ORAL DISEASES

Oral Diseases (2011) 17, 154–161 doi:10.1111/j.1601-0825.2010.01726.x

www.wiley.com

INVITED MEDICAL REVIEW

Sialoadenitis secondary to ^{131}I therapy for well-differentiated thyroid cancer

D Van Nostrand

Division of Nuclear Medicine, Department of Medicine, Washington Hospital Center and Professor of Medicine, Georgetown University School of Medicine, Washington, DC, USA

Radioiodine (^{131}I) is an important therapy for patients who have well-differentiated thyroid cancer. However, ^{131}I may also result in side effects in multiple organs and glands. The glands that are frequently affected are the salivary glands with the major untoward effects including sialoadenitis and increased risk of second primary malignancy. This report will review sialoadenitis secondary to ^{131}I therapy including (1) proposed mechanisms, (2) incidence and clinical presentations, (3) possible approaches to improve prevention, (4) management, and (5) sequelae of sialoadenitis (e.g. xerostomia and salivary duct obstruction). A discussion of second primary malignancies is beyond the scope of this review. With a better understanding of the above, dentists, oral surgeons, otolaryngologists, endocrinologists, nuclear medicine physicians, and nuclear radiologists will be more likely to implement more effective preventive measures to reduce the incidence and severity of ^{131}I-induced sialoadenitis, and if it does occur, to identify and treat sialoadenitis sooner, thereby potentially reducing not only the severity of the initial symptoms, but also the severity of subsequent sequelae.

Oral Diseases (2011) **17**, 154–161

Keywords: Sialoadenitis; ^{131}I, thyroid cancer

Introduction

Radioiodine (^{131}I) therapy was first used for the treatment of Graves' disease in humans in 1942 (Hertz and Roberts, 1942) and for the treatment of well-differentiated thyroid cancer (WDTC) in humans in 1946 (Seidlin *et al*, 1946). Over the years, this has become an important tool in the management of these diseases, and specifically WDTC. Unfortunately, untoward effects in multiple organs and glands secondary to ^{131}I therapy have been identified (Van Nostrand *et al*, 2006). One frequently affected and important group of glands are the salivary glands with radiation-induced sialoadenitis occurring frequently. The objective of this report is to review sialoadenitis secondary to ^{131}I therapy in patients with WDTC including its (1) proposed mechanisms, (2) incidence and clinical presentations, (3) possible approaches to improve prevention, (4) management, and (5) sequelae of sialoadenitis (e.g. xerostomia and salivary ductal obstructions).

Mechanism of radiation-induced sialoadenitis

The parotid, submandibular, and sublingual glands have been reported to concentrate iodine as high as 7–700 times the plasma levels (Freinkel and Ingbar, 1953; Myant, 1960; Rice, 1984; Schiff *et al*, 1947). As a result these glands can receive a significant radiation absorbed dose from the ^{131}I treatment resulting in a sialoadenitis. The radiation exposure to the salivary glands has not been well studied. However, Donachi (1978) reported approximately 250 rads (250 cGy) to the salivary gland from a 5 mCi (185 MBq) dose, and Goolden *et al* (1957) estimated 707 rad (cGy) and 680 rads (700 cGy) to the salivary glands during the first 12 h in two patients who were administered 100 mCi (3.7 GBq) and 150 mCi (5.55 GBq), respectively. However, the mechanisms by which the salivary glands take up the iodine are not well described. Although a major mechanism of salivary iodide transport may be the sodium/iodide symporter, several publications have suggested that the salivary accumulation of radioiodine does not appear to be affected by thyroid-stimulating hormone level or the state of thyroid function (Freinkel and Ingbar, 1953; Myant, 1960; Jhiang *et al*, 1998). Regardless of the mechanism, the serous cells appear to have a greater ability to concentrate radioiodine than the mucous cells.

Incidence and clinical presentation

The reported incidence of acute radiation sialoadenitis is very variable because of many factors (see Table 1) and ranges from 2% to 67% (see Table 2) (Benua *et al*, 1962;

Correspondence: Douglas Van Nostrand, MD, FACP, FACNM, Division of Nuclear Medicine, Washington Hospital Center, 110 Irving Street, NW, Suite GA60B, Washington, DC 20010, USA. Tel: +1 202 877 0348, Fax: +1 202 877 6601, E-mail: douglas.van.nostrand@medstar.net
Received 2 March 2010; revised 10 May 2010; accepted 10 May 2010

Table 1 Factors contributing to the variability in reported incidence and severity of sialoadenitis

- Range of prescribed activity of ^{131}I administered
- Cumulative prescribed activity of ^{131}I administered
- Interval between repeated ^{131}I therapies
- Factors affecting uptake of ^{131}I in the salivary glands
- Previous history of other salivary gland disease
- Administration of drugs that potentially cause xerostomia
- Diligence of the patient and physician in implementation of preventive measures to reduce the radiation absorbed dose to the salivary gland prior to and shortly after ^{131}I therapy
- Diligence in looking for signs and symptoms of sialoadenitis or xerostomia and
- Length of follow up

Reproduced with permission from Humana Press, Van Nostrand and Freitas (2006).

