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PRACTICE GUIDELINES

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Salivary and lacrimal dysfunction after radioactive iodine for differentiated thyroid cancer: American Head and Neck Society Endocrine Surgery Section and Salivary Gland Section joint multidisciplinary clinical consensus statement of otolaryngology, ophthalmology, nuclear medicine and endocrinology

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Abstract

Background: Postoperative radioactive iodine (RAI) administration is widely utilized in patients with differentiated thyroid cancer. While beneficial in select patients, it is critical to recognize the potential negative sequelae of this treatment. The prevention, diagnosis, and management of the salivary and lacrimal complications of RAI exposure are addressed in this consensus statement.

Methods: A multidisciplinary panel of experts was convened under the auspices of the American Head and Neck Society Endocrine Surgery and Salivary Gland Sections. Following a comprehensive literature review to assess the current best evidence, this group developed six relevant consensus recommendations.

Results: Consensus recommendations on RAI were made in the areas of patient assessment, optimal utilization, complication prevention, and complication management.

Conclusion: Salivary and lacrimal complications secondary to RAI exposure are common and need to be weighed when considering its use. The recommendations included in this statement provide direction for approaches to minimize and manage these complications.

KEYWORDS

lacrimal, radioactive iodine, recommendations, salivary, thyroid cancer

1 | INTRODUCTION

The incidence of thyroid cancer has steadily increased over the last four decades. This has occurred without a similar corresponding rise in mortality rates.[1] Radioactive iodine (RAI) treatment has been employed for patients with thyroid cancer since the 1940s. In the United States, the proportion of patients with differentiated thyroid cancer who received RAI treatment rose from 40% in 1990 to 56% in 2008.[2] Since then, however, in at least some regions, this trend has started to reverse.[3] Based upon recent research, the 2015 edition of the American Thyroid Association guidelines on thyroid nodules and cancer recommend remnant ablation with RAI in fewer circumstances and, when utilized, at lower administered activities.[4] Currently, postoperative RAI administration is recommended for all patients with high-risk differentiated thyroid cancer for whom it may improve survival, and for a subset of patients with intermediate-risk thyroid cancer who may be at higher risk of recurrence. Despite the availability of these evidence-based recommendations on the optimal utilization of RAI, wide variability exists in its usage.[2]

From an oncologic perspective, select patients with thyroid cancer benefit from RAI therapy. However, it is critical to acknowledge the potential negative sequelae of this

treatment. While it is widely recognized that RAI can have an adverse impact on the salivary glands, the precise incidence and presentation of salivary gland dysfunction is less clearly understood. Furthermore, while less common, the lacrimal glands and nasolacrimal system can also be impacted leading to a range of ocular complaints.

2 | METHODS

In this clinical consensus statement, we review the potential sequelae of RAI on the salivary and lacrimal glands and lacrimal outflow system. The current state of knowledge regarding the incidence and presentation of RAI-induced salivary gland disease and lacrimal dysfunction as well as risk factors for disease development are discussed. This statement also provides direction regarding how best to mitigate those risks, as well as state-of-the-art recommendations for the optimal management of patients with xerostomia, sialadenitis, or epiphora. We also introduce new innovations in salivary gland management including the emerging field of sialendoscopy.

Reflecting the range of physicians involved in the care of patients undergoing RAI treatment, this consensus statement was purposely developed by convening a multidisciplinary group of authors. Experts from the Endocrine Surgery Section and Salivary Gland Section of the American Head and Neck Society (AHNS) were joined by leading physicians invited from ophthalmology, endocrinology, nuclear medicine and general surgery. Additionally, several of the world's authorities on salivary gland diseases and their management (including sialendoscopy) were included in the author panel.

Evidence-based support for the recommendations was drawn from the literature and the authors' expert opinions. Reviews of the literature, performed to provide critical reference material for the author panel, were conducted in August 2018. Computerized and manual searches were performed to identify relevant publications. Computerized searches for studies published between January 1966 and August 2018 were performed using PubMed, Cochrane Library, Cochrane Central Register of Controlled Trials, and Medline. First, a search using the terms radioiodine, RAI, ^{131}I, and thyroid cancer was conducted. These articles were then cross-referenced with those found with the search terms: salivary gland, sialadenitis, salivary gland dysfunction, sialendoscopy, xerostomia, lacrimal gland, lacrimal outflow, and nasolacrimal duct. These studies were limited to those published in English examining humans. Members of the expert panel were also asked to supplement this search by submission of additional references they thought were most relevant and of high quality.

