Int. J. Radiation Oncology Biol. Phys., Vol. 56, No. 1, pp. 136–144, 2003

0360-3016/03/$–see front matter

ELSEVIER

doi:10.1016/S0630-3016(03)00093-2

3D-CRT

DOSIMETRIC PREDICTORS OF XEROSTOMIA FOR HEAD-AND-NECK CANCER PATIENTS TREATED WITH THE SMART (SIMULTANEOUS MODULATED ACCELERATED RADIATION THERAPY) BOOST TECHNIQUE

CHAD M. AMOSSON, M.D.,* BIN S. TEH, M.D.,* T. JOHN VAN, M.D.,* NATHAN UY, M.D.,* EUGENE HUANG, M.D.,* WEI-YUAN MAI, M.D.,* ANNA FROLOV, M.S.,† SHIAO Y. WOO, M.D., F.A.C.R.,* J. KAM CHIU, M.D.,* L. STEVEN CARPENTER, M.D.,* HSIN H. LU, M.D.,* WALTER H. GRANT III, PH.D.,* AND E. BRIAN BUTLER, M.D.*

*Department of Radiology/Section of Radiation Oncology and the †Scott Department of Urology, Baylor College of Medicine and The Methodist Hospital, Houston, TX

Purpose: **To evaluate the predictors of xerostomia in the treatment of head-and-neck cancers treated with intensity-modulated radiation therapy (IMRT), using the simultaneous modulated accelerated radiation therapy (SMART) boost technique. Dosimetric parameters of the parotid glands are correlated to subjective salivary gland function.**

Methods and Materials: **Between January 1996 and June 2000, 30 patients with at least 6 months follow-up were evaluated for subjective xerostomia after being treated definitively for head-and-neck cancer with the SMART boost technique. Threshold limits for the ipsilateral and contralateral parotid glands were 35 Gy and 25 Gy, respectively. Dosimetric parameters to the parotid glands were evaluated. The median follow-up time was 38.5 months (mean 39.9 months). The results of the dosimetric parameters and questionnaire were statistically correlated.**

Results: **Xerostomia was assessed with a 10-question subjective salivary gland function questionnaire. The salivary gland function questionnaire (questions 1, 2, 3, 4, 6, and 9) correlated significantly with the dosimetric parameters (mean and maximum doses and volume and percent above tolerance) of the parotid glands. These questions related to overall comfort, eating, and abnormal taste. Questions related to thirst, difficulty with speech or sleep, and the need to carry water daily did not correlate statistically with the dosimetric parameters of the parotid glands.**

Conclusions: **Questions regarding overall comfort, eating, and abnormal taste correlated significantly with the dosimetric parameters of the parotid glands. Questions related to thirst, difficulty with speech or sleep, and the need to carry water daily did not correlate statistically with the dosimetric parameters of the parotid glands. Dosimetric sparing of the parotid glands improved subjective xerostomia. IMRT in the treatment of head-and-neck cancer can be exploited to preserve the parotid glands and decrease xerostomia. This is feasible even with an accelerated treatment regimen like the SMART boost. More patients need to be evaluated using IMRT to identify relevant dosimetric parameters.** **© 2003 Elsevier Inc.**

Dosimetric predictors, Xerostomia, Head-and-neck cancer, Radiation therapy, IMRT, Parotid sparing.

INTRODUCTION

Radiation therapy for head-and-neck cancer is evolving from generous treatment fields encompassing large volumes of normal tissue to conformal techniques that focus on areas of disease. Conformal radiation also allows the radiation oncologist to spare normal tissue. The primary goal of treatment is still targeting the tumor for disease control, but perhaps the most significant benefit has been seen with improved quality of life. Quality of life after radiation is largely related to xerostomia (1–3). Other institutions are applying conformal radiation therapy to the goal of parotid preservation (4–7). Improved results have been seen in subjective and objective salivary gland function. Parotid-sparing irradiation can even improve nutrition and body weight (8).

Intensity-modulated radiation therapy (IMRT) with the

Reprint requests to: E. Brian Butler M.D., Department of Radiation Oncology, The Methodist Hospital, 6565 Fannin, MS 121-B, Houston, TX 77030. Tel: (713) 790-2637; Fax: (713) 793-1300; E-mail: ebutler@bcm.tmc.edu

Presented at the 3rd S. Takahasi Memorial International Workshop on 3-Dimensional Conformal Radiotherapy, December 8–10, 2001, Nagoya, Japan.

Presented, in part, at the 44th Annual Meeting of the American Society for Therapeutic Radiology and Oncology (ASTRO), New Orleans, LA, October 6–10, 2002.

Acknowledgments—The authors wish to thank Shirley Clark for her assistance in the preparation of this manuscript.

Received Feb 22, 2002, and in revised form Nov 1, 2002. Accepted for publication Nov 8, 2002.

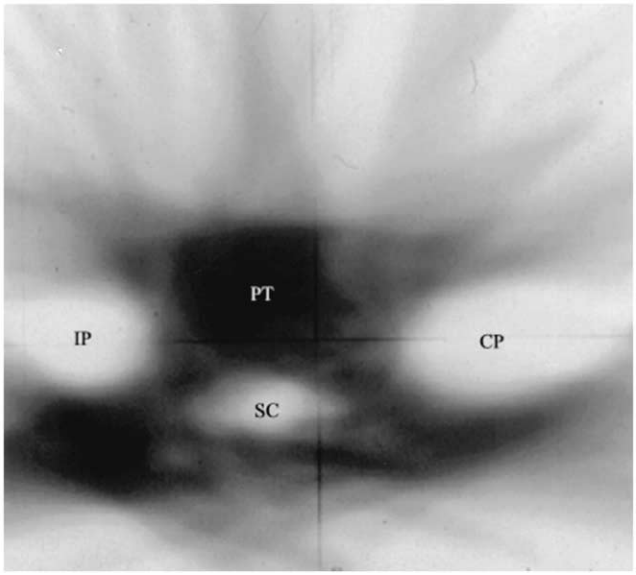

Fig. 1. Film verification of a treatment plan covering the primary target and lymphatics with dosimetric sparing of the parotid glands and spinal cord. *Abbreviations:* PT = primary target; SC = spinal cord; IP = ipsilateral parotid; CP = contralateral parotid.

