

Role of magnetic resonance sialography in diagnosis of salivary gland diseases: a meta-analysis

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Objectives

To establish the diagnostic accuracy of magnetic resonance sialography (MRS) when compared with the gold standard conventional sialography (CS) in patients with suspected salivary gland disease.

Background

This is a systematic review and meta-analysis to compare both studies. CS is still considered the standard modality for assessing ductal abnormalities. MRS has been applied as an alternative.

Methods

We searched PubMed, Cochrane CENTRAL, Scopus, Science Direct, and Web of Science for all studies that compared MRS versus CS regarding radiological outcomes and diagnostic performance as primary outcomes. Combined outcomes were pooled as risk ratios in a fixed model or diagnostic odds ratio (DOR) in a random model, using Reviewer Manager 5.3 and Meta-DiSc 1.4 for Windows.

Results

Eight studies ($n = 285$ patients) were included in the final analysis. Our results showed that MRS was effective in the detection of main duct according to patients more than CS [risk ratio = 0.84, 95% confidence interval (CI), 0.71–1, $P = 0.05$]. However, it showed no significant difference between the two groups in detection of main duct according to glands. Moreover, there are no significant differences between MRS and CS regarding detection of sialolithiasis, sialectasis, stenosis with stones, or strictures. The diagnostic performance in the detection of sialolithiasis according to glands was as follow: the pooled sensitivity was 0.88 (95% CI, 0.75–0.95), the pooled specificity was 0.98 (95% CI, 0.93–1.00), and the pooled DOR under random effect was 181.64 (95% CI, 39.420–837). Moreover, the diagnostic performance in the detection of the stenosis with stones according to patients was as follows: the pooled sensitivity was 0.727 (95% CI, 0.498–0.893), the pooled specificity was 0.979 (95% CI, 0.889–0.99), and the diagnostic odds ratio under random effect was 78.73 (95% CI, 2.18–508.81).

Conclusion

There is no difference between MRS and CS in radiological findings except in case of detection of main duct according to patients, which indicates that MRS is more effective in revealing the proper information about main salivary ducts. Moreover, MRS provides a noninvasive alternative to CS especially if acute sialadenitis is present or cannulation is not successful.

Keywords:

conventional sialography, magnetic resonance sialography, salivary gland diseases

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Introduction

Saliva reflects the physiologic state of the body. Salivary gland diseases may be inflammatory, noninflammatory, non-neoplastic, or neoplastic lesions [1].

Advances in imaging have led to improved sensitivity in the diagnosis of diseases that involve the major salivary glands. Ultrasound, plain radiography, sialography, MRI, computed tomography (CT), and nuclear scintigraphy/positron emission tomography all play a part [2].

Conventional or digital subtraction sialography has long been considered the gold standard for imaging the salivary ductal system. Although this technique offers excellent anatomical detail and spatial resolution,

it carries significant disadvantages [3]. Owing to the complex nature of the procedure, patient cooperation and operator experience are required for success. The reported failure rate is as high as 4%, especially in patients with a small submandibular duct opening or papillary stenosis.

MRS has become an alternative method for imaging the salivary gland and duct [4]. MRS is a noninvasive method for evaluating the ductal structures of the major salivary glands. Although the technique and

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its applications have evolved greatly from its initial description in the mid-1990s, it remains rooted in the simple concept that stationary fluid, such as saliva, has intrinsic high T2 signal intensity, obviating instillation of contrast material to 'opacify' the salivary ducts [5].

The purpose of our study was to establish the diagnostic accuracy of MRS when compared with the gold standard of conventional sialography (CS) in a large group of patients with suspected salivary duct disease.

Methods

We conducted this systematic review and meta-analysis according to PRISMA flow diagram guidelines [6] and Cochrane Handbook for Systematic Reviews of Intervention [7].

Literature search

We performed a comprehensive search of five electronic databases (PubMed, Scopus, ISI Web of Science of clinical trials, Science Direct, and Cochrane Library) for all eligible studies using the following search building: salivary gland disease and magnetic resonance sialography (MRS), and CS. There was no restriction by the year of publication or the language of study.

Eligibility criteria

We included all studies either randomized clinical trials or observational that met our following inclusion criteria: (a) population: patients with salivary gland diseases; (b) intervention: MRS; (c) comparator: CS as gold standard; (d) outcomes: efficacy end points (detection of sialolithiasis, stenosis with stones, sialectasis, stricture, and main duct) and diagnostic performance of sialolithiasis and stenosis with stones; and (e) study design: randomized clinical trials and observational studies. We excluded all papers not related to our inclusion criteria. Eligibility screening was conducted in a two-step wise manner (title/abstract screening and full-text screening). All reviewers preformed each step, and consensus was reached upon discussion among all reviewers.