The specific goals of the clinical consensus statement were reviewed with the entire group. Draft statements and relevant text were circulated among these members for commentary. These comments were then were incorporated by the lead author (M.S.) and a final draft of the manuscript and recommendations was distributed to all authors for review. Recommendations were categorized according to the American College of Physicians grading system for evidence-based guidelines.[5] After the author panel provided its approval, it received final approval from the AHNS Education Service and thus has full AHNS organizational support as a statement of the AHNS.

3 | NORMAL SALIVARY GLANDS: ANATOMY AND PHYSIOLOGY

The primary salivary glands in humans are the paired parotid, submandibular, and sublingual glands.[6] In addition, distributed throughout the oral cavity and pharynx are numerous minor salivary glands. The parotid glands produce saliva, representing approximately 30% of total daily production, primarily during meals. The submandibular (60%), sublingual (5%) and minor salivary (5%) glands are responsible for the basal production of saliva necessary for continuous upper aerodigestive tract hydration and lubrication.

The fundamental unit for all salivary tissue consists of acini producing saliva that then drains into a progressively widening ductal system. Acinar cells have specialized functions and are classified according to the quality of the saliva that they produce: serous, mucinous, or mixed. These cells are present in the major salivary glands in different distributions: the parotid glands are predominately composed of serous acini, the sublingual glands primarily mucinous acini, and the submandibular glands contain an equal mix mucinous and serous acini.

The 1-2 L of saliva produced daily is made up of approximately 99% water. Saliva also contains a complex blend of organic substances (including proteins, enzymes, mucin, and immunoglobulins) and inorganic molecules such as iodine, sodium, potassium, and calcium. The saliva can contain iodide levels that are 7-700 times plasma iodide levels.[7,8]

Saliva has a multitude of functions, including lubrication of food and oral cavity structures (critical for dental health), facilitation of chewing, tasting, and swallowing, initiating digestion, assisting in antimicrobial efforts, and optimizing taste receptor function. The precise role of iodine in these tasks remains unclear, although antioxidant functions have been postulated to play an important role in oral immune defense.[9] When salivary production

is impaired all of these functions can be compromised, resulting in xerostomia, decreased taste, impaired swallowing and digestion, and increased susceptibility to dental and periodontal disease.

4 | PATHOPHYSIOLOGY

RAI-associated parotitis was first reported by Rigler and Scanlon.[10] Despite this long known association, no precise understanding of the exact pathophysiology of RAI-induced salivary gland dysfunction has been elucidated.

The sodium/iodide symporter, which is highly expressed along the basolateral membrane of epithelial cells of the striated salivary ducts (as opposed to the acini), allow concentration of iodine in the saliva.[11,12] After uptake and concentration within the cytoplasm of these ductal cells, iodide is later secreted by the intralobular ductal epithelium into the salivary gland ducts. When RAI is administered and concentrated into salivary gland cells, damage to the ductal epithelium and surrounding tissue (including adjacent vascular endothelial damage) may occur immediately or in a delayed fashion. Ultimately, histologic changes associated with RAI exposure include periacinoductal inflammation and fibrosis.[13,14]

In the immediate phase, an increase in capillary permeability results in the leakage of plasma proteins and electrolytes into the surrounding interstitial tissues.[7] The intralobular ducts lose their ability to filter and prevent plasma proteins from entering the saliva. This results in elevated protein and sodium chloride levels along with decreased phosphate and prostaglandin levels in the saliva.[7,8,13]

Serous salivary cells concentrate iodide to a greater extent than mucinous acini, and as noted, the parotid glands have the highest concentration of serous cells.[15] Consequently, although all salivary glands are involved in RAI transport into the saliva, the parotid glands are most adversely affected by RAI.[16] Additionally, the sodium iodide symporters located in submandibular glands continuously transport RAI out of the parenchymal cells and into the ducts. This contrasts with the parotid glands in which symporter function is less continuous. Thus, transit time in the parotid glands is longer, leading to greater exposure of the parotid parenchyma to RAI.[17,18] As a result, these glands are most susceptible to the adverse effects of RAI.

An early response to irradiation can result in decreased salivary flow rates within the first week following RAI treatment.[11,19] Narrowing of the duct lumen from inflammation results in the formation of a jelly-like plug consisting of radiation induced inflammatory cells and mucus. If acute sialadenitis results from this obstruction, swelling and pain are most marked during eating and periods of increased salivary production.[7,20,21] Within a few days, resolution of this acute inflammatory phase occurs and initial symptoms subside. The sensation of oral dryness can occur when a person's normal, unstimulated flow rate is reduced by ~45%-50% and is dependent on the extent of parenchymal RAI damage.[17] The exact etiology for some of the other frequently seen sequelae of RAI, such as distortion or loss of taste, remains unclear.

