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Radioactive Iodine and the Salivary Glands

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Abstract and Introduction

Abstract

Radioactive iodine (^{131}I) targets the thyroid gland and has been proven to play an effective role in the treatment of differentiated papillary and follicular cancers. Simultaneously, this radioisotope hones in on the salivary glands where it is concentrated and secreted into the saliva. Dose related damage to the salivary parenchyma results from the ^{131}I irradiation. Salivary gland swelling and pain, usually involving the parotid, can be seen. The symptoms may develop immediately after a therapeutic dose of ^{131}I and/or months later and progress in intensity with time. In conjunction with the radiation sialadenitis, secondary complications reported include xerostomia, taste alterations, infection, increases in caries, facial nerve involvement, stomatitis, candidiasis, and neoplasia. Prevention of the ^{131}I sialadenitis may involve the use of sialogogic agents to hasten the transit time of the radioactive iodine through the salivary glands. However, studies are not available to delineate the efficacy of this approach. Recently, amifostine has been advocated to prevent the effects of irradiation. Treatment of the varied complications that may develop encompass numerous approaches and include gland massage, sialogogic agents, duct probing, antibiotics, mouthwashes, good oral hygiene, and adequate hydration.

Introduction

Radiation damage to the salivary glands is a known short-term and long-term complication of radioactive iodine (^{131}I) therapy for patients with differentiated thyroid cancer.^[1-4] This morbid aspect of ^{131}I therapy has caused significant patient distress and warrants measures designed to circumvent this commonly experienced salivary gland impairment. Consequently, the purpose of this review paper is to further focus attention on the problem. Emphasis is placed on the mechanisms involved in the evolution of the sialadenitis and the therapeutic steps that can be taken to inhibit or limit its onset, or treat the condition if it develops.

Salivary Glands

The salivary glands also have the capacity to concentrate iodide selectively for unknown reasons (Fig. 1). The iodide is then secreted into saliva such that its salivary concentration has been reported to vary from 20 to 100 times that found in the serum.^[5-10] It is this critical ability that causes glandular damage when ^{131}I is used. The principal site of the iodide transport into saliva is the epithelium of the parotid salivary gland's intralobular ducts.^[11,12] Iodide is extracted from periductal capillaries and concentrated by the ductal epithelium, whereupon it is secreted into the duct lumen and transported into the oral cavity. It has been

calculated that up to 24% of the administered ^{131}I dose for thyroid cancer therapy is lost in the saliva.^[13]

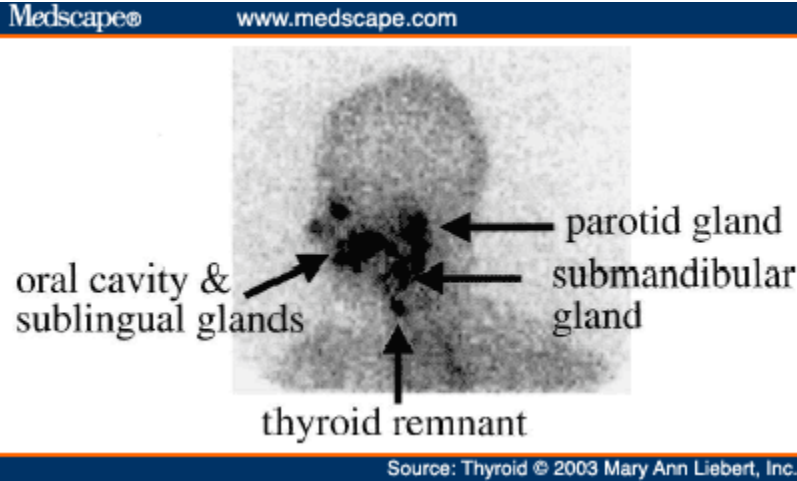


Figure 1. Lateral head and neck planar view acquired with a low energy collimator 24 hours after oral administration of 2.0 mCi ^{123}I in a patient with papillary thyroid cancer undergoing diagnostic scanning prior to ^{131}I therapy for thyroid remnant ablation. Normal physiologic uptake of radioiodine by the salivary glands is indicated.

In the process of concentrating the radioactive iodine, the salivary glands are exposed to the damaging effects of irradiation. Although all salivary glands are involved in the transport of the radioactive iodine into the saliva, the parotid gland is most active and its serous cells are more susceptible than mucous acini to the deleterious effects of ionizing radiation. Therefore, the serous parotid gland will demonstrate a more intense radiation sialadenitis than the mixed mucous and serous cell-containing submandibular and sublingual salivary glands.^[5,14] Serous cells are particularly concerned with secretion of salts and zymogen, the precursor of amylase. The mucous cells secrete mucin, a lubricant that eases swallowing and act as a protective oral mucosal barrier.

