Evaluation of Salivary Gland Lesions by Real Time Sonoelastography: Diagnostic Efficacy and Comparative Analysis with Conventional Sonography

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ABSTRACT

Introduction: Imaging of salivary gland lesions is a major challenge for radiologists and differentiation of malignant and benign lesions is extremely important. The current modalities ultrasonography, Computed Tomography (CT) and Magnetic Resonance Imaging (MRI), despite being highly sensitive, lack the accuracy in differentiating benign and malignant lesions. Sonoelastography is a novel imaging modality that identifies elasticity of tissues. Most of the malignant lesions are harder due to desmoplastic reaction, making sonoelastography, a paramount non-invasive technique and its importance needs no further emphasis.

Aim: To investigate the diagnostic efficacy of Sonoelastography in the evaluation of major salivary gland lesions and comparative analysis of its sensitivity and specificity with conventional Sonography.

Materials and Methods: A total of fifty-one patients with salivary gland lesions (including inflammatory, reactive, benign and malignant) were evaluated from December 2015-June 2017 by conventional sonography and sonoelastography. The sonoelastography image was evaluated using colour coding ranging from blue (soft) through green and red (hard) and strain ratios were calculated. Then, grading was done according to the 4-point elastography score and results compared with histopathology findings. Statistical analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0. Receiver Operating Characteristic (ROC) analysis, Fisher's-exact test and Chi-square tests were used statistically and best cut-off value of strain ratio and elastography score for predicting malignancy was determined. p-value of <0.05 was considered as statistically significant.

Results: Of the 51 lesions (21 in females and 30 in males) mean age of subjects 39.3±12.9 years, 35 were located in parotid and 16 in submandibular gland; 39 being benign and 12 malignant. The diagnostic accuracy of sonography, elastography score and strain ratio was determined in comparison to pathological diagnosis. It was found that the value of elastography score alone is not significant (p=0.308) with low sensitivity and negative predictive value (41.67% and 82.93%, respectively). However, strain ratio showed statistically significant difference (p<0.0001) with high sensitivity and Negative Predictive Value (NPV) (100% each) in differentiating benign and malignant lesions.

Conclusion: The parameters used in sonoelastography are strain ratio (Semi quantitative) and Elastography score (Qualitative). Strain ratio adds to the diagnostic efficacy of conventional sonography by attaining high sensitivity and NPV while Elastography score has a limited role in enhancing the diagnostic efficacy of conventional ultrasound.

Keywords: Benign, Imaging, Lesions, Malignant, Pathology

INTRODUCTION

Salivary gland neoplasms constitute up to 5% of all head and neck tumours. The incidence of salivary gland neoplasms as a whole is approximately 2.5-3 cases per 100,000 individuals per year with malignant neoplasms accounting for 0.9 cases per 100,000 [1]. Mortality from malignant salivary gland neoplasms varies with stage and pathology, the overall 5-year survival rate being 72% [1].

The majority of salivary gland neoplasms arise in the parotid glands (80%) and rest (10-15%) in the submandibular glands [1]. About 80% of parotid neoplasms are benign, with higher proportion of malignancy in the smaller glands [2]. The most common benign tumour of parotid and submandibular gland is pleomorphic adenoma, which represents about 60% of all parotid neoplasms. The most common malignant tumours are mucoepidermoid and adenoid cystic carcinoma in parotid and submandibular gland respectively [3]. The preoperative demarcation between malignant and benign salivary tumour is important for surgical preparation [4].

Currently, ultrasonography (USG), CT and MRI are the imaging modalities for evaluation of salivary gland lesions. Ultrasonography is a time and cost-effective, easy to apply, and radiation free method which needs no contrast agent administration. CT and MRI provide more information about the relationship with surrounding tissues of the tumour but, are time consuming, costly and occupied in all settings. Despite high sensitivity of these imaging modalities, the accuracy in predicting the histopathology of lesions is limited because of considerable overlap between the imaging features of benign and malignant salivary gland lesions [2].

If there is a doubt regarding malignancy, then superficial or total parotidectomy and neck dissection are the treatment approaches [5]. Therefore, presuming the characteristics of the tumour before surgery is of utmost importance [6,7].