Data extraction

We extracted data from related studies on standard excel sheet. We abstracted data as follows: list of authors, year of publication, sample size, study design, and baseline characteristics of enrolled patients. Moreover, we extracted outcomes if reported as follows: detection of sialolithiasis, stenosis with stones, sialectasis, stricture and main duct and the diagnostic accuracy

of sialolithiasis and stenosis with stones according to glands; in addition, the same outcomes according to patients.

Risk-of-bias assessment

We evaluated the methodological quality of included studies using Quality Assessment of Diagnostic Accuracy Studies (QUADAS) [8] and Standards for Reporting Studies of Diagnostic Accuracy (STARD) [9], to assess the risk of bias among included studies. The QUADAS tool includes the following domains: patient selection, index and comparator test, reference standard, and flow and timing. The judgment of authors are 'Yes,' 'No,' and 'unclear risk.' According to Egger and colleagues, the assessment of publication bias using the funnel plot method and the Egger's test is unreliable for less than 10 included studies. Therefore, in the present study, we could not assess for publication bias owing to the small number of included studies [10,11].

Data synthesis

Dichotomous data of efficacy outcomes were pooled as risk ratio (RR) using the Mantel-Haenszel method. We performed all statistical analysis in this study by RevMan software package (version 5.3; Cochrane Collaboration, Oxford, UK) and Meta-DiSc (version 1.4). We assessed the statistical heterogeneity using the χ^2 test and its extent measured by I^2 test. We used random effect model between all studies to minimize the heterogeneity if present; otherwise, the fixed-effects model was used. We performed a sensitivity analysis to assess the contribution of each study to the pooled estimation by excluding one trial at a time and recalculating the combined mean difference estimation for the remaining studies.

Results

Results of the literature search

After searching five databases, we obtained 149 citation after removing duplicates. We started records title and abstract screening, and 37 studies were eligible for full-text screening then we involved about eight studies [12–19], which met our inclusion criteria (as shown in PRISMA follow diagram (Supplementary File No. 1).

Characteristics of the included studies

The included studies were randomized clinical trials and observational studies with a total number of 285 patients. Included studies compared the diagnostic performance of MRS and CS in detection of radiological

findings in salivary gland diseases. The summary of included studies and the baseline characteristics of their population are shown in Table 1.

Quality of the evidence

The quality of included studies was high quality according to Quality Assessment of Diagnostic Accuracy Studies (QUADAS) and Standards for Reporting Studies of Diagnostic Accuracy (STARD). Quality assessment domain summary is shown in Fig. 1 (authors' judgment with justifications is shown in Supplementary File No. 2).

Outcomes

Our primary outcomes are detection of radiological findings (sialolithiasis, stenosis with stones, sialectasis, strictures, and main duct) and the diagnostic performance of these findings (sialolithiasis and stenosis with stones).