The ^{131}I irradiation of the salivary glands also causes endothelial damage to the glandular vasculature.^[9] An increase in capillary permeability results in the leakage of plasma proteins and electrolytes into the surrounding interstitial tissues. The simultaneously injured irradiated intralobular ducts lose their ability to filter and prevent plasma proteins from entering the saliva. As a result of these two mechanisms, elevated protein values are evident in parotid saliva.^[9,15] Elevated sodium and chloride levels are also found in parotid saliva because a radiation-damaged duct does not have the normal duct's ability to resorb these electrolytes secreted by the terminal acinar cells as saliva progresses through the duct system. Furthermore, salivary phosphate levels are decreased when the damaged epithelium of the intralobular duct's wall fails in its normal function to transport phosphate into the saliva. Biochemical changes in saliva can be expected in all patients receiving therapeutic ^{131}I ,^[9,10] the extent of which is obviously dose dependent.

Early and Late Sialadenitis

Sialadenitis is the most frequent complication of ^{131}I therapy for thyroid cancer. Almost immediately after ^{131}I therapy transient swelling (Fig. 2) and pain with decreased salivary flow, usually bilateral and involving the parotid glands, have become a known problem.^[1,4,5,16-19] The radiation-induced swelling from the inflammatory infiltrate causes increased periductal pressure with duct constriction. This results in salivary retention and adds to the swelling and pain. As can be anticipated, the effect is rapid and dose related. Within a few days, resolution of this posttherapeutic inflammatory process occurs and symptoms subside.^[18,20] Unfortunately, no data are available regarding the frequency of this immediate post- ^{131}I

sialadenitis.



Figure 2. Clinical view of right parotid swelling (arrows).

Initially, not all salivary glands were thought to be impaired while those glands that demonstrated damage seemed to heal spontaneously without further subjective and objective symptomatology. Such assumptions were probably derived from the observation that the initial and immediate parotid swellings were transient in nature. Longitudinal studies of this specific problem were not performed. Numerous reports of permanent harm and the associated symptomatology have now appeared.^[10,21-23] Allweiss et al.^[8] reported that 10 of 87 patients (11.5%) returned on their own volition over various periods of time with complaints compatible with chronic sialadenitis after ¹³¹I therapy. Alexander et al.^[24] examined 203 patients within 3 months of ¹³¹I therapy (100-200 mCi) and found that 67 patients (33%) had symptoms of sialadenitis usually manifesting itself as bilateral parotid swelling. Thirty-one of the 67 patients also had submandibular gland swellings. One year later, persistent salivary complaints were present in 87 of the patients. The longer elapsed time allowed for continued progression of gland degeneration. More severe symptoms develop with time as the effects of the incorporated ionizing radiation in the cell's genetic structure make their appearance in succeeding cell generations.

The first gland symptom that prompts a voluntary post-¹³¹I therapy visit is usually obstructive in nature. Duct lumen narrowing from inflammatory stricturing (Fig. 3) is instrumental in the formation of a jelly-like plug. The plug results when a nidus of radiation-induced inflammatory cells and/or the narrowed duct lumen creates an obstruction with stagnation and mucus precipitation. Obstructive symptomatology with swelling and pain will then develop from salivary retention, most marked during periods of increased salivary production (eating). Because the plug is soft, increased retrograde pressure eventually results in its spontaneous extrusion and the symptoms subside. Simultaneously, the patient becomes aware of a salty taste because the intralobular ducts have not adequately resorbed sodium and chloride ions from the saliva. Furthermore, because salivary lavage is impeded, an orally ascending secondary duct infection can develop and lead to an intensification of the obstructive symptoms of swelling and pain. Continued exacerbations, facilitated by the scarred duct wall and decreased salivary lavage, can be expected.