Table 2 Reported incidence of sialoadenitis after ^{131}I therapy

Alexander *et al* (1998)	33%	67/203
Allweiss *et al* (1984)	12%	10/87
Benua *et al* (1962)	2%	3/122
Edmonds and Smith (1986)	10%	26/258
Grewal *et al* (2009)	39%	102/262
Kahn (1994)	34%	17/50
Maier and Bihl (1987)	8%	3/37
Pan (2004)	5%	16/342
Silberstein (2008)	5%	3/60
Van Nostrand *et al* (1986)	67%	9/15

Reproduced with permission from Humana Press, Van Nostrand and Freitas (2006).

Albrecht and Creutzig, 1976; Allweiss *et al*, 1984; Edmonds and Smith, 1986; Van Nostrand *et al*, 1986; Maier and Bihl, 1987; Kahn *et al*, 1994; Alexander *et al*, 1998; Pan, 2004; Van Nostrand *et al*, 2006; Grewal *et al*, 2009). The signs and symptoms may range from severely swollen and painful salivary glands to asymptomatic sialoadenitis, that latter implicated by the subsequent manifestation of xerostomia many months later (Alexander *et al*, 1998). Swelling and pain may begin as early as several hours after treatment with ^{131}I or as long as several weeks later, and the duration may last hours to several days. Infrequently, these signs and symptoms may last several weeks and occasionally persist for a year. Fortunately, most signs and symptoms resolve spontaneously within hours to several days without any specific treatment. The signs and symptoms may be unilateral or bilateral but occur more frequently in the parotid glands than the submandibular and lingual glands. As noted above, the serous cells appear to have a greater ability to concentrate radioiodine than the mucous cells, and because the parotid glands are predominately serous cells, this may be one reason that the parotid glands appear to have a higher frequency of radiation-induced sialoadenitis than the submandibular and sublingual salivary glands (Honour *et al*, 1952). Alexander *et al* (1998) reported that 81% (54/67) of patients with sialoadenitis involved the parotid glands of which 14 were unilateral and 40 were bilateral. Signs and symptoms of sialoadenitis in the submandibular glands were seen in 46% (31/67) of patients with sialoadenitis, of which eight were unilateral and 23 were bilateral. Albrecht and Creutzig (1976) found 59% (30/51) of the patients had involvement of the parotid gland with 25 bilateral and 5 unilateral. Sixteen per cent (8/51) of the patients had involvement of the submandibular glands. Studies have suggested that the incidence and severity of sialoadenitis appears to correlate with the individual prescribed activity (Tollefsen *et al*, 1964; Tubiana *et al*, 1975), as well as the cumulative prescribed activity of ^{131}I (Albrecht and Creutzig, 1976). Grewal *et al* (2009) should a statistically significant dose response between administered radioactivity and salivary gland swelling but not xerostomia, altered taste or salivary gland pain.

Prevention

Prevention by reduction of radiation absorbed dose to the salivary is preferable to managing sialoadenitis, but many of the proposed approaches for achieving the reduction of radiation absorbed dose to the salivary glands are controversial. An overview is shown in Table 3.

Pre ^{131}I therapy

Assessment of salivary glands on pre-ablation or pre-treatment radioiodine whole body scans. Evaluation of radioiodine uptake in the salivary glands on pre-ablation whole body scans has been proposed as potentially useful in helping to predict a radiation-induced sialoadenitis (Kulkarni *et al*, 2004). Significant uptake may suggest a higher likelihood of sialoadenitis while little to no uptake may suggest a lower likelihood. Higher uptake may encourage more structured and diligent preventive care. However, this needs further evaluation, and even if this assessment is helpful, I believe that a structured and diligent preventive care for side effects is warranted in every patient unless that care is associated with its own untoward effects.

Patient education. Patient education is paramount. Not only is it important that the patient understand the potential side effects of ^{131}I in order to give informed

Table 3 Approaches to mitigate radiation sialoadenitis and its consequences

- Pre ^{131}I Therapy
  - Assessment of salivary glands on pre-ablation or pre-treatment radioiodine whole body scans
  - Patient education about prevention
  - Suspension of anticholinergic medications
- Post ^{131}I Therapy
  - Hydration
  - Frequent sialagogues (e.g. lemon candies, sugarless chewing gum, lemon juice) during the day and night
  - Massage of salivary glands
  - Use of one or more of the following:
    - Cholinergic agents
    - Prophylactic non-steroidal, anti-inflammatory agents
    - Prophylactic steroids
    - Amifostine
    - Reserpine

consent for the treatment, but it is also important for the patient to understand the seriousness of the potential side effects in order to comply with the physician's recommendations to help prevent and/or minimize radiation-induced sialoadenitis and it sequelae.

Hydration. To my knowledge, no significant data has been published that assesses the positive or negative effects of hydration on the radiation absorbed dose to the salivary glands. However, I would submit that hydration would be beneficial for two intuitive reasons. First, dehydration decreases salivation, which in turn may decrease ^{131}I clearance from the salivary glands and increase the radiation absorbed dose to the salivary glands. However, whether or not dehydration also reduces uptake of ^{131}I in the salivary glands has not been well studied. Second, dehydration decreases ^{131}I renal clearance, thereby resulting in higher blood levels of ^{131}I for a longer period of time. This may result – at least theoretically – in higher uptake of ^{131}I by the salivary glands. Until proven otherwise, I believe good hydration is appropriate and helpful.