NOMOS Peacock system (NOMOS Corp., Sewickley, PA), an advanced form of conformal radiation using inverse planning, provides a sophisticated method of dose deposition and avoidance. Using IMRT in the treatment of head-and-neck cancer, radiation oncologists are now able to create dose deposition patterns around tumor and dose–avoidance patterns around normal tissue. Applying this concept of dose avoidance to the preservation of parotid glands to diminish the incidence of xerostomia can have a major impact on quality of life.

The simultaneous modulated accelerated radiation therapy (SMART) boost technique was initiated at Baylor College of Medicine in January 1996 (9). The primary tumor is treated with accelerated fractionation (2.4 Gy/fraction), whereas regions at risk for microscopic disease are treated at conventional fractionation (2.0 Gy/fraction). Treatment is completed in 25 fractions over 5 weeks. It can only be achieved with IMRT because of the conformal treatment of tumor and avoidance of normal tissue. Threshold limits are prescribed to important normal tissues, and structures are weighted based on relative importance. Target is always given priority over normal structures (i.e., parotid glands). An example of dosimetric sparing of the parotids and spinal cord is seen in Fig. 1.

The purpose of the current study is to correlate subjective salivary gland function with dosimetric parameters of the parotid glands for head-and-neck cancer patients treated with the SMART boost.

METHODS AND MATERIALS

Between January 1996 and June 2000, 30 evaluable patients with at least 6 months of follow-up were treated with the SMART boost technique with IMRT via the NOMOS Peacock system at The Methodist Hospital in Houston, Texas, and evaluated with a subjective salivary gland function questionnaire.

Table 1. Patient characteristics

Age	
Mean	60.5
Median	63.0
Range	43–73
Sex	
Male	24 (80.0%)
Female	6 (20.0%)
Tumor site	
Oropharynx	16 (53.3%)
Nasopharyx	4 (13.3%)
Oral cavity	2 (6.7%)
Larnyx	4 (13.3%)
Hypopharynx	1 (3.3%)
Paranasal sinus	2 (6.7%)
Unknown primary	1 (3.3%)
T stage	
T1	7 (23.3%)
T2	12 (40.0%)
T3	5 (16.7%)
T4	4 (13.3%)
Recurrent	1 (3.3%)
Unknown	1 (3.3%)
N stage	
N0	11 (36.7%)
N1	9 (30.0%)
N2	6 (20.0%)
N3	3 (10.0%)
Unknown	1 (3.3%)
Stage	
1	3 (10.0%)
2	7 (23.3%)
3	9 (30.0%)
4	9 (30.0%)
Recurrent	1 (3.3%)

The workup included an extensive history and physical examination on all patients. Triple endoscopy was performed under anesthesia. All patients had a biopsy performed to confirm the diagnosis. Five patients had excisional biopsy or resection performed on their primary tumors. Four patients underwent neck dissections. The breakdown of primary tumor sites is listed in Table 1, with most patients having oropharyngeal primaries. All patients had a computed tomography (CT) neck scan, chest X-ray, complete blood count, and liver function tests. Dental evaluation with appropriate extraction and care were performed on all patients. The American Joint Committee on Cancer TNM classification system was used for staging purposes (10). Patient characteristics are shown in Table 1.

The patient population consisted of histologically confirmed squamous cell carcinomas, adenocarcinomas, and adenoid cystic carcinomas in the head-and-neck region treated with the SMART boost. Criteria for treatment included *(1)* no evidence of metastatic disease at the time of

diagnosis, *(2)* good performance status (ECOG 0-1), and *(3)* informed consent.

Immobilization

Thirteen patients were initially immobilized using the "Talon" fixation device (NOMOS Corp., Sewickley, PA) (9). The neurosurgeon secured the device to the inner table of the skull using intracranial screws. Movement was limited to 1–2 mm. Screw site infection was minimized using antibiotics and aggressive screw site care. We later changed our immobilization technique to a reinforced Aquaplast face mask (Medtech, Orange City, CA). This device was noninvasive, required less maintenance, and did not require a surgical procedure. Movement was limited to 2–3 mm. Seventeen patients were immobilized with a reinforced Aquaplast mask.

Treatment planning and delivery

Axial CT slices were obtained at 3-mm intervals and the images were transferred to the NOMOS Peacock treatment planning system. After review of the images with the ear, nose, and throat (ENT) surgeons and radiologists, target and avoidance structures were delineated using the SMART charts (axial images created by ENT surgeons and diagnostic radiologist at Baylor College of Medicine to delineate anatomic sites in the head-and-neck area). These structures were outlined on each axial slice. The normal structures were delineated first, followed by the target volume. The target doses and normal tissue threshold limits were prescribed. The ipsilateral and contralateral parotid glands had threshold limits of 35 Gy and 25 Gy, respectively, but some variation occurred based on the preference of the treating physician, location of tumor, and outcome of the treatment plan. The submandibular lymph nodes were commonly included in the target volumes, and no attempts were made to avoid the submandibular glands. The structures were weighted, with target being given priority over normal structures. A treatment plan was generated, reviewed, and revised or accepted. Each axial image was evaluated for dosimetric coverage of the target and avoidance of normal structures. Dose–volume histograms were analyzed for both target structures and normal tissues. The treatment plan was verified using a phantom. Figure 2 shows an axial slice through an oropharyngeal cancer demonstrating the conformal treatment of the primary and secondary targets with avoidance of spinal cord and parotid glands.

