands are illustrated in Fig. 2. Flow rates decreased over time in treated glands, and were significantly lower 1 yr after the completion of radiotherapy, compared with baseline values ($p = 0.04$). Conversely, stimulated flow rates did not change as dramatically in spared glands, and were statistically indistinguishable compared with baseline at 1 yr after radiotherapy ($p > 0.05$). Direct comparisons of the flow rates between treated and spared glands showed significant differences at most collection periods during radiation treatment and at all collection periods after the completion of radiotherapy, with the exception of baseline (Table 4).

Salivary flow rates were also converted into percentages of baseline flow rates to control for inter-individual differences. The results for percentages of baseline unstimulated (Fig. 3) and stimulated (Fig. 4) parotid flow rates revealed similar trends as absolute values. Treated unstimulated and stimulated flow rates dropped dramatically after the first week of radiation and remained close to 0% of baseline values. Alternatively, function from spared glands was evident throughout the course of treatment. At 1 yr after the completion of radiotherapy, median flow rates were 67% and

Table 2. Radiation dose

Radiation Dose (cGy)	Spared Gland (n = 11)	Treated Gland (n = 11)	p-Value
Mean ± SD	1986 ± 713	5745 ± 472	0.0001
Range	1300 - 3500	4700 - 6700	

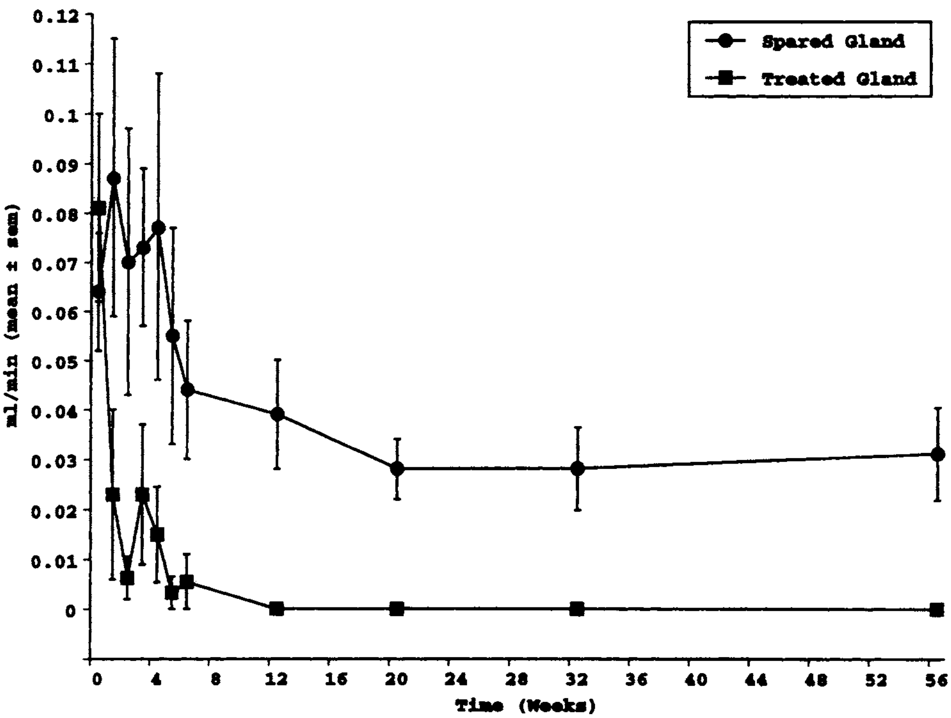

Figure 1. One-year data for unstimulated parotid salivary flow rates in treated and spared glands in 11 cancer patients receiving bilateral head and neck radiation. Flow rates were significantly lower in treated glands compared with spared glands at every visit except baseline.

46% of baseline values, respectively, of baseline unstimulated and stimulated flow rates.

Discussion

Head and neck radiation therapy has a deleterious effect on salivary gland function (Dreizen *et al.*, 1977; Marks *et al.*, 1981; Mira *et al.*, 1981; Larson *et al.*, 1983; Stephens *et al.*, 1986, 1991; Greenspan, 1990; Hazuka *et al.*, 1993; Valdez *et al.*, 1993; Parsons, 1994; Semba *et al.*, 1994; Jones *et al.*, 1996). There is a dose-dependent relationship between the amount of radiation delivered to oral tissues and the damage that eventually occurs (Marks *et al.*, 1981; Mira *et al.*, 1981; Valdez *et al.*, 1993; Semba *et al.*, 1994). It has also been documented that bilateral conventional radiotherapy causes greater oral discomfort and increased complaints of xerostomia compared with unilateral radiation therapy (Mira *et al.*, 1981; Franzen *et al.*, 1992).