Sonoelastography is a new dynamic imaging technique that measures tissue stiffness with qualitative, quantitative and semi-quantitative parameters. Most of the malignant lesions are harder than benign lesions due to associated desmoplastic reaction. Elastography is mainly focused on this principle and determines the stiffness of mass by measuring the degree of strain related distortion under the application of an external force, thereby differentiating the nature of the lesions [8]. However, the application of sonoelastography is relatively new and still evolving. Further studies are still required to validate and establish its role in salivary gland imaging.

Hence, the aim of this study was to investigate the diagnostic efficacy of sonoelastography in characterisation of major salivary gland lesions and analyse its role as an adjunct modality to grey scale ultrasound using histopathology as gold standard.

MATERIALS AND METHODS

This prospective cross-sectional study included 51 subjects presenting with salivary gland lesion to the Department of Radiodiagnosis, VMMC and Safdarjung Hospital, for a duration of 18 months (December 2015-June 2017). A written bilingual informed consent was taken before enrolling the subject for the study.

Inclusion criteria: All patients with clinically suspected lesions of parotid or submandibular glands of all age groups and both sexes were included.

Exclusion criteria: Those who had mass with ulcerated or raw surface or involvement of whole of the gland by the lesion were excluded from the study. The study was approved by the institution's Ethics and Research Committee (IEC/VMMC/SJH/S. No:976).

Sample size was calculated by using qualitative variables based on the study by Li C et al., and with its values as reference, the minimum sample size of 51 was determined with desired precision of 25% and 5% level of significance [9].

Grey scale ultrasound of the concerned salivary gland was performed with linear array transducers of frequency 5-17 MHz and 3-9 MHz and the shape, size, margin and echo-pattern of the lesions were determined. Doppler assessment was also done to evaluate the presence and pattern of vascularity.

Subsequently, sonoelastography was performed using linear array transducer of frequency between 5 and 17 MHz with same depth focus and gained settings as for grey scale imaging. The grey scale and sonoelastography images were displayed side by side on a dual screen. The elastogram image of the detected lesion, was evaluated using colour coding ranging from blue (soft) [Table/Fig-1] through green (intermediate/average hardness) [Table/Fig-2,3] and red (hard) [Table/Fig-4]. All lesions were scored on elastogram in terms of their stiffness compared to normal parenchyma using a 4-grade system like the grading presented by Dumitriu D et al., [10].
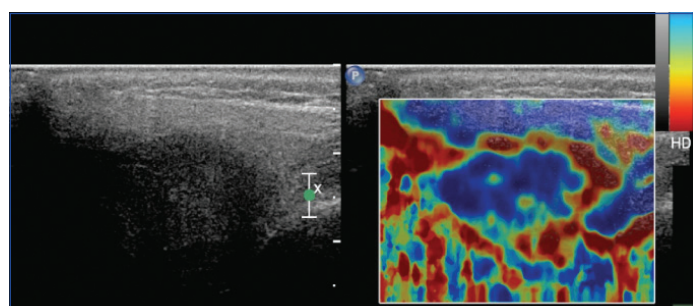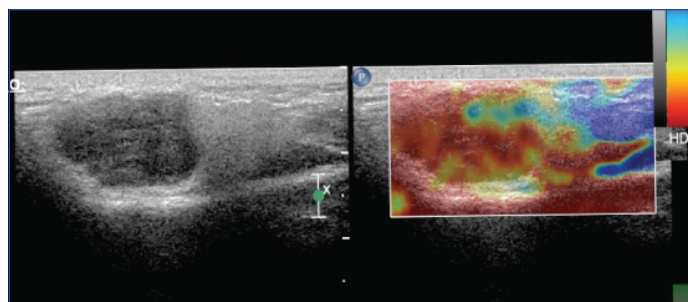

[Table/Fig-1]: Conventional sonography of salivary gland lesion and corresponding elastogram showing a solid mass with soft areas (blue:elasticity) -pattern1.
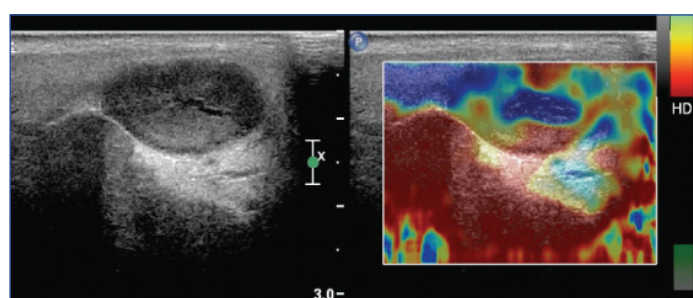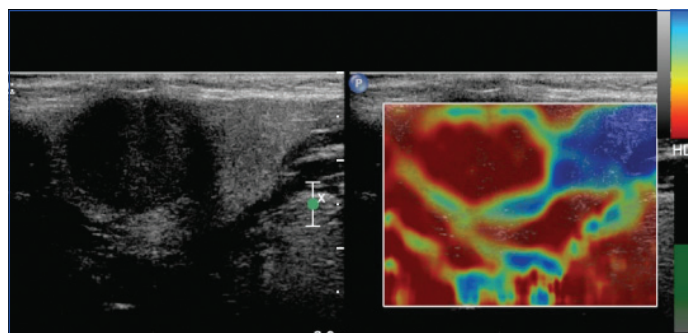

