Influence of Vitamin C on Salivary Absorbed Dose of ^{131}I in Thyroid Cancer Patients: A Prospective, Randomized, Single-Blind, Controlled Trial

Bin Liu, Anren Kuang, Rui Huang, Zhen Zhao, Yu Zeng, Jiantao Wang, and Rong Tian

Department of Nuclear Medicine, West China Hospital, Sichuan University, Chengdu, China

In this study, vitamin C was administered at various times as a sour stimulant to thyroid cancer patients, and the effect on salivary absorbed dose of therapeutic radioiodine (^{131}I) was investigated. **Methods:** Patients with differentiated thyroid cancer who had been prepared for thyroid remnant ablation after total thyroidectomy were prospectively recruited and, using a random-number table, were divided into 4 groups. In the hypothyroid condition, the patients in groups A, B, C, and D began sucking vitamin C (100 mg every 4 h in the daytime over 6 d) at 1, 5, 13, and 25 h, respectively, after receiving 3.7 GBq of ^{131}I. Scintigraphic images of the head and neck were serially acquired after ^{131}I administration to assess biokinetics in the salivary glands. Calculation of salivary absorbed dose was based on the MIRD schema of the Society of Nuclear Medicine. **Results:** Seventy-two patients (18, 18, 19, and 17 patients from groups A, B, C, and D, respectively) were eligible for the analysis of salivary dosimetry. Differences in absorbed doses to the parotid salivary gland (0.18 ± 0.11, 0.16 ± 0.07, 0.16 ± 0.09, and 0.16 ± 0.12 mGy/MBq in groups A, B, C, and D, respectively; $P = 0.37$) and submandibular salivary gland (0.19 ± 0.05, 0.17 ± 0.05, 0.18 ± 0.07, and 0.17 ± 0.06 mGy/MBq, respectively; $P = 0.28$) were not statistically significant among groups. Salivary cumulated activities arising from the first 24 h after ^{131}I administration accounted for 86.08% ± 7.89% (range, 75%–98%) of total cumulated activities. Differences in salivary absorbed dose during the first 24 h were not statistically significant among the 4 groups either ($P = 0.32$ and 0.24, respectively, for the parotid and submandibular salivary glands). **Conclusion:** Salivary stimulation with vitamin C at any time after ^{131}I administration has only a limited effect on salivary absorbed dose in thyroid cancer patients.

Key Words: thyroid cancer; ^{131}I; vitamin C; salivary gland; dosimetry

J Nucl Med 2010; 51:618–623
DOI: 10.2967/jnumed.109.071449

Received Oct. 8, 2009; revision accepted Dec. 21, 2009.
For correspondence or reprints contact: Anren Kuang, Department of Nuclear Medicine, West China Hospital, Sichuan University, Guo Xuexiang 37, Chengdu 610041, China.
E-mail: kuanganren@263.net

The radioiodine (^{131}I) used to treat thyroid cancer patients is taken up not only by thyroid tissue but also by the salivary glands because both have similar sodium iodine symporters (*1,2*). Consequently, β-radiation from ^{131}I exerts cytotoxic effects in the salivary glands. Salivary glands are highly radiosensitive (*3*). Radiation sialadenitis and xerostomia have become the most frequent complication of high-activity ^{131}I therapy for thyroid cancer (*2,4–9*). Additionally, salivary gland injury can be observed even when the administered ^{131}I activity is relatively low (*7–9*). Recent reviews of adverse salivary effects after ^{131}I therapy have indicated an incidence of acute sialadenitis ranging from 24% to 67%, with chronic sialadenitis in 11%–43% of those treated (*2,8,9*). Clinically relevant xerostomia, with dry mouth, swallowing difficulties, and a loss of taste, has, to a certain extent, impaired the quality of life of thyroid cancer patients (*2,4–9*). Therefore, prevention of salivary gland injury in ^{131}I therapy becomes an important issue.

The use of sour stimulation after administration of ^{131}I, such as ascorbic acid (vitamin C) stimulation, which can increase the flow of saliva and accelerate ^{131}I washout from salivary glands, has always been presumed helpful in preventing salivary gland injury in ^{131}I therapy. Yet, no established evidence has demonstrated that sour stimulation actually reduces salivary gland injury after ^{131}I therapy. Moreover, the optimal regimen of sour stimulation in ^{131}I therapy is still a subject of ongoing debate (*10–16*).