The patients were treated with a megavoltage linear accelerator using 10 MV photons. IMRT from the Peacock system was delivered using sequential arc therapy. Treatment was delivered through the MIMiC (multivane intensity modulating collimator). The MIMiC consists of two rows of 20 vanes measuring 1×1 cm or 2×1cm on isocenter; therefore, arcs were treated with a 2 cm or 4 cm width. The vanes were made of 8 cm thick tungsten. Each vane was individually controlled and could be opened or closed for increments of 10% every 5° of rotation. An optimization program was used to create dose deposition and avoidance patterns. Laser alignment was used daily. Treatment generally required 3–6 arcs to cover the defined volume. The table was indexed between each arc using a Crane (NOMOS Corp., Sewickley, PA) with a micrometer to verify the position. The crane precisely locates the table with respect to the treatment machine. The supraclavicular fossa was treated bilaterally in most patients. A junctional block was used. This single anterior field was treated with 6 MV photons.

Dosimetric parameters

Dosimetric analysis was performed on all treatment plans. Normal tissue was given threshold limits (i.e., ipsilateral parotid 35 Gy, contralateral parotid 25 Gy, spinal cord 40 Gy, and mandible 58 Gy) based on the treating physician. Axial images were evaluated slice by slice for dosimetric coverage of the targets and avoidance of normal tissue. Special attention was given to ipsilateral and contralateral parotid mean and maximum doses. The volume of each parotid gland was also analyzed. The volume and percentage of the parotid glands above the prescribed threshold were also evaluated and recorded.

Assessment of xerostomia

Xerostomia was evaluated with a questionnaire, as shown in Table 2. The questionnaire was administered at the time of most recent follow-up in an attempt to address long-term xerostomia. The median time from completion of treatment to questionnaire administration was 38.5 months (mean 39.9 months) with a range of 16.6 to 71.4 months.

The first question was a subjective assessment of RTOG/EORTC (Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer) late salivary gland toxicity (11), which asks, "What is the overall comfort of your mouth?" There were four possible responses. Very comfortable implied no noticeable change compared with pretreatment function. Slight dryness correlated to the RTOG Grade 1 toxicity. These patients had a noticeable change in salivary gland function but it did not affect quality of life. Moderate dryness represented RTOG Grade 2 toxicity. Severe dryness referred to patients with a profound change in quality of life resulting from xerostomia. This corresponded to RTOG Grade 3 toxicity. RTOG Grade 4 toxicity is a clinical assessment of salivary gland fibrosis and was not seen in this group.

Questions 2, 3, 4, and 6 were validated by Fox *et al.* (12). They correlated basal and poststimulation saliva levels in patients with subjective xerostomia. These questions concern dryness while eating, difficulty swallowing dry foods, and need to sip liquids correlated with salivary dysfunction. Questions 2 through 4 address mouth dryness when eating. Question 2 addresses the general dryness of the mouth when eating. The responses range from no dryness to severe dryness. Question 3 focuses on difficulty with swallowing certain foods (i.e., dry food such as toast or chicken). Question 4 addresses the need for liquids when eating dry foods. Combining these questions with questions 5 and 6,