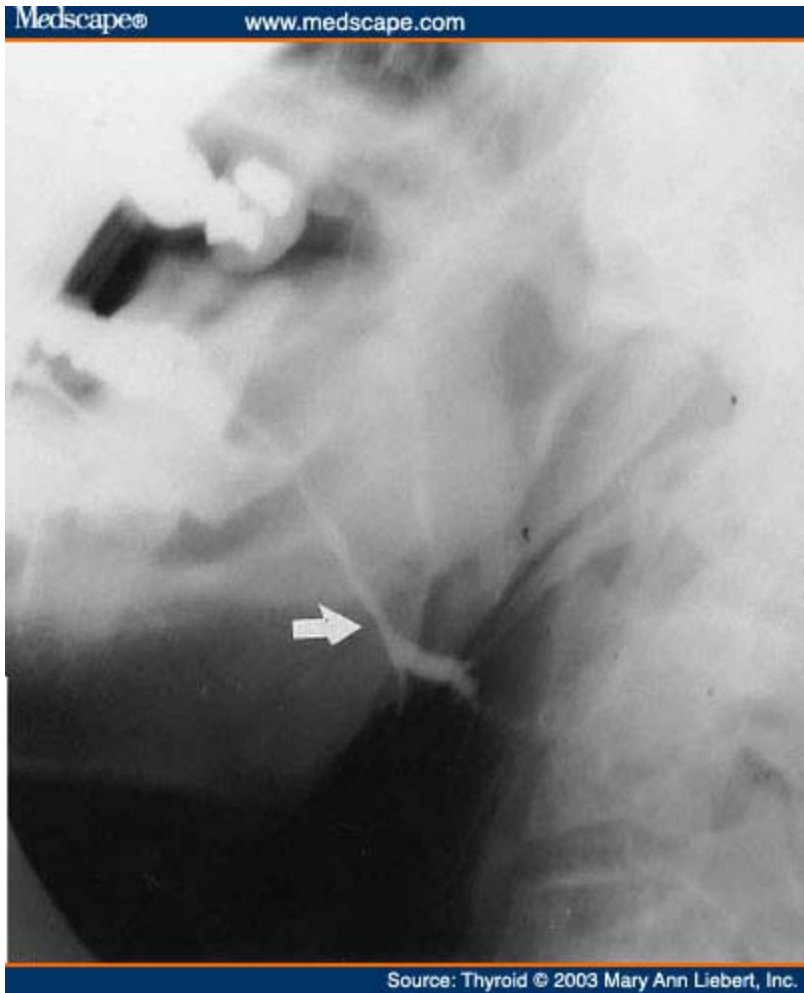


Figure 3. Right parotid sialogram. Patient received radioactive iodine therapy 17 months ago and has recently developed obstructive parotid symptomatology. Arrow indicates duct stricture with proximal duct dilatation evident.

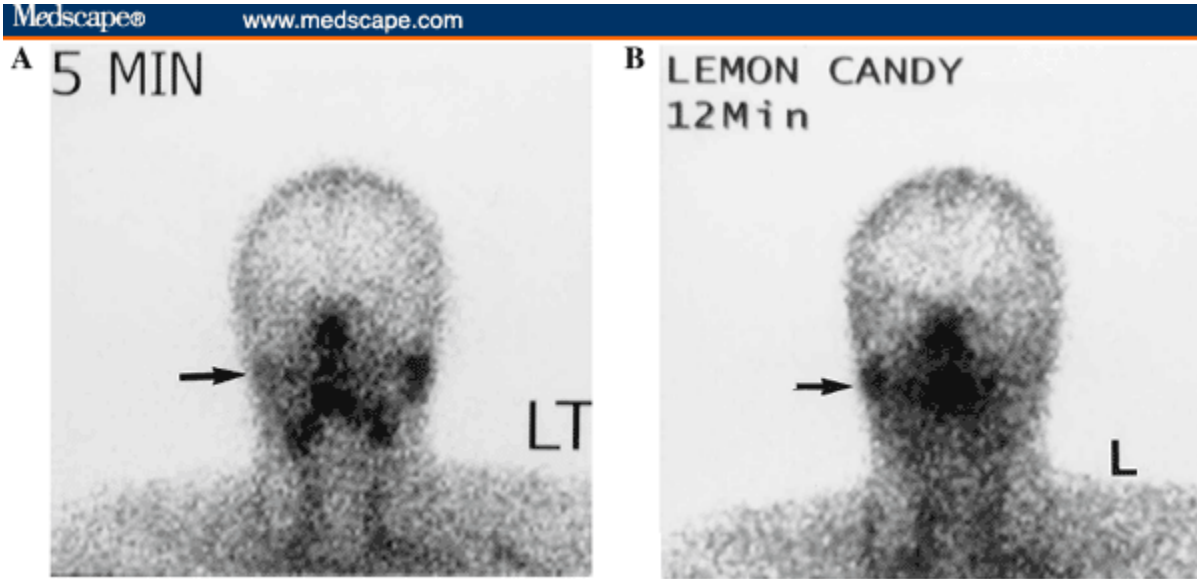
Diagnosis of chronic sialadenitis can readily be accomplished when the patient's history of having received radioactive iodine is factored into the patient's clinical symptomatology. Computerized tomography scans, in an attempt to identify sialoliths, almost certainly will be negative (Fig. 4). Because parotid stones are uncommon, this procedural approach is not cost effective.



Figure 4. Computerized tomography scan. Patient developed radiation parotitis (right) 10 months after treatment with radioactive iodine. Note increased right parotid density (P), particularly when compared to the normal appearing left parotid.