To date, published data involving salivary gland injury and the effects of protective measures have largely been based on short- and long-term follow-up, and few studies have evaluated the effects of these protective measures from the perspective of internal radiation dosimetry. As is well recognized, normal-tissue radiation-absorbed dose delivered by an administered radiopharmaceutical correlates with attendant tissue toxicity (*17–19*). Dosimetry is thus important both for determining the limit beyond which administered radiation would cause harmful side effects

and for enabling assessment of the effects of various protective measures.

The objective of this prospective, randomized, single-blind, controlled study was to administer vitamin C at various times as a sour stimulant to thyroid cancer patients and investigate the effect on salivary absorbed dose of therapeutic ^{131}I.

MATERIALS AND METHODS

Patient Population

To be included in the study, patients had to be at least 18 y old, have a case of recently diagnosed differentiated papillary or follicular thyroid cancer, have undergone total thyroidectomy, and have been referred to the Department of Nuclear Medicine, West China Hospital, for ablation of remnant thyroid tissue, stage pT1–T3, N0–N1, M0. For women of childbearing potential, a negative result on serum human chorionic gonadotropin pregnancy testing was required.

The exclusion criteria were the presence of distant metastases; a previous history of salivary gland disorders, collagen tissue disease, diabetes, previous ^{131}I therapy, or external radiation to the head or neck; or difficulty drinking a large amount of water.

The study was approved by the institutional review board, and written informed consent was obtained from patients before they enrolled.

Study Design

The study was prospective, randomized, single-blind, and controlled.

Patients were divided into 4 groups by means of a random-number table. While in the hypothyroid condition, all patients were treated with 3.7 GBq (100 mCi) of ^{131}I at 4–6 wk after thyroidectomy without preceding diagnostic scanning and after maintaining a low-iodine diet for 2 wk. Levothyroxine therapy was initiated after the last salivary dosimetric measurements.

Patients in groups A, B, C, and D were instructed to start sucking vitamin C at 1, 5, 13, and 25 h, respectively, after ingestion of ^{131}I, 100 mg every 4 h for 6 d, the common dose used in our department. The exact timing for the sucking of vitamin C in each group is illustrated in Figure 1.

During the study (6 d after ingestion of ^{131}I), all patients were required to stop taking lemon candy, gum, or any other sialogogues except for the study-associated sucking of vitamin C. Anticholinergic or antidepressant medications were temporarily discontinued if patients had been taking them before the study. All patients received 10 mg of prednisone every 8 h and ingested at least 3,000 mL of nondairy liquid daily.

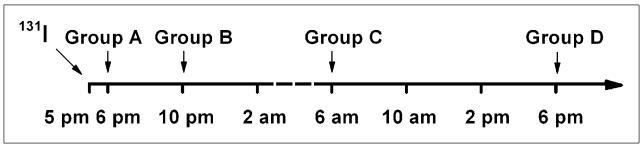

FIGURE 1. Timing of start of vitamin C stimulation for each group. Ingestion of ^{131}I was almost always at 5 PM for all patients. Groups A and B began sucking vitamin C at 6 PM and 10 PM, respectively, on day of ^{131}I ingestion. Groups C and D began sucking vitamin C at 6 AM and 6 PM, respectively, on second day of ^{131}I ingestion. Because of nocturnal rest, no patients sucked vitamin C from 2 AM to 6 AM.

Salivary Gland Dosimetry

Scintigraphy. Serial planar images of the head and neck were obtained on a dual-head γ-camera (Skylight; Philips) equipped with a set of high-energy parallel-hole collimators. Salivary absorbed dose was estimated from conjugate (anterior and posterior) counts of the salivary glands in these images. Before each patient was imaged, dead-time correction was made, when necessary, to allow for high counting rates (*20*). Patients were placed supine in Waters' position. Detectors were positioned to cover an area from the brain to the level of the thyroid gland. The time points, chosen from pilot studies, were 1, 2, 3, 4, 5, 13, 25, and 48 h after ^{131}I ingestion. Each 20-min imaging study was performed using a peak of 364 keV, a 20% window, two 10% windows on either side to allow for triple-energy window scatter correction (*21*), and a 128 × 128 matrix. Elliptic regions of interest covering the parotid and submandibular salivary glands were marked on the 1-h anterior images and then flipped to the posterior images and copied to the corresponding later scans. The cerebrum was selected for background subtraction (*22*). All images were reviewed by one physician who was unaware of any information about the patient.