Suspension of anticholinergic medications. Although anticholinergic drugs may in some patients reduce the early radioiodine uptake in the salivary glands based on salivary gland scintigraphy (personal observation), all anticholinergic drugs are typically discontinued. However, further evaluation is warranted.

Post ^{131}I therapy

Hydration. Good hydration is again typically recommended prior to and for several days after ^{131}I therapy, and this has been discussed above.

Sialagogues. The use of sialagogues is presently one of the most controversial areas regarding the reduction of the frequency and/or severity of ^{131}I radiation-induced sialoadenitis.

Prior to 2005, sialagogues during the early post-treatment period had been almost universally recommended (Van Nostrand *et al*, 2006). Sialagogues such as sour candies, lemon juice, lemon drops, sugarless chewing gum, or anything else that would cause the patient to salivate were initiated ~2–4 h after the administration of the ^{131}I therapy. Instructions typically included continuation of the sialagogues at least while the patient was awake, and sometimes the recommendation included continuation of the sialagogues for an additional one to several days.

Nakada *et al* (2005) published a report in which they evaluated one group of patients who were administered sialagogues every 2–3 h while awake for the first 24-h period after ^{131}I therapy and a second group of patients who received no sialagogues during the first 24-h period after ^{131}I therapy. They reported in several patients using Doppler flow assessment that salivation increased blood flow to the salivary glands and hypothesized that this increased flow increased delivery and uptake of ^{131}I to the salivary glands, resulting in increased radiation absorbed dose to the salivary glands. Van Nostrand *et al* (2009) have referred to this as a 'rebound effect'. Nakada *et al* observed that the second group who did not received any sialagogues for the first 24-h period had a lower incidence of sialoadenitis [38% (52/139)] than the group that received sialagogues [64% (74/116)]. Hypogeusia or taste loss also decreased from 39% to 25.4%, and dry mouth decreased from 23.8% to 11.1%. Irreversible xerostomia was reduced from 14.3% to 5.6%. Based on this data, Nakada *et al* recommended that sialogogues should not be administered during the first 24-h period after ^{131}I therapy. One letter to the editor, one case report, and two subsequent articles have challenged Nakada's report (Lam and van Isselt, 2005; Silberstein, 2008, Van Nostrand *et al*, 2009, 2010). Lam and van Isselt (2005) in a letter to the editor stated that (1) '… [some] patients [with higher salivary gland side effects] … tended to be treated more intensively…', (2) '… the reported incidence of salivary gland injury [varied] considerably depending on the diagnostic criteria', and (3) '… the author's concept of salivary gland function has not been studied physically'. In a study to evaluate the utility of pilocarpine, Silberstein (2008) administered continuous sialagogues while the patient was awake and intermittently during the night. In these patients he reported a frequency of sialoadenitis that was 5%, which was much lower than the frequency report by Nakada *et al* (i.e. 38–64%). However, in this study, Silberstein also administered dexamethasone to all his patients, and as a result one cannot differentiate how much of the lower incidence of ^{131}I induced sialoadenitis might have been due to the continuous administration of sialagogues or use of steroids. Van Nostrand *et al* (2009) demonstrated in a case report that re-accumulation of radioiodine in the salivary glands begins soon after the washout of ^{131}I from the salivary glands after administration of lemon juice. However, despite re-accumulation of the radioiodine in the salivary glands, the radioactivity did not exceed the level at the time of the administration of the sialagogue over 1 h of observation. In addition, the subsequent administration of sialagogues repeatedly every 20 min resulted in significantly decreased overall uptake of radioiodine in the salivary glands. Subsequently, Van Nostrand *et al* (2010) reported the use of sialagogues in 23 patients over two 1 h periods beginning 2 h after the administration of radioiodine. Based on this study, if sialagogues were to be given repeatedly at a time interval corresponding to when the radioiodine in the salivary glands would re-accumulate back to the level prior to the administration of the sialagogue, the average potential reduction in radiation absorbed dose was in the range of 40–50%. The average times for the radioiodine to re-accumulate back to the pre-lemon juice level of activity were 21 and 38 min for each phase, respectively. Thus, this study strongly suggested that the frequent administration of sialagogues can significantly reduce the radiation absorbed dose to the salivary gland relative to the administration of sialagogues every 2–3 h. This study also documented what we all know from our own personal experience that spontaneous salivation may occur in the absence of any sialagogues. Spontaneous salivation might be induced simply from the thought or