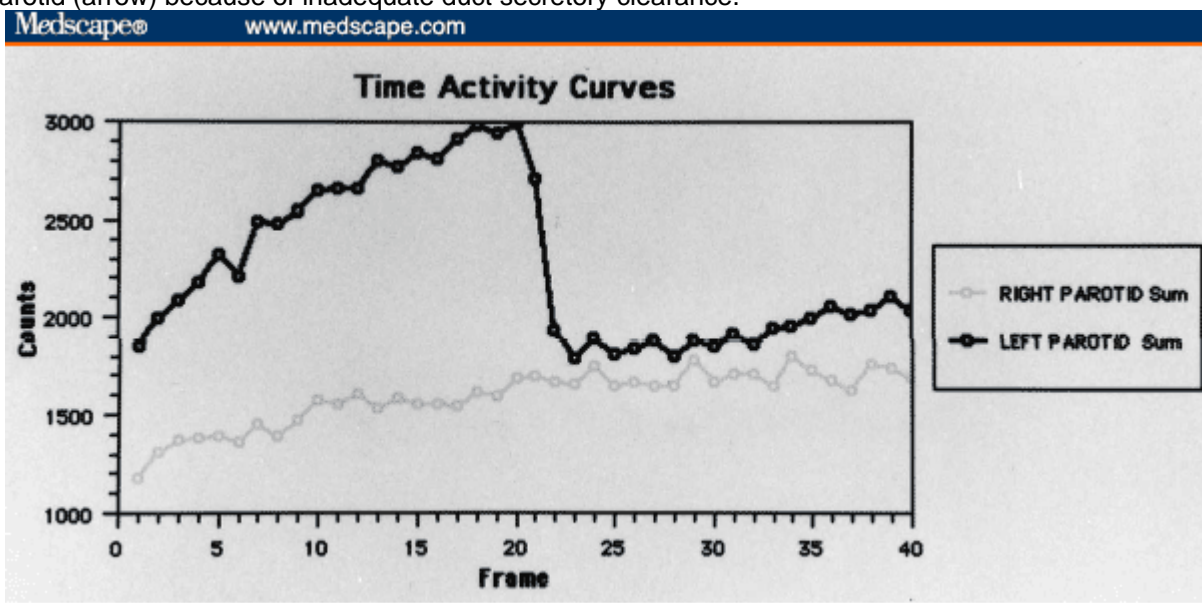
Evaluation of gland function is best accomplished via a scintigraphic examination with the intravenously introduced radioisotope, technetium-99 m pertechnetate (TPT). The TPT, a radioisotope of molybdenum, is considered safe because it only has a 6-hour half-life and does not produce any destructive beta radiation. It emits a nondestructive gamma radiation that can be imaged by a gamma camera. This tracer is effectively concentrated and secreted by salivary gland tissue, thus affording the opportunity to study gland function in real-time.

The effect of ^{131}I on the parenchyma and on the excretory ducts are independent of each other. Abnormal parenchymal uptake, duct secretory clearance or both (Fig. 5) were observed with a TPT study in 73% of patients who received an average of 375 mCi ^{131}I and whose dose-related symptoms became evident over a period of several months^[25] Initially, TPT salivary gland uptake may be normal, but because of early damage to the duct wall, TPT clearance is delayed resulting in increased TPT retention. Later, diminished TPT uptake results from vascular fibrosis caused by the destructive effect of the ^{131}I and becomes manifest slowly over a prolonged period. TPT investigations have revealed that dosages of 500 mCi caused abnormal salivary gland function in as many as 80% of the patients^[26] and approached 100% when more was used.^[27-29] Because the dose-dependent effect of ^{131}I is delayed, salivary secretion tends to gradually decrease with time.^[25] The dysfunction that develops can be mild, asymmetric (Fig. 6) and subjectively asymptomatic in its presentation.



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Figure 5. A: Distribution of the technetium-99m pertechnetate (TPT) radioisotope 5 minutes after injection. Note the decreased right parotid uptake (arrow) when compared to left parotid. **B:** Same patient 12 minutes after receiving TPT and 2 minutes after using lemon candy. There is TPT retention in the right parotid (arrow) because of inadequate duct secretory clearance.



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Figure 6. Technetium-99m pertechnetate (TPT) time activity graph performed for patient who developed recurrent right parotitis after radioactive iodine therapy 8 months previously. Each frame represents 30 seconds. Lemon candy was given after 10 minutes (20 frames). Note normal uptake and secretion of the TPT radioisotope by the left parotid while the right parotid demonstrates minimal uptake and no secretory clearance.

