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A Phase II Study of Submandibular Gland Transfer Prior to Radiation for Prevention of Radiation-Induced Xerostomia in Head and Neck Cancer (Rtog 0244)s

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Abstract

Purpose—We report the results of a phase II study to determine reproducibility of surgical technique of submandibular salivary gland transfer (SGT) for prevention of radiation (XRT) induced xerostomia in a multi-institutional setting and to assess severity of xerostomia.

Methods and Materials—Eligible patients had surgery for primary, neck dissection, and SGT followed by XRT during which the transferred salivary gland was shielded. IMRT, amifostine, and pilocarpine were not allowed, but postoperative chemotherapy was allowed. Each operation was reviewed by two and radiation by one reviewer. If 13 or more (out of 43) were “not per protocol”, then technique would be considered not reproducible as per study design. The secondary endpoint was the rate of acute xerostomia, Grade 2 or higher and a rate of ≤ 51% was acceptable.

Results—44 of the total 49 patients were analyzable: male (81.8%), oropharynx (63.6%), stage IV (61.4%), median age 56.5 years. SGT was “per protocol” or with acceptable variation in 34 patients (77.3%) and XRT in 79.5%. 9 patients (20.9%) developed grade II acute xerostomia; 2 had grade 0 -1 xerostomia (4.7%) but started on amifostine/pilocarpine. These 11 patients (25.6%)

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were considered failures for the xerostomia endpoint. 13 patients have died; median follow-up for 31 surviving patients is 2.9 years. Two-year overall and disease-free survival rates are 76.4% and 71.7%, respectively.

Conclusions—the technique of submandibular salivary gland transfer procedure is reproducible in a multicenter setting. Seventy-four percent of patients had prevention of XRT induced acute xerostomia.

Keywords

Salivary gland transfer procedure; xerostomia; radiation; prevention; head and neck cancer

Introduction

Over 40,000 individuals are diagnosed as having head and neck cancer every year in the United States. Radiation treatment is a primary or secondary therapeutic modality with most cases resulting in xerostomia and adversely affecting patient's quality of life.[1] Xerostomia impairs mastication, deglutition, gustation, causes nutritional compromise, sleep disruptions and change in oral microbial flora leading to caries. [1] Several strategies such as amifostine, [2] intensity modulated radiation therapy (IMRT),[3,4] pilocarpine [5,6] and acupuncture have been tried over the years in an attempt to reduce xerostomia.

A new surgical procedure for the prevention of xerostomia through submandibular gland transfer (SGT) to the submental space has been recently described. The transferred gland is then shielded during radiation treatment. [7-9] Jha, Seikaly et al did a prospective, phase II study for management of xerostomia by surgical transfer of submandibular salivary gland (SMG) to the submental space prior to starting XRT.[7-9] Surgery was the prime modality of the management, followed by XRT. Eighty-one percent of patients had no or minimal xerostomia and 19% had moderate to severe xerostomia. Long-term results were also published showing preservation of saliva in 83% of patients 2 years after XRT. These results have been confirmed by other investigators. [10,11]

The purpose of this study was to determine reproducibility of surgical technique of SGT for prevention of XRT induced xerostomia in a multi-institutional setting and to assess severity of xerostomia. Quality of life outcomes (QOL), pattern of recurrence, disease-free and overall survival were also evaluated.

Methods and Materials

A phase II multi-center trial was initiated after the appropriate institutional review board approval was obtained. Viewing of a teaching video / CD-Rom detailing submandibular salivary gland transfer procedure was mandatory for all investigators prior to accrual of patients. All simulator films and treatment plans were evaluated centrally by the principal investigator and surgery by two reviewers.

Eligibility criteria included biopsy-confirmed squamous cell carcinoma of oropharynx, hypopharynx, larynx, or unknown primary tumor with unilateral neck nodes. The radiation treatment volumes were to include ≥ 80% of major salivary glands (parotids) and this

volume received ≥ 50 Gy. Patients greater than 18 years with Zubrod status 0-1; no prior XRT to the head and neck; no salivary gland malignancy or disease, e.g., Sjögren's syndrome. Patients using cholinergic, anti-cholinergic, and tricyclic drugs were ineligible as were pregnant women. Carcinomas of oral cavity, nasopharynx, N3 disease, bilateral neck node involvement or a suspicious neck node (on CT or MRI scan) on the contralateral neck or the side chosen for salivary gland transfer, pre-epiglottic space involvement, involvement of level 1 nodes and recurrent disease were ineligible.