Residence Time. The following equation was used for calculating salivary activity (A) (*21*):

$$A = \sqrt{\frac{I_A \times I_P}{e^{-\mu_e t}}} \times \frac{f}{C} \qquad \text{Eq. 1}$$

where I_A and I_P are the number of counts on the salivary region of interest in the anterior and posterior images, respectively, after correcting for scatter, dead time, and background. Buijs' background correction method was applied (*23*), where the anterior–posterior thickness of the body across the salivary gland and the salivary gland itself were measured on the CT scanner (Brilliance; Philips), μ_e is the linear attenuation coefficient (0.11/cm), t is the body anterior–posterior thickness across the salivary gland, f is the salivary self-absorption coefficient (1), and C is the camera calibration factor (43 cps/MBq).

The time–activity curves used to calculate salivary residence times were fit by minimizing χ^2. The activities beyond 48 h were small, and their contribution to the cumulated activities (<1%) could be neglected (*22*).

Absorbed Dose. It was assumed that all nonpenetrating radiation of ^{131}I deposited in the salivary glands would be completely absorbed by the glands and that all penetrating radiation would have no contribution to salivary absorbed dose. Based on the MIRD schema, salivary absorbed dose (D) was calculated as follows:

$$D \approx A_0 \times \tau \times \frac{\Delta}{m} \qquad \text{Eq. 2}$$

where A_0 is the administered ^{131}I activity (3.7 GBq), τ is the salivary residence time, Δ is the equilibrium dose constant for nonpenetrating radiation of ^{131}I (0.11 Gy·g/MBq·h), and m is the salivary gland mass (g).

The masses of the salivary glands were determined by CT. The cylindric model for the parotid glands and the ellipsoid model for the submandibular glands were applied to determine the salivary

volumes of each patient as proposed by Jentzen et al. (*22*), where the density was considered to be approximately 1.0 g/cm^3.

Statistics

Categoric variables were described as frequencies. Continuous variables were described as mean ± SD. The χ^2 test was used to compare the difference in categoric variables. The Kruskal–Wallis test was used to compare the difference in continuous variables. Statistically significant differences were assumed at a P value of less than 0.05.

RESULTS

Patients

From October 2006 to December 2008, 80 consecutive patients were initially recruited. Eight consecutive patients were excluded: 5 of these 8 did not complete salivary dosimetry measurements (2 from group A and 3 from group D), and the others showed distant metastases on posttherapy scans (2 with lung metastases from group B and 1 with bone metastases from group C). The final number of patients eligible for the analysis of salivary dosimetry was 72. The main characteristics of each group are indicated in Table 1.

At baseline, the groups were comparable in age, sex, pathologic types of thyroid cancer (papillary or follicular), and levels of thyroid-stimulating hormone at ^{131}I therapy.

Time–Activity Curves

Representative time–activity curves of the salivary glands are presented in Figure 2.

Salivary Absorbed Dose

Figure 3 shows a box plot of mean salivary absorbed dose for each group. For the single parotid gland, the values in groups A, B, C, and D were 0.18 ± 0.11, 0.16 ± 0.07, 0.16 ± 0.09, and 0.16 ± 0.12 mGy/MBq, respectively (P = 0.37). For the single submandibular gland, the respective values were 0.19 ± 0.05, 0.17 ± 0.05, 0.18 ± 0.07, and 0.17 ± 0.06 mGy/MBq (P = 0.28).

Salivary Absorbed Dose During First 24 h After ^{131}I Ingestion

Salivary cumulated activities arising from the first 24 h after ^{131}I ingestion accounted for 86.08% ± 7.89% of total cumulated activities and ranged from 75% to 98% among patients (Table 2). There was no significant difference in salivary absorbed dose during the first 24 h after ^{131}I ingestion among the 4 groups (Table 3).