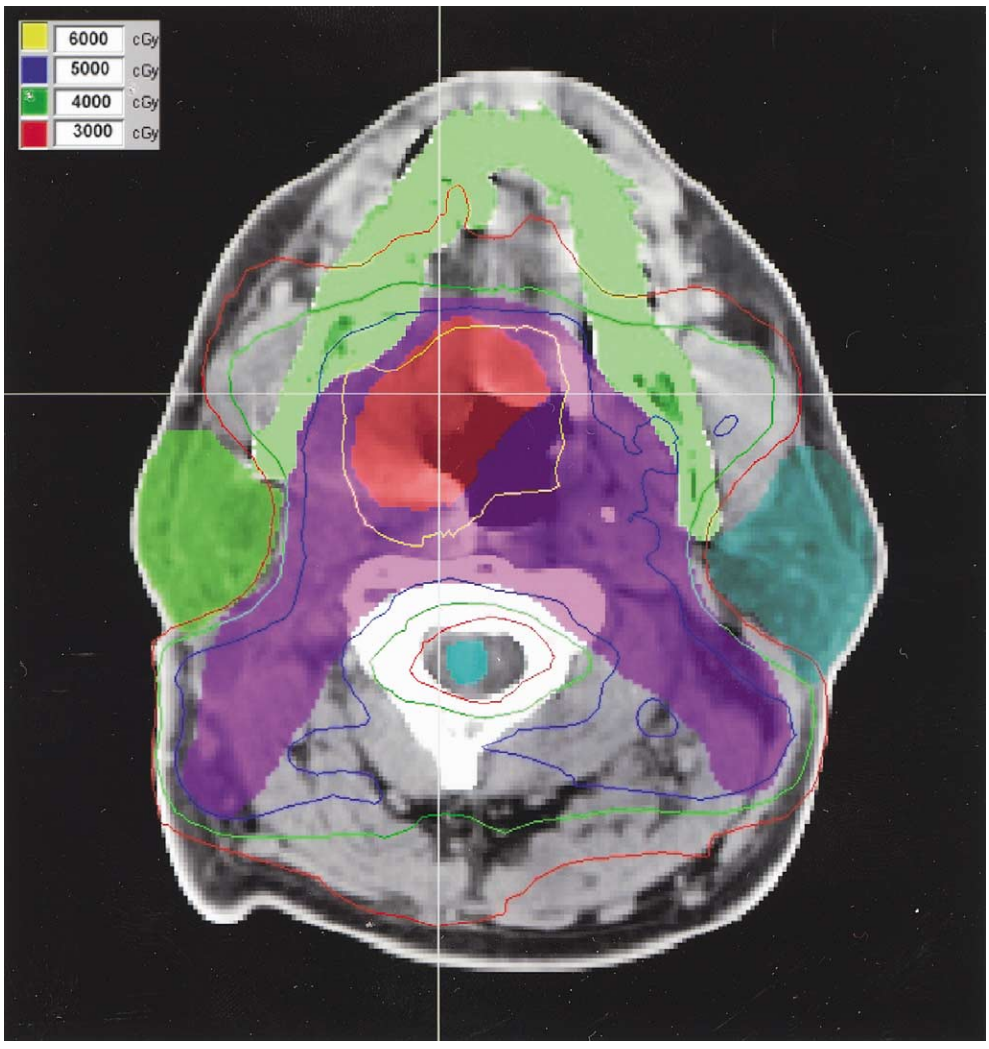

Fig. 2. Axial slice through a treatment plan for a patient with oropharyngeal cancer. The primary tumor and draining lymphatics are treated with sparing of the spinal cord and parotid glands. Isodose lines are displayed for 6000 cGy, 5000 cGy, 4000 cGy, and 3000 cGy.

Eisbruch *et al.* examined salivary gland function in patients receiving conformal radiation for their head-and-neck cancer (13). The results were validated through salivary flow rate measurements. Question 5 asks, "Are you thirsty all the time?" Many patients with xerostomia complain of being chronically thirsty. Question 6 has previously been shown to correlate well with quantity of saliva.

Table 2. Salivary gland function questionnaire

1. What is the overall comfort of your mouth?
2. Does your mouth feel dry when eating?
3. Do you have difficulty swallowing any foods?
4. Do you need to sip liquids to swallow dry food?
5. Do you feel thirsty all the time?
6. Do you feel the amount of saliva in your mouth is too little, too much, or adequate?
7. Do you have problems with speech because of dry mouth?
8. Does dry mouth interfere with your ability to sleep all the time?
9. Has you taste changed as a result of salivary gland function?
10. Do you need to carry water daily?

The visual analog scale (VAS) has been previously validated and used in Phase III trials (14, 20, 21). This scale is used at baseline and multiple intervals to assess changes in xerostomia over time. Unfortunately, this study administers the questionnaire at a single follow-up visit so no changes can be detected. Questions 1–4 are addressed in the VAS, but were directly taken from other sources. Questions 7 and 8 are extrapolated from the VAS, but have been altered to be answered in a simple, concise questionnaire. They address common problems with xerostomia, which affect everyday life. They also assess problems with speech and sleep that are directly related to xerostomia. Questions 9 and 10 also assess the quality of life, but have not been previously validated in quality-of-life studies. Taste changes are frequently associated with salivary gland function, and patients with xerostomia commonly carry water on a daily basis.

Statistical analysis

The dosimetric parameters of the parotid glands and the results of the questionnaire were entered into a database.

Table 3. Dosimetric parameters ipsilateral and contralateral parotid glands for the SMART*

Parotid glands	Dose limit (Gy)	Mean dose delivered (Gy)	Maximum dose delivered (Gy)	Volume of parotids above threshold doses	
				(cc)	(%)
Ipsilateral	35	24.2 (4.2–34.2) Median 25.3	56.1 (13.3–66.4) Median 57.2	10.6 (.21–30.7) Median 10.3	30.4 (1.3–52.6) Median 34.6
Contralateral	25	19.1 (3.7–29.9) Median 21.0	47.4 (7.3–63.2) Median 52.4	8.22 (0.0–31.8) Median 7.4	23.4 (0.0–52.3) Median 24.4

* Average, range, and median are listed for each parameter.

The data were analyzed using SPSS software (Chicago, IL), version 10.1. Categoric variables were analyzed with the 2-sided chi-squared test. Continuity variables were computed using analysis of variance tables and Fisher's exact test. The threshold for statistical significance was a p value ≤ 0.05.

RESULTS

Dosimetric parameters

The ipsilateral parotid glands received an average mean dose of 24.2 Gy (median 25.3 Gy), with an average maximum dose of 56.1 Gy. The average volume of ipsilateral parotid gland above threshold was 10.6 cc (30.4%). The average mean dose to the contralateral parotid glands was 19.1 Gy (median 21.0), with an average maximum dose of 47.4 Gy. The average volume of contralateral parotid gland above the threshold dose was 8.22 cc (23.4%). These results are shown in Table 3.

Xerostomia

A questionnaire was used to assess long-term xerostomia (Table 4). Thirty patients responded to the questionnaire. The first question was a subjective assessment of mouth dryness derived from the RTOG/EORTC late radiation morbidity scoring for salivary glands, which asks, "What is the overall comfort of your mouth?" With 30 patients responding, 9 patients (30%) felt that their mouth was very comfortable. Eleven patients (36.7%) had slight dryness (RTOG Grade 1), six (20%) had moderate dryness (RTOG Grade 2), and four (13.3%) developed severe dryness (RTOG Grade 3). A statistically significant correlation was seen with mouth dryness and contralateral parotid mean and maximum doses ($p = 0.008$ and 0.038, respectively).

The maximum dose to the contralateral parotid gland also correlated ($p = 0.031$) with question 2: "Does your mouth feel dry when eating?" The maximum dose to the contralateral parotid gland for patients who answered "no" was 35.5 Gy; "mild," 50.7 Gy; "moderate," 54.7 Gy; and "severe," 57.5 Gy. Patients who replied "yes" to questions regarding difficulty swallowing and sipping liquids to swallow dry food (questions 3 and 4) had significantly higher mean and maximum doses to both ipsilateral and contralateral parotid glands (Table 5).