Radiological findings outcomes

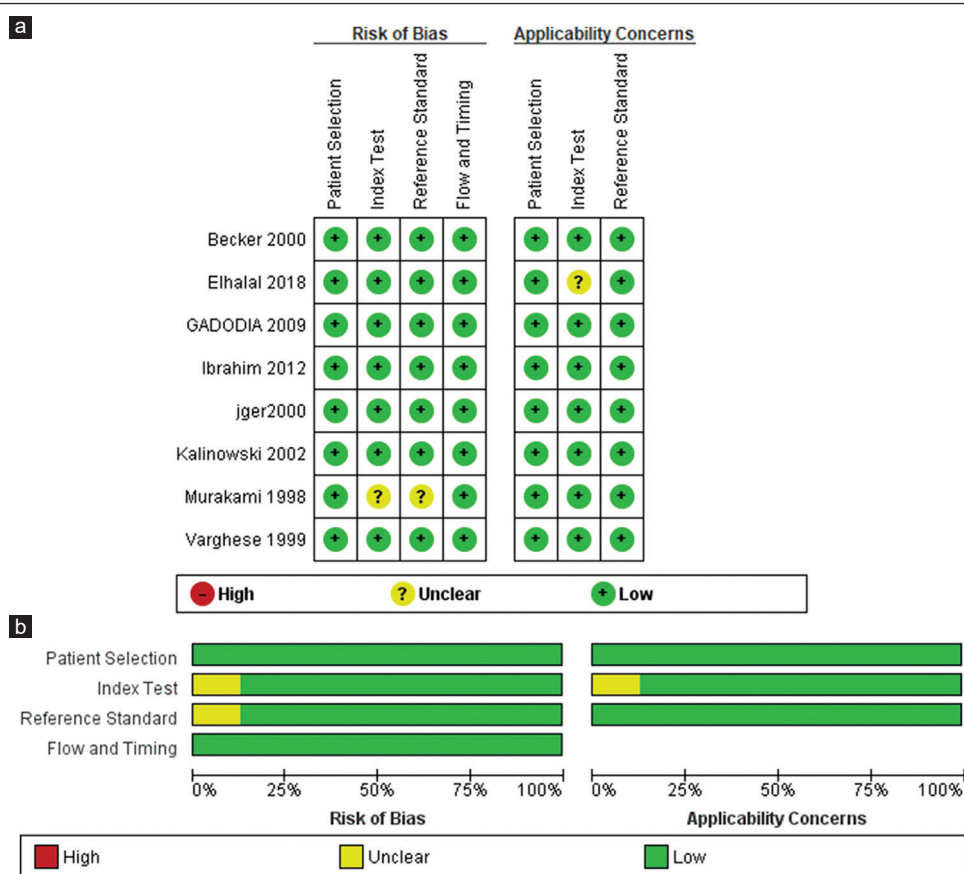
Data according to number of glands: four included studies with a total of 61 glands in MRS and 61 glands in CS recorded sialolithiasis. The subgroup analysis showed no significant difference between MRS and CS in term of sialolithiasis [RR = 0.93, 95% confidence interval (CI), 0.83–1.04, $P = 0.23$]. Although two studies reported stenosis with stones, the subgroup analysis showed no significant difference between the two groups in term of stenosis with stones (RR = 0.93, 95% CI, 0.81–1.08, $P = 0.34$). The analysis of subgroups showed no significant difference between MRS and CS in term of sialectasis (RR = 0.92, 95% CI, 0.74–1.15, $P = 0.47$) and in term of stricture (RR = 1, 95% CI, 0.54–1.86, $P = 1$). Moreover, the overall effect estimate showed no significant difference between the two groups in term of radiological findings according to glands (RR = 0.93, 95% CI, 0.86–1.01, $P = 0.11$). All pooled studies and subgroups were homogenous ($P = 0.76$); $I^2 = 0\%$ ($P = 1$); $I^2 = 0\%$; except stenosis with stones, which showed

Table 1 Baseline characteristics of the population and studies

ID	Study groups	Number of patients	Age mean (range)	Sex [n (%)]		Type of gland [n (%)]			Patients
				Male	Female	Parotid	Submandibular	Total (n)	
Ibrahim 2012	MRS and CS	28	47 (NA)	20	8	NA	NA	25	The presenting symptoms were recurrent: painful salivary gland swelling in 6 patients, swelling in the floor of the mouth in 4 patients, pain and swelling during mastication in 7 patients, recurrent submandibular or parotid swelling in 5 patients and swelling of the salivary gland related to eating in 6 patients
Becker <i>et al.</i> [15]	MRS and CS	61	44 (6-85)	42	19	25	39	64	Patients with acute or recurrent salivary glandular swelling and no palpable mass
Gadodia 2009	MRS and CS	26	31 (3-65)	19	9	NA	NA	34	Patients with suspected inflammatory salivary glandular swelling
Kalinowski <i>et al.</i> [16]	MRS and CS	65	47 (9-78)	34	31	48	33	81	All patients had swelling and/or pain of one or more salivary glands. Indication for digital subtraction sialography was to verify sialolithiasis or inflammatory ductal changes. Patients suspected of having sialadenitis were investigated only if all clinical signs of acute inflammation had disappeared
Jäger <i>et al.</i> [13]	MRS and CS	20	NA	NA	NA	NA	NA	NA	Patients who were clinically suspected of having of sialolithiasis of the submandibular duct
Elhalal <i>et al.</i> [17]	MRS and CS	24	22 (22-69)	14	10	NA	NA	NA	Patients sharing some signs and symptoms as swelling of the submandibular or parotid regions, pain during mastication, feeling of a hard object in the oral cavity near the orifices and/or feeling of discharging duct artifices
Murakami <i>et al.</i> [18]	MRS	12	NA	NA	NA	NA	NA	NA	Patients with possible or definite abnormalities of the salivary glands were studied with a 1.5-T superconductive unit with a 25 mT/m maximum gradient capability (Magnetom Vision; Siemens, Erlangen, Germany) and a standard head coil
Varghese <i>et al.</i> [14]	MRS and CS	49	47 (16-78)	23	26	29	20	49	All patients were referred from the otolaryngology outpatient clinic for CS with presenting symptoms of intermittent pain and swelling of the salivary glands related to eating (61%), persistent facial swelling (33%), chronic parotitis (6%), and dry mouth (6%)

CS, conventional sialography; MRS, magnetic resonance sialography; NA, not available in the published paper.