All patients had baseline CT/MRI scan of the head and neck, salivary scan using sodium pertechnetate (Na-99mTcO4-) and completed a University of Washington Quality of Life Questionnaire.

All patients were treated with surgery as prime modality of treatment. The patients had surgery for the primary, neck nodes and had submandibular salivary gland transfer procedure followed by XRT within 4-6 weeks. The XRT doses ranged from 54-70 Gy over 5.5 – 7 weeks, 2.0 Gy/fraction. Patients were treated with standard three field techniques. Simulation films, initial port films, and the calculation form were sent to RTOG Headquarters for radiation therapy quality assurance review.

The transferred salivary gland is identified with the help of the CT scans done in the treatment position and a wire placed around the gland at the time of surgery. The volume of the transferred salivary gland was drawn on each slice of the CT scan showing the transferred submandibular salivary gland. The shielding was then drawn to cover > than 70% of the transferred submandibular salivary gland, and the major part of the sublingual salivary glands (explained in the CD-ROM/video).

Sometimes, if the permanent pathology were to reveal disease (missed at frozen section) in level I lymph nodes or on the side chosen for the salivary gland transfer (contralateral to the primary site), no attempt was to be made to shield the transferred salivary gland in order to remain oncologically sound. In this study, however, there were no such cases.

The choice of the side for submandibular salivary gland transfer was dependent on: 1) the side of uninvolved neck and 2) side of primary tumor. For well lateralized primary cancer with unilateral neck involvement or N0 neck, transfer was performed on the contralateral N0 neck; for midline primary cancer with unilateral neck involvement, transfer was performed on the contralateral N0 neck and for midline primary cancer with no neck involvement, transfer was performed on either one of the N0 neck.

Photographs

Photographs (35 mm slides or prints) were mandatory for each transfer. Photographs of anterior & lateral view of the submental space after transfer were sent to the RTOG for central review.

IMRT, Amifostine & Pilocarpine

IMRT treatment techniques, and prophylactic use of amifostine or pilocarpine were not allowed. Administration of pilocarpine and its derivatives was discouraged before six

months post-treatment. However, pilocarpine could be used if there was no salivary flow during the first post-treatment sialometry study. Any use of these agents and their derivatives including start dates was reported on the case report forms.

Postoperative chemoradiotherapy was allowed; the choice of chemotherapy was at the discretion of the treating physician. Neoadjuvant chemotherapy was not permitted.

Quality of Life

A patient self-assessed questionnaire, University of Washington QOL was used for QOL evaluation. The QOL assessments included a baseline assessment, and at 3, 6, and 12 months from start of XRT.

Toxicity

Acute radiotherapy toxicities (≤ 90 days from start of XRT) and systemic effects at any time were scored using the Common Toxicity Criteria (CTC) version 2.0. Late RT toxicities were scored by the RTOG/EORTC criteria.

Statistical Methods

The primary endpoint was reproducibility of the salivary gland transfer technique. Each case was examined by two reviewers. Procedures scored as per protocol or with acceptable variation by both reviewers were considered “per protocol” and all others “not per protocol”. Simon's two-stage design was used with unacceptable/acceptable rates set at 60%/80%, type I error 5%, and 80% power. The first stage required 11 patients. If 4 or more operation in the first 11 patients were scored “not per protocol” then discontinuation would have been requested. The second stage required 43 patients (including the initial 11). If 13 or more of the 43 operations were scored “not per protocol” the technique would have been considered not reproducible. Allowing for 10% of patients to be ineligible or not start protocol therapy, the total sample size was 48 patients.

An important secondary endpoint was the rate of acute xerostomia, defined as Grade 2 or higher acute xerostomia. Based on the U.S. Bioscience phase III amifostine trial, a rate of ≤ 51% would be considered acceptable. Toxicities due to XRT and/or surgery, and salivary gland function via scintigraphy were also evaluated as secondary endpoints.