Patients who felt that the amount of saliva in their mouth was "too little" received significantly higher mean and maximum doses to the contralateral parotid glands, as shown in Table 6. Question 9 ("Has your taste changed

Table 4. Actual results of the salivary gland function questionnaire

Salivary Gland Function Questionnaire
Questions with significant correlation to dosimetric parameters:
1. What is the overall comfort of your mouth?
   Very comfortable = 9 (30%)
   Slight dryness = 11 (36.7%)
   Moderate dryness = 6 (20%)
   Significant dryness = 4 (13.3%)
2. Does your mouth feel dry when eating?
   No = 9 (30%)
   Mild = 12 (40%)
   Moderate = 5 (16.7%)
   Severe = 4 (13.3%)
3. Do you have difficulty swallowing any foods?
   Yes = 19 (63.3%)
   No = 11 (36.7%)
4. Do you need to sip liquids to swallow dry food?
   Yes = 23 (76.7%)
   No = 7 (23.3%)
6. Do you feel that the amount of saliva in your mouth is...
   Too little = 14 (46.7%)
   Adequate = 16 (53.3%)
   Too much = 0 (0%)
9. Has your taste changed due to salivary gland function?
   Yes = 13 (43.4%)
   No = 17 (56.7%)

Questions without significant correlation to dosimetric parameters:
5. Do you feel thirsty all the time?
   Yes = 6 (20%)
   No = 24 (80%)
7. Do you have problems with speech because of dry mouth?
   Yes = 10 (33.3%)
   No = 20 (66.7%)
8. Does dry mouth interfere with your ability to sleep all the time?
   No = 17 (56.7%)
   Occasionally = 10 (33.3%)
   Frequently = 3 (10%)
10. Do you need to carry a water bottle daily?
   No = 15 (50%)
   Occasionally = 4 (13.3%)
   Frequently = 4 (13.3%)
   All the time = 7 (23.3%)

Table 5. Results of questions 3 and 4

	Do you have difficulty swallowing any foods?			Do you need to sip liquids to swallow dry food?		
Dosimetric parameters	Yes	No	*p* value	Yes	No	*p* value
Ipsilateral parotid mean dose	26.5 Gy	20.3 Gy	0.016	26.2 Gy	17.8 Gy	0.003
Ipsilateral parotid maximum dose	59.5 Gy	50.2 Gy	0.013	59.1 Gy	46.4 Gy	0.002
Contralateral parotid mean dose	21.5 Gy	14.7 Gy	0.017	21.3 Gy	12.6 Gy	0.005
Contralateral parotid maximum dose	53.6 Gy	36.2 Gy	0.003	51.8 Gy	34.1 Gy	0.007

because of salivary gland function?") also correlated with dosimetric parameters of the parotids, as shown in Table 7. Patients who felt their taste had changed because of salivary gland function had higher mean doses and volumes treated above threshold for the ipsilateral parotid glands and higher mean doses, maximum doses, and volumes treated above threshold for the contralateral parotid glands.

Questions relating to a constant sense of thirst, problems with speech, difficulty sleeping, and needing to carry water daily did not significantly correlate with the dosimetric parameters of the parotid glands.

This study correlates the dosimetric parameters of the parotid glands with a subjective assessment of xerostomia. Multiple statistically significant correlations were discovered (Table 8). The mean and maximum doses to the ipsilateral and contralateral parotid glands correlated with multiple questions regarding salivary gland function. Examining the mean ipsilateral parotid doses (standard deviation [SD]) for patients who responded negatively (i.e., complained of xerostomia) to questions 3, 4, and 9 (i.e., questions that significantly correlated with ipsilateral mean parotid dose) reveals values of 26.5 Gy (4.3), 26.2 Gy (5.0), and 28.3 Gy (3.8). Patients who responded positively (i.e., no xerostomia) had mean ipsilateral parotid doses (SD) of 20.3 Gy (9.1), 17.8 Gy (9.0), and 21.1 Gy (7.4). Similar results are seen when evaluating the contralateral parotid mean dose. Patients who responded negatively to questions 1, 3, 4, 6, and 9 had mean doses (SD) of 22.1 Gy (3.6), 21.5 Gy (5.0), 21.3 Gy (6.1), 22.5 Gy (3.0), and 24.5 Gy (3.3), respectively. Patients who responded positively had mean doses (SD) of 13.0 Gy (7.8), 14.7 Gy (9.3), 12.6 Gy (7.7), 16.2 Gy (8.8), and 15.1 Gy (7.2).

A similar clustering of doses was seen when examining the average maximum doses. The contralateral parotid gland maximum dose correlated with questions 1, 2, 3, 4, 6, and 9. These questions addressed overall mouth comfort, problems with eating, difficulty swallowing dry food, quantity of saliva, and abnormal taste. Patients who responded negatively had mean doses (SD) of 57.5 Gy (3.9), 57.5 Gy (3.9), 53.6 Gy (9.9), 51.8 Gy (12.1), 55.8 Gy (4.1), and 55.6 Gy (4.2), whereas patients who responded positively had average doses (SD) of 35.9 Gy (19.3), 35.5 Gy (19.8), 36.2 Gy (18.4), 46.4 Gy (18.7), 40.0 Gy (18.4), and 41.2 Gy (18.4). Similar results were seen when evaluating the ipsilateral parotid gland maximum dose with regards swallowing difficulties (questions 3 and 4). Patients who responded "yes" had average doses (SD) of 59.5 Gy (5.3) and 59.1 Gy (5.0), whereas patients who responded "no" had average doses of 50.2 Gy (13.8) and 46.4 Gy (16.2). Multivariate analysis was performed to evaluate the contribution of other factors including primary tumor site, chemotherapy, and treatment time, but no significant factors could be discovered.

