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ORIGINAL RESEARCH

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# Gadolinium as a contrast agent for infusion sialograms in patients with iodine allergy

Ryan P. Sabotin MD[1] | Ryan Thorpe MD[1] | Joan E. Maley MD[2] | Bruno Policeni MD[2] | Henry T. Hoffman MD[1]

[1]Department of Otolaryngology, University of Iowa Hospitals and Clinics, Iowa City, Iowa, USA

[2]Department of Radiology, University of Iowa Hospitals and Clinics, Iowa City, Iowa, USA

**Correspondence**
Ryan P. Sabotin, Department of Otolaryngology, University of Iowa Hospitals and Clinics, 21151 Pomerantz Family Pavilion, Iowa City, IA, USA.
Email: sabotinent@gmail.com

## Abstract

**Objectives:** To assess the adequacy of gadolinium in sialography as an alternative contrast agent for patients with iodine allergies. To directly compare images taken with gadolinium versus iodine-based contrast agents using the Iowa Sialography Classification System.

**Methods:** Retrospective chart review was performed on patients undergoing sialography between February 2008 and July 2022. Patients with sialograms obtained with gadolinium were identified and matched to similar sialograms obtained with iodine-based contrast agent. Patients were matched based on duct location, duct side, and initial radiology findings. Blinded reevaluation of sialograms was performed first independently and then by consensus by two head and neck radiologists to evaluate overall image adequacy and grade using the Iowa Sialography Classification System.

**Results:** Four patients with six sialograms (one bilateral parotid and one parotid + submandibular) obtained with gadolinium were identified and reevaluated. Five patients with six sialograms (one bilateral parotid) obtained with iodine-based were matched to the gadolinium sialograms. The overall adequacy of images for gadolinium sialograms was graded at an average of 4.25 (4 = good and 5 = excellent); whereas, the overall adequacy of iodine-based sialograms was graded at an average of 5. Interobserver variability was observed in three sialograms obtained with gadolinium (50%), while no interobserver variability was observed in sialograms obtained with iodine-based contrast agent.

**Conclusion:** Gadolinium is an adequate alternative to use in sialography for patients with iodine allergies undergoing contemporary digital infusion sialography. Adverse reactions to iodine contrast agents are rare in sialography; however, the precautionary use of gadolinium is acceptable for the diagnostic and therapeutic benefits in sialography.

Level of Evidence: IV

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KEYWORDS
gadolinium, infusion sialography, iodine allergy, parotid gland, submandibular gland

## 1 | INTRODUCTION

Retrograde injection of contrast dye into the ductal system of a major salivary gland (sialography) is a technique that has been used for the radiographic analysis of the architecture of the ductal system since the early 1900's.[1] With high spatial resolution providing detailed analysis of the salivary ducts and acini, contemporary high quality digital infusion sialography is an important tool in the investigation of salivary gland pathology.[2,3] The use of sialography has been reported in defining and characterizing multiple disease processes, such as Sjogrens, sialolithiasis, sialosis, juvenile recurrent parotitis, and radioiodine-associated sialadenitis.[4–6]

Sialography has also been reported to provide therapeutic effects in addition to its diagnostic capabilities through mechanical dilations and irrigation with contrast agent.[7,8] Additionally, sialography may identify parenchymal disease in the absence of significant ductal strictures to permit in-office steroid insufflation. This approach permits drug delivery to a gland not already permeated by the saline infused during sialography. Findings on sialography provide a useful road map to direct more invasive treatments such as sialendoscopy or mechanical duct dilation.[9]

Contemporary digital infusion sialography typically utilizes water-soluble iodinated contrast agents. Pretreatment with oral steroids and diphenhydramine is an option for patients with reported iodine allergy but may be either not tolerated or refused by patients.[10] Anaphylactic reactions from iodinated contrast are rare; however, delayed reactions involving edema of the mouth and neck causing respiratory distress, as well as macropapular rashes with significant edema and shoulder/back pain have been reported.[11–13]

Magnetic resonance (MR) sialography has emerged as an alternative to contemporary sialography to bypass use of iodinated contrast, but suffers from absence of therapeutic benefit, poorer ductal definition, and inability to provide dynamic imaging.[14,15] Additionally, ultrasound imaging avoids the need for iodinated contrast, yet provides an even-less clear image of ductal structures. Contemporary digital infusion sialography provides a detailed view of the ductal anatomy to include the tertiary ducts extending into the parenchyma. The shortcomings of MR sialography and ultrasonography warrant provision of an alternative method for digital infusion sialography when there are concerns about managing iodine allergies.