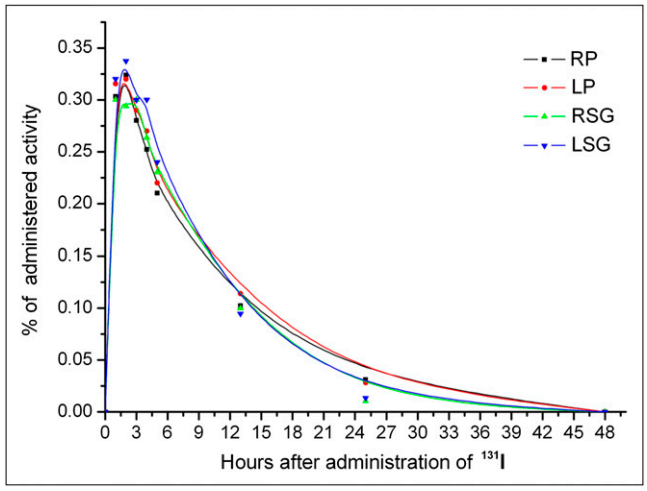

FIGURE 2. In 49-y-old woman with differentiated papillary thyroid cancer, salivary time–activity curves after ingestion of 3.7 GBq of ^{131}I for ablating postsurgical thyroid remnant. LP = left parotid; LSG = left submandibular gland; RP = right parotid; RSG = right submandibular gland.

DISCUSSION

On the assumption that ^{131}I uptake by the salivary glands, just like thyroid tissue, would not plateau until 24 h after administration and that an early start of sour stimulation would further deliver ^{131}I by increased blood flow to the salivary glands, Nakada et al. (*10*) proposed that sour stimulation should not be initiated until 24 h after ^{131}I administration. Although the reported incidence of sialadenitis in the paper of Nakada et al. was higher in the early-candy-sucking group (1 h after ^{131}I ingestion) than in the late-sucking group (24 h after ^{131}I ingestion) (64% and 37%, respectively, $P < 0.05$), 81% of the late-sucking group received ibuprofen or a steroid for radiation sialadenitis, versus 52% in the early-sucking group (*10–14*).

TABLE 1. Patient Characteristics

Characteristic	Group A	Group B	Group C	Group D
Start of vitamin C stimulation*	1 h	5 h	13 h	25 h
Patients available (*n*)	18	18	19	17
Age (y)	44 ± 14	42 ± 14	43 ± 13	39 ± 12
Sex (*n*, M/F)	2/16	3/15	7/12	2/15
Papillary/follicular (*n*)	17/1	15/3	18/1	17/0
Thyroid-stimulating hormone† (mU/L)	85.2 ± 15.2	91.0 ± 16.3	86.9 ± 12.2	83.2 ± 13.5

*After ^{131}I ingestion.
†Normal range = 0.27–4.2 mU/L.
For all comparisons, $P > 0.05$.

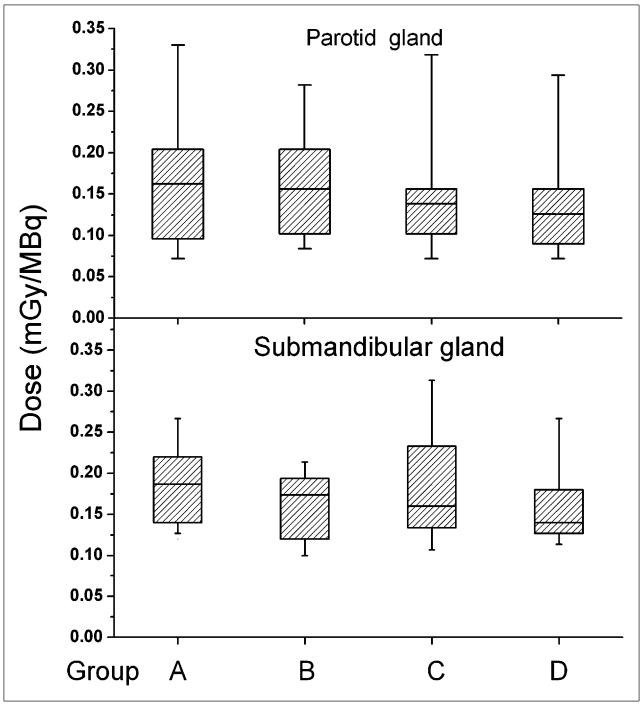

FIGURE 3. Box plot of absorbed dose (average of left and right glands) to parotid and submandibular salivary glands in 4 groups. Errors bars are 10th and 90th percentiles, gray box itself is boundary of 25th and 75th percentiles, and solid line indicates median.

