# Radioiodine Sialadenitis

8

Andrew T. Day and David W. Eisele

**Key Points**

1. Sialadenitis is the most common side effect of radioiodine therapy occurring in 10–60% of treated patients.
2. The major salivary glands concentrate radioiodine at 20–100 times the level of serum.
3. Predominantly serous salivary glands such as the parotid are more susceptible to radioiodine damage than mixed or mucinous-predominant glands.
4. Pretreatment with recombinant thyroid-stimulating hormone (rTSH) may reduce radioiodine-related salivary toxicity.
5. Therapeutic sialendoscopy reduces symptoms and obstructive episodes in the majority (>50%) of patients with radioiodine-related sialadenitis.

## Introduction

### Radioiodine

Radioiodine ($^{131}$I) is a radioactive isotope of iodine, a naturally occurring chemical element that is preferentially taken up by and stored within the thyroid gland to serve a critical role in thyroid physiology and human metabolism [1–4]. An isotope is "any of two or more species of atoms of a chemical element with the same atomic number and nearly identical chemical behavior but with differing atomic mass or mass number and different physical properties" [5]. Isotopes may be either stable or unstable. Nuclei of unstable, or radioactive, isotopes dissipate excess energy by spontaneously emitting radiation in the form of alpha, beta, and gamma rays [6]. Among the 37 different isotopes of iodine ($^{108}$I–$^{144}$I), only $^{127}$I is stable [7]. Given its preferential uptake by the thyroid gland, 8-day half-life, and toxic beta wave emission during decay, radioiodine ($^{131}$I) has been effectively harnessed for the treatment of benign and malignant thyroid disorders via the destruction of thyroid follicular cells [3, 7, 8].

Today, radioiodine ($^{131}$I) administration is indicated in certain patients with well-differentiated thyroid cancer and hyperthyroidism due to Graves' disease, toxic adenoma, or toxic nodular goiter [9, 10]. Given the increased frequency of incidental radiologically identified thyroid nodules, the United States has seen a significant increase in the detection of well-differentiated thyroid cancer and its subsequent treatment with surgery and radioactive iodine when indicated [11]. Indeed, Davies et al. identified a near threefold increase in the incidence of thyroid cancer in the United States from 1973 to 2002, from 2.7

A.T. Day, M.D. • D.W. Eisele, M.D., F.A.C.S. (✉)
Department of Otolaryngology-Head and Neck Surgery, Johns Hopkins University School of Medicine, 601 N. Caroline Street, Suite 6210, Baltimore, MD 21287, USA
e-mail: deisele1@jhmi.edu


M.B. Gillespie et al. (eds.), *Gland-Preserving Salivary Surgery*,
https://doi.org/10.1007/978-3-319-58335-8_8

to 7.7 cases per 100,000 [12]. Approximately 38–61% of patients received radiobiologic treatment during this period [13].

Radioiodine is administered orally as a single dose of $^{131}$I–labeled sodium iodide ($Na^{131}I$) in liquid or capsule form. Patients with well-differentiated thyroid cancer treated with a total thyroidectomy may be given radioiodine for remnant ablation, adjuvant therapy, or therapy for known disease, with doses ranging from 30 millicuries (mCi) to 200 mCi [13]. While radioiodine is generally well-tolerated, increased attention has been drawn to its adverse effects. Early toxicities include gastrointestinal symptoms, radiation thyroiditis, sialadenitis/xerostomia, bone marrow suppression, gonadal damage, dry eye, painless neck edema, tumor hemorrhage, and nasolacrimal duct obstruction. Late toxicities include second primary cancers, pulmonary fibrosis, and permanent bone marrow suppression [14, 15]. Among these, sialadenitis/xerostomia and nausea/vomiting occur most frequently, with an incidence of approximately 30% [14, 16].

## Radioiodine Sialadenitis

Sialadenitis is defined as inflammation of the salivary glands and may present in acute, recurrent, or chronic forms [17, 18]. Chronic sialadenitis is the most common disorder of the major salivary glands, affecting approximately 1 in 20,000 patients [19]. Causes of chronic sialadenitis include sialolithiasis, ductal scar tissue and previous parenchymal damage from previous sialolithiasis, radiation exposure or radioiodine administration, ductal trauma, autoimmune disorders (such as Sjogren's syndrome and juvenile recurrent parotitis), anatomic anomalies, and foreign bodies [20]. Symptoms of chronic sialadenitis include recurrent, often postprandial, swelling and pain of the involved gland. This disorder is occasionally complicated by bacterial superinfection with mucopurulent drainage [19–21].