DISCUSSION

Radiation therapy for head-and-neck cancer can profoundly affect quality of life (1–3, 15). Xerostomia affects every aspect of life including speech, nutrition, taste, and sleep. Patients live with a constant reminder of their diminished quality of life. Subjective assessment of salivary gland function is an important criterion to consider when delivering definitive radiation therapy for head-and-neck cancer.

This study correlates the dosimetric parameters of the parotid glands with a subjective assessment of xerostomia. Multiple statistically significant correlations were discovered (Table 8). The mean and maximum doses to the ipsilateral and contralateral parotid glands correlated with multiple questions regarding salivary gland function. Examining the mean ipsilateral parotid doses for patients who responded negatively to questions 3, 4, and

Table 6. Do you feel the amount of saliva in your mouth is . . .

	Do you feel the amount of saliva in your mouth is . . .		
Dosimetric parameters	Too little	Adequate	*p* value
Contralateral parotid mean dose	22.5 Gy	16.2 Gy	0.021
Contralateral parotid maximum dose	55.8 Gy	40.0 Gy	0.005
Contralateral parotid volume above threshold	11 cc	5 cc	0.017

Table 7. Has your taste changed due to salivary gland function?

Dosimetric parameters	Has your taste changed due to salivary gland function? Yes	No	*p* value
Ipsilateral parotid mean dose	28.3 Gy	21.1 Gy	0.004
Ipsilateral parotid volume above tolerance	14 cc	8 cc	0.014
Ipsilateral parotid percentage above threshold	38%	24%	0.005
Contralateral parotid mean dose	24.5 Gy	15.1 Gy	<0.001
Contralateral parotid maximum dose	55.6 Gy	41.2 Gy	0.014
Contralateral parotid volume above threshold	13 cc	5 cc	0.001
Contralateral parotid percentage above threshold	34%	16%	0.001

9 (i.e., questions that significantly correlated with ipsilateral mean parotid dose) reveals range of 26.2 Gy to 28.3 Gy. Patient who responded positively had mean ipsilateral parotid doses in the range of 17.8 Gy to 21.1 Gy. Similar results are seen when evaluating the contralateral parotid mean dose. Patients who responded negatively to questions 1, 3, 4, 6, and 9 had mean doses ranging from 21.3 Gy to 24.5 Gy. Patients who responded positively had mean doses ranging from 12.6 Gy to 16.2 Gy. The narrow range of doses for each dosimetric parameter may provide guidelines for evaluating treatment plans. A larger cohort will be required to answer this question.

A similar clustering of doses was also seen when examining the average maximum doses. The contralateral parotid gland maximum dose correlated with questions 1, 2, 3, 4, 6, and 9. These questions addressed overall mouth comfort, problems with eating, difficulty swallowing dry food, quantity of saliva, and abnormal taste. Patients who responded negatively had mean doses ranging from 51.8 Gy to 57.5 Gy, whereas patients who responded positively had average doses ranging from 35.5 Gy to 41.2 Gy. Similar results were seen when evaluating the ipsilateral parotid gland maximum dose with regard to swallowing difficulties (questions 3 and 4). Patients who responded "yes" had average doses of 59.5 Gy and 59.1 Gy, whereas patients who responded "no" had average doses of 50.2 Gy and 46.4 Gy. The significance of these average dose groupings should be evaluated with a larger cohort of patients, because it may have implications on treatment plan evaluation.

Other institutions have examined the impact of conformal radiation on xerostomia. Eisbruch *et al.* have suggested that the mean parotid dose be limited to 26 Gy (16). They have also calculated partial volume data. Equivalent uniform dose (EUD) is another method of evaluating dose to the parotid glands. Chao *et al.* examined EUD and mean dose and found that mean dose to the parotids was a reasonable indicator for parotid gland outcome (17). The results of our study certainly show a strong correlation of subjective salivary gland function and mean dose to the parotids. The exact threshold dose for the parotid glands is uncertain. Most likely, however, the lower the mean dose to the parotid glands the better. Mean dose, maximum dose, and threshold volumes and percentages above tolerances for the parotid glands are likely to be closely related. Of these, maximum dose is highly variable. Threshold volumes and percentages above goal correlated with subjective xerostomia but not as well as did mean dose. Therefore, mean dose appears to be the most important parameter to examine. Using the NOMOS system, the parotid anatomy and volume can be affected by target delineation. At our institution,

Table 8. Statistical correlation of the dosimetric parameters of the ipsilateral and contralateral parotid glands with the salivary gland function questionnaire

	Ipsilateral parotid mean dose	Ipsilateral parotid maximum dose	Contralateral parotid mean dose	Contralateral parotid maximum dose
Question 1	NS	NS	0.008	0.038
Question 2	NS	NS	NS	0.031
Question 3	0.016	0.013	0.017	0.003
Question 4	0.003	0.002	0.005	0.007
Question 5	NS	NS	NS	NS
Question 6	NS	NS	0.021	0.005
Question 7	NS	NS	NS	NS
Question 8	NS	NS	NS	NS
Question 9	0.004	NS	0.000	0.014
Question 10	NS	NS	NS	NS

Abbreviation: NS = not significant.

normal structures are drawn before target delineation; therefore, the parotid volume does not change after target delineation except in cases in which the tumor invades the parotids. This was not seen in this population. Evaluation of partial volume data is limited at our institution because of a departmental flood that destroyed records necessary for analysis. As more patients are treated, partial volume data will be forthcoming. Another factor that must be considered is the correlation of fraction size to xerostomia. Considering an ipsilateral parotid mean dose of 24.2 Gy over 25 fractions, the fraction size was 0.97 Gy/day, half the size of conventional fractionation. The significance of fraction size in salivary gland function is uncertain. Other factors, such as concurrent chemotherapy and baseline parotid function, may also have significance with respect to xerostomia.