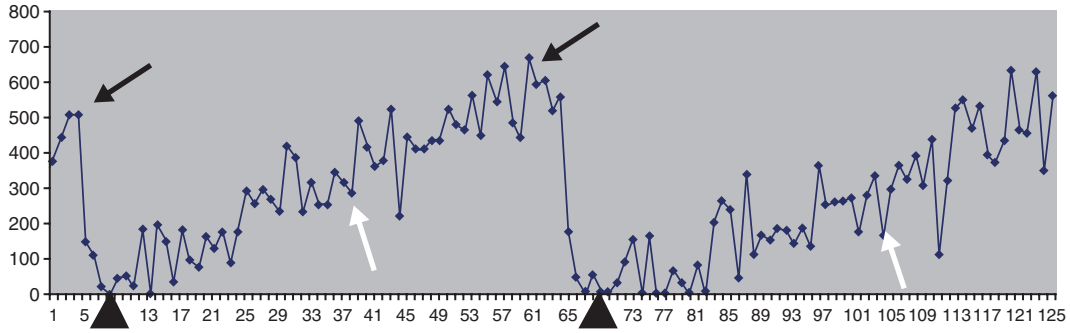

Figure 1 Starting 2 h after the administration of ^{123}I or ^{131}I orally, anterior images of the head and neck were obtained for two subsequent hours. Regions of interest were placed around each parotid gland, and the time activity curves (TACs) for each parotid gland were obtained. The above graph demonstrates a typical patient background-corrected TAC for one of the parotid glands. The black arrows denote the two time points at which a bolus of lemon juice was administered orally without moving the patient. The black arrow heads demonstrate the nadir of washout of the radioiodine from the parotid gland after the administration of the lemon juice. The white arrows point to the re-accumulation phase of the radioiodine back in to the parotid gland, which for this patient required approximately 60 min to return to baseline

smell of food or the sight of food such as on television. Thus, even though Nakada *et al* may not have administered sialagogues during the first 24-h period after ^{131}I therapy, those patients still most likely experienced spontaneous salivation and/or ate during that period.

So, should sialagogues be administered or withheld during the first 24-h period after the therapeutic administration of ^{131}I? The question remains and the controversy continues. However, based on my experience, sialagogues should continue to be administered routinely during the first 24-h period at a frequent interval such as every 20–40 min or even continuously as recommended by Silberstein (2008). Further, even if Nakada *et al*'s theory of a 'rebound effect' resulting in a subsequent greater increase in the ^{131}I concentration in the salivary glands after sialagogues is correct, Van Nostrand *et al*'s study presents strong evidence that if the sialagogues are given at a short enough time intervals, then a 'rebound effect' can be preempted (see Figure 1).

Anti-inflammatory medication

The prophylactic use of anti-inflammatory agents including non-steroidal and steroidal agents to prevent sialoadenitis of the salivary glands is also controversial with little data available. Silberstein (2008) has reported the routine use of steroids along with one the lowest reported incidences of signs and symptoms of sialoadenitis. However, as noted above, he also administered sialagogues continuously not only while the patient was awake but also intermittently after the patient had retired.

Massage of parotid glands

Massage of the parotid glands may also be of value, especially if there may be a partial flow obstruction (see Figure 2; Van Nostrand, 2006).

Administration of cholinergic medications

Cholinergic drugs such as pilocarpine, cevimeline HCl, anetholetrithione, and bromhexine have been used to stimulate salivation and hopefully increase the turn over

Figure 2 For antegrade massage, push with the fingers mildly on the parotid gland cephalad and then anteriorly. (Concept adopted from Mandel and Mandel, 2003). (Image reproduced with permission from Keystone Press from the book entitled 'Thyroid Cancer: A Guide for Patients.')

and/or throughput of ^{131}I in the salivary gland (Davies, 1997; Ericson and Lindberg, 1982; Nakada *et al*, 2004). However, Alexander *et al* (1998) and more recently Silberstein (2008) showed no benefit to the administration of cholinergic drugs.

Reserpine

Because the salivary glands are also innervated by the sympathetic system, anti-sympathomimetic agents have been investigated. In order to evaluate the potential role of reserpine as a protective agent by reducing the uptake of radioiodine in the salivary glands, Levy and Park

(1987) administered reserpine and measured a significant decrease in the ratio of radioiodine uptake in the parotid glands compared to a baseline value. However, in this report it is unclear whether the reduced salivary gland uptake was in response to the reserpine or secondary to a 'radiation stunning' from the 10 mCi (370 MBq) diagnostic prescribed activities of ^{131}I and/or partial treatment of the salivary gland from the prescribed activities of 100–150 mCi (3.7–5.55 GBq) ^{131}I administered for the therapy.

Amifostine

Amifostine (WR-2721, Ethyol) has been shown to protect the salivary gland from the damaging effects of ionizing radiation from external radiotherapy for head and neck tumors (Dorr and Holmes, 1999; Shaw *et al*, 1999; Werner-Wasik, 1999). Amifostine is an organic thiophosphate that is dephosphorylated into its active metabolite WR-1065. This metabolite is a scavenger of oxygen-free radicals, the latter being one of the major affects of radiation resulting in tissue damage, and this metabolite may have a greater effect in normal tissue than in tumor tissue for several reasons. First, amifostine can concentrate as much as 100 times more in normal tissue than tumor tissue (Hall *et al*, 1992), and second, the dephosphorylation of the amifostine to its active metabolite is more effective in the alkaline environment of normal tissue than in the more acidic environment in tumor tissue (Utley *et al*, 1976).