While sialolithiasis is the most common cause of chronic sialadenitis, the increased use of radioiodine has resulted in an increased incidence of radioiodine sialadenitis [19]. Symptoms of radioiodine sialadenitis are characteristically pain, swelling, and xerostomia [22]. A range of 10–60% of patients report symptoms of acute or chronic salivary gland dysfunction after exposure [23]. The salivary glands experience greater toxicity than other tissues because the parenchymal and ductal cells contain a sodium/iodine symporter that accumulates $^{131}$I in the saliva at concentrations of 20–100 times the levels found in plasma. Ultimately, an estimated 24% of radioiodine is lost through the saliva [24]. Due to exposure to radiation, the ductal epithelial cells as well as the salivary parenchymal cells experience acute and chronic inflammatory changes with subsequent duct lumen narrowing, stricture formation, and altered, more viscous saliva. These factors contribute to ductal blockage and salivary stasis [22]. Since serous acini are most susceptible to this injury, the parotid gland tends to be more affected than the submandibular gland [23].

## Prevention

Methods of preventing radioiodine sialadenitis are debated. Van Nostrand originally proposed pretreatment and posttreatment approaches to mitigation of radioiodine sialadenitis. He suggested assessment of radioiodine uptake in the salivary glands on preablation whole body scans with potential treatment adjustment as indicated, patient education, aggressive hydration, and suspension of anticholinergic medications. After therapy, he recommended aggressive hydration, frequent sialogogues, gland massage, and use of one or more of the following medications: cholinergic agents, nonsteroidal anti-inflammatory agents, prophylactic steroids, amifostine, and reserpine [25]. Other studies, however, questioned the efficacy of these recommendations, particularly with regard to frequent sialogogues, pilocarpine, and reserpine [26–28].

Recent studies of patients receiving radioiodine for well-differentiated thyroid cancer suggest the use of recombinant human thyroid-stimulating hormone (rhTSH) postoperatively may induce less salivary gland toxicity as opposed to thyroid hormone withdrawal because

the latter group experienced transiently impaired renal function and subsequent decreased renal clearance of radioiodine. In fact, in one prospective study, only 5.4% of 148 patients receiving rhTSH experienced adverse oral symptoms [29]. Ultimately, however, uniform consensus regarding successful preventative measures for radioiodine sialadenitis has yet to be achieved.

## Management

Management of radioiodine sialadenitis is first medical. Medical therapy is intended to reduce the severity of symptoms and includes hydration, gland massage, application of warm heat, anti-inflammatories, and cholinergic medications. Antibiotics are administered should bacterial infection occur [23, 25, 30].

Interventional sialendoscopy is beneficial to most patients whose symptoms are refractory to medical management. In our experience, the procedure is best performed under general anesthesia. The ductal lumen is inspected thoroughly with a diagnostic sialendoscope. Typical endoscopic findings included pale ductal mucosa, thick mucus plugs, ductal debris, and ductal stenosis (Fig. 8.1). Salivary dilators and the sialendoscope may mechanically expand the duct

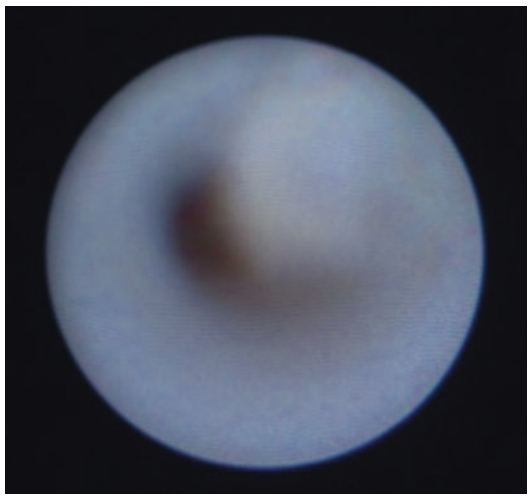

**Fig. 8.1** Sialendoscopic appearance of parotid duct with characteristic findings of narrowed, pale duct with mucous plug due to radioiodine sialadenitis

**Fig. 8.2** Hydraulic expansion of the parotid gland

while sterile saline is introduced to hydraulically expand the ducts and engorge the gland (Fig. 8.2). Steroids can be instilled although the benefits of steroids are not well characterized. Some patients may benefit from several sequential procedures. Sialadenectomy is reserved for patients with severe symptoms that do not resolve with sialendoscopy.