Whether this more aggressive treatment altered the outcome of the late-sucking group is unknown.

Despite expressing sodium iodine symporters similar to those of thyroid tissue, salivary glands do not have thyroperoxidase and thus have an extremely short residence time of ^{131}I. The present study clearly showed that it is at 1–2 h after ^{131}I ingestion that uptake in the salivary glands is highest (Fig. 2). Afterward, ^{131}I rapidly washes out from the glands. Little ^{131}I remains in the glands 24 h after ingestion. To determine the optimal regimen of sour stimulation, one should thus consider starting the sour stimulation at varied times, especially during the first 24 h after ^{131}I ingestion, and then observe if the salivary absorbed dose or the prevalence of salivary side effects changes.

Our study demonstrated that the start of vitamin C stimulation at various times after ^{131}I ingestion has little effect on salivary absorbed dose. The sour prescription of Nakada et al. (*10*) was a little more stringent than ours. We instructed patients to suck vitamin C every 4 h for 6 d, whereas Nakada et al. asked patients to suck lemon candy every 2–3 h over 5 d. Neither prescription included nocturnal salivary gland stimulation. Because of ethical considerations, we did not set up a control group of patients who would not be given vitamin C stimulation at any time after ^{131}I ingestion. Salivary cumulated activities in the first 24 h after ^{131}I ingestion did, however, amount to 86.08% ± 7.89% (range, 75%−98%) of total cumulated activities. As a result, salivary absorbed dose during the first 24 h accounted for a large proportion of total absorbed dose and may substitute for total absorbed dose; in addition, salivary absorbed dose during the first 24 h did not significantly differ among groups. Unlike patients in group D, all patients in groups A, B, and C had been given vitamin C stimulation in the first 24 h after ^{131}I ingestion. Group D can thus act as a control group. Therefore, the use of vitamin C stimulation at any time after ^{131}I ingestion has only a limited effect on salivary absorbed dose. The possible mechanisms underlying this finding follow:

Salivary glands have a high rate of metabolism and a high blood flow; both are proportional to the rate of saliva formation. The blood flow of the maximally secreting salivary gland is approximately 10 times that of an equal mass of actively contracting skeletal muscle (*24,25*). Color Doppler sonographic studies have shown that there is a close correlation between the increase in minimum velocity of the submandibular glands and that of saliva secretion after sour stimulation (*26,27*). In thyroid cancer patients, because ^{131}I uptake by the remnant thyroid tissue or metastatic thyroid cancer is much lower than that of normal thyroid tissue, and clearance of ^{131}I from the blood is substantially delayed because of a reduced glomerular filtration rate in the hypothyroid state, the blood concentration of ^{131}I early after ^{131}I ingestion is considerably high (*28*). Therefore, sour stimulation not only can accelerate ^{131}I washout from the salivary glands by enhancing saliva flow but also can increase the amount of ^{131}I arriving at the glands by enhancing blood flow, which may partially or completely compensate for emptying effects. After sour stimulation, it can be postulated that, if the amount of ^{131}I secreted through increased saliva flow is greater than the amount arriving through increased blood flow, salivary absorbed dose would be reduced. In contrast, if the amount secreted is less than the amount arriving, salivary absorbed dose would be increased. However, if the amount secreted is equal or equivalent to the

TABLE 2. Salivary Cumulated Activities in First 24 Hours, Divided by Total Cumulated Activities

	Group				
Salivary gland	A	B	C	D	*P*
Parotid	0.82 ± 0.07	0.87 ± 0.05	0.85 ± 0.12	0.88 ± 0.10	0.21
Submandibular	0.83 ± 0.09	0.80 ± 0.05	0.96 ± 0.09	0.94 ± 0.08	0.16

Data are mean ± SD.