Because of the success of the use of amifostine in reducing sialoadenitis in patients undergoing external radiotherapy, amifostine was proposed for use in patients receiving ^{131}I therapy for WDTC. Subsequently, Ma *et al*. (2010) reviewed the literature regarding amifostine and its protective affect from ^{131}I, and out of 92 articles published on the subject, Ma *et al*. accepted only two randomized controlled clinical trials by Bohuslavizki *et al*. (1999) and Kim *et al*. (2008) for analysis. Based on these two studies, Ma *et al*. concluded that amifostine had no significant radioprotective effects on the salivary glands after ^{131}I therapy. Amifostine is also not without sides effects. Amifostine may significantly decrease the patient's blood pressure – albeit this is usually temporary requiring suspension of the infusion of the amifostine. Finally, it is important to be aware that the drug insert for amifostine states that amifostine should not be administered to '… patients in other settings where chemotherapy can produce a significant survival benefit or cure, or in patients receiving definite radiotherapy, except in the context of a clinical study'.

Management

If sialoadenitis does occur post therapy, it is reasonable to administer anti-inflammatory agents, although there is no definitive data to confirm that this reduces the signs, symptoms, severity, and/or duration of ^{131}I radiation-induced sialoadenitis. Likewise, neither is there any significant data regarding the reduction of the sequelae secondary to radiation-induced sialoadenitis. Nevertheless, if the signs and symptoms of sialoadenitis are severe or persist longer than a short period of time, the administration of anti-inflammatory agents would be reasonable. If the signs and symptoms are severe and/or persistent, then steroids and the referral of the patient to a dentist, oral surgeon, and/or otolaryngologist should be considered. Suggested guidelines for the use of non-steroidal and steroidal anti-inflammatory agents are noted in Table 4. However, there is no data to indicate that these guidelines are more effective than any other guidelines or even effective. If there is a suppurative sialoadenitis, antibiotics may be necessary. In three patients, Allweiss *et al*.

Table 4 Proposed guidelines for the management of sialoadenitis[a,b] based on the severity of the signs and symptoms

Category	*Description*	*Treatment*
Mild	▪ Mild Pain (NCI[c] Grade 1 = mild pain not interfering with function with a duration of < 1 h) ▪ No swelling▪ No tenderness to the touch	Non-steroidal, anti-inflammatory medication for 3 days
Moderate (One or more of the following)	▪ Moderate Pain (NCI Grade 2 = moderate pain or analgesics for pain interfering with function, but not interfering with activities of daily living of ≥ 1 h of duration) ▪ Any swelling ▪ Any tenderness to the touch	Anti-inflammatory medication for 7 days
Severe (One or more of the following)	▪ Severe Pain (NCI Grade 3 = pain or analgesics severely interfering with activities of daily living of any duration) ▪ Moderate to severe swelling (very subjective) ▪ Moderate to severe tenderness to the touch (very subjective)	▪ Anti-inflammatory medication for 7 days ▪ Methylprednisolone dose pack or equivalent, and ▪ Referral to dentist, oral surgeon, or otolaryngologist
Extreme	Suppurative sialoadenitis	▪ Emergency referral to otolaryngologist, oral surgeon, and/or dentist with special expertise in salivary gland management

[a]Hydration is not listed, because this should already be encouraged and continued.
[b]No data is available to suggest that these guidelines are any more or less effective than any other guidelines.
[c]National Cancer Institute.

(1984) reported a suppurative sialoadenitis that required antibiotics.

Sequelae

Xerostomia

One important sequelae of ^{131}I radiation-induced sialoadenitis is xerostomia, which may also be associated with burning oral discomfort, difficulty in eating dry foods, dysphagia, decreased taste sensitivity, and mucosal ulcerations. The reported frequency of xerostomia ranges from 2% to 43% (see Table 5; Benua *et al*, 1962; Albrecht and Creutzig, 1976; Leeper, 1982; Allweiss *et al*, 1984; Edmonds and Smith, 1986; Maier and Bihl, 1987; Kahn *et al*, 1994; Lin *et al*, 1996; Solans *et al*, 2001; Pan, 2004; Van Nostrand *et al*, 2006), and the frequency and severity is again multi-factorial. Xerostomia may begin several weeks or months after ^{131}I therapy but usually resolves within several months (Brown *et al*, 1984; Alexander *et al*, 1998; Van Nostrand *et al*, 2006). However, xerostomia may last greater than one year in 4.4–7% of patients (Tollefsen *et al*, 1964; Allweiss *et al*, 1984; Lin *et al*, 1996; Van Nostrand *et al*, 2006) and not infrequently it may be permanent (Mandel and Mandel, 1999; Schneyer and Tanchester, 1954). The presence of initial symptoms of sialoadenitis (e.g. pain and/or swelling) is not predictive of subsequent xerostomia. In 63 of 96 patients (66%), Alexander *et al*. (1998) diagnosed xerostomia in patients who had no clinical evidence of sialoadenitis initially. Malpani *et al*. (1996) also was unable to demonstrate any relationship of significant reduction in function of the salivary glands to symptoms of sialoadenitis, whereas, Spiegel *et al*. (1985) reported a dose-dependent decrease in salivary gland function. The same group specifically reported reduction of parotid gland function by 40% after prescribed activities of 270 mCi (9.99 GBq), while Solans *et al*. (2001) demonstrated no relationship of xerostomia to cumulative prescribed activity.

Xerostomia may also result in additional sequelae including dental caries and candidiasis. Walter *et al*. (2007) followed 176 patients and reported a 99% increased risk of xerostomia ($P = 0.003$) with an 8% increased risk of tooth extraction per gigabecquerel administered ($P = 0.02$). Candidiasis is a rare side effect of xerostomia, which may be severe enough to require treatment such as with nystatin and clotrimazole (Busnell *et al*, 1992). Several recommendations for the management of xerostomia and preventive care to minimize dental caries are noted in Table 6.