Our review of the literature identified a single case-study documenting the use of gadolinium as an alternative contrast for sialography in patients with iodine allergies.[16] We compared the use of gadolinium in a series of six sialograms with similar sialograms performed with traditional iodinated contrast agents, using the University of Iowa sialogram classification system as an objective reference, adapted previously from the Iowa parotid sialogram classification system.[17–19]

## 2 | METHODS

### 2.1 | Data Collection

Following approval from the University of Iowa Institutional Review Board (IRB), identification number 201909820, a retrospective chart review was performed to identify all sialograms performed by a single surgeon at the University of Iowa from 2008 to 2022. Four hundred and eighty-five patients who underwent sialography at the University of Iowa were included. Written informed consent was obtained from all patients included. Systematic chart review was performed, identifying four patients with six sialograms that were performed using gadolinium-based contrast, Gadovist (gadobutrol, Bayer Healthcare Pharmaceuticals, Whippany, NJ). Sialograms using gadolinium were matched to six comparable sialograms using iodinated contrast, Isovue 370 (Iopamidol, Bracco Diagnostics) from five patients, based upon sialogram location, reason for sialography, and radiology impression. For those nine patients identified (12 sialograms), the following variables were analyzed: patient age at time of sialogram, gender, reason for sialography, BMI, type of symptoms, duration of symptoms, contrast agent used, and volume of contrast used.

### 2.2 | Sialography Technique

All sialograms were performed in the fluoroscopy suite by the senior investigator with a consistent technique employing a microscope to help with the direct placement of a 22 or 24-gauge angiocatheter into the parotid or submandibular duct orifice, as previously described.[20] Gadolinium or iodine-based contrast was then instilled into the duct under direct fluoroscopic guidance, and radiographs were taken. The required volume of contrast as determined by injection under fluoroscopic guidance and stopping with the patient's sensation of increased preauricular pressure or pain. Contrast retention was then evaluated by giving the patient a small amount of lemon juice to swish and expectorate along with gland massage, with delayed radiographs obtained.

### 2.3 | Sialography Analysis

All 12 sialograms were reassessed by two radiologists (each with >13 years of experience interpreting sialograms) after reviewing the University of Iowa sialogram classification and grading system. The radiologists reviewed the predetermined 12 sialograms in random order and scored independently. The radiologists were informed that some sialograms were obtained using iodinated contrast while others were obtained using gadolinium but were otherwise blinded to contrast used for each specific sialogram and all other variables.

**TABLE 1** University of Iowa sialogram classification scale.

| Score | Location of ductal stenosis/stricture | Degree of ductal stenosis/stricture | Retention of contrast | Peripheral duct dilation |
|---|---|---|---|---|
| 0 | No stenosis/stricture | No stenosis/stricture | No retention | No dilation |
| 1 | Tertiary or quaternary ducts | Minimal; <25% stenosis/stricture | Focal retention pockets | Punctate dilation; <1 mm in size |
| 2 | Secondary ducts | Mild; 25%–50% stenosis/stricture | Indistinct retention | Globular dilation; 1–2 mm in size |
| 3 | Primary/main duct | Moderate; 50%–75% stenosis/stricture | N/A | Coalescent, irregularly shaped globules; >2 mm in size |
| 4 | N/A | Severe; >75% stenosis/stricture | N/A | Invasion/destruction of gland parenchyma |

The University of Iowa sialogram classification system has previously been employed for the classification of parotid ducts, and subsequently modified for the use with submandibular ducts.[6,18] This classification system describes location of ductal stenosis, degree of ductal stenosis, retention of contrast, and peripheral duct dilation (Table 1). The 1°, or main duct, was defined as extending from the oral papilla to the first major ductal bifurcation; 2° ducts were defined as the ducts proximal to the first major bifurcation, but distal to any second bifurcations; and 3° ducts were defined as any ducts proximal to second bifurcations. Branches to accessory lobes were classified as 2° ducts. Additionally, the radiologists were asked to independently grade the overall adequacy of the ductal imaging on a scale from zero to five: 0 (no image viewable), 1 (poor), 2 (marginal), 3 (adequate), 4 (good), and 5 (excellent) for each sialogram observed.