Few long-term longitudinal studies have examined salivary function after completion of radiotherapy. Several studies reported permanent salivary dysfunction which was not reversible with time (Dreizen *et al.*, 1977; Mira *et al.*, 1981; Mossman *et al.*, 1982). Conversely, several studies demonstrated partial salivary function recovery which was dependent on radiation dose, field of treatment, and length of follow-up after the completion of therapy (Eneroth *et al.*, 1972; Franzen *et al.*, 1992).

Using conventional bilateral radiation techniques, Dreizen *et al.* (1977) treated 26 patients with a minimum dose of 5000 cGy, and all patients showed a progressive loss of salivary function during and after treatment. Compared with baseline values, mean whole stimulated flow rates were 67% lower at the end of radiation therapy, 89% lower 1 yr post-radiation, and continued to decrease 3 yrs post-radiation (Dreizen *et al.*, 1977). Dreizen *et al.* (1977) concluded that radiation-induced salivary dysfunction was irreversible. Valdez *et al.* (1993) examined unstimulated and stimulated parotid salivary flow rates and demonstrated that patients in the lowest radiation dose quartile (< 5000 cGy) had significantly greater salivary flow rates compared with those in the highest dose quartile (> 6800 cGy). This study and others suggest that if the amount of radiation to the contralateral parotid gland can be minimized, some salivary function can be spared.

The one-year results of the present study demonstrate that contralateral parotid gland function can be spared in patients requiring bilateral radiation for head and neck cancers if 3-DTP and dose-delivery techniques are used. Through the use of 3-DTP, beam's-eye-view displays were used to design beam and blocking arrangements that excluded the contralateral parotid gland (Hazuka *et al.*, 1993). Consequently, spared glands received an average radiation dose of only 1986 cGy, 65.4% lower than that received by treated glands. This permitted a partial preservation of contralateral parotid function to occur, while nearly all output was lost in

Table 3. Average unstimulated flow rates[a]

	Spared Gland (n = 11) (mL/min)	Treated Gland (n = 11) (mL/min)	p Value
Baseline	0.064 ± 0.039	0.081 ± 0.063	NS[b]
Completion of radiation	0.044 ± 0.048	0.006 ± 0.018	0.009
3 months	0.028 ± 0.020	0.000 ± 0.000	0.0009
6 months	0.028 ± 0.026	0.000 ± 0.000	0.008
12 months	0.031 ± 0.031	0.000 ± 0.000	0.008

[a] Mean ± SD.
[b] NS = Not statistically significant.

treated glands. Complete preservation of contralateral parotid glands is not possible in all patients, since the tail of the contralateral parotid gland may be fully irradiated to treat subdigastric and jugular neck nodes.

Unstimulated parotid salivary secretions play a vital role in the maintenance of oral health (Mandel, 1989). Alterations in these unstimulated fluids can impair oral and systemic health, since they confer protection to the host all day and night. Spared parotid glands in the present study received 65.4% less radiation than treated glands, which allowed for at least partial preservation of unstimulated parotid flow rates 12 months after the completion of radiation treatment. While preservation of unstimulated function was not 100%, the presence of some unstimulated function will allow for subsequent stimulation with mechanical, gustatory, and pharmacological agents (Greenspan, 1990; Johnson *et al.*, 1993; LeVeque *et al.*, 1993; Atkinson and Wu, 1994).

Stimulated salivary fluids reflect the functional capacity of the gland, and play a major role during mealtime for mastication and deglutition. The median parotid stimulated flow rates 12 months after completion of radiation treatment in spared glands were 64% lower than baseline values, compared with 100% lower in treated glands. When non-sparing bilateral parotid radiation techniques were used, Dreizen *et al.* (1977) demonstrated that mean whole stimulated saliva flow rates were 89% lower than baseline values 1 yr post-irradiation, and that flow rates progressively decreased through 3 yrs post-irradiation. Conversely, the results from the present study demonstrate that mean stimulated flow rates increased slightly up to 12 months after the completion of radiation therapy (Table 4). Perhaps in some individuals, the radiation-induced loss of stimulated saliva function in spared glands may be partially reversible with time.