Table 5 Frequency of Xerostomia

Albrecht and Creutzig (1976)	22%	(11/51)
Alexander *et al* (1998)	43%	(87/203)
Allweiss *et al* (1984)	30%	(3/10)
Benua *et al* (1962)	2%	(3/122)
Edmonds and Smith (1986)	10%	(26*/258) (*calculated)
Kahn *et al* (1994)	18%	(10/55)
Leeper (1982)	*Common	
Lin *et al* (1996)	5.4%	(3/56)
Silberstein (2008)	5%	(3/60)
Solans *et al* (1986)	33%	(26/79)
Van Nostrand *et al*, 2006	13%	(2/15)

*No frequency reported; simply stated by the Author as 'common'. Reproduced with permission from Humana, Van Nostrand and Freitas (2006).

Stomatitis

Stomatitis is rare and may be very painful, which if severe may require treatment with dexamethasone elixir mouthwash and/or mouthwash containing viscous lidocaine, diphenhyrdramine and aluminum, and magnesium hydroxides (Mandel and Mandel, 1999). Referral to a dentist, oral surgeon, or otolaryngologist is recommended.

Salivary duct obstruction

The frequency of salivary duct obstruction is not well documented, and I believe that with more careful histories, future studies will demonstrate that this is more common than originally suspected. Salivary duct obstruction may first present 1 month to 1 year after ^{131}I therapy with the sudden onset of swelling and pain in

Table 6 Options for the management of xerostomia and dental caries

- Maintain good hydration
- Refer patient to a dentist, oral surgeon, or otolaryngologist
- Treat causes other than radiation-induced xerostomia such as changing a drug or the dose of a drug that is causing xerostomia
- Take frequent sips of sugar free water or drinks
- Drink frequently while eating
- Keep a glass of water by one's bedside for dryness during the night or on awakening
- Pause often while speaking to sip some liquids
- Avoid coffee, tea and soft drinks
- Chew sugarless gum
- Suck sugarless mints or hard sugarless candy allowing them to dissolve in your mouth (Cinnamon and mint are often more effective)
- Avoid tobacco and alcohol
- Avoid spicy, salty and highly acidic foods that may irritate the mouth
- Use a humidifier, particularly at night
- Maintain impeccable dental hygiene with regular checkups (3–6 months)
- Use fluoride toothpaste routinely
- Use non-alcoholic mouth washout such as a non-alcoholic mouthwash mixed with hydrogen peroxide
- Consider fluoride therapy in the form of topical fluoride applications, fluoride mouthwashes, and fluoride toothpastes
- Artificial saliva swirled in the mouth and swallowed every 3–4 h
- Avoidance of anticholinergic medications
- Administration of sialagogues (Davies, 1997)
  - Pilocarpine, (Salagen®), 5–10 mg p.o. t.i.d. Oral tablet may need to be taken for 6–12 weeks before full benefit realized
  - Cevimeline (Nakada *et al*, 2004) (Evoxac®), cholinesterase inhibitor, 30 mg p.o. t.i.d.
  - Anethole Trithione (Hepasulfol®, Mucinol®, Sialor®, Sonicur®, Sufralem®). The standard dose is 37.5–75 mg typically in divided doses before meals. Doses of up to 150 mg daily have been used
  - Trial of saliva stimulating tablets (SST) (Ericson and Lindberg, 1982) including potential agents as disaccharides and low-dose interferon-alfa lozenges
- Acupuncture (Blom and Lunderberg, 2000), and
- Antibiotics for suppurative sialoadenitis

one or more salivary glands when the patient eats or spontaneous salivations such as when seeing or thinking of food. These signs and symptoms may resolve within minutes but typically last longer and as long as several hours. Unlike sialoadenitis, which is the acute effects of radiation from the ^{131}I, the mechanism proposed is a combination of stricture of the salivary ducts secondary to scarring from the previous radiation and reduced volume of saliva secondary to the previous radiation-induced sialoadenitis (i.e. xerostomia), dehydration, and/or xerostomia secondary to other medications. With reduced flow and thickened saliva, there may be mucus precipitation resulting in a mucous plug causing an obstruction. Although the natural history of this side effect has not been well described, in my experience these symptoms frequently and slowly resolve over several months. In the short term, increased retrograde or antegrade pressure with massage may resolve the symptoms by helping the normal or thickened saliva to pass by the ductal narrowing or to help spontaneously extrude a plug (see Figure 2). However, persistent signs and symptoms may require intervention which might include ductal dilation of Stensen's or Wharton's duct. In 12 patients, Bomeli *et al*. (2009) used sialoendoscopy for the treatment of recalcitrant pain/swelling after ^{131}I therapy, and symptoms were improved in 75% of the patients with no serious complications. Xu *et al*. (2010) evaluated ^{99m}Tc pertechnetate scintigraphy to determine which patients should have sialoendoscopy to relieve obstruction of the submandibular gland. Based on eleven patients, they successfully predicted whether or not the sialendoscopy would significantly relieve the patients' signs and symptoms in all eleven patients. In rare cases, tympanic neurectomy may be considered. Although excision of the gland should be avoided, Allweiss *et al*. (1984) reported one patient who required a parotidectomy because of intractable salivary gland pain and discomfort.