### 2.4 | Statistical Analysis

Calculation of weighted kappa and confidence intervals for interobserver agreement were performed using R Statistical Software (v4.2.1),[21] with the vcd package.[22,23] Due to the small sample size and presumed non-Gaussian distribution of volume of contrast used during sialogram, body mass index (BMI) at time of sialogram, age at time of sialogram, and duration of symptoms at time of sialogram, two-tailed Mann–Whitney test were used to compare values between sialograms performed with gadolinium-based contrast versus iodinated contrast. These analyses were performed using GraphPad Prism v9.4.1 software (San Diego, CA).

## 3 | RESULTS

### 3.1 | Demographics

Nine patients evaluated with 12 sialograms (two bilateral parotid and one parotid + submandibular) underwent chart review and reevaluation of sialogram images (Table 2). All patients evaluated were female (100%). The average age at time of sialogram was 48 years old, with unspecified sialadenitis listed as the most common reason for sialography (77.8%). The second most common reason for sialography included sialosis (11.1%) and Sjogren's Syndrome (11.1%) reported symptoms predating sialography included gland swelling and pain (100%), with five of nine patients experiencing dry mouth (55.6%), and five of nine patients experiencing dry (55.6%). The average duration of symptoms before performing sialography was 1215 days (3.3 years) among all patients. The mean amount of contrast agent used was 2.7 cc, with an average of 3 cc used in gadolinium sialograms, and 2.4 cc used in iodine-based sialograms.

Two-tailed Mann–Whitney test demonstrated no significant difference in age ($p = .2186$), BMI ($p = .2251$), duration of symptoms ($p = .4524$), or volume of contrast ($p = .4481$) between patients receiving gadolinium-based contrast agent compared to patients receiving iodine-based contrast agent.

### 3.2 | Adequacy of Imaging

Among the six sialograms performed with gadolinium, three displayed interobserver variability ($\kappa = -0.2857$, CI $-0.7014$ $-0.1300$). The average adequacy of imaging in the sialograms performed with gadolinium was rated at 4.25/5, where 4 = good overall imaging and 5 = excellent overall imaging. On all six sialograms performed with gadolinium, radiologist comments noted lesser density of contrast compared to the other six done with iodine-based contrast—but that imaging was still adequate for interpretation (Figure 1). Among the six sialograms performed with iodinated contrast, there was zero interobserver variability ($\kappa = 1$). The average adequacy of imaging in the sialograms performed with iodinated contrast was rated at 5/5, with excellent imaging overall. There were no technical problems reported with infusion of either gadolinium or iodinated contrast.

### 3.3 | Identification and Classification of Ductal Stenosis

Ductal stenosis was identified in three sialograms overall (25%), with two instances of ductal stenosis identified with gadolinium (16.7%) and one instance of ductal stenosis identified with iodinated contrast (8.3%) (Figure 2). Ductal stenosis was only identified within the primary duct within our sample. Among the two ductal stenoses identified within the gadolinium sialograms, there was interobserver disagreement regarding the degree of ductal stenosis in one sialogram,

**TABLE 2** Matched sialograms with patient characteristics, presenting symptoms, and overall adequacy of imaging.

| Gadolinium Contrast Agent | | | | | | Iodine Contrast Agent | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| ID | Age | Reason for Sialography | Symptoms | Adequacy of Ductal Imaging | Duct | ID | Age | Reason for Sialography | Symptoms | Adequacy of Ductal Imaging |
| 1 | 51 | Sialadenitis, possible SS | S, P, X, D | 4 | Parotid | 5 | 55 | Sialosis, possible SS | S, P, X, D | 5 |
| 2a | 57 | Sialadenitis, unspecified | S, P, D | 4.5 | Parotid | 6a | 39 | Sialadenitis, possible SS | S, P | 5 |
| 2b | * | * | * | 4.5 | Parotid | 6b | * | * | * | 5 |
| 3 | 73 | Sialadenitis, unspecified | S, P | 4.5 | Parotid | 7 | 58 | Sialadenitis, unspecified | S, P, X | 5 |
| 4a | 42 | SS | S, P, X, D | 4 | Submandibular | 8 | 43 | Sialadenitis, unspecified | S, P, D | 5 |
| 4b | * | * | * | 4 | Parotid | 9 | 23 | Sialadenitis, possible SS | S, P, X | 5 |

*Note*: Each row represents a pairing of sialograms with gadolinium contrast agent (left) compared to iodine contrast agent (right) and variables used to match.