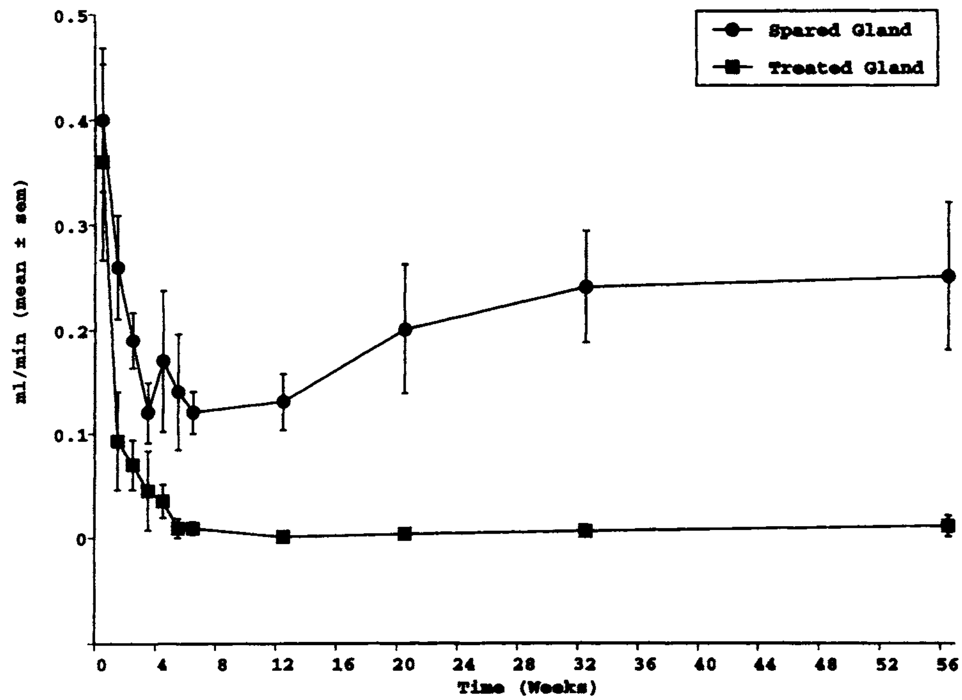

Figure 2. One-year data for stimulated parotid salivary flow rates in treated and spared glands in 11 cancer patients receiving bilateral head and neck radiation. Flow rates were significantly lower in treated glands compared with spared glands at every visit except baseline.

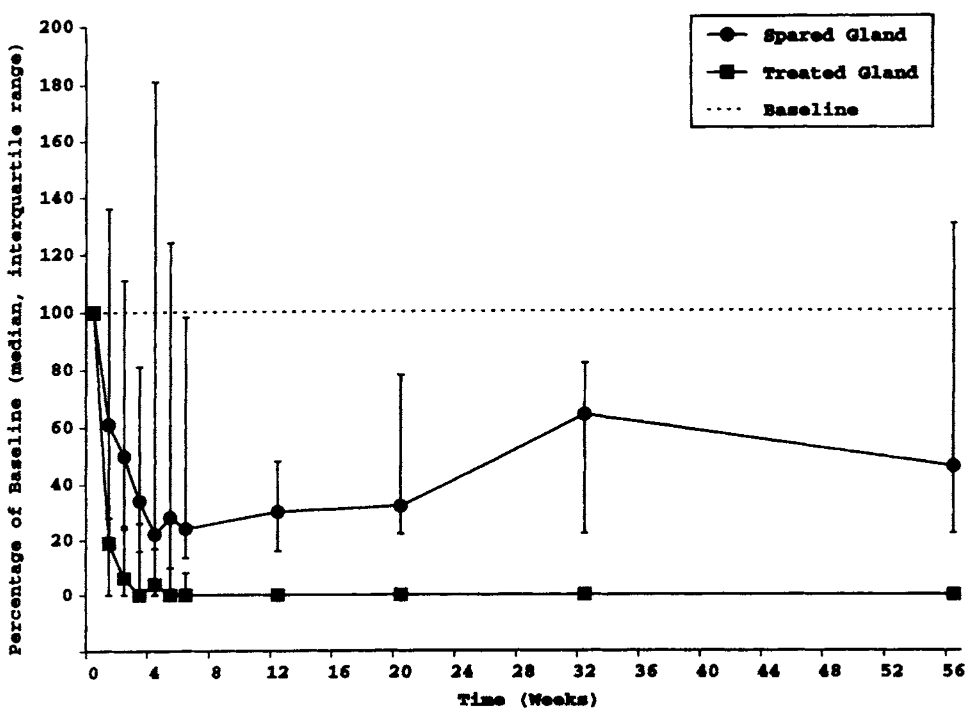

Figure 3. One-year data for percentages of baseline unstimulated parotid salivary flow rates in treated and spared glands in 11 cancer patients receiving bilateral head and neck radiation. Flow rates were significantly lower in treated glands compared with spared glands at every visit except baseline.