The lacrimal glands are embryologically related to the major salivary glands and also contain the sodium/iodide symporter. There is a small body of literature evaluating the effect of RAI treatment on lacrimal gland function, manifesting typically as eye dryness, pruritus and other secondary ocular surface abnormalities. Often patients with ocular symptoms demonstrate minimal or no objective findings that correlate with their disease.[22-25] Fortunately, in most patients, these ophthalmic symptoms tend to decrease over the first 3 years after treatment.[25]

Epiphora can also occur after RAI treatment through several mechanisms. In patients with dry eyes, there is a reflexive increase in tear production without an accompanying increase in ocular surface mucous and oil, resulting in tear overflow. In addition, frank lacrimal outflow obstruction may also occur in patients receiving high activity RAI. Both mechanisms are responsible for RAI-associated epiphora.[26]

Nasal symptoms, including dryness, pain, and epistaxis, can also occur after treatment with RAI. Three months after RAI treatment, approximately 10% of patients complain of nasal symptoms.[27] While cells within the nasolacrimal ducts express the sodium iodine symporter, nasal tissues do not.[24,28-30] Thus, the mechanism of nasal-induced RAI symptoms is still not entirely understood.

The risk of developing a secondary primary malignancy associated with treatment with RAI is one of the primary concerns of physicians and patients.[31-37] Several cancer database epidemiological investigations have analyzed the risk of secondary primary malignancy development. The findings of these studies are divergent. While some have shown no significant increased risks with RAI exposure,[32,38,39] numerous others have demonstrated a significantly elevated risk, at least of salivary gland malignancies, in selected cohorts.[31,33-36,40-42]

Given the concentration of RAI in salivary gland tissue, these glands are potentially particularly at risk of developing a secondary primary malignancy. RAI can theoretically induce genetic alterations in salivary gland cells, resulting in tumor development. There have been at least six reported cases of mucoepidermoid carcinoma of the salivary glands following RAI exposure.[43-46] However, more generally, the risk of salivary gland malignancy appears to be increased.[40-42] Two studies have reported that when compared to similar patients not

treated with RAI, those with exposure had an increased standardized incidence ratio of 11.13:34.1.[40,41]

It does appear that there is a correlation between RAI dosing and risk of secondary primary malignancy.[31,35-37,47,48] Additionally, patients treated with RAI at younger ages have been shown to be those most at risk of development of secondary primary malignancy.[33,48,49] A number of studies have shown that patients exposed to RAI are at increased risk of leukemia, with reported standardized incidence ratios of between 2.74 and 5.68.[33,35,41] The risk of hematologic malignancies specifically appears to increase with age, smoking, and radiation exposure.[41,49] There is retrospective evidence that suggests that increasing activity of RAI may be associated with clonal hematopoiesis, a precursor clonal state that may eventually lead to the development of myeloid malignancies.[50] These findings must be viewed in the context of other studies that have demonstrated that patients with thyroid cancer are at greater risk of developing a secondary primary malignancy irrespective of treatment received.[51,52] Clearly further research is needed to more comprehensively understand the risks of RAI as it relates to secondary primary malignancy.

Recommendation #1

Given the potential for salivary and lacrimal side effects as well as secondary primary malignancy, patients in whom RAI therapy is being considered should receive pretreatment education regarding the prevalence and nature of these complications. Xerostomia, sialadenitis, dry eyes, epiphora, nasal symptoms and, in rare instances, secondary primary malignancy should be discussed. [Strong recommendation, moderate-quality evidence]

Recommendation #2

Physicians should be aware that secondary primary malignancies can be associated, rarely, with the use of RAI and relates to RAI activity and patient age. Given this small but possible risk of a secondary malignancy, including of the salivary glands, kidneys and bone marrow, judicious, evidence-based use of RAI is warranted. In addition, these risks should be considered when determining optimal follow-up. [Weak recommendation, low-quality evidence]

5 | INCIDENCE/RISK

The reported incidence of salivary gland dysfunction after treatment with RAI appears quite common but varies significantly between studies because of heterogeneous patient cohorts, variability in administered activity and number of treatments, timing of salivary gland assessment, definition of salivary gland dysfunction, and method of determining dysfunction.