[Table/Fig-2]: Conventional sonography of salivary gland lesion and corresponding elastogram showing a predominantly solid lesion with soft areas (blue: elasticity) in larger part of lesion, with inconstant appearance of hard (red: anelastic) areas-pattern 2.

Strain ratio values of all the lesions were calculated individually [Table/Fig-5]. Ultrasound guided fine needle biopsy was done in all the patients under complete aseptic precautions. In patients

[Table/Fig-3]: Conventional sonography of salivary gland lesion and corresponding elastogram showing a solid mass with few soft areas (blue: elasticity), with constant appearance of predominant hard areas (more than 50%; red: anelastic) areas -pattern 3.

[Table/Fig-4]: Conventional sonography of salivary gland lesion and corresponding-elastogram showing a solid lesion with uniformly hard (red: anelastic) areas -pattern 4.
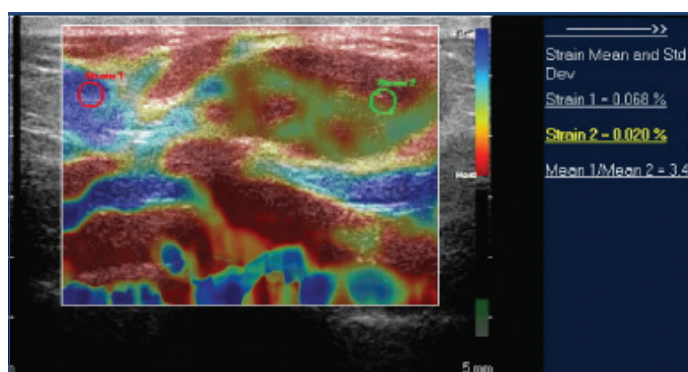
[Table/Fig-5]: Strain elastography of a lesion in parotid gland shows the predominantly red colour of the lesion on colour map and a strain ratio of 3.45.

who underwent surgery, histopathology was considered as the gold standard. Elasticity scores and strain ratio calculations were compared with histopathology results.

STATISTICAL ANALYSIS

The data was entered in MS EXCEL spreadsheet and analysis was done using SPSS version 21.0. Interpretation of the diagnostic modalities i.e., Ultrasound including Doppler and Elastography was compared with the pathology findings with regard to specificity, sensitivity, Positive Predictive Values (PPV) and Negative Predictive Values (NPV). Categorical variables were expressed in number and percentage (%) and continuous variables as mean±SD and median. Qualitative variables were correlated using Fisher's-exact test. Inter-rater kappa agreement was used to find out the strength of agreement of ultrasound and elastography with FNAC and agreement value was good. A combined approach using both ultrasound and strain ratio was also analysed using paired t-test. ROC curve was used to find out best cut-off point of elastography score and strain ratio for predicting malignancy. p-value of <0.05 was considered as statistically significant.

RESULTS

A total of 51 patients (21 females and 30 males; age ranging from 6 to 70 years and mean age 39.3±12.9 years) with one salivary gland lesion each were evaluated with grey scale ultrasound and sonoelastography. FNAC/histopathology was performed

in all of them. Fourteen patients had lesions in left parotid and 21 in right parotid, 6 in right submandibular gland and 10 in left submandibular gland.

The echogenicity, internal structure, margins and vascularity characteristics of the masses that have been observed on grey-scale ultrasound and Doppler are shown in [Table/Fig-6]. The spectrum of pathological diagnosis of the lesions based on histopathology is tabulated in [Table/Fig-7].