Once radiation damage to the gland has occurred, no permanent cure can be offered. Treatment becomes symptomatic. Aggressive external massage of the parotid gland is advised to milk out the retained saliva, increase salivary lavage, and flush out ductal debris (Fig. 7). Antibiotics may be used if infection is present as evidenced by a suppurative salivary return and/or fever. If swelling and pain do not resolve, duct probing to break up plug blockage is helpful. Home care must be continuous and should

include good oral hygiene and the constant use of sialogogic agents such as sugarless sour candy or chewing gum, followed by massage. Whatever the reason, dehydration must be avoided because it leads to decreased salivary lavage and recurrent exacerbations. Adequate daily fluid intake must be maintained. Consideration should also be given to any use of anticholinergic agents (antidepressants, antihistamines, some cardiovascular drugs, sedatives, etc.) because they decrease salivation.

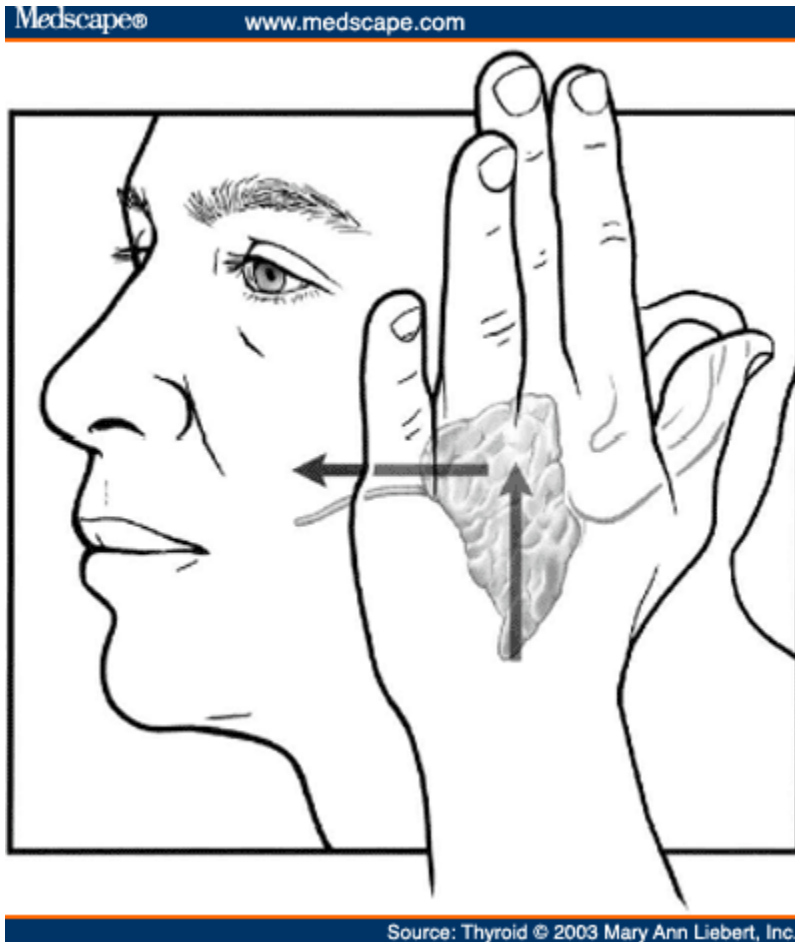


Figure 7. Sketch demonstrates method of massaging parotid gland.

Despite a relative xerostomia caused by the ^{131}I and secondary infection, there usually is sufficient functioning gland parenchyma present to respond to sour candy and gum. However, patients with significant xerostomias are candidates for the cholinergic medications, pilocarpine, or cevimeline. Increased salivary flow and patient comfort can be expected.

The postsurgical management of thyroid cancer demands recognition of the existence of sialadenitis because a whole-body ^{131}I scan can demonstrate intense tracer uptake in an affected salivary gland.^[30,31] The presence of inflammation, whether it be acute or chronic sialadenitis, is the problem. Two processes associated with glandular inflammation are in play and cause the "hot spot." First, the increased capillary permeability inherent in the inflammatory reaction enhances transmigration of the radioactive isotope into the salivary parenchyma. Second, duct wall damage and lumen obstruction, consequences of inflammation, promote ^{131}I retention. An awareness of any existing sialadenitis avoids an inaccurate interpretation of the presence of metastatic cervical lymph nodes.

Taste

Often, immediately after ^{131}I ingestion for thyroid cancer, transient taste alterations develop concurrently with the initial but temporary parotid symptomatology. Distorted taste perception has been reported in 16% of the patients who received 150 mCi ^{131}I ^[27] and 27% of those who received 200 mCi ^{131}I ,^[24] and may last several weeks. With higher therapeutic doses of ^{131}I , the loss of taste can occasionally become permanent. The explanation for taste dysfunction rests mostly with the von Ebner's serous glands that are situated in the immediate vicinity of the taste bud-containing circumvallate papilla. As with all salivary serous acini, radioactive iodine also hones in on the von Ebner glands and creates a radiation sialadenitis with a diminished ability, albeit often temporary, of these structures to secrete serous saliva. Salivary fluid from von Ebner's glands functions to carry the food chemicals that facilitate taste to taste buds. With the loss of this salivary transport, the ability of the chemical tastants to activate the taste buds is inhibited. Furthermore, a damaged duct's inability to adequately resorb salivary sodium and chloride ions results in a salty taste and plays into the mix of altered taste.