In the immediate post-treatment phase, the incidence of acute sialadenitis ranges from 10% to 41%.[53-56] One year after RAI exposure sialadenitis is reported in 5%-43% of patients.[57,58] Sialadenitis affects the parotid glands in 59%-81% of cases and when involved both parotid glands are typically affected. The submandibular glands are affected in 16%-46% of cases.[59]

Xerostomia symptoms appear between 3 months and 1 year after RAI treatment. The reported incidence varies between 15% and 54%.[12,60] Studies show an apparent diminution of prevalence with time: 17%-33% at 1 year, 15% at 3 years, and 13% at 7 years.[25,57] Importantly, in the general population, xerostomia has an overall prevalence ranging from 8% to 13%.[61,62]

Taste alterations also appear to be common following RAI therapy. The prevalence of dysgeusia ranges from 13% to 27%.[7,57] This typically occurs soon after treatment. While in most patients, this issue resolves, in some patients, the taste change is permanent.

Ocular symptoms appear between 2 months and 1 year after RAI treatment and their prevalence ranges from 8% to 25.3%[23,25] for dryness and between 2.5% and 11%[23,63] for epiphora. Over time, the incidence of both of these symptoms appears to decrease.[25,64]

A number of risk factors for the development of salivary dysfunction after RAI have been identified (Table 1). The risk of experiencing symptoms of sialadenitis and xerostomia appears to be activity-dependent and cumulative with multiple RAI exposures.[15,17] Two studies suggest that the inflection point for a marked increase in risk occurs at approximately 100 mCi for xerostomia[20] and 150 mCi for sialadenitis.[56] Importantly, the risk of developing salivary gland related complications is significantly less with administration of a single activity of 30 mCi.[58,65]

Age and gender have also been reported to impact salivary gland function, with women and those over age

TABLE 1 Risk factors that have been associated with salivary gland dysfunction following RAI exposure

Risk factors for salivary gland dysfunction
RAI dosage >100 mCi for xerostomia
RAI dosage >150 mCi for sialadenitis
Use of thyroid hormone withdrawal rather than recombinant TSH for preparation for RAI treatment
Age > 45 years
Shorter intervals between exposures
Medications that induce xerostomia
Comorbid diseases: Sjögren's syndrome, IgG4-related disease, and so on

Abbreviations: Ig, immunoglobulin; RAI, radioactive iodine; TSH, thyroid stimulating hormone.

45 years old at increased risk of salivary gland dysfunction after RAI exposure.[15] Van Nostrand suggested that the variability of sialadenitis is due to numerous factors, including dosage, intervals between treatments, factors affecting gland uptake, comorbid disease, xerostomic medications, and preventive measures.[59]

Several studies have concluded that the use of recombinant thyroid stimulating hormone (TSH) to facilitate RAI treatment seems to reduce the risk of developing salivary gland dysfunction. Utilization of recombinant TSH for preparation of RAI ablation as compared to thyroid hormone withdrawal is associated with a lower incidence of salivary gland dysfunction.[65-67]

Risk factors for nasolacrimal side effects also include higher activity of RAI.[28] A single study found an inverse relationship between body mass index and risk of nasolacrimal symptoms.[28] Interestingly, in contrast to other symptoms, studies of dry eyes have shown no correlation between complaints and administered activity of RAI.

Recommendation #3a

Given the association between administered activity of RAI, particularly greater than 100 mCi, and the frequency and severity of side effects, the minimum effective, individualized RAI activity should be utilized. Thyroid remnant ablation with 30 mCi of RAI has significantly less risk of inducing complications. Additionally, in patients with thyroid cancer, whose tumors are considered iodine-refractory, unless efforts at redifferentiation are attempted, RAI use should be avoided. [Strong recommendation, moderate-quality evidence]

Recommendation #3b

The use of recombinant TSH rather than thyroid hormone withdrawal to prepare for RAI therapy appears to reduce both the risk of salivary and lacrimal gland complications. This should be considered when determining the optimal protocol for patient RAI preparation. [Weak recommendation, low-quality evidence]

Recommendation #3c

Other factors such as age, interval between RAI treatments, factors relating to salivary gland uptake, preexisting salivary gland disease, and xerostomic medication impact the risk of RAI related complications. These should be considered when determining the risk-benefit calculation of RAI treatment for individual patients. [Strong recommendation, low-quality evidence]

6 | PREVENTION

Given the frequency of symptomatic sequelae of treatment with RAI, a range of approaches has been utilized by clinicians in an attempt to reduce their incidence and severity. In addition to aggressive hydration, interventions that are often recommended include the use of medications, supplements, sialagogues, and massage.

6.1 | Amifostine

Amifostine has been used as a radioprotectant for patient with head and neck cancer receiving external beam radiation and has been touted as a promising preventive therapy for sialadenitis in patients receiving RAI treatment. In a comprehensive review of the medical literature in 2010, Ma et al reviewed 92 pertinent studies and found two randomized controlled trials involving the comparative use of amifostine and salivary stimulants to prevent post-RAI sialadenitis.[68-70] Their meta-analysis found no significant radioprotective effects on the salivary glands of the 130 patients in these two trials.