Characterstics of the lesions	Benign/Malignant on FNAC/ Histopathology		Total	p-value
	Benign	Malignant		
Echogenecity				
Heteroechoic	14	25		
Hypoechoic	10	0	51	0.049
Isoechoic	02	0		
Margins				
Poorly defined	5	6	51	0.006
Well defined	34	6		
Internal components				
Cystic	11	0	51	0.048
Solid	28	12		
Vascularity				
Central	0	2		
Mixed	5	19	51	0.005
Peripheral	25	0		

[Table/Fig-6]: Ultrasound and Doppler characteristics of the Lesions according to Histological subtypes.

Pathological diagnosis	No. of lesions	Percentage
Abscess	3	5.88%
Adenoid cystic carcinoma	3	5.88%
Epidermal inclusion cyst	2	3.92%
Lymphangioma	2	3.92%
Mucocele	4	7.84%
Mucoepidermoid carcinoma	8	15.69%
Mucus retention cyst	1	1.96%
Pleomorphic adenoma	26	50.98%
Squamous cell carcinoma	1	1.96%
Warthin tumour	1	1.96%
Total	51	100%

[Table/Fig-7]: Spectrum of Pathological diagnosis of the lesions based on HP/FNAC. Qualitative variables were correlated using Fisher's-exact test

The imaging results of conventional sonography were compared with pathological diagnosis [Table/Fig-8] and the diagnostic accuracy was determined using histopathology as gold standard, which showed a sensitivity of 66.67%, specificity of 97.44%, PPV of 88.89% and NPV of 90.48%.

Types of tumour	Pathology diagnosis		Total (n=51)
	Benign	Malignant	
Benign	38 (74.51%)	4 (7.84%)	42 (82.35%)
Malignant	1 (1.96%)	8 (15.69%)	9 (17.65%)
Total	39 (76.47%)	12 (23.53%)	51 (100%)

[Table/Fig-8]: Cross tabulation conventional sonography and pathological diagnosis. Inter rater kappa agreement to find out the strength of agreement of sonography with pathology and diagnostic test to assess the sensitivity, specificity, NPV and PPV and agreement value was good

Further, the imaging results of sonoelastography were compared with pathological diagnosis and the diagnostic accuracy of elastography score and strain ratio was determined [Table/Fig-9,10]. Elastography score showed a sensitivity of 41.67%, specificity of 87.18%, PPV of 50% and NPV of 82.93%. The value of

elastography score alone was not found to be significant (p=0.308) with low sensitivity. However, strain ratio shows statistically significant difference (p<0.0001) with high sensitivity and NPV in differentiating benign and malignant lesions. Mean strain ratio of malignant lesions was 3.19±2.6 and strain ratio of >3 showed sensitivity 100%, specificity 84.62%, PPV 66.67% and NPV 100% as an indicator of malignancy. When we used both ultrasound and strain ratio using paired t-test the specificity was 100%, PPV 100% and NPV 86.67%, however sensitivity was reduced to 50%, hence ROC curves were used to find out best cut-off point and diagnostic accuracy of strain ratio [Table/Fig-11] and elastography score [Table/Fig-12] for predicting malignancy. A cut-off value of >3.7 for strain ratio and >3 for elastography score was determined to predict malignant lesion [Table/Fig-13].

		Benign/Malignant on FNAC/HP			p-value
		Benign	Malignant	Total	
Strain ratio	≤3	33 (84.62%)	0 (0%)	33 (64.71%)	<0.0001
	>3	6 (15.38%)	12 (100%)	18 (35.29%)	
Total		39 (100%)	12 (100%)	51 (100%)	

[Table/Fig-9]: Cross tabulation of Strain ratio and Pathological diagnosis. Inter rater kappa agreement to find out the strength of agreement of sonoelastography with pathology and diagnostic test to assess the sensitivity, specificity, NPV and PPV and agreement value was good