Abbreviations: D, dry eyes; Gad, gadolinium; P, pain; SS, Sjogren's syndrome; S, swelling; X, xerostomia.

*Indicates that the demographics/symptoms are identical to the above line, as the ducts are from the same patient.

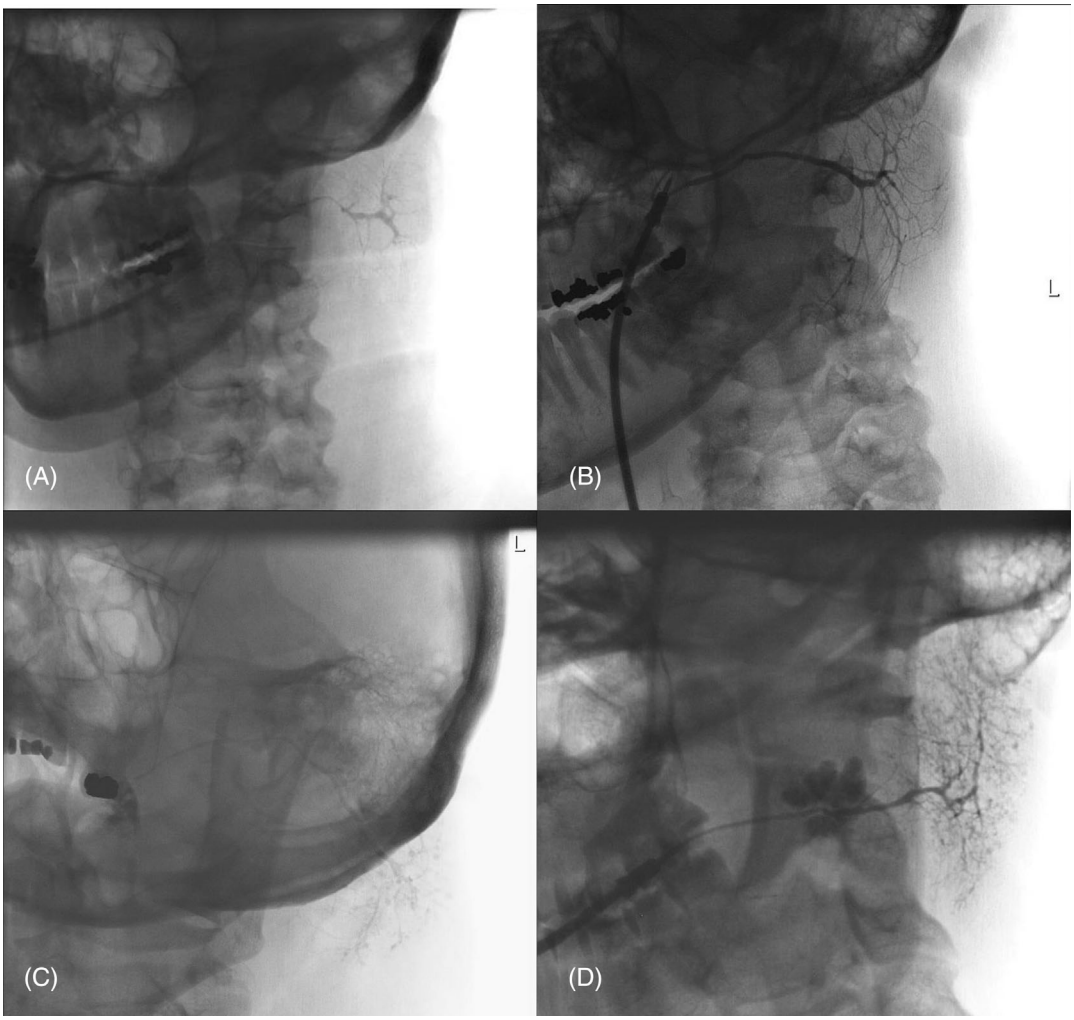


**FIGURE 1** Fluoroscopic contemporary digital infusion sialography of the left parotid duct taken with gadolinium-based contrast agent (A,C) matched with similar sialograms of the left parotid duct taken with iodine-based contrast agents (B,D). Sialogram images taken with gadolinium contrast demonstrate decreased density when compared to those taken with iodinated contrast; however, secondary and tertiary ducts are still identifiable for analysis in images taken with gadolinium.