6.2 | Sialagogues

The use of sialagogues, such as sour/lemon candies or lemon juice, which increase salivation appears to have a protective effect on the salivary glands in patients treated with RAI.[71] Greater salivation results in a more rapid transit of the RAI through the salivary glands. Theoretically, a shorter exposure period with less radioactive absorption reduces the risk of salivary gland injury.

While sialagogues after RAI exposure are widely recommended, several critical questions regarding their optimal use remain controversial. Significant disagreement exists concerning the appropriate time to initiate their consumption after exposure. Additionally, once initiated, the ideal frequency of use once started is debated.

One study suggested that lemon candy stimulation should only begin 24 hours after RAI dosing, because early administration actually increases the salivary glands' avidity for RAI accumulation, whereas later use increases RAI clearance from the salivary glands.[72] This cohort of 255 patients treated with an average of 105 mCi of RAI after thyroid hormone withdrawal was divided into two lemon drop treatment groups, one starting on 1-2 lemon drops every 2-3 hours immediately after receiving ^{131}I and another who started with the candy 24 hours after treatment. Of the group who started the candy immediately, 64% experienced sialadenitis, hypogeusia, taste loss or dry mouth as opposed to only 37% of patients who were started 24 hours after RAI administration. However, other studies have provided data that do not support these results and imply that immediate and repetitive sialagogue administration may be best.[73]

Van Nostrand et al demonstrated that the pharmacokinetics of iodine in the parotid glands changes dramatically after administration of sialagogues and that this finding has potential management consequences.[74] In 23 patients, they demonstrated that after sialagogue administration, the iodine in the parotid gland was rapidly and significantly secreted. Interestingly, the parotid glands re-accumulated iodine back to their pre-sialagogue level in 21-40 minutes. However, the same rapid and significant secretion followed repeated administration of the sialagogues. Van Nostrand et al calculated that with repeated administration of the sialagogues the absorbed dose of radiation to the parotid gland would be reduced by as much as 37%-45%, supporting the use of sialagogues continuously during the day and intermittently at night.[59,74] Nakada et al subsequently validated the pharmacokinetics of iodine in the salivary glands as reported by Van Nostrand et al.[75]

As noted earlier, debate also exists over the optimal time to start the use of sialagogues following RAI exposure. Nakada et al assert that due to a "rebound effect" of increased radioiodine accumulation from salivation, avoiding sialagogues during the first 24 hours after therapy would reduce side effects. Kulkarni et al evaluated whether or not a "rebound" occurs after administration of sialagogues by performing a prospective study in which I-123 scans were performed with and without sialagogues with the patients being their own control.[76] In this study, no "rebound effect" was identified, suggesting that sialagogues use should be initiated immediately.

6.3 | Supplements

Vitamin E has also been assessed as a possible protectant from the side effects of RAI. One study examined the potential benefit of pretreatment with vitamin E supplement.[77] The groups receiving vitamin E exhibited statistically better salivary gland function by scintigraphy when compared to the control group. A second smaller study resulted in similar outcomes.[78]

The use of selenium as a protective agent has also been considered. One small study suggested that it might provide a benefit in terms of salivary gland symptoms, particularly at 6 months.[79] A separate randomized trial on 72 patients receiving vitamin C after RAI did not show any benefit regardless of the timing.[80]

6.4 | Massage

Massage of the glands, often recommended to any patient with salivary gland issues, potentially appears to be effective in patients receiving RAI as well. A controlled study of 60 patients demonstrated its efficacy, especially in younger patients.[81]

Recommendation #4a

The use of lemon candies/juice and massage as RAI protectants should be considered. The exact optimal time to start, frequency, duration, and particular sialagogue and method of massage to use remains unclear. [Weak recommendation, moderate-quality evidence]

Recommendation #4b

There is insufficient data to recommend the use of other interventions, including the use of amifostine, vitamin E, selenium, or vitamin C as RAI protectants. [Weak recommendation, low-quality evidence]

7 | EVALUATION AND MANAGEMENT

7.1 | Diagnosis

The use of patient surveys to assess subjective complaints of salivary dysfunction, whether xerostomia or sialadenitis, has been studied extensively. Although many of these focus solely on xerostomia,[82-85] others specifically include items focused on sialadenitis.[27,64,79,86-88]

There are a host of options available to objectively evaluate the function of the salivary glands and determine anatomic causes for related complaints.