Summary

Radiation-induced sialoadenitis is an important untoward effect secondary to ^{131}I therapy for WDTC. With (1) a better understanding of the mechanism of ^{131}I accumulation within the salivary glands, (2) a heightened awareness of the incidence, clinical presentation, and sequelae of sialoadenitis including xerostomia, stomatitis, and duct obstruction, and (3) an assiduous preventive care program prior to and immediately after ^{131}I therapy, the incidence and severity of ^{131}I radiation-induced sialoadenitis can be hopefully reduced. However, if sialoadenitis and/or its sequelae occur, appropriate management can reduce the effects such as xerostomia and ductal obstruction.

References

Albrecht HH, Creutzig H (1976). Salivary gland scintigraphy after radioiodine therapy. Functional scintigraphy of the salivary gland after high dose radioiodine therapy. *Fortschr Rontgenstr* **125:** 546–551.

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.

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.

Benua RS, Cicale NR, Sonenberg M, Rawson RW (1962). The relation of radioiodine dosimetry to results and complications in the treatment of metastatic thyroid cancer. *AJR* **87:** 171–182.

Blom M, Lunderberg T (2000). Long term follow up of patients treated with acupuncture for xerostomia and the influence of additional treatment. *Oral Dis* **6:** 15–24.

Bohuslavizki KH, Klutmann S, Jenicke L, *et al*. (1999). Salivary gland protection by S-2-(3-amiopropylamino)-ethylphosphorothioic acid (amifostine) in high-dose radioiodine treatment: results obtained in a rabbit animal model and in a double blind multi-arm trial. *Cancer Biother Radiopharm* **13:** 337–347.

Bomeli SR, Schaitkin B, Carrau RL, Walvekar RR (2009). Interventional sialendoscopy for treating of radioiodine-induced sialadenitis. *Laryngoscope* **119:** 864–867.

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.

Busnell 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.

Davies AN (1997). The management of xerostomia: a review. *Eur J Cancer Care* **6:** 209–214.

Donachi I (1978). Biologic effects of radiation on the thyroid. In: Werner SC, Ingbar SH, eds *The thyroid*. Harper & Row: New York, pp. 274–283.

Dorr RT, Holmes BC (1999). Dosing considerations with amifostine: a review of the literature and clinical experience. *Semin Oncol* **26:** 108–119.

Edmonds CJ, Smith T (1986). The long-term hazards of the treatment of thyroid cancer with radioiodine. *Br J Radiol* **59:** 45–51.

Ericson T, Lindberg A (1982). Clinical trial of a saliva stimulating tablet SST. *Tandjakartidningen* **74:** 713–716.

Freinkel N, Ingbar SH (1953). Concentration gradients for inorganic I-131 and chloride in mixed human saliva. *J Clin Invest* **32:** 1077–1084.

Goolden AWG, Mallard JR, Farran HEA (1957). Radiation sialitis following radioiodine therapy. *Br J Radiol* **30:** 210–212.

Grewal RK, Larson SM, Pentlow CE, *et al*. (2009). Salivary gland side effects commonly develop several weeks after initial radioactive iodine ablation. *J Nucl Med* **50:** 1605–1610.

Hall P, Holm L-E, Lundell G, Ruden BI (1992). Tumors after radiotherapy for thyroid cancer. *Acta Oncol* **31:** 403–407.

Hertz S, Roberts A (1942). Application of radioactive iodine in therapy of Graves' disease. *J Clin Invest* **1:** 624.

Honour AJ, Myant NB, Rowland EN. (1952). Secretion of radioiodine in digestive juices and milk in man. *Clin Sci* **11:** 447–462.

Jhiang SM, Cho JY, Ryu KY, *et al*. (1998). An immunohistochemical study of Na+/I-symporter in human thyroid tissues and salivary gland tissues. *Endocrinology* **139:** 4416–4419.

Kahn S, Waxman A, Ramanna L, Ashok G, Nagaraq N, Braunstein G (1994). Transient radiation effects following high dose I-131 therapy for differentiated thyroid cancer (DTC). *J Nucl Med* **35:** 15P.

Kim SJ, Choi HY, Kim IJ, *et al*. (2008). Limited cytoprotective effects of amifostine in high-dose radioactive iodine 131-treated well-differentiated thyroid cancer patients: analysis of quantitative salivary scan. *Thyroid* **18:** 325–331.

Kulkarni K, Kim SM, Intenzo C (2004). Can salivary gland uptakes on a diagnostic I-131 scan predict acute salivary gland dysfunction in patients receiving radioiodine therapy for thyroid cancer? *J Nucl Med* **5S:** 291P.

Lam MGEH, van Isselt JW (2005). Does lemon candy decreased salivary gland damage after radioiodine therapy for thyroid cancer? *Letter to the editor*. *J Nucl Med* **46:** 2118–2119.

Leeper R (1982). Controversies in the treatment of thyroid carcinoma: The New York Memorial Hospital approach. *Thyroid Today* **4:** 1–6.

Levy HA, Park CH (1987). Effect of reserpine on salivary gland radioiodine uptake in thyroid cancer. *Clin Nucl Med* **12:** 303–307.