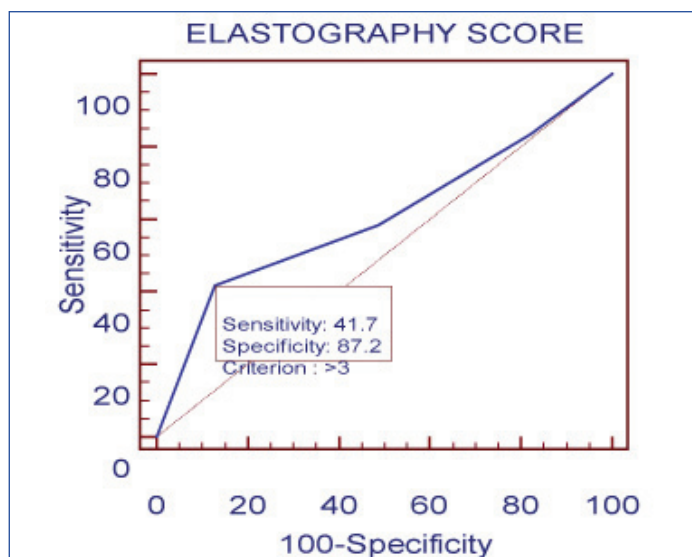|		Pathological diagnosis			p-value
		Benign	Malignant	Total	
Elastography score	1	7 (17.95%)	2 (16.67%)	9 (17.65%)	
	2	13 (33.33%)	3 (25%)	16 (31.37%)	
	3	14 (35.90%)	2 (16.67%)	16 (31.37%)	0.3083
	4	5 (12.82%)	5 (41.67%)	10 (19.61%)	
Total		39 (100%)	12 (100%)	51 (100%)	

[Table/Fig-10]: Cross tabulation of Elastography score and Pathological diagnosis. Inter rater kappa agreement to find out the strength of agreement of sonoelastography with pathology and diagnostic test to assess the sensitivity, specificity, NPV and PPV and agreement value was good
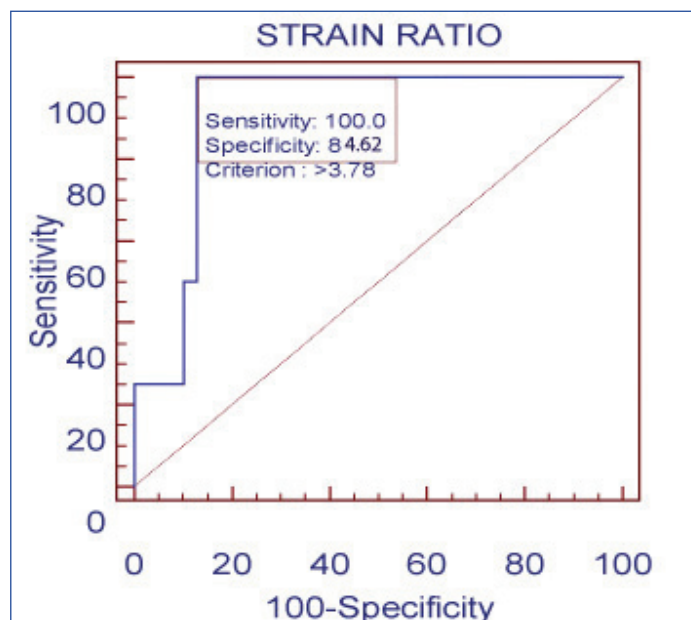
[Table/Fig-11]: ROC of strain ratio.

DISCUSSION

Imaging and differentiation of benign and malignant salivary gland lesions is still a challenge to radiologists. The conventional sonographic features which suggest probably malignant nature of a lesion include irregular shape, ill-defined margins, heterogeneous appearance and increased vascularity. The sonographic features of probably benign lesion include round or ovoid shape, circumscribed well-defined margins and homogeneous appearance [11]. Pre-

ELASTOGRAPHY SCORE

Sensitivity: 41.7
Specificity: 87.2
Criterion : >3

[Table/Fig-12]: ROC of elastography score.

for malignancy [15]. The present study found that the mean strain ratio of malignant lesions was 3.19±2.6. Using SR >3 as an indicator of malignancy we found 33 benign and 18 malignant lesions (p-value <0.0001 which was statistically significant). However, out of these 18 malignant lesions, 6 were found to be benign on pathological examination. All the false positive lesions were pleomorphic adenomas. This can be explained by the fact that pleomorphic adenomas, can have an important fibrous, stiff component which results in a higher strain ratio and elastography score; which was also observed in the first study by Dumitriu D et al., [10].