Facial Nerve and Stomatitis

Facial Nerve

Levinson et al.^[10] reported two patients who rapidly developed transient facial paralysis after having received high doses of ^{131}I . It can be theorized that the inflammatory process associated with sialadenitis secondarily involved the facial nerve as it passed through the parotid. After the remission of the acute inflammation, the facial palsy resolved.

Stomatitis

Recently, one of the authors (S.M.) examined a patient who had received 200 mCi ^{131}I for thyroid cancer. Seven days later, the patient returned with a severe painful stomatitis, the origin of which can only be hypothesized. It is possible that the patient had a mucosal radiation reaction to the ^{131}I , which was concentrated in the oral cavity by secretions from all the major and minor salivary glands. An idiosyncratic reaction to iodine can also be theorized as the source of the problem. Subsequent questioning of colleagues indicated that two additional cases have been observed, but a literature search revealed no such reports. Effective treatment of the stomatitis can be attained with the use of a dexamethasone elixir mouthwash or one containing viscous lidocaine, diphenhydramine and aluminum and magnesium hydroxides.

Candidiasis and Caries

Candidiasis

Oral candidiasis has been reported after the use of ^{131}I .^[32] The fungal infection is facilitated by the reduced salivary flow that follows secretory cell injury from high ^{131}I dosages. Xerostomia is a known cause of such a fungal infection. Clotrimazole troches function as effective therapeutic agents to combat candidiasis.

Caries

Saliva, through its buffering power, serves to protect the dentition from dental decay. Clinical substantiation of this function is derived from the rampant caries that develop in association with the marked xerostomia after cancericidal doses of external beam radiation to the oral cavity. Statistical increases in dental caries have not been reported^[22] after ^{131}I therapy probably because the intensity of the xerostomia is not as severe as that seen with external beam radiation. Such an event may be authenticated in the future, but long-term longitudinal studies are necessary. Fluoride therapy in the form of topical fluoride applications, fluoride mouthwashes and fluoride toothpaste can prevent the onset of any

such radiation carries.

Salivary Gland Neoplasms and Strategies for Prevention

Salivary Gland Neoplasms

Because radiation can be carcinogenic, the incidence of salivary neoplasms after ^{131}I therapy has been investigated. A small but statistically meaningful neoplastic increase years after ^{131}I therapy has been demonstrated.^[1,33,34] Reports include the development of pleomorphic adenoma,^[35] non-Hodgkin's lymphoma,^[36] and mucoepidermoid carcinoma.^[37] Although definitive evidence is scant regarding neoplastic change, its occurrence would seem to be in direct proportion to the dosage of ^{131}I .

Strategies for Prevention

Rather than accept the salivary gland damage produced by ^{131}I , the use of sour candy^[1,4] or lemon juice^[28] has been recommended to increase salivation during ^{131}I administration in an attempt to reduce salivary gland damage. These interventions increase salivary flow and thereby decrease both the transit time of ^{131}I through the parotid and the salivary ^{131}I concentration. However, whether this results in a decrease in the overall salivary gland exposure to ^{131}I is unknown. Transit time through the salivary glands can also be decreased with the cholinergic drugs pilocarpine or cevimeline using an empiric 5 day dosage regimen (2 days before, the day of and 2 days after ^{131}I treatment). As a supplement, sugarless sour candy can be used at the time of treatment. Regrettably, there are no studies that have investigated the long-term efficacy of salivary stimulants (sour candy and/or cholinergic medications) in preventing salivary gland damage in patients receiving radioactive iodine. If medically possible, the temporary suspension of the use of any anticholinergic medications is also helpful.

Intravenous amifostine, an organic thiophosphate, is a recent addition to the drug armamentarium to combat the effects of irradiation.^[38-41] Within the tissues, amifostine undergoes dephosphorylation to its active metabolite WR-1065. Alkaline phosphatase, present in all tissues, is necessary for this change. The conversion is more effective in the alkaline environment of normal tissue rather than the acid environment of tumor tissue. In addition, the concentration of alkaline phosphatase is 100 times greater in normal tissue than in tumor tissue.^[33] Once the WR-1065 becomes available, it acts as a scavenger of oxygen-free radicals, which are the cause of radiation induced tissue damage.