Figure 1



(a) Methodological quality summary. (b) Methodological quality graph.

some heterogeneity; therefore, the fixed-effects model was used as shown in Fig. 2a.

Two studies reported detection of the main duct. The two studies showed some heterogeneity ($P = 0.1$), $I^2 = 63\%$; therefore, the random effects model was used. There is no significant difference between MRS versus CS (RR = 0.98, 95% CI, 0.9–1.06, $P = 0.62$) as shown in Fig. 3a.

Data according to number of patients: some papers reported the same outcomes but according to the number of patients. The subgroup analysis reported by two papers showed no significant difference between MRS and CS in terms of sialolithiasis (RR = 0.93, 95% CI, 0.81–1.07, $P = 0.31$). As two papers recorded stenosis with stones, the analysis of subgroup showed no significant difference between MRS and CS (RR = 0.75, 95% CI, 0.34–1.65, $P = 0.47$). Moreover, two studies reported sialectasis and stricture, and the analysis of subgroup showed no significant difference in term of either sialectasis (RR = 1.23, 95% CI, 0.53–2.86, $P = 0.64$) or stricture (RR = 1.05, 95% CI, 0.73–1.51, $P = 0.79$). The overall effect estimate showed no significant difference between the two groups in term of radiological findings according to patients (RR = 1, 95% CI, 0.84–1.18, $P = 0.98$). These

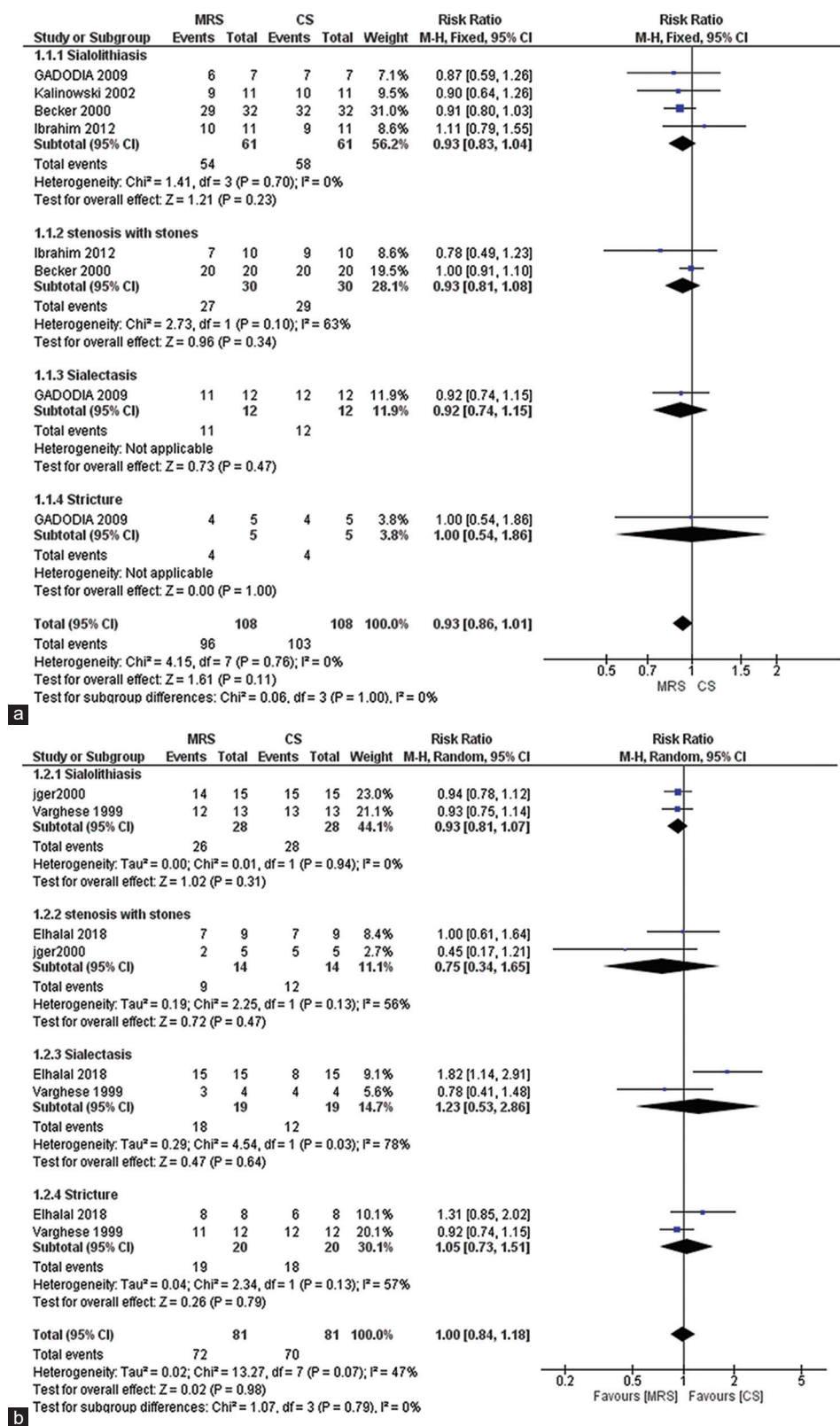
studies were statistically heterogeneous ($P = 0.07$), $I^2 = 47\%$; therefore, the random effect model was used as shown in Fig. 2b.