IMRT for head-and-neck cancer can have a positive impact on xerostomia. It has the capability to create dose–deposition patterns around the target and dose–avoidance patterns around normal structures (i.e., parotid glands). In this study, the submandibular glands were not labeled as avoidance structures. Eisbruch *et al.* found that oral cavity mean dose, representing radiation effect on the minor salivary glands, was related to xerostomia (18). At our institution, the submandibular lymph nodes are included as target; therefore, the submandibular glands receive large doses of radiation.

Pilocarpine and amifostine have been successfully used to decrease postirradiation xerostomia (19–22). Amifostine can be given by subcutaneous injection, which has increased its application (23). Some patients experience a profound improvement in their quality of life with these medications. Unfortunately, both medications are associated with certain side effects and can be costly. Amifostine causes nausea, vomiting, and hypotension. These symptoms can be severe. Patients with head-and-neck cancer are already prone to weight loss, malnutrition, and dehydration. The addition of amifostine can worsen these problems. The logistics, convenience, and timing of administration with respect to radiation treatment are also problematic. Pilocarpine can also be associated with a wide variety of side effects that can limit its use.

The SMART boost was developed at the Baylor College of Medicine in 1996. We treated the primary target at 2.4 Gy per day to a total dose of 60 Gy (mean dose 63.8 Gy), whereas areas at risk for microscopic disease were treated at conventional fraction sizes of 2.0 Gy per day to a total dose of 50 Gy (mean dose 54.8 Gy). The fraction size was based on the treatment time and number of fractions. A similar fractionation scheme had previously been used in Toronto (24). The biologic effective dose (BED) of the SMART boost was 80.0 Gy based on a mean dose of 63.8 Gy and fraction size of 2.55 Gy, with a tumor alpha/beta ratio of 10 Gy. We delivered a similar BED to conventional fractionation (84 Gy) or concomitant boost (84.4 Gy) (25), hoping that the decreased treatment time would improve the therapeutic ratio. Normal tissue was prescribed threshold doses. The threshold doses for the ipsilateral and contralateral parotid glands were usually 35 Gy and 25 Gy.

Xerostomia was expected to be reduced as a result of the small fraction sizes and diminished total doses to the parotids. The SMART boost results for xerostomia can be compared with the four arms in RTOG 9003 (26) based on RTOG late salivary gland toxicity. We experienced 13% Grade 3 toxicity compared with 6–10% in the four arms of RTOG 9003. Our Grade 2 toxicity was 21% compared with 53–62% in RTOG 9003. The comparison is definitely limited by the small sample in our population, but we are optimistic that a larger cohort will compare favorably.

The ability to reduce the dose to the parotid glands is limited by multiple factors. The primary site of disease will alter our ability to preserve the parotid glands. Laryngeal and hypopharynx primaries are anatomically inferior to the parotid glands and have the potential for excellent parotid sparing. Oropharyngeal cancers and pathways of spread of disease are located in closer proximity to the parotid glands. Parotid preservation is difficult with primary tonsil cancers that spread along the pterygoid muscles as a result of the close proximity. Parotid sparing depends on the proximity of the tumor and involved lymph nodes to the parotid glands. Bulky level 2 lymphadenopathy will limit the ability to minimize parotid dose. Another factor to consider is the limits of technology. Because of limitations of our table, our IMRT system can only treat patients with 270° arcs. This leaves 90° of treatment angles that could be exploited to improve the dose distribution. As new technology becomes available, more sophisticated optimization algorithms may be able to generate improved dose avoidance patterns.

Evaluation of salivary gland function through a standardized questionnaire provides valuable clinical correlation to the treatment given. Xerostomia significantly affects quality of life. Quantitative data regarding the stimulated and unstimulated saliva flow are more objective, but the important issue is patient satisfaction with his or her degree of xerostomia. Statistical correlation of the dosimetric parameters with the degree of xerostomia provides guidelines for evaluation of treatment plans. We discovered that contralateral parotid mean and maximum doses strongly correlated with many aspects of subjective salivary gland function (questions 1, 3, 4, 6, and 9). The volume of contralateral parotid gland above the prescription tolerance was related to amount of saliva and taste changes as in questions 6 and 9. The ipsilateral parotid mean and maximum doses demonstrated statistically significant correlation with salivary gland function in question 3, 4, and 9. A complete examination of the data was performed evaluating many factors. Statistically significant observations may be the result of multiple testing. These results need to be verified in a larger cohort of patients.

In the future, treatment plan evaluation will continue to focus on parotid mean and maximum doses. These data are being used in evaluation of treatment plans to serve as guidelines for salivary gland sparing. Because of the small sample size, multivariate analysis could not further delineate the important variables. Larger numbers of patients need to be evaluated to better define the relationship between salivary gland function and dosimetric parameters of the parotid glands. This study includes patients treated with

the SMART boost. At our institution, we are evaluating the salivary gland function questionnaire and dosimetric parameters for all patients treated with IMRT for head-and-neck cancer to expand the population size.

CONCLUSIONS

The salivary gland function questionnaire (questions regarding overall comfort, eating, and taste) correlated significantly with the dosimetric parameters (mean and maximum doses and volume and percent above tolerance) of the parotid glands. Questions regarding thirst, speech, sleep, and need to carry water showed no significantly correlation with the dosimetry of the parotid glands. Dosimetric sparing of the parotid glands improved subjective xerostomia. IMRT in the treatment of head-and-neck cancer can be exploited to preserve the parotid glands and decrease xerostomia. This is feasible even with an accelerated treatment regimen like the SMART boost. More patients need to be evaluated using IMRT to identify relevant dosimetric parameters.