7.2 | Salivary gland scintigraphy

Salivary gland scintigraphy can be employed to determine the functionality of the salivary glands.[25] A correlation has been demonstrated between measured salivary gland function and sialadenitis[55] and xerostomia symptoms.[15,17] After RAI treatment with high activities, the uptake or excretion of the salivary glands is abnormal in approximately 70% of patients at 18-20 months following exposure.[15,89] Scintigraphy allows early detection of glandular dysfunction, before sialometry becomes abnormal. Importantly, however, scintigraphy has no role in evaluating strictures or sialoliths.

7.3 | Sialometry/sialography

Sialometry, a functional exam, and sialography, an anatomical study, were historically used to evaluate patients with salivary disorders. Due to inconsistent results, sialometry is no longer employed. Sialography is the classical method to assess salivary ductal pathologies, with

excellent sensitivity for detection of sialolithiasis and, to a lesser extent, stenosis.[90,91] However, because of the associated risks, this imaging modality has been largely abandoned in favor of magnetic resonance (MR) sialogram (see below).

7.4 | Ultrasound

Ultrasound is a cost-effective and reliable method to image the salivary glands. It is considered a first-line modality in cases of sialadenitis, with good sensitivity for stone detection (71.9%),[90] even as small as 2-3 mm (accuracy of 94%),[91] and identification of stenosis.[92,93] However, ultrasound has limitations for the diagnosis of strictures.[90,91] Importantly, the changes that occur in the ultrasound features of the major salivary glands after RAI do not have a statistically significant association with the development of xerostomia[94] or sialadenitis.[95]

7.5 | Computed tomography

Computed tomography is a widely used method to assess for the presence and location of salivary stones. However, it has limited sensitivity for identifying salivary strictures such as those present in RAI-related chronic sialadenitis.

7.6 | MR sialogram

MR sialogram with its T2-weighted sequences allows for the generation of excellent quality three-dimensional reconstructions of the salivary gland ducts and their pathologies. This is done without any ductal injection of contrast media. MR sialogram is an excellent method to assess ductal stenosis and chronic sialadenitis.[96,97] However, it is expensive and time-consuming.

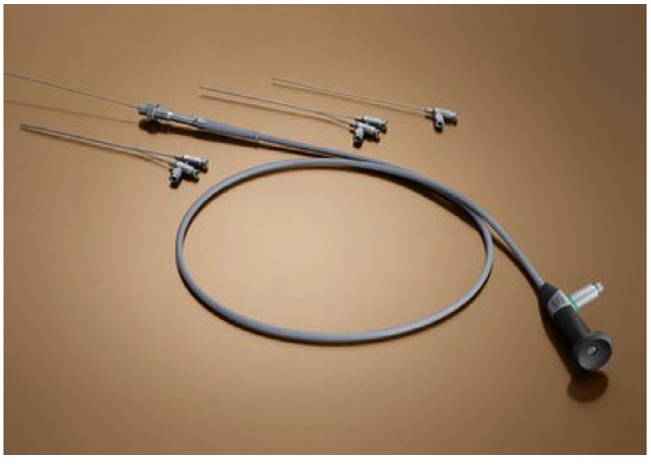

FIGURE 1 To perform diagnostic and interventional sialendoscopy specialized, miniature sialendoscopes and instruments (as shown) are utilized [Color figure can be viewed at wileyonlinelibrary.com]

7.7 | Sialendoscopy

Sialendoscopy offers both diagnostic and therapeutic functions. First described in the early 1990s, the technique has gained wider adoption among otolaryngologists since the turn of the century.

Initially, salivary probes, specifically designed for this procedure, are introduced through the respective gland's duct ostium. The duct papilla is cannulated and is sequentially dilated. After adequate dilation, a sialendoscope (with a diameter of only between 0.89 and 1.6 mm) can then be introduced to begin the endoscopy. These miniature endoscopes can be used for both diagnostic and interventional purposes (Figure 1).

Sialendoscopy provides 100% sensitivity for the assessment of salivary strictures and represents an excellent first-line diagnostic tool in cases of RAI sialadenitis.[90] As long as the sialendoscope passes the given stricture, they can be theoretically dilated mechanically or via fluid pressure.

7.8 | Lacrimal evaluation

Patients with complaints of dry eye or epiphora should be referred to an ophthalmologist for examination including slit lamp biomicroscopy, to assess the cornea and tear film, as well as Schirmer testing of tear production. In patients with epiphora, the lacrimal outflow system should be probed and irrigated to assess for partial or complete nasolacrimal obstruction. Dacryoscintigraphy or dacryocystography may be useful in determining the specific location of nasolacrimal obstruction if there is uncertainty after clinical evaluation.