Three studies reported detection of the main duct. The three studies showed no heterogeneity ($P = 0.70$), $I^2 = 0\%$; therefore, the fixed-effect model was used. There is a significant difference between MRS versus CS favoring the MRS over CS (RR = 0.84, 95% CI, 0.71–1, $P = 0.05$), as shown in Fig. 3b.

Diagnostic performance

Sialolithiasis: three studies [14,17,18] reported sensitivity and specificity for detection of sialolithiasis according to the number of glands. The sensitivity for Becker *et al.* [15], Gadodia *et al.* [12], and Kalinowski *et al.* [16] was 0.91 (95% CI, 0.75–0.98), 0.86 (95% CI, 0.42–1.00), and 0.8 (95% CI, 0.44–0.97), AbdelMaboud Ibrahim NM [19] respectively. The pooled sensitivity was 0.88 (95% CI, 0.75–0.95) with no heterogeneity ($P = 0.68$), $I^2 = 0\%$, whereas the specificity of these three studies was as follows: 0.97 (95% CI, 0.84–1.00), 1.00 (95% CI, 0.29–1.00), and 0.98 (95% CI, 0.92–1.00), respectively. The pooled specificity was 0.98 (95% CI, 0.93–1.00) with no heterogeneity ($P = 0.82$), $I^2 = 0\%$.

Figure 2

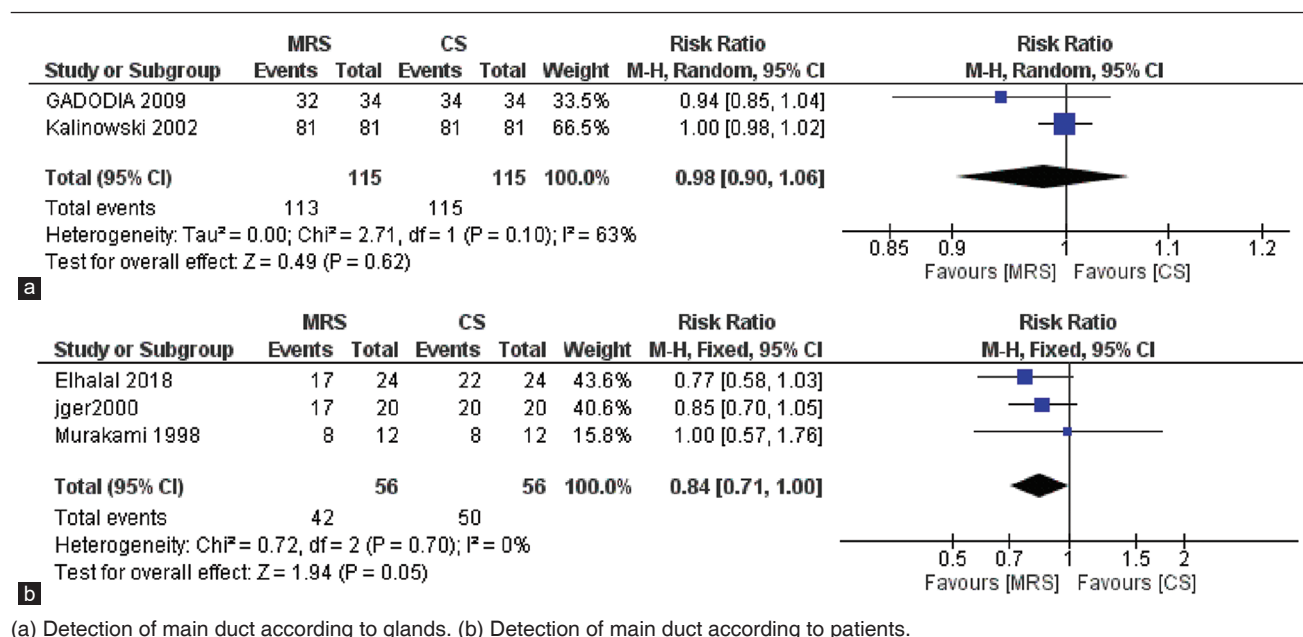


(a) Radiological findings according to glands. (b) Radiological findings according to patients.