TABLE 3. Salivary Dosimetry During First 24 Hours

	Group				
Salivary gland	A	B	C	D	*P*
Parotid	0.15 ± 0.06	0.14 ± 0.07	0.12 ± 0.08	0.14 ± 0.11	0.32
Submandibular	0.16 ± 0.04	0.14 ± 0.04	0.16 ± 0.07	0.16 ± 0.06	0.24

Data are mean mGy/MBq ± SD.

amount arriving—that is to say, the amount retained in the glands is balanced—then whether sour stimulation is given, and its timing, after ^{131}I ingestion would have little effect on salivary absorbed dose.

Our study had strengths and limitations. First, to our knowledge, this was the first prospective, randomized, controlled dosimetry-based trial to investigate the effect of sour stimulation on the salivary glands. Salivary parenchymal functions and symptoms after ^{131}I therapy were not studied. Although it is accepted that radiation-absorbed dose to normal tissue in radionuclide therapy is able to predict toxicity (*17–19*), investigations of the dose–effect relation for the salivary glands in ^{131}I therapy remain essential. Second, we investigated the effect of only the timing of salivary gland stimulation, and if the sour prescription in the study had been less stringent, the study would have been insufficiently powerful to detect the effect of sour stimulation on salivary absorbed dose. In view of the high incidence of salivary gland injury and the easy availability of sour stimulation, future controlled studies are needed to determine not only whether sour stimulation is necessary and when it is to be started but also how the dose and frequency are to be titrated. Third, it has become common practice in some areas to prepare thyroid cancer patients with recombinant human thyroid-stimulating hormone rather than traditional thyroid hormone withdrawal for ^{131}I therapy (*9,28,29*). The optimal regimen of sour stimulation in that group is also worth investigating.

CONCLUSION

This prospective, randomized, single-blind, controlled study demonstrated that salivary stimulation with vitamin C at any time after ^{131}I administration has little effect on salivary absorbed dose in thyroid cancer patients.

ACKNOWLEDGMENTS

We thank the staff of the Department of Nuclear Medicine, West China Hospital, particularly Luyi Zhou and Xiaochuan Yang, for their technical support. This work was supported by the National Natural Science Fund of China (grants 30670585 and 30870724).