8 | TREATMENT

8.1 | Xerostomia

Management of xerostomia consists of conservative interventions with adequate hydration, tobacco avoidance and appropriate oral hygiene.[98] Systemic salivary stimulants such as pilocarpine and cevimeline and several topical medications can also help these patients, although they may be associated with unsatisfactory systemic side effects.[99] While the use of sour candies, sugar-free

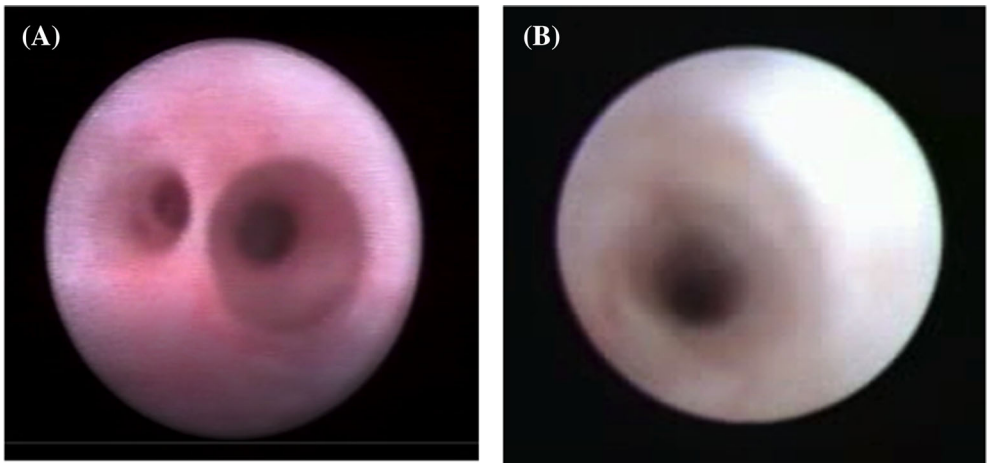

FIGURE 2 A, An endoscopic view of a normal appearing duct. B, An endoscopic view of a strictured duct following radioiodine exposure. The duct is reduced in caliber and exhibits white, fibrotic walls [Color figure can be viewed at wileyonlinelibrary.com]

chewing gum and lemon juice are widely recommended, there is limited data demonstrating the actual value of these interventions.[59] Importantly, particular attention should be paid to the possible development of oral candidiasis in patients with xerostomia as its colonization is facilitated by salivary flow reduction.[7]

8.2 | Acute sialadenitis

Acute sialadenitis is characterized by the rapid onset of salivary gland inflammation, which can be associated with pain, tenderness, induration, and swelling.

The treatment of acute sialadenitis should consist of nonsteroidal anti-inflammatory medications or oral corticosteroid therapy for the symptomatic period. In cases in which there is persistent painful swelling, erythema or pus seen at the papilla, a broad-spectrum antibiotic, such as amoxicillin-clavulanate or clindamycin, should be prescribed as the typical infectious flora includes gram-positive and anaerobic organisms.[59]

To date, there is no evidence in the literature regarding the utility of massage or warm compresses for acute sialadenitis. Importantly, sialagogues in the acute phase of sialadenitis are contraindicated as they can worsen the symptoms.

8.3 | Chronic sialadenitis

Chronic sialadenitis, typified by repeated episodes of salivary gland swelling and pain (frequently occurring with meals), can either result from recurrent episodes of acute sialadenitis damaging the salivary gland or can be due to a progressive reduction in function of the glands due to ductal strictures.[7] This second scenario is typical of patients following RAI exposure.

In contrast to acute sialadenitis treatment, an underlying important dynamic in the treatment of chronic sialadenitis is stimulation of the hypofunctional salivary tissue. Therefore, all salivary stimulants are potentially beneficial in these patients. Additionally, due to the predisposition to dental caries in the setting of xerostomia, oral hygiene should be optimized.[100]

8.4 | Sialendoscopy

Sialendoscopy offers a minimally invasive approach to address strictures in a safe and effective manner.[101] After diagnostic assessment with a sialendoscope, strictures can be immediately addressed. Repeated sialendoscopies may be offered for persistent or recurrent symptoms.[102]

With a sialendoscope, instillation of a NaCl solution allows dilation of the ductal branches, which can then be visually inspected. When seen, strictures appear white and fibrotic (Figures 2 [normal duct] and B [stricture]). At the end of a sialendoscopy procedure, a corticosteroid solution can be infused into the duct system.[103]