Efficacy endpoints were disease-free survival (where failure was defined as local, regional, or distant recurrence/progression, second primary tumor, or death due to any cause), and overall survival, where failure was defined as death due to any cause. Rates were estimated using the Kaplan-Meier method.

Results

Eight institutions enrolled 49 patients between August, 2003 and August, 2007. Forty-four patients were analyzable (3 patients were ineligible and 2 received no protocol treatment). Distributions of patient and tumor characteristics are shown in Table 1. Patients were

predominantly male (81.8%), Zubrod 0 (79.5%), oropharynx (63.6%), and stage IV (61.4%); median age was 56.5 years.

Nine patients (20.9%) developed Grade 2 acute xerostomia. In addition, 2 had Grade 1 xerostomia (4.7%) but started on amifostine/pilocarpine yielding an acute xerostomia rate of 25.6%. Per the study design, this rate was acceptable. Seventy-four percent did not have any xerostomia. One patient (2.3%) experienced Grade 4 acute toxicity (anorexia). Fifteen patients (34.9%) experienced at least one Grade 3-4 acute toxicity (Table 2). Three patients (7.9%) experienced Grade 3 late toxicity [pneumonia; supraglottic edema; trismus (Table 3)]. The most common surgical complication was edema, in 13.6% (Tables 4).

RT was per protocol or with acceptable variation in 79.5%. One patient did not receive RT and 3 patients had unacceptable deviations (IMRT). The salivary gland transfer was “per protocol” in 34 patients (77.3%); per the study design this rate was acceptable. Three patients (6.8%) did not have the transfer. Twenty-two patients (50%) had chemotherapy concurrent with RT; the most common drug was single-agent cisplatin (13/22; 59.1%).

Thirteen patients have died; median follow-up for 31 surviving patients is 2.9 years (range 0.2-5.6). Estimated 2-year overall and disease-free survival rates are 76.4% (95% confidence interval: 63.6-89.2) and 71.7% (58.2-85.3), respectively. First failure was local & regional in 1 patient, local & distant in 1, distant only in 3, second primary in 4, and death in 7. Seven of 13 deaths (53.8%) were due to study cancer.

Discussion

Humans produce approximately 600 mls of saliva per day. Parotid secretions are primarily serous and predominate when stimulated during eating, whereas submandibular salivary gland secretions are relatively more mucinous, and represent the majority of basal, unstimulated saliva. Parotids contribute only about 20% of the total volume of unstimulated saliva, while the submandibular salivary gland contributes 65% and the sublingual 7-8%. At high flow rates, the parotids contribute about 50% of the whole saliva. Unstimulated saliva (resting state) is more important in the subjective feeling of xerostomia. Stimulated saliva is produced during eating, which lasts for approximately 54 minutes per day.[19] In our opinion, the submandibular salivary glands contribution is the most important in perception of xerostomia.

Jha, Seikaly et al performed a prospective, phase II study for management of xerostomia by surgical transfer of submandibular salivary gland (SMG) to the submental space prior to starting XRT. [7-9] Surgery was the prime modality of the management, followed by XRT. Eighty-one percent of patients had no or minimal xerostomia and 19% had moderate to severe xerostomia. Long-term results were also published showing preservation of saliva in 83% of patients 2 years after XRT. These results have been duplicated by other investigators. [10-11]

IMRT strategies have focused primarily on diminishing radiation dose to one or both the parotid glands.[3,4] Investigators are now, however, focusing their attention on the importance of submandibular salivary gland salivary contributions. Eisbruch et al. are investigating the

possibility of sparing both the parotid and the submandibular salivary gland by the combined use of IMRT (for parotids) and amifostine for the cytoprotection of the submandibular salivary gland.[12] Saarilahti et al. recently demonstrated the importance of sparing the contralateral submandibular salivary gland using IMRT.[13] In a selected subset of patients (n=18), the mean unstimulated saliva flow was 60% of the baseline vs. 25% (p=0.006) among patients with one submandibular salivary gland spared. Patients in whom both the submandibular and the parotid salivary glands were spared, reported less grade 2 or 3 xerostomia (p= 0.018).[12] Therefore, to further alleviate patient's xerostomia, future studies should focus on better sparing of the submandibular salivary gland in addition to parotids. [13]