REFERENCES

1. De La Viejo A, Dothan O, Levy O, Carrasco N. Molecular analysis of the sodium/iodide symporter: impact on thyroid and extrathyroid pathophysiology. *Physiol Rev.* 2000;80:1083–1105.
2. Mandel SJ, Mandel L. Radioactive iodine and the salivary glands. *Thyroid.* 2003;13:265–271.
3. Konings AW, Coppes RP, Vissink A. On the mechanism of salivary gland radiosensitivity. *Int J Radiat Oncol Biol Phys.* 2005;62:1187–1194.
4. Ish-Shalom S, Durleshter L, Segal E, Nagler RM. Sialochemical and oxidative analyses in radioactive I-131 treated patients with thyroid cancer. *Eur J Endocrinol.* 2008;158:677–681.
5. Hyer S, Kong A, Pratt B, Harmer C. Salivary gland toxicity after radioiodine therapy for thyroid cancer. *Clin Oncol (R Coll Radiol).* 2007;19:83–86.
6. Walter MA, Turtschi CP, Schindler C, Minnig P, Muller-Brand J, Muller B. The dental safety profile of high-dose radioiodine therapy for thyroid cancer: long-term results of a longitudinal cohort study. *J Nucl Med.* 2007;48:1620–1625.
7. Kita T, Yokoyama K, Higuchi T, et al. Multifactorial analysis on the short-term side effects occurring within 96 hours after radioiodine-131 therapy for differentiated thyroid carcinoma. *Ann Nucl Med.* 2004;18:345–349.
8. Silberstein EB. Reducing the incidence of I-131 induced sialadenitis: the role of pilocarpine. *J Nucl Med.* 2008;49:546–549.
9. Grewal RK, Larson SM, Pentlow CE, et al. Salivary gland side effects commonly develop several weeks after initial radioactive iodine ablation. *J Nucl Med.* 2009;50:1605–1610.
10. Nakada K, Ishibashi T, Takei T, et al. Does lemon candy decrease salivary gland damage after radioiodine therapy for thyroid cancer? *J Nucl Med.* 2005;46:261–266.
11. Lam MGEH, van Isselt JW. Does lemon candy decrease salivary gland damage after radioiodine therapy for thyroid cancer? [letter]. *J Nucl Med.* 2005;46:2118–2119.
12. Lam MG, van Isselt JW. Re: does lemon candy decrease salivary gland damage after radioiodine therapy for thyroid cancer? [reply]. *J Nucl Med.* 2005;46:2118–2119.
13. Van Nostrand D, Atkins F, Bandaru VV, et al. Salivary gland protection with sialagogues: a case study. *Thyroid.* 2009;19:1005–1008.
14. Kloos RT. Protecting thyroid cancer patients from untoward effects of radioactive iodine treatment. *Thyroid.* 2009;19:925–928.
15. Luster M, Clarke SE, Dietlein M, et al. Guidelines for radioiodine therapy of differentiated thyroid cancer. *Eur J Nucl Med Mol Imaging.* 2008;35:1941–1959.
16. Cooper DS, Doherty GM, Haugen BR, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid.* 2009;19:1–48.
17. Meredith R, Wessels B, Knox S. Risks to normal tissues from radionuclide therapy. *Semin Nucl Med.* 2008;38:347–357.
18. Stabin MG. The case for patient-specific dosimetry in radionuclide therapy. *Cancer Biother Radiopharm.* 2008;23:273–284.
19. Brans B, Bodei L, Giammarile F, et al. Clinical radionuclide therapy dosimetry: the quest for the "Holy Gray." *Eur J Nucl Med Mol Imaging.* 2007;34:772–786.
20. Becker S, Laffont S, Vitry F, et al. Dosimetric evaluation and therapeutic response to internal radiation therapy of hepatocarcinomas using iodine-131-labelled lipiodol. *Nucl Med Commun.* 2008;29:815–825.
21. Siegel JA, Thomas SR, Stubbs JB, et al. MIRD pamphlet no. 16: techniques for quantitative radiopharmaceutical biodistribution data acquisition and analysis for use in human radiation dose estimates. *J Nucl Med.* 1999;40:37S–61S.
22. Jentzen W, Schneider E, Freudenberg L, et al. Relationship between cumulated radiation dose and salivary gland uptake associated with radioiodine therapy of thyroid cancer. *Nucl Med Commun.* 2006;27:669–676.
23. Buijs WCAM, Siegel JA, Boerman OC, Corstens FHM. Absolute organ activity estimated by five different methods of background correction. *J Nucl Med.* 1998;39:2167–2172.
24. Kutchai HC. The gastrointestinal system. In: Berne RM, Levy MN, Koeppen BM, et al. *Physiology.* 5th ed. St. Louis, Missouri: Mosby; 2003:566–570.
25. Lingappa VR, Farey K. Gastrointestinal physiology. In: Lingappa VR, Farey K. *Physiological Medicine: A Clinical Approach to Basic Medical Physiology.* 1st ed. New York, NY: McGraw-Hill Co. Inc.; 2000:209–210.

26. Martinoli C, Derchi LE, Solbiati L, Rizzatto G, Silvestri E, Giannoni M. Color Doppler sonography of salivary glands. *AJR.* 1994;163:933–941.
27. Ariji Y, Yuasa H, Ariji E. High-frequency color Doppler sonography of the submandibular gland: relationship between salivary secretion and blood flow. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 1998;86: 476–481.
28. Hanscheid H, Lassmann M, Luster M, et al. Iodine biokinetics and dosimetry in radioiodine therapy of thyroid cancer: procedures and results of a prospective international controlled study of ablation after rhTSH or hormone withdrawal. *J Nucl Med.* 2006;47:648–654.
29. Remy H, Borget I, Leboulleux S, et al. ^{131}I effective half-life and dosimetry in thyroid cancer patients. *J Nucl Med.* 2008;49:1445–1450.