Lin WY, Shen YY, Wang SJ (1996). Short-term hazards of low-dose radioiodine ablation therapy in postsurgical thyroid cancer patients. *Clin Nucl Med* **21:** 780–782.

Ma C, Xie J, Jiang X, Wang G, Zuo S (2010). Does amifostine have radioprotective effects on salivary glands in high-dose radioactive iodine-treated differentiated thyroid cancer. *Eur J Nucl Med Mol Imaging* February 4, e-pub ahead of print.

Maier H, Bihl H (1987). Effect of radioactive iodine therapy on parotid gland function. *Otolaryngology* **103:** 318–324.

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.

Mandel S, Mandel L (1999). Persistent Sialadenitis after radioactive iodine therapy: report of two cases. *J Oral Maxillofac Surg* **57:** 738–741.

Mandel S, Mandel L (2003). Radioactive iodine and the salivary glands. *Thyroid* **13:** 265–271.

Myant NB (1960). Iodine metabolism of salivary glands. *Ann NY Acad Sci* **85:** 208.

Nakada K, Hirata K, Ishibashi T, *et al*. (2004). Cevimeline hydrochloride hydate in treating salivary gland dysfunction following radioiodine therapy for thyroid cancer. *J Nucl Med* **45S:** 17P.

Nakada K, Ishibashi T, Takei T, *et al*. (2005). Dose lemon candy decrease salivary gland damage after radioiodine therapy for thyroid cancer? *J Nucl Med* **46:** 261–266.

Pan MS (2004). Follow-up study of side effects for iodine-131 treatment in patients with differentiated thyroid cancer. *J Nucl Med* **5S:** 386P.

Rice DH (1984). Advances in diagnosis and management of salivary gland diseases. [Medical Progress]. *West J Med* **140:** 238–249.

Schiff L, Stevens CD, Molle WE, Steinberg H, Kumpe CW, Stewart P (1947). Gastric (and salivary) excretion of radioiodine in man (preliminary report). *J Nat Cancer Inst* **7:** 349–354.

Schneyer LH, Tanchester D (1954). Some oral aspects of radioactive iodine therapy for thyroid disease. *NYJ Dent* **24:** 308–309.

Seidlin SM, Marinelli LD, Oshry E (1946). Radioactive iodine therapy: effect on functioning metastases of adenocarcinoma of the thyroid. *JAMA* **132:** 838–847.

Shaw LM, Bonner HS, Schuchter L, Schiller J, Lierberman R (1999). Pharmacokinetics of amifostine: effects of dose and method of administration. *Semin Oncol* **26:** 34–36.

Silberstein EB (2008). Reducing the incidence of 131-I-induced sialadenitis: The role of pilocarpine. *J Nucl Med* **49:** 546–549.

Solans R, Bosch JA, Galofre P, *et al*. (2001). Salivary and lacrimal gland dysfunction (sicca syndrome) after radioiodine therapy. *J Nucl Med* **42:** 738–743.

Spiegel W, Reiners Chr, Borner W (1985). Sialadenitis following iodine-131 therapy for thyroid carcinoma. *J Nucl Med* **26:** 816.

Tollefsen HR, DeCosse JJ, Hutter RVP (1964). Papillary carcinoma of the thyroid. A clinical and pathological study of 70 fatal cases. *Cancer* **17:** 1035–1043.

Tubiana M, Lacour J, Monnier JP, *et al*. (1975). External radiotherapy and radioiodine in the treatment of 359 thyroid cancers. *Br J Radiol* **48:** 894–907.

Utley JF, Phillips TL, Kane LJ (1976). Protection of normal tissues by WR-2721 during fractionated irradiation. *AACN Clin Issues* **1:** 699–703.

Van Nostrand D, Atkins F, Bandaru VV, *et al*. (2009). Salivary gland protection with sialagogues. *A Case Report*. *Thyroid* **19:** 1005–1008.

Van Nostrand D, Bandaru V, Chennupati V, *et al*. (2010). Reduction of radiation absorbed dose to the parotid glands after the administration of lemon juice. In press

Van Nostrand D, Freitas J (2006). Side effects of I-131 for ablation and treatment of well-differentiated thyroid carcinoma. In: Wartofsky L, Van Nostrand D, eds *Thyroid Cancer: A Comprehensive Guide to Clinical Management*. Humana Press: Totowa, New Jersey, pp. 459–484.

Van Nostrand DV, Neutze J, Atkins F (1986). Side effects of ''rational dose'' iodine-131 therapy for metastatic well differentiated thyroid carcinoma. *J Nucl Med* **27:** 1519–1527.

Walter MA, Turtschi CP, Schinderl C, Mining P, Müller-Brand J., Müller B (2007). The dental safety profile of high-dose radioiodine therapy for thyroid cancer: long-term results of a longitudinal cohort study. *J Nucl Med* **48:** 1620–1625.

Werner-Wasik M (1999). Future development of amifostine as a radioprotectant. *Semin Oncol* **26:** 129–1234.

Xu JH, Su YX, Cheng MH, *et al*. (2010). Using Tc-99m pertechnetate scintigraphy to predict the outcome of sialendoscopy in obstructive submaxillaritis. *Clin Nucl Med* **35:** 77–79.