## Sialendoscopy Outcomes

According to the studies listed in Table 8.1, 50–100% of patients undergoing sialendoscopy for radioiodine sialadenitis report improvement in sialadenitis symptoms [22, 23, 30–35]. Three studies reported complete resolution of symptoms in 55–100% of patients [22, 23, 31]. While almost all studies validated the use of sialendoscopy for these patients, a study of 12 patients by Kim et al. demonstrated that sialendoscopy consistently provided no benefit in some sialadenitis outcome measures. Their patients reported a significant improvement in obstructive symptoms but no improvement in xerostomia symptoms, unstimulated salivary flow rate, or salivary gland scintigraphy [35]. Among patients within all studies, the cumulative doses of radioiodine administered ranged from 125 to 250 mCi [33, 34]. Four studies demonstrated follow-up of greater than 1 year in some of their patients, suggesting symptom relief may be long-lasting [22, 23, 30, 31]. According to

**Table 8.1** Selected studies assessing interventional sialendoscopy for patients with radiation sialadenitis

| Group | Year | Sample size | Total glands | Additional interventions | Follow-up | % Improved symptoms | % Symptom free | Other |
|---|---|---|---|---|---|---|---|---|
| Nahlieli et al. | 2006 | 15 | NR | Hydrocortisone 100 mg irrigation | Range: 1–4 years | 100% | 100% | |
| Kim et al. | 2007 | 6 | NR | None | Range: 8–10 months | 50% | NR | |
| Bomeli et al. | 2009 | 12 | NR | Triamcinolone 40 mg | Median: 6 months | 75% | NR | Balloon dilation used |
| Prendes et al. | 2012 | 11 | 28 | None | Mean: 7–18 months | 91% | 55% | |
| DeLuca et al. | 2014 | 30 | 75 | Hydrocortisone solution irrigation | Range: 2 weeks–84 months | 77% | NR | |
| Bhayani et al. | 2015 | 26 | 68 | Kenalog-40 irrigation | Median: 23.4 +/− 12.1 months | 92% | 64% | Improved unstimulated saliva production at 6 months |
| Wu et al. | 2015 | 12 | 19 | Gentamicin irrigation | NR | 92% | NR | Stent left in for 2 weeks postoperatively |
| Kim et al. | 2016 | 10 | 15 | NR | 3 months | NR | NR | See text |

De Luca et al. and Bomelli et al., the most common causes of recurrence were ductal stenosis and mucus plugs [30, 33].

Ultimately, while all studies to date report improved symptoms in at least half of patients undergoing sialendoscopy, additional higher-powered studies are needed to further assess the degree, quality, and length of symptom improvement. The studies are further limited by the lack of a validated objective measure of symptoms and the various administered treatments prohibiting direct comparison of outcomes.

**Conclusion**

Sialendoscopy is effective in providing symptomatic relief to a majority of patients with radioiodine sialadenitis not responding to conservative medical therapy.