In the present multi center study, the salivary gland transfer was “per protocol” in 34 patients (77.3%) and XRT was per protocol or with acceptable variation in 79.5%. Twenty-one percent of patients experienced grade 2 acute xerostomia and 26% grade 1. Per our protocol definition, the acute xerostomia rate was 25.6% (grade 2: 21%; grade 0-1 but started amifostine or pilocarpine: 4.7%). Per the study design, this rate was acceptable and consistent with the results published by other investigators with submandibular salivary gland transfer procedure. [10,11] We will be reporting patient's self assessed quality of life questionnaire as a separate manuscript.

Several authors, using IMRT or amifostine have reported the acute & late xerostomia rate using the same RTOG late toxicity reporting criteria (Table 5). [3, 14-19] We have chosen the studies that have used the same RTOG criteria for reporting late toxicity. The time period of reported late toxicity varied and that time is mentioned in Table 6. Our results of acute & late xerostomia compare quite favorably to the results reported by other investigators using IMRT or amifostine (Table 6). Lee et al reported acute xerostomia results, but for late xerostomia results at 2 years, only 61% of patients were evaluable and hence late xerostomia results are not incorporated in table 6. Most common surgical complications were related to submental fullness or facial edema. This is primarily due to the location of the transferred salivary gland. Shoulder weakness and numbness were observed in 4.5% of the patients. Submental fullness was also noted as the late surgical complications in 19% of patients.

The recurrence pattern was not altered by the salivary gland transfer procedure and there was no submental space recurrence noted.

The technique of submandibular salivary gland transfer procedure is reproducible in a multicenter setting. Seventy-four percent of patients had prevention of XRT-induced acute xerostomia. Other investigators have also reproduced good results of salivary gland transfer procedure. [10,11]

Recently in a phase III multicenter randomized study comparing SGT with pilocarpine for management of xerostomia, we convincingly showed superiority of submandibular salivary gland transfer.[20] At our institution, we are conducting a phase II prospective study combining salivary gland transfer procedure and IMRT using tomotherapy to protect both the parotid and the “transferred submandibular salivary gland” for the prevention of XRT-induced xerostomia.

There are two issues that have prevented the wider use of submandibular salivary gland transfer procedure for the prevention of XRT-induced xerostomia despite its good results. There is no surgical code for this procedure in North America and the surgeons are not easily compensated for performing it. The second reason is that the paradigm of head and neck cancer treatment has shifted in favor of chemoradiation treatment as the primary management with surgery mostly reserved for salvage.

The major part of the global burden of head and neck cancers is located in the developing world. Even in the cancer centers with no access to IMRT/tomotherapy or other image-guided radiation treatment techniques, SGT can be used with standard three field techniques, for the prevention of XRT-induced xerostomia.

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Submandibular salivary gland transfer – RTOG – 0244 study

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70,000 individuals are diagnosed with head and neck cancer annually in United States. Radiation treatment adversely affects salivary gland function and quality of life. Several strategies have been explored to address problem of xerostomia: Amifosine, intensity modulated radiation treatment, Pilocarpine. Salivary gland transfer (SGT) procedure proved to be effective for management of XRT induced xerostomia, in a phase III randomized Canadian study. SGT now has shown excellent results in a phase II, multicenter study (RTOG-0244).

Table 1

Pretreatment Characteristics (n=44)

Age		
Median	56.5	
Range	42-74	
	n	%
Gender		
Male	36	81.8
Female	8	18.2
Zubrod Performance Status		
0	35	79.5
1	9	20.5
Primary Site		
Oropharynx	28	63.6
Hypopharynx	3	6.8
Larynx	3	6.8
Unknown	10	22.7
T Stage		
T0	1	2.3
T1	12	27.3
T2	16	36.4
T3	4	9.1
T4	2	4.5
Tis	1	2.3
Tx	8	18.2
N Stage		
N0	5	11.4
N1	14	31.8
N2a	12	27.3
N2b	13	29.5

Table 2

Chemotherapy and Acute Radiotherapy Toxicity Reported as Definitely, Probably, or Possibly Related to Treatment * (n=43)**