Table 4. Average stimulated flow rates[a]

	Spared Gland (n = 11) (mL/min)	Treated Gland (n = 11) (mL/min)	p Value
Baseline	0.400 ± 0.220	0.360 ± 0.310	NS[b]
Completion of radiation	0.120 ± 0.065	0.008 ± 0.020	0.0004
3 months	0.200 ± 0.210	0.003 ± 0.010	0.05
6 months	0.240 ± 0.170	0.006 ± 0.017	0.001
12 months	0.250 ± 0.023	0.011 ± 0.034	0.006

[a] Mean ± SD.
[b] NS = Not statistically significant.

There are some limitations to this study. First, this paper presents data on only 11 patients treated with bilateral 3-DTP up to 12 months after radiotherapy. Nevertheless, there are distinct and significant differences between spared and treated parotid glands. There are even slightly detectable trends of salivary gland recovery from spared glands with time. However, more patients are needed over a longer time period if we are to determine whether the trends observed are statistically significant in larger populations. Finally, subjective data on patients' xerostomia complaints are not included in this report. Responses to standardized xerostomia questions (Fox *et al.*, 1987) have been collected, but due to the small sample size and large individual response variations, results to date have yielded no statistical significance.

The data from this study have some important clinical ramifications. Total loss of parotid salivary gland function may no longer be inevitable in patients with head and neck cancers who require bilateral radiation therapy. Parotid gland function can be partially preserved by 3-DTP, resulting in a decrease in radiation-induced dysfunction. Consequently, the use of gustatory, masticatory, and pharmacological saliva stimulants as well as aggressive oral hygiene techniques can be used to help preserve oral health.

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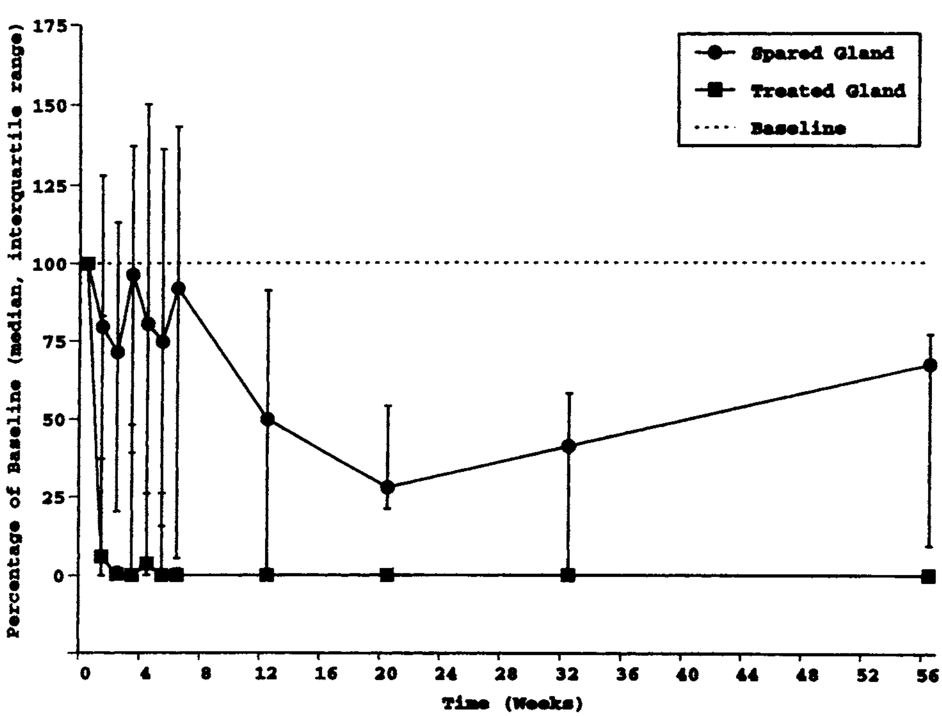

Figure 4. One-year data for percentages of baseline stimulated parotid salivary flow rates in treated and spared glands in 11 cancer patients receiving bilateral head and neck radiation. Flow rates were significantly lower in treated glands compared with spared glands at every visit except baseline.

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