A recent double-blind scintigraphic study examined the effect of amifostine on salivary gland function in 25 patients after amifostine infusion and 25 patients who received placebo prior to ^{131}I therapy.^[38] In conjunction with amifostine therapy, all 50 patients received salivary stimulation with ascorbic acid, and antiinflammatory therapy with an extremely high dose of dexamethasone (40 mg). One year after the ^{131}I therapy, parotid and submandibular function was reduced by 40% in the placebo group and remained unchanged in the amifostine group. The one amifostine complication encountered was a decrease in mean blood pressure, which necessitated a temporary suspension of the infusion. Regardless of the safety record, there is some hesitancy to prescribe amifostine because many practitioners are not convinced that the amifostine does not inhibit the radioactive iodine's efficacy in the treatment of the cancer.

Patients should be made aware of the salivary gland damage that follows ^{131}I therapy for thyroid cancer. The need for lifelong secondary prevention must be understood by the patient. Emphasis should be placed on the need to preserve salivary flow with glandular massage (Fig. 7) and to practice caution when anticholinergic drugs are used. Avoidance of any form of dehydration and the maintenance of an acceptable daily fluid intake must be impressed on the patient.

Although attention is legitimately directed toward achieving a cancer cure with the ^{131}I , procedures should be implemented to negate the patient distress that is encountered from the radioisotope's harmful effect

on salivary glands. The available techniques to prevent or diminish such injury should be part of the practitioner's knowledge base. In addition, early recognition and treatment of sialadenitis serve to lessen patient morbidity.

References

1. Mazzaferri E. Carcinoma of the follicular epithelium. In Braverman LE, Utiger RD (eds) 2000 Werner and Ingbar's The Thyroid, Lippincott, Philadelphia, pp. 904-929.
2. Bland WH 1979 Treatment of malignant thyroid disease. *Semin Nucl Med* 9:95-99.
3. DeGroot IJ, Larsen PR, Hennemann G (eds) 1996 The Thyroid and Its Diseases, 6th ed. Churchill Livingstone, New York, pp. 658-696.
4. Freitas JE, Gross MD, Ripley S, Shapiro B 1985 Radionuclide diagnosis and therapy of thyroid cancer: current status report. *Semin Nucl Med* 15:106-131.
5. Rigler RG, Scanlon PW 1955 Radiation parotitis from radioactive iodine therapy. *Proc Staff Meet Mayo Clin* 30:149-153.
6. Myant NB 1960 Iodine metabolism of salivary glands. *Ann NY Acad Sci* 85:208-214.
7. Mason DK, Harden R McG, Alexander WD 1967 The salivary and thyroid glands: A comparative study in man. *Br Dent J* 122:485-489.
8. Allweiss P, Braunstein GD, Katz A, Waxman A 1984 Sialadenitis following I-131 therapy for thyroid carcinoma: Concise communication. *J Nucl Med* 25:755-758.
9. Maier H, Bihl H 1987 Effect of radioactive iodine therapy on parotid gland function. *Acta Otolaryngol* 103:318-324.
10. Levenson D, Coulec S, Sonnenberg M, Lai E, Goldsmith SJ, Larson SM 1994 Peripheral facial nerve palsy after high-dose radioiodine therapy in patients with papillary thyroid carcinoma. *Ann Int Med* 120:576-578.
11. Gates GA, Work WP 1967 Radioisotope scanning of the salivary glands. *Laryngoscope* 77:861-875.
12. Mishkin FS 1981 Radionuclide salivary gland imaging. *Semin Nucl Med* 11:258-265.
13. McCall MS, Timm, L, Frenkel EP 1967 Chewing tobacco and radioiodine [letter]. *Lancet* 1:902.
14. Abramson AL, Levy LM, Goodman M 1969 Salivary gland scinti-scanning with technetium 99m pertechnetate. *Laryngoscope* 79:1105-1117.
15. Deeg M, Maier H, Bihl H, et al 1988 Klinisches Bild and mogliche Ursachen der Funktionsstorungen der Glandular parotis bei der Radiojodtherapie des differenzierten Schilddrusenkarzinoms. *Laryng Rhinol Otol* 67:362-366.
16. Schneyer LH 1953 Effect of administration of radioactive iodine in human salivary gland function. *J Dent Res* 32: 146.
17. Hilton G, Pochin EE, Cunningham RM, Halnan KE 1956 The role of radioiodine in the treatment of carcinoma of the thyroid. *Br J Radiol* 29:297-310.
18. Goolden AWG, Malland JR, Farran HEA 1957 Radiation sialadenitis following radioiodine therapy. *Br J Radiol* 30:210-212.
19. Van Nostrand D, Neutze J, Atkins F 1986 Side effects of "rational dose" iodine-131 therapy for metastatic well-differential thyroid carcinoma. *J Nucl Med* 27:1519-1527.
20. Khan S, Waxman L, Ramanna G, Ashok N, Nagaraj G, Braunstein G 1994 Transient radiation effects following high-dose I-131 therapy for differentiated thyroid cancer [Abstract]. *J Nucl Med* 35 Suppl:15p.
21. Weisenfeld D, Webster G, Cameron F, Ferguson MM, MacFayden EE, MacFarlane TW 1983 Salivary gland dysfunction following radioactive iodine therapy. *Oral Surg Oral Med Oral Pathol* 55:138-141.
22. Laupa MS, Toth BB, Keene HJ 1993 Effect of radioactive iodine therapy on salivary flow rates and oral streptococcus mutants prevalence in patients with thyroid cancer. *Oral Surg Oral Med Oral Pathol* 75:312-317.
23. Mandel SJ, Mandel L 1999 Persistent sialadenitis after radioactive iodine therapy: Report of two cases. *J Oral Maxillofac Surg* 57:738-741.
24. Alexander C, Bader JB, Schaefer A, Finke C, Kirsh CM 1998 Intermediate and long-term side effects of high-dose radioiodine therapy for thyroid carcinoma. *J Nucl Med* 39:1551-1554.