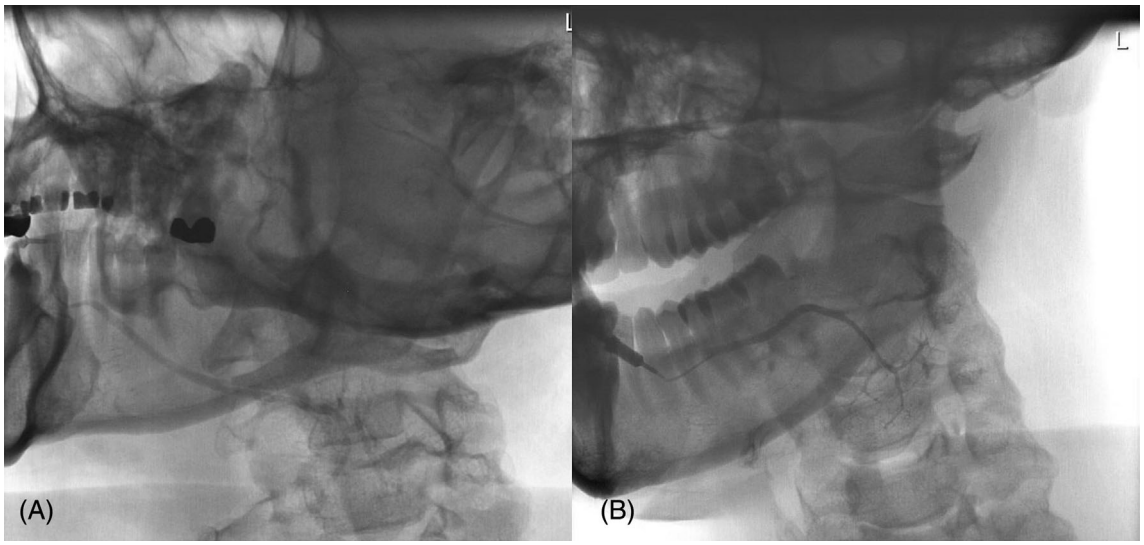


**FIGURE 2** Fluoroscopic contemporary digital infusion sialography of the left parotid duct taken with gadolinium-based contrast agent (A); mild to moderate stricture appreciated within the primary duct. Globular peripheral duct dilation (1–2 mm) additionally noted. (B) Multiple moderate to severe strictures viewed on left parotid digital sialogram images taken with iodine-based contrast agent, with additional globular peripheral duct dilation (1–2 mm).

with discrepancies between classifying stenosis as mild versus moderate. There were no other instances of interobserver disagreement for all other gadolinium or iodinated contrast sialograms.

## 4 | DISCUSSION

Sialography remains an important tool in the diagnosis of salivary gland disease, further refined with introduction of the Iowa sialogram classification system to offer consistency in classifying pathology within parotid and submandibular ducts.[6,18,19] Contemporary high quality digital infusion sialography is primarily designed as a diagnostic tool to direct care but often provides ancillary benefit as a therapeutic measure in the course of duct dilation with irrigation.[5,9]

Although adverse effects to iodinated contrast are rare during sialography, the standard precaution involving pretreatment with steroids and diphenhydramine may be either refused or not tolerated by patients.[24] Salerno et al. describes an instance in which a patient developed delayed edema and pain surrounding the mouth and neck, prompting admission to the emergency department after sialography of the submandibular gland.[12] Similarly, Cockrell and Rout documented a delayed reaction to iodine-based sialography, in which the patient experienced severe shoulder and back pain 24 h after administration of the contrast agent.[13] These rare allergic reactions to iodinated contrast agents in association with sialography warrant exploration of a safe alternative.