Farasat M et al., conducted a study on 27 lesions (25 in parotid and 2 in submandibular gland including 20 benign and 7 malignant lesions) and found no statistically significant difference between elastography scores and strain ratios of benign and malignant lesions (p = 0.708 for score and p = 0.698 for ratio) [16]. However, this study involved a small number of malignant lesions, which might influence the results. In the present study, strain ratio shows statistically significant difference between benign and malignant lesions (p<0.0001). The mandibular bone might affect the elastography score and strain

	AUC	Standard error	95% Confidence interval	p-value	Cut-off	Sensitivity	Specificity
Strain ratio	0.910256	0.0416	0.796 to 0.97	**<0.0001**	>3.78	100	84.62
Elastography score	0.606838	0.105	0.46 to 0.74	0.3083	>3	41.67	87.18

[Table/Fig-13]: Diagnostic accuracy of strain ratio and elastography score based on ROC parameters.
Receiver operating characteristic curve to find out best cut off point of strain ratio/elastography score for predicting malignancy and diagnostic test to assess the sensitivity and specificity; AUC: Area under curve

treatment lesion characterisation is of utmost importance as the management differs from conservative to superficial/partial or total parotidectomy depending on the diagnosis. In the present study, sonoelastography was used to evaluate the changes in tissue hardness in response to external forces and predicting biological character of salivary gland lesions and we found that it is a new promising tool for evaluation of salivary gland lesions further adding upon the diagnostic accuracy of conventional ultrasound.

Dumitriu D et al., published the first study in 2010 as to use of sonoelastography in evaluation of salivary gland lesions [12]. They studied 70 lesions and observed that most of the lesions demonstrated heterogeneous elastography image along with significant overlap of findings in pleomorphic adenoma and malignant lesions. The most specific finding they showed was lobulated contour which has not been seen in other benign tumours, but rarely seen in some malignant tumours.

Another study by Dumitriu D et al., on 74 salivary gland tumours (18 malignant and 56 benign tumours), using a four-point elasticity score showed statistically significant difference between benign and malignant lesions [10].

On the contrary, the results of present study showed that benign-malignant differentiation by elastography score alone is not significant (p = 0.308 for score), however the recent semi-quantitative analysis using strain ratio shows statistically significant difference between benign and malignant lesions (p<0.0001).

The results of present study were also concordant with Bhatia KS et al., in which 65 salivary gland lesions were studied with qualitative elastography scores alone and accomplished that this method is weak for differentiating benign lesions particularly pleomorphic adenoma from malignant ones [13]. In the present study blurred edge was defined in 6 malignant lesions, whereas 34 benign lesions showed well-defined edges and this finding was statistically significant (p=0.006).

In a similar study by Klintworth N et al., on 57 parotid mass lesions it was found that blurred edge is the main differentiating feature between malignant and benign tumours on conventional sonography [14].

Coman MM et al., concluded that strain ratio (SR) of >3 is suspicious

ratio of salivary gland lesions as it restricts the compression which limits the usage of elastography [16].

Sonoelastography is moderately accurate in differentiating benign and malignant salivary gland tumours as stated by Ghajarzadeh M et al., in a literature review which showed pooled sensitivity of 63% and pooled specificity of 59% [17]. The present study showed a comparable sensitivity of 66.67%, however, the specificity was much higher i.e., 97.44% for conventional sonography.

In another recent literature review by Zhang Y et al., analysing total ten studies that included a total sample of 725 salivary gland lesions, sonoelastography showed a pooled sensitivity of 0.67, specificity of 0.64 and an AUC of 0.77 [18].

In contradiction, the present study shows that strain ratio of >3 has a sensitivity of 100% and specificity 84.62% (p<0.0001) which is higher than that of study by Zhang Y et al., hence carries higher diagnostic accuracy.

Thus, concluding that overall, sonoelastography has a limited role in differentiating between malignant and benign salivary gland lesions. Quantitative and semi-quantitative methods prove to be better tool/parameters than the qualitative ones.

Limitation(s)

As sonography is operator dependent and elastography is a new method in evaluating superficial glands such as lesions located in salivary glands. Maybe, more experience and precise definition of elastography method and application should be introduced to radiologist.

CONCLUSION(S)

Real time sonoelastography is an innovative supplement to conventional sonography for evaluation of salivary gland lesions. However, the present study asserts that its overall accuracy is less assuring, and cannot replace biopsy, which is still necessary to differentiate benign and malignant salivary gland lesions in routine clinical practice.

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AUTHOR DECLARATION:
• Financial or Other Competing Interests: None
• Was Ethics Committee Approval obtained for this study?   Yes
• Was informed consent obtained from the subjects involved in the study?   Yes
• For any images presented appropriate consent has been obtained from the subjects.   Yes