Moreover, the positive likelihood ratio for these studies was 29 (95% CI, 4.2–200.26), 6.5 (95% CI, 0.48–88.76), and 52.8 (95% CI, 7.37–378.46), respectively, and the pooled LR + was 26.35 (95% CI, 7.78–89.25) with no heterogeneity ($P = 0.449$),

$I^2 = 0\%$. However, the negative likelihood ratio was 0.097 (95% CI, 0.03–0.29), 0.21 (95% CI, 0.05–0.95), and 0.2 (95% CI, 0.06–0.7), respectively, and the pooled LR – was 0.149 (95% CI, 0.07–0.304), with no heterogeneity ($P = 0.58$), $I^2 = 0\%$.

Figure 3



(a) Detection of main duct according to glands. (b) Detection of main duct according to patients.

In addition, the diagnostic odds ratio under random effect was 299.67 (95% CI, 29.48–3046.7), 30.3 (95% CI, 0.959–959.68), and 260 (95% CI, 21.12–32.2). These three studies showed no heterogeneity ($P = 0.71$), $I^2 = 0\%$. The pooled diagnostic odds ratio (DOR) was 181.64 (95% CI, 39.420–837), as shown in Supplementary File No. 3.

There was a paper by Jeger *et al.* [15] which reported sialolithiasis according to the number of patients. The sensitivity and specificity were 0.77 (95% CI, 0.55–0.92) and 0.00 (95% CI, 0.00–0.84), respectively.

Stenosis with stones: two studies [16,19] reported sensitivity and specificity for detection of stenosis with stones according to the number of patients. The sensitivity for Elhalal *et al.* [17] and Varghese *et al.* [14] was 0.78 (95% CI, 0.40–0.97) and 0.69 (95% CI, 0.39–0.91), respectively. The pooled sensitivity was 0.727 (95% CI, 0.498–0.893), with no heterogeneity ($P = 0.656$), $I^2 = 0\%$. However, the specificity was 1 (95% CI, 0.78–1.00) and 0.97 (95% CI, 0.84–1.00), respectively, and the pooled specificity was 0.979 (95% CI, 0.889–0.99), with no heterogeneity ($P = 0.39$), $I^2 = 0\%$.

Moreover, the positive likelihood ratio for these studies was 24 (95% CI, 1.532–376) and 22.846 (95% CI, 3.206–162.81), and the pooled LR + was 23.229 (95% CI, 4.697–114.87), with no heterogeneity ($P = 0.977$), $I^2 = 0\%$. However, the negative likelihood ratio was 0.258 (95% CI, 0.088–0.758) and 0.317 (95% CI, 0.14–0.719), respectively, and the pooled LR – was 0.294 (95% CI, 0.153–0.564), with no heterogeneity ($P = 0.764$), $I^2 = 0\%$.

In addition, the diagnostic odds ratio under random effect was 93 (95% CI, 3.949–2190) and 72

(95% CI, 7.127–727.34). These two studies showed no heterogeneity ($P = 0.898$); $I^2 = 0\%$. The pooled DOR was 78.73 (95% CI, 2.18–508.81), as shown in Supplementary File No. 4.

There was a paper by Becker *et al.* [17] which reported the stenosis with stones according to the number of glands. The sensitivity and specificity were 1 (95% CI, 0.83–1.00) and 0.98 (95% CI, 0.88–1.00), respectively.

Discussion

The common clinical indications of salivary gland imaging are pain and swelling. Imaging methods for the salivary glands include plain radiography, sialography (conventional, CT, and MRI), high-resolution ultrasonography, CT, MRI, and radionuclide scintigraphy [20]. It is important to choose the best imaging modality regarding cost, radiation, accuracy, reliability, and patient satisfaction [21].

Yet, CS still is the method that provides high-spatial resolution images for examining the anatomical features of the salivary ducts and assessing their ductal abnormalities. CS indications are sialoliths, strictures, diverticula, autoimmune diseases, and sialosis [22]. However, it is an invasive examination that may cause inconvenience and a risk of complications, such as dye retention, inability to duct cannulation, and intraprocedural or postprocedural pain [23]. The examination is contraindicated in acute sialadenitis and in cases of former allergic reactions to iodine-containing contrast agent [20].

For us too, this explains the need of a noninvasive diagnostic method like MRS.