	Grade				
Category	1	2	3	4	5
Allergy/immunology	1	0	0	0	0
Auditory/Hearing	2	2	1	0	0
Blood/bone marrow	2	1	0	0	0
Cardiovascular (General)	2	0	0	0	0
Constitutional symptoms	5	14	4	0	0
Dermatology/skin	7	9	2	0	0
Endocrine	0	1	0	0	0
Gastrointestinal	9	14	11	1	0
Hemorrhage	1	1	0	0	0
Hepatic	0	1	0	0	0
Infection Febrile Neutropenia	2	3	0	0	0
Lymphatics	2	1	0	0	0
Metabolic/laboratory	1	0	0	0	0
Musculoskeletal	3	2	0	0	0
Category	1	2	3	4	5
Neurology	3	1	0	0	0
Pain	4	5	3	0	0
Pulmonary	4	2	0	0	0
Renal/genitourinary	0	1	0	0	0
Sexual/reproductive function	1	0	0	0	0
Worst non-hematologic	5 (11.6%)	16 (37.2%)	14 (32.6%)	1 (2.3%)	0 (0.0%)
Worst overall	5 (11.6%)	16 (37.2%)	14 (32.6%)	1 (2.3%)	0 (0.0%)

*Includes toxicities where relationship to treatment is missing.

** One patient did not receive radiation therapy.

Table 3

Late Radiotherapy Toxicity (n=38)

	Grade				
Toxicity	1	2	3	4	5
Esophagus	2	2	0	0	0
Joint	2	1	0	0	0
Larynx	6	0	0	0	0
Mucous membrane	7	2	0	0	0
Salivary gland (xerostomia, taste impairment)	16	6	0	0	0
Skin (within RT field)	6	0	0	0	0
Subcutaneous tissue (within RT field)	4	2	0	0	0
Other	2	5	3	0	0
Worst overall	13 (34.2%)	9 (23.7%)	3 (7.9%)	0 (0.0%)	0 (0.0%)

Table 4
Surgical Complications (within 30 days of surgery) (n=44)

	n	%
Bleeding/hematoma	2	4.5
Wound infection	2	4.5
Facial edema	6	13.6
Facial edema on the transfer side	6	13.6
Shoulder weakness	2	4.5
Shoulder weakness on the transfer side	1	2.3
Neck numbness	3	6.8
Neck numbness on the transfer side	2	4.5
Gland movement out of position	1	2.3
Nerve injury: hypoglossal	1	2.3
Nerve injury: hypoglossal on the transfer side	1	2.3
Nerve injury: lingual	1	2.3
Cerebral embolism/CVA	1	2.3
Other	4	9.1

Table 5

Acute and Late Xerostomia

	Acute Xerostomia		Late Xerostomia	
Study	**Grade 1**	**Grade 2**	**Time point**	**Grade 2**
RTOG 0244	25.6%	20.9%	1 year	5.9%
RTOG 0022 (IMRT)	38.8%	49.3%	1 year	22.7%
Brizel et al. phase III amifostine study	NR	51%	1 year	34%
Koukourakis et al. s/C amifostine, phase II study	NR	58%	NR	NR
Lee et al. (IMRT), UCSF experience	28%	64%	NR	NR
Buentzel et al. I/V (amifostine), phase III study	46%	39%	>90 days	39%
Nangia et al. (IMRT), IJROBP, 2010	NR	NR	>1 year	36%
Vergee et al. (IMRT), IJROBP, 2009	NR	NR	6 months	32%
Wasserman et al.I/V (amifostine), IJROBP, 2005	NR	NR	1 year	34%

NR = not reported for all patients on the study.

Table 6

Acute and Late Xerostomia

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Study	**Grade 1**	**Grade 2**	**Time point**	**Grade 2**
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RTOG 0022 (IMRT)	38.8%	49.3%	1 year	22.7%
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Buentzel et al. I/V (amifostine), phase III study	46%	39%	>90 days	39%
Nangia et al. (IMRT), IJROBP, 2010	NR	NR	>1 year	36%
Vergee et al. (IMRT), IJROBP, 2009	NR	NR	6 months	32%
Wasserman et al.I/V (amifostine), IJROBP, 2005	NR	NR	1 year	34%

NR = not reported for all patients on the study.