To our knowledge, this report provides the largest analysis of gadolinium as a contrast agent in sialography and offers a direct comparison of gadolinium to iodinated contrast agents. Williams et al. documented a single case report in which gadolinium was used successfully as an alternative agent for sialography in a patient with iodine allergy.[16] Gadolinium has also been reported as an adequate alternative to iodine-based contrast in iodine-allergic patients undergoing vascular and hepatobiliary procedures.[25–27] However, it is reported that caution must be exercised in the use of gadolinium in patients with renal insufficiency, with rare associations to nephrogenic systemic sclerosis limiting the use in patients with chronic kidney disease.[28]

This study further confirmed gadolinium as an adequate alternative agent for sialography in patients with contraindications to iodine-based contrast agents. In all instances where gadolinium was used for sialography, radiologists rated the overall adequacy of ductal imaging as "good" or "excellent." Additionally, there were no technical problems or adverse effects noted after the instillation of gadolinium.

A greater degree of interobserver variability was observed with use of gadolinium when assessing adequacy of ductal imaging and the degree of stenosis within the duct compared to iodinated imaging. Furthermore, the radiologists rated the adequacy of imaging as "excellent" in all patients receiving iodinated contrast, with zero interobserver variability in any categories of the Iowa sialogram classification system.

Subjective comments from the radiologists when reevaluating the images obtained with gadolinium include: "Decreased density; adequate but less intense; contrast less intense, but adequate; Mildly decreased density of contrast, but adequate." The comments written when reevaluating the sialograms obtained with iodinated contrast include: "Contrast much better; really nice contrast density." There was no significant difference in volume of contrast administered or intraoperative complications between the groups receiving gadolinium versus iodinated contrast.

Our findings suggest that gadolinium is an adequate alternative to iodinated contrast in patients with iodine-allergies undergoing contemporary digital infusion sialography. The results further support iodine-based contrast agents as the gold standard for infusion sialography; however, when indicated, gadolinium offers good to excellent

diagnostic capabilities with the same therapeutic outcomes via instillation of contrast agent.

Limitations of our study include a small sample size of gadolinium sialograms, the use of patient-reported symptoms, and retrospective design of the study. Additionally, matching of patients receiving gadolinium versus patients receiving iodinated contrast was limited based on availability of images. Larger studies documenting the use gadolinium in contemporary digital sialogram may provide further insight into the adequacy and/or pitfalls of using gadolinium in sialography.

## 5 | CONCLUSION

Contemporary high quality digital infusion sialography employing gadolinium-based contrast agents provides an adequate alternative in patients with iodine allergies. Based on our limited data showing sialograms obtained with gadolinium yield images interpreted as "good" or "excellent," we conclude that gadolinium is a safe and adequate alternative in iodine-allergic patients for the diagnostic and therapeutic benefits in contemporary digital infusion sialography.

### CONFLICT OF INTEREST STATEMENT

Dr. Henry T. Hoffman reported personal fees as an author from UpToDate and personal fees as a research consultant from Cook Medical outside the submitted work.

### ORCID

*Ryan P. Sabotin* https://orcid.org/0000-0003-0794-6029
*Ryan Thorpe* https://orcid.org/0000-0002-8046-407X
*Henry T. Hoffman* https://orcid.org/0000-0003-4486-855X