Diagnostic imaging of salivary glands has been revolutionized with the advent of cross-sectional imaging modalities like MRI, avoiding most of the complications and contraindications of CS [24]. MRS is based on the rule of imaging stationary fluids using single-shot RARE sequence as it was first described by Lomas *et al.* [25]. Since then, various investigators performed MRS by using other sequences such as fast spin echo [26–28], constructive interference in steady state (CISS) [29], and half-Fourier acquisition single-shot turbo spin-echo (HASTE) [30].

In this systematic review and meta-analysis, we found that there is no significant difference in radiological findings between MRS and CS regarding detection of sialolithiasis. Gadodia *et al.* [12] may support this sentence as it showed no significant difference between MRS and CS in sialolithiasis. However, in the same paper when they combined CISS sequence with HASTE sequence, it showed that MRS was superior to CS in seven glands, because it enabled the upstream imaging of the ductal system which was not seen at CS owing to near-total obstruction by distal calculus (Fig. 4).

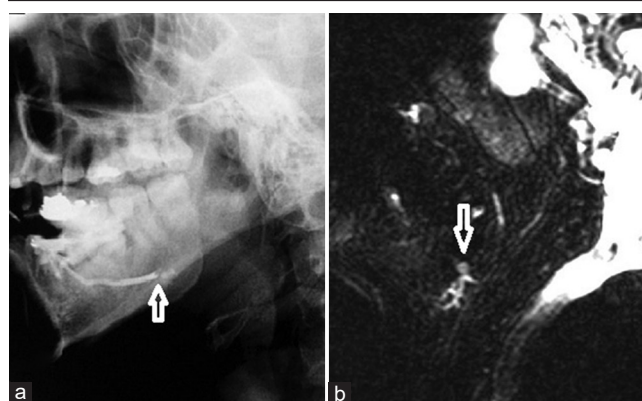
Furthermore, Jäger and colleagues compared three techniques in MRS which were 3D CISS, RARE, and T1-T2 turbo fast spin echo, and they conclude that 3D CISS showed superior significance to RARE and T1-T2 turbo spin-echo for detecting the gland sialoliths. The major advantage of 3D CISS is the ability to yield oblique images with the multiplanar reconstruction procedure. Moreover, they reported a higher sensitivity of 3D CISS than other techniques; however, in one case, fibrous tissue was missed resulting in the reduction of specificity [13]. The sensitivity and

specificity of detection of calculi using different MR sequences by different investigators ranged from 80 to 100% and 80 to 94% [13–16], because the diagnosis of sialolithiasis is based on indirect signs such as areas with complete obstruction. Therefore, small nonobstructing ducts will be missed in most cases, especially the sialoliths close to orifice which are difficult to be diagnosed with MR using HASTE. However, Gadodia *et al.* [12] combined CISS and HASTE sequences and concluded with 100% sensitivity and 100% specificity for detection of sialolithiasis.

In stenosis with stones, we found that there is no significant difference in revealing stenosis with stones according to either glands or patients in the included studies. However, according to Varghese and colleagues they found that MRS had poor sensitivity of duct stenosis with stones because there was no rim of high signal intensity saliva which makes them stand out against the soft tissue background. Although when they combined the control radiographs to MRS, they revealed stenosis with stones with 100% sensitivity and specificity, because control radiographs showed the calcification but not the localization. Moreover, administration of sialogogues may lead to pooling the saliva around stenosis with stones, hence making them more obvious in MRS [14].

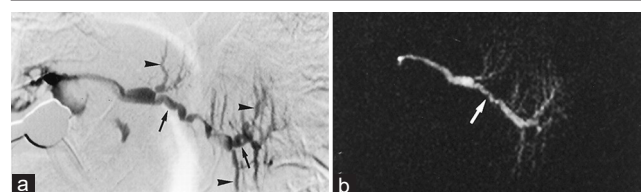
Regarding strictures and sialectasis (Fig. 5), we found no difference between MRS compared with CS in either patients or glands. Gadodia and colleagues were the only ones who reported them according to glands; however, they were able to diagnose all strictures in all patients when they combined CISS with HASTE, where MRS was useful in tight strictures and was superior to CS, as the opacification of the strictures and the proximal dilated duct was difficult on CS. This combination makes detection easier because of CISS three-dimensional nature and the pathology of diseases is confirmed in multiple views. On combining the two