In a systematic review from 2017, in patients complaining of sialadenitis symptoms, 89.3% reported improvement after sialendoscopy.[104] In regard to xerostomia, the data have been inconsistent regarding the benefits of sialendoscopy. Some studies have shown no improvement in oral dryness[87,105] while others have demonstrated that in some patients subjective xerostomia complaints decreased.[106] It does appear that earlier intervention with sialendoscopy provides improved outcomes.[107] This likely is due to the greater ease of dilating less severe strictures. Several studies have examined the impact of sialendoscopy on RAI-induced salivary gland symptoms in patients who have failed medical management.[105,108,109] These series have reported that sialendoscopy is often

TABLE 2 List of recommendations

Recommendation #1	Given the potential for salivary and lacrimal side effects as well as secondary primary malignancy, patients in whom RAI therapy is being considered should receive pretreatment education regarding the prevalence and nature of these complications. Xerostomia, sialadenitis, dry eyes, epiphora, nasal symptoms and, in rare instances, secondary primary malignancy should be discussed.	Strong recommendation, moderate-quality evidence
Recommendation #2	Physicians should be aware that secondary primary malignancies can be associated, rarely, with the use of RAI and relates to RAI activity and patient age. Given this small but possible risk of a secondary malignancy, including of the salivary glands, kidneys and bone marrow, judicious, evidence-based use of RAI is warranted. In addition, these risks should be considered when determining optimal follow-up.	Weak recommendation, low-quality evidence
Recommendation #3a	Given the association between administered activity of RAI, particularly greater than 100 mCi, and the frequency and severity of side effects, the minimum effective, individualized RAI activity should be utilized. Thyroid remnant ablation with 30 mCi of RAI has significantly less risk of inducing complications. Additionally, in patient with thyroid cancer, whose tumors are considered iodine-refractory, unless efforts at redifferentiation are attempted, RAI use should be avoided.	Strong recommendation, moderate-quality evidence
Recommendation #3b	The use of recombinant TSH rather than thyroid hormone withdrawal to prepare for RAI therapy appears to reduce both the risk of salivary and lacrimal gland complications. This should be considered when determining the optimal protocol for patient RAI preparation.	Weak recommendation, low-quality evidence
Recommendation #3c	Other factors such as age, interval between RAI treatments, factors relating to salivary gland uptake, preexisting salivary gland disease, and xerostomic medication impact the risk of RAI-related complications. These should be considered when determining the risk-benefit calculation of RAI treatment for individual patients.	Strong recommendation, low-quality evidence
Recommendation #4a	The use of lemon candies/juice and massage as RAI protectants should be considered. The exact optimal time to start, frequency, duration, and particular sialagogue and method of massage to use remains unclear.	Weak recommendation, moderate-quality evidence
Recommendation #4b	There are insufficient data to recommend the use of other interventions, including the use of amifostine, vitamin E, selenium, or vitamin C as RAI protectants.	Weak recommendation, low-quality evidence
Recommendation #5	In patients experiencing symptoms after RAI exposure timely referral, to an otolaryngologist for salivary gland and an ophthalmologist for nasolacrimal gland dysfunction, is recommended.	Strong recommendation, low-quality evidence
Recommendation #6	Sialendoscopy should be considered in patients with RAI induced salivary gland sialadenitis that has not responded to conservative or medical management or that is recurrent or chronic in nature.	Strong recommendation, low-quality evidence

effective at reducing and sometimes fully alleviating their symptoms.

8.5 | Ophthalmologic treatment

The treatment of patients found to have dry eye is focused on ocular surface lubrication with preservative-free artificial tear replacement drops and gels. Those with epiphora due to nasolacrimal obstruction can be encouraged to undergo dacryocystorhinostomy, in which a surgical bypass is created to allow tear drainage directly from the lacrimal sac into the nasal cavity, in order to improve their symptoms and decrease the risk of dacryocystitis. However, patients should be counseled that previous RAI treatment decreases the success rate of dacryocystorhinostomy.[110,111]

Recommendation #5

In patients experiencing symptoms after RAI exposure timely referral, to an otolaryngologist for salivary gland and an ophthalmologist for nasolacrimal gland dysfunction, is recommended. [Strong recommendation, low-quality evidence]

Recommendation #6

Sialendoscopy should be considered in patients with RAI induced salivary gland sialadenitis that has not responded to conservative or medical management or that is recurrent or chronic in nature. [Strong recommendation, low-quality evidence]

9 | FUTURE WORK

The recommendations in this statement are based on the best available multidisciplinary evidence related to the adverse sequelae of RAI exposure (Table 2). To date there are few high-quality, randomized control trials examining these side effects. Due to the variability in study design and at times inconclusive data, there is a need to better understand the true incidence, optimal treatments and importantly prevention of salivary gland and lacrimal dysfunction following RAI use.

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