### REFERENCES

1. Holt JF. Sialography. *Radiology*. 1957;68(4):584-585.
2. Sobrino-Guijarro B, Cascarini L, Lingam RK. Advances in imaging of obstructed salivary glands can improve diagnostic outcomes. *Oral Maxillofac Surg*. 2013;17(1):11-19.
3. Rinast E, Gmelin E, Hollands-Thorn B. Digital subtraction sialography, conventional sialography, high-resolution ultrasonography and computed tomography in the diagnosis of salivary gland diseases. *Eur J Radiol*. 1989;9(4):224-230.
4. Rzymska-Grala I, Stopa Z, Grala B, et al. Salivary gland calculi–contemporary methods of imaging. *Pol J Radiol*. 2010;75(3):25-37.
5. Kalk WW, Vissink A, Spijkervet FK, Bootsma H, Kallenberg CG, Roodenburg JL. Parotid sialography for diagnosing Sjogren syndrome. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2002;94(1):131-137.
6. Thorpe RK, Foggia MJ, Marcus KS, Policeni B, Maley JE, Hoffman HT. Sialographic analysis of radioiodine-associated chronic sialadenitis. *Laryngoscope*. 2021;131(5):E1450-E1456.
7. Eisenbud L, Cranin N. The role of sialography in the diagnosis and therapy of chronic obstructive sialadenitis. *Oral Surg Oral Med Oral Pathol*. 1963;16:1181-1199.
8. Lee C, Kim JE, Huh KH, et al. Therapeutic effect of intraductal irrigation of the salivary gland: a technical report. *Imaging Sci Dent*. 2017;47(2):123-127.
9. Diggelmann HR, Hoffman HT. Intraductal infusion of steroids in patients with Sjogren syndrome to treat painful salivary swelling: report of 2 cases. *Ear Nose Throat J*. 2015;94(6):238-239.
10. Katayama H, Yamaguchi K, Kozuka T, Takashima T, Seez P, Matsuura K. Adverse reactions to ionic and nonionic contrast media. A report from the Japanese committee on the safety of contrast media. *Radiology*. 1990;175(3):621-628.
11. Davis PL. Anaphylactoid reactions to the nonvascular administration of water-soluble iodinated contrast media. *AJR Am J Roentgenol*. 2015;204(6):1140-1145.
12. Salerno S, Cannizzaro F, Lo Casto A, Speciale R. Late allergic reaction following sialography. *Dentomaxillofac Radiol*. 2002;31(2):154.
13. Cockrell DJ, Rout PG. An adverse reaction following sialography. *Dentomaxillofac Radiol*. 1993;22(1):41-42.
14. Karaca Erdogan N, Altay C, Ozenler N, et al. Magnetic resonance sialography findings of submandibular ducts imaging. *Biomed Res Int*. 2013;2013:417052.
15. Lomas DJ, Carroll NR, Johnson G, Antoun NM, Freer CE. MR sialography. Work in Progress. *Radiology*. 1996;200(1):129-133.
16. Williams MD, Moody AB, Newlands CA, Howlett DC. Gadolinium an alternative contrast agent for sialography in patients with iodine sensitivity. *Int J Oral Maxillofac Surg*. 2003;32(6):651-652.
17. University of Iowa Health Care. *Classification of salivary duct stenosis (parotid duct stricture–submandibular duct stricture) University of Iowa sialogram classification and grading scale*. University of Iowa Health Care. https://medicine.uiowa.edu/iowaprotocols/classification-salivary-duct-stenosis-parotid-duct-stricture-submandibular-duct-stricture-university; 2020 Accessed September 14, 2022.
18. Foggia MJ, Peterson J, Maley J, Policeni B, Hoffman HT. Sialographic analysis of parotid ductal abnormalities associated with Sjogren's syndrome. *Oral Dis*. 2020;26(5):912-919.
19. Moore AE, Marcus KS, Rajan KA, Maley JE, Hoffman HT. Ultrasound and Sialogram correlates to parotid immunoglobulin G4-related disease. *Ear Nose Throat J*. 2021;0(0):14556132110516.
20. Truong K, Hoffman HT, Policeni B, Maley J. Radiocontrast dye extravasation during sialography. *Ann Otol Rhinol Laryngol*. 2018;127(3):192-199.
21. R Core Team. *R: A Language and Environment for Statistical Computing [Computer Program]*. R Foundation for Statistical Computing; 2022.
22. Meyer D, Zeiles A, Hornik K. *vcd: Visualizing Categorical Data*. R package version 1.4-11. 2022.
23. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics*. 1977;33(1):159-174.
24. Nadler C, Rettman A, Benvenisty N, Ribak Y, Hershko AY, Tal Y. Iodinated contrast media allergy is rare in patients undergoing sialography. *Asian Pac J Allergy Immunol*. 2020. doi:10.12932/AP-190720-0923
25. Lawrence C, Cotton PB. Gadolinium as an alternative contrast agent for therapeutic ERCP in the iodine-allergic patient. *Endoscopy*. 2009;41(6):564-567.
26. Matuszczyk A, Hahn S, Bose D, et al. Gadolinium as an alternative contrast agent during cardiac catheterization in patient with iodine-induced hyperthyroidism. *Exp Clin Endocrinol Diabetes*. 2006;114(6):336-338.
27. Zeller T, Muller C, Frank U, et al. Gadodiamide as an alternative contrast agent during angioplasty in patients with contraindications to iodinated media. *J Endovasc Ther*. 2002;9(5):625-632.
28. Nadolski GJ, Stavropoulos SW. Contrast alternatives for iodinated contrast allergy and renal dysfunction: options and limitations. *J Vasc Surg*. 2013;57(2):593-598.

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