Figure 4



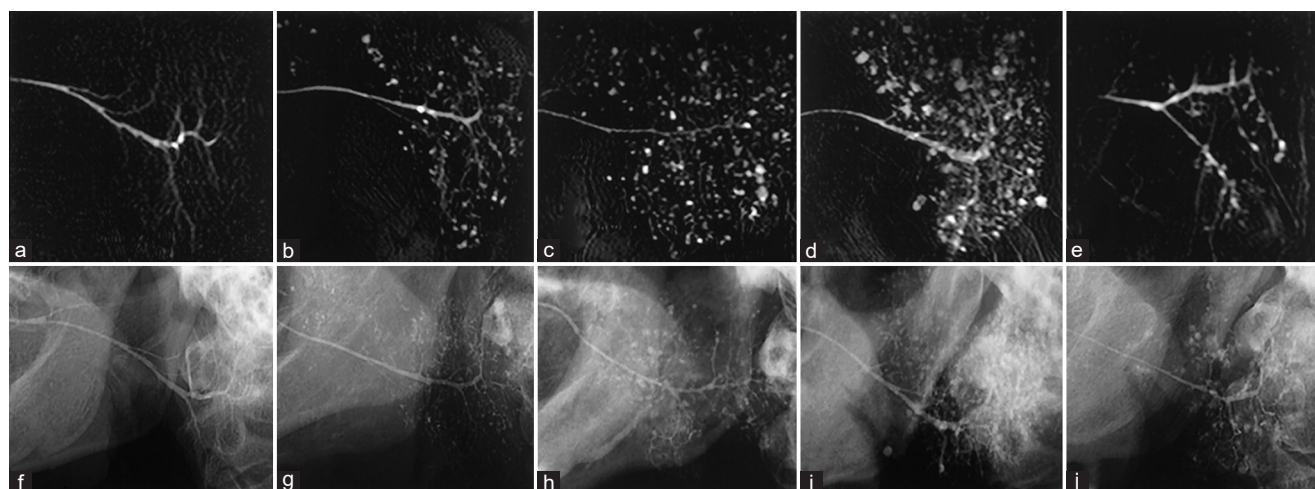
Sialolith in the proximal main duct of right submandibular gland. (a) Right lateral view of conventional sialogram showing cessation of contrast in the proximal main submandibular duct. (b) Sagittal MR sialogram of the right submandibular gland reveals the mild dilatation with beading of the intraglandular branches with the stone (arrow) in the proximal part of the right submandibular duct [17].

Figure 5



A 59-year-old man with a history of chronic sialadenitis of the left parotid gland. (a) Lateral digital subtraction sialogram shows multiple strictures, sialectasis, and prestenotic dilatation of the Stensen duct (arrows) and also of secondary and tertiary branching intraglandular ducts (arrowheads). (b) Lateral MR sialogram shows the same abnormal findings but at lesser spatial resolution. Subtle strictures are more difficult to visualize and sialectasis is not as prominent (arrow). The enlargement of the ductal system is demonstrated up to secondary branching ducts [16].

Figure 6



(a–j) MR sialograms (a–e) and conventional sialograms (f–j) of the parotid glands in patients with xerostomia with or without Sjögren's syndrome: grade 0 (a and f), grade 1 (b and g), grade 2 (c and h), grade 3 (d and i), and grade 4 (e and j). Note apparent differences in sialographic features at grade 4 (e vs. j) [31].

sequences, the sensitivity and specificity were 93 and 100%, respectively [12]. These results are in line with Varghese *et al.* [14], Elhalal *et al.* [17], and Kalinowski *et al.* [16] where MRS showed the extent of strictures and excluded the proximal stricture as tandem lesion or calculi. Owing to the better visualization of the upstream portions of salivary glands and strictures involving the distal third of the main duct, MRS was superior to CS. However, CS was superior to MRS in demonstration of the distal ducts, concretions, and changes of sialodochitis [12].

In addition, Varghese and colleagues showed that MRS gave full clear delineation of sialectasis compared with CS; however, CS is highly sensitive in showing sialectasis (Fig. 6), but the necessity of injection of contrast materials causes exacerbation of the process of inflammation leading to increase in pain and discomfort. Thus, MRS proves to be a valuable noninvasive alternative to CS in these patients [14].

This is the first meta-analysis that compares between MRS with different sequences and CS. Our limitations in our study are the small number of included studies that might have played an essential role in our outcomes and our heterogeneity, and some outcomes are not measured by some papers.

Moreover, the small sample size in our studies makes a need for more studies in this field. Furthermore, we excluded non-English studies. However, recent evidence suggests that excluding non-English studies does not produce a bias to meta-analysis [32]. Our recommendations are to increase the number of studies comparing different sequences of MRS with CS to conclude better results about that.

Conclusion

Our study reveals that MRS is a potentially diagnostic tool that can replace invasive imaging methods such as CS.

Moreover, overall CS continues to be the standard technique of imaging. However, when the insertion of cannula is not successful or there is an acute sialadenitis, an alternative way is required, which can be MRS, especially when it is performed with a combination of CISS and HASTE sequences.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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