REFERENCES

1. Bjordal K, Kaasa S, Mastekaasa A. Quality of life in patients treated for head-and-neck cancer: A follow-up study 7 to 11 years after radiotherapy. *Int J Radiat Oncol Biol Phys* 1994; 28:847–856.
2. Cooper JS, Fu K, Marks J, *et al.* Late effects of radiation therapy in the head-and-neck region. *Int J Radiat Oncol Biol Phys* 1995;31:1141–1164.
3. Jensen AB, Hanse O, Jorgensen K, *et al.* Influence of late side-effects upon daily life after radiotherapy for laryngeal and pharyngeal cancer. *Acta Oncol* 1994;33:487–491.
4. Chao KSC, Majhail N, Huang CJ, *et al.* Intensity-modulated radiation therapy reduces late salivary toxicity without compromising tumor control in patients with oropharyngeal carcinoma: A comparison with conventional techniques. *Radiother Oncol* 2001;61:275–280.
5. Marsh L, Eisbruch A, Watson B, *et al.* Treatment planning for parotid sparing in the patient requiring bilateral neck irradiation. *Med Dosimetry* 1996;21:7–13.
6. Nishioka T, Shirato H, Arimoto T, *et al.* Reduction of radiation-induced xerostomia in nasopharyngeal carcinoma using CT simulation with laser patient marking and three-field irradiation technique. *Int J Radiat Oncol Biol Phys* 1997;38:705–712.
7. Wu Q, Mannin M, Schmidt-Ullrich R, *et al.* The potential for sparing of parotids and escalation of biologically effective dose with intensity-modulated radiation treatments of head-and-neck cancers: A treatment design study. *Int J Radiat Oncol Biol Phys* 2000;46:195–205.
8. Reddy SP, Leman CR, Marks JE, *et al.* Parotid-sparing irradiation for cancer of the oral cavity: Maintenance of oral nutrition and body weight by preserving parotid function. *Am J Clin Oncol* 2001;24:341–346.
9. Butler EB, Teh BS, Grant WH, *et al.* SMART (simultaneous modulated accelerated radiation therapy) boost: A new accelerated fractionation schedule for the treatment of head-and-neck cancer with intensity modulated radiotherapy. *Int J Radiat Oncol Biol Phys* 1999;45:21–32.
10. Strong EW, Batsakis JG, Cassisi NJ, *et al.* Head-and-neck sites. In: Fleming ID, Cooper JS, editors. AJCC cancer staging manual, 5th ed. Philadelphia: Lippincott-Raven; 1997. p. 21–58.
11. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys* 1995;31:1341–1346.
12. Fox PC, Busch KA, Baum BJ. Subjective reports of xerostomia and objective measures of salivary gland performance. *J Am Dent Assoc* 1987;115:581–584.
13. Eisbruch A, Ship JA, Martel MK, *et al.* Parotid gland sparing in patients undergoing bilateral head-and-neck irradiation techniques and early results. *Int J Radiat Oncol Biol Phys* 1996;36:469–480.
14. Zimmerman RP, Marks RJ, Tran LM, *et al.* Concomitant pilocarpine during head-and-neck irradiation is associated with decreased post-treatment xerostomia. *Int J Radiat Oncol Biol Phys* 1997;37:571–575.
15. Harrison LB, Zelefsky MJ, Pfister DG, *et al*. Detailed quality of life assessment in patients treated with primary radiotherapy for squamous cell cancer of the base of the tongue. *Head & Neck*. 169–175.
16. Eisbruch A, Ten Haken RK, Kim HM, *et al.* Dose, volume, and function relationships in parotid salivary glands following conformal and intensity-modulated irradiation of head-and-neck cancer. *Int J Radiat Oncol Biol Phys* 1999;45:577–587.
17. Chao KSC, Deasy JO, Markman J, *et al.* A prospective study of salivary function sparing in patients with head-and-neck cancers receiving intensity-modulated or three-dimensional radiation therapy: Initial results. *Int J Radiat Oncol Biol Phys* 2001;49:907–916.
18. Eisbruch A, Kim HM, Terrell JE, *et al.* Xerostomia and its predictors following parotid-sparing irradiation of head-and-neck cancer. *Int J Radiat Oncol Biol Phys* 2001;50:695–704.
19. Rieke JW, Hafermann MD, Johnson JT, *et al.* Oral pilocarpine for radiation-induced xerostomia: Integrated efficacy and safety results from two prospective randomized clinical trials. *Int J Radiat Oncol Biol Phys* 1995;31:661–669.
20. Johnson JT, Ferretti GA, Nethery WJ, *et al*. Oral pilocarpine for post-irradiation xerostomia in patients with head-and-neck cancer. *N Engl J Med* 1993;329:390–395.
21. LeVeque FG, Montgomery M, Potter D, *et al.* A multicenter, randomized, double-blind, placebo-controlled, dose-titration study of oral pilocarpine for treatment of radiation-induced xerostomia in head-and-neck cancer patients. *J Clin Oncol* 1993;11:1124–1131.
22. Brizel DM, Wasserman TH, Henke M, *et al.* Phase III randomized trial of amifostine as a radioprotector in head-and-neck cancer. *J Clin Oncol* 2000;18:3339–3345.
23. Koukourakis MI, Kyrias G, Kakolyris S, *et al.* Subcutaneous administration of amifostine during fractionated radiotherapy: A randomized phase II study. *J Clin Oncol* 2000;18:2226–2233.
24. Harwood AR. Cancer of the larynx: The Toronto Experience. *J Laryngol* 1982;11:1–21.
25. Hall EJ. Time, dose and fractionation. In: John JR, Sutton P, Marino D, editors. Radiobiology for the radiologist. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2000. p. 397–418.
26. Fu KK, Pajak TF, Trotti A, *et al.* A Radiation Therapy Oncology Group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head-and-neck squamous cell carcinomas: First report of RTOG 9003. *Int J Radiat Oncol Biol Phys* 2000;48:7–16.