25. Malpani BL, Samuel AM, Ray S 1996 Quantification of salivary gland function in thyroid cancer patients treated with radioiodine. *Int J Radiat Oncol Biol Phys* 35:535-540.
26. Albrecht HH, Creutzig H 1976 Funktions zintigraphie der Speicheldrüsen nach hochdorsierter Radiojodtherapie. *Fortschr Roentgenstr* 125:546-553.
27. Brown AP, Greening WP, McCready VR, Shaw HJ, Harmer CL 1984 Radioiodine treatment of metastatic thyroid carcinoma: The Royal Marsden Hospital experience. *Br J Radiol* 57:323-327.
28. Spiegel W, Reiners C, Borner W 1985 Sialadenitis following iodine-131 therapy for thyroid carcinoma [letter]. *J Nucl Med* 26:816.
29. Newkirk KA, Ringel MD, Wartofsky L, Burman KD 2000 The role of radioactive iodine in salivary gland dysfunction. *Ear Nose Throat J* 79:460-468.
30. Mitchell G, Pratt BE, Vini L, McCready VR, Harmer CL 2000 False-positive ¹³¹I whole-body scans in thyroid cancer. *Br J Radiol* 73:627-635.
31. Kim S, Park CH, Yoon SN, Hwang K 2001 A false-positive I¹³¹ whole-body scan in chronic parotitis: A case report. *Clin Nucl Med* 26:536-537.
32. Bushell DL, Boles MA, Kaufman GE, Wadas MA, Barnes WE 1992 Complications, sequela and dosimetry of iodine-131 therapy for thyroid carcinoma. *J Nucl Med* 33:2214-2221.
33. Hall P, Holm L-E, Lundell G, Ruden BI 1992 Tumors after radiotherapy for thyroid cancer. *Acta Oncology* 31:403-407.
34. Dottorini ME, Lomuscio G, Mazzucchelli L, Vignati A, Colombo L 1995 Assessment of female fertility and carcinogenesis after iodine-131 therapy for differentiated thyroid cancer. *J Nucl Med* 36:21-28.
35. Edmonds CJ, Smith T 1986 The long-term hazards of the treatment of thyroid cancer with radioiodine. *Br J Radiol* 59:45-51.
36. Wiseman JC, Hales IB, Joasoo A 1982 Two cases of lymphoma of the parotid gland following ablative radioiodine therapy for thyroid carcinoma. *Clin Endocrinol* 17:85-89.
37. Henze M, Hittel JP 2001 Mukoepidermoid-Karzinom der Speicheldrüsen nach hochdosierter Radiojodtherapie. *Laryngo Rhinol Otol* 80:253-256.
38. Bohuslavizki KH, Klutmann S, Brenner W, Kroger S, Buchert R, Bleckmann C, Mester J, Henze E, Clausen M 1999 Radioprotection of salivary glands by amifostine in high-dose radioiodine treatment. *Strahlenther Onkol* 175(Suppl 4):6-12.
39. Bohuslavizki KH, Klutmann S, Bleckmann C, Brenner W, Cassmann S, Mester J, Henze E, Clausen M 1999 Salivary gland protection by amifostine in high-dose radiotherapy of differentiated thyroid cancer. *Strahlenther Onkol* 175:57-61.
40. Bohuslavizki KH, Brenner W, Klutmann S, Hubner RH, Lassmann S, Feyerabend B, Lutgges J, Tinnemeyer S, Clausen M, Henze E 1998 Radioprotection of salivary glands by amifostine in high-dose radioiodine therapy. *J Nucl Med* 39:1237-1242.
41. Bohuslavizki KH, Klutmann S, Brenner W, Mester J, Henze E, Clausen M 1998 Salivary gland protection in high-dose radioiodine treatment: Results of a double blind placebo-controlled study. *J Clin Oncol* 16:3542-3549.

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