## References


1. Ahad F, Ganie SA. Iodine, Iodine metabolism and iodine deficiency disorders revisited. Indian J Endocrinol Metab. 2010;14(1):13–7.
2. Cavalieri RR. Iodine metabolism and thyroid physiology: current concepts. Thyroid. 1997;7(2):177–81.
3. American Thyroid Association. Radioactive iodine. http://www.thyroid.org/radioactive-iodine/. Accessed 31 Jan 2016.
4. Van Dyke M, Punja M, Hall MJ, Kazzi Z. Evaluation of toxicological hazards from medical radioiodine administration. J Med Toxicol. 2015;11(1):96–101.
5. Merriam-Webster. Isotope. http://www.merriam-webster.com/dictionary/isotope. Accessed 1 June 2016.
6. Encyclopædia Britannica. Radioactive isotope. 2016. http://www.britannica.com/science/radioactive-isotope. Accessed 31 Jan 2016.
7. Audi GWA, Thibault C, Blachot J, Bersillon O. The NUBASE evaluation of nuclear and decay properties. Nucl Phys A. 2003;729:3–128.
8. Suwinski R, Gawkowska-Suwinska M. Radiobiologic basis for using 131I to treat patients with thyroid cancer. Wiad Lek. 2001;54(Suppl 1):266–77.
9. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid. 2016;26(1):1–133.
10. Ross DS. Radioiodine therapy for hyperthyroidism. N Engl J Med. 2011;364(6):542–50.
11. Alexander EK, Larsen PR. Radioiodine for thyroid cancer--is less more? N Engl J Med. 2012;366(18):1732–3.
12. Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973-2002. JAMA. 2006;295(18):2164–7.
13. Patel SS, Goldfarb M. Well-differentiated thyroid carcinoma: the role of post-operative radioactive iodine administration. J Surg Oncol. 2013;107(6):665–72.
14. Fard-Esfahani A, Emami-Ardekani A, Fallahi B, Fard-Esfahani P, Beiki D, Hassanzadeh-Rad A, et al. Adverse effects of radioactive iodine-131 treatment for differentiated thyroid carcinoma. Nucl Med Commun. 2014;35(8):808–17.
15. Sherman SI. Thyroid carcinoma. Lancet. 2003;361(9356):501–11.
16. Klein Hesselink EN, Links TP. Radioiodine treatment and thyroid hormone suppression therapy for differentiated thyroid carcinoma: adverse effects support the trend toward less aggressive treatment for low-risk patients. Eur Thyroid J. 2015;4(2):82–92.
17. Francis CL, Larsen CG. Pediatric sialadenitis. Otolaryngol Clin N Am. 2014;47(5):763–78.
18. Wilson KF, Meier JD, Ward PD. Salivary gland disorders. Am Fam Physician. 2014;89(11):882–8.
19. Vashishta R, Gillespie MB. Salivary endoscopy for idiopathic chronic sialadenitis. Laryngoscope. 2013;123(12):3016–20.
20. Gillespie MB, O'Connell BP, Rawl JW, McLaughlin CW, Carroll WW, Nguyen SA. Clinical and quality-of-life outcomes following gland-preserving surgery for chronic sialadenitis. Laryngoscope. 2015;125(6):1340–4.
21. Aubin-Pouliot A, Delagnes EA, Eisele DW, Chang JL, Ryan WR. The chronic obstructive sialadenitis symptoms questionnaire to assess sialendoscopy-assisted surgery. Laryngoscope. 2016;126(1):93–9.
22. Prendes BL, Orloff LA, Eisele DW. Therapeutic sialendoscopy for the management of radioiodine sialadenitis. Arch Otolaryngol Head Neck Surg. 2012;138(1):15–9.
23. Bhayani MK, Acharya V, Kongkiatkamon S, Farah S, Roberts DB, Sterba J, et al. Sialendoscopy for patients with radioiodine-induced Sialadenitis and Xerostomia. Thyroid. 2015;25(7):834–8.
24. Mandel SJ, Mandel L. Persistent sialadenitis after radioactive iodine therapy: report of two cases. J Oral Maxillofac Surg. 1999;57(6):738–41.
25. Van Nostrand D. Sialoadenitis secondary to $^{131}$I therapy for well-differentiated thyroid cancer. Oral Dis. 2011;17(2):154–61.
26. Nakada K, Ishibashi T, Takei T, Hirata K, Shinohara K, Katoh S, et al. Does lemon candy decrease salivary gland damage after radioiodine therapy for thyroid cancer? J Nucl Med. 2005;46(2):261–6.
27. Silberstein EB. Reducing the incidence of 131I-induced sialadenitis: the role of pilocarpine. J Nucl Med. 2008;49(4):546–9.
28. Kim SJ, Choi HY, Kim IJ, Kim YK, Jun S, Nam HY, et al. Limited cytoprotective effects of amifostine

in high-dose radioactive iodine 131-treated well-differentiated thyroid cancer patients: analysis of quantitative salivary scan. Thyroid. 2008;18(3):325–31.
29. Rosario PW, Calsolari MR. Salivary and lacrimal gland dysfunction after remnant ablation with radioactive iodine in patients with differentiated thyroid carcinoma prepared with recombinant human thyrotropin. Thyroid. 2013;23(5):617–9.
30. De Luca R, Vicidomini A, Trodella M, Tartaro G, Colella G. Sialoendoscopy: a viable treatment for I(131) induced sialoadenitis. Br J Oral Maxillofac Surg. 2014;52(7):641–6.
31. Nahlieli O, Nazarian Y. Sialadenitis following radioiodine therapy—a new diagnostic and treatment modality. Oral Dis. 2006;12(5):476–9.
32. Kim JW, Han GS, Lee SH, Lee DY, Kim YM. Sialoendoscopic treatment for radioiodine induced sialadenitis. Laryngoscope. 2007;117(1):133–6.
33. Bomeli SR, Schaitkin B, Carrau RL, Walvekar RR. Interventional sialendoscopy for treatment of radioiodine-induced sialadenitis. Laryngoscope. 2009;119(5):864–7.
34. CB W, Xi H, Zhou Q, Zhang LM. Sialendoscopy-assisted treatment for radioiodine-induced sialadenitis. J Oral Maxillofac Surg. 2015;73(3):475–81.
35. Kim YM, Choi JS, Hong SB, Hyun IY, Lim JY. Salivary gland function after sialendoscopy for treatment of chronic radioiodine-induced sialadenitis. Head Neck. 2016;38(1):51–8.