RESEARCH ARTICLE

Does acoustic radiation force elastography improve the diagnostic capability of ultrasound in the preoperative characterization of masses of the parotid gland?

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Objectives: Ultrasound is the method of choice for preoperative evaluation of tumours of the parotid glands. However, existing methods do not allow for clear differentiation between the most common benign tumours and malignant tumours. The aim of our study was to evaluate if acoustic radiation force, Virtual Touch Quantification (VTQ) elastography helps to improve the preoperative evaluation of parotid masses.

Methods: We investigated the parenchyma of 102 parotid glands, 14 lymph nodes of healthy volunteers and 51 tumours of the parotid gland via ultrasound, colour Doppler ultrasound and VTQ. The results were matched with histopathology and analyzed.

Results: The perfusion in pleomorphic adenoma, the most frequent benign tumour of the parotid gland, was significantly lower in comparison to malignant tumours. All tumours showed statistically significant higher perfusion in comparison to the parenchyma or the lymph nodes of the gland. Shear wave velocity of the user-defined region of interest was statistically significant more frequently an overflow value higher than 8.5 m/s in total tumours in comparison to parenchyma or lymph nodes. The different tumour types presented no significant difference in the shear wave velocity.

Conclusions: VTQ in combination with classical ultrasound examination provides additional data useful in distinguishing between benign and malignant tumours and thus shows promise for integration into preexisting ultrasound protocols. However, despite the improvement, clear differentiation of tumours is still not possible and further investigation is recommended.

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Introduction

Evaluation of salivary gland tumours of head and neck masses is challenging because of the variability of the histopathology. 3–6% of the tumours found in the head and neck region are located in the salivary gland. 80% of these are located in the parotid gland. Although most lesions are benign, it is nevertheless essential to properly identify all malignant tumours.¹ Proper diagnosis is

often very demanding as there is a huge range of potential differential diagnoses and currently neither clinical nor imaging investigation allows for reliable differentiation between malignant and benign tumours. Despite decades of research, technical progress and growing clinical experience, the diagnosis of masses of the salivary glands is still a great challenge.

In addition to the progressive possibilities of therapy and aftercare, a safe, minimally invasive, cost-effective and low-radiation diagnostic method is increasingly crucial. The total parotidectomy is indicated sometimes

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including the resection of the facial nerve and the lymph nodes of the neck if a tumour is malignant, which dramatically influences the patient's psychologically. It is of great clinical value to characterize the tumour correctly because it directly influences the aggressiveness of the surgical approach and patient morbidity associated with extensive surgical situations, such as nerve palsy and Frey syndrome.² There exist numerous studies in the search for non-invasive imaging methods capable of differentiating malignant and benign tumours. On the basis of a variety of different benign tumour entities for simplification, many studies only formed two subgroups consisting of pleomorphic adenomas (PAs) tumours, which have significant pre-malignant potential, and Warthin tumours (WTs), thus potentially allowing patients in the WT group to avoid surgery especially in the elderly.

Sonography is largely accepted as the initial imaging investigation of choice. Imaging techniques alone can achieve diagnostic accuracy rates of approximately 90% in an experienced investigator. However, imaging of salivary gland tumours by less experienced examiners may be very challenging, and the differentiation between healthy lymph nodes in parenchyma, cysts and tumours very difficult. Thus, fine-needle aspiration cytology guided by ultrasound is widely used, albeit with variable success; sensitivity ranges vary from 57 to 98% and specificity from 56 to 100%, where both depend primarily on the experience of the pathologist.^{3,4} These techniques are invasive and could possibly cause pain, haemorrhage and other complications.⁵ Therefore, an imaging technique that provides additional information for differentiation between salivary gland lesions would be of great value as it is faster and free of pain or complications.

It is known that tissue changes in its nature in the context of pathological transformation. Early on, this characteristic was exploited in order to differentiate pathological from physiological tissues by means of palpatory findings. However, as palpation is a very subjective method of examination and is only accessible to tissues that are located near the body surface, ultrasound elastography is generally the preferred method. However, new technologies now allow for objective and quantitative data. Because tissue compression with ultrasound pulses is similar to palpation and shear waves can be simultaneously generated in the tissue and their speed effectively measured, the values of which correlate with the tissue stiffness, it is now possible to derive quantitative values for tissue differentiation.

The primary focus of our study was on quantitative tissue differentiation using the novel Shear Wave Elastography, which has recently yielded promising clinical results in the study of many other tissues. Due to the superficial location of the large salivary glands, the ultrasound investigation using high-resolution transducers and state-of-the-art software has generally become more and more of an imaging gold standard. This progress allows for more and more accurate diagnoses and

distinctions of the present pathologies concerning the species, size, vascularization and positional relationship to the surrounding tissue.

Acoustic radiation force impulse (ARFI) imaging is a new elastic imaging technology that can assess the stiffness of tissue qualitatively and quantitatively. In contrast, previous external pressure elastography techniques only use semi-quantitative methods and are highly dependent of the investigator skills.⁶ ARFI is a technical approach that has been proven to be useful in other areas for the evaluation of malignant tumours, thyroid pathologies and liver fibrosis.^{7–10}

In addition, ARFI can be integrated into conventional real-time ultrasound equipment and thereby, be performed along with B-mode imaging. ARFI utilizes short duration acoustic pulses that are emitted into the tissue under investigation. Subsequently, the impulses induce localized microshifts within the tissue, which cause transverse waves to spread centrifugally from the centre of excitation. The shear wave velocity, which can be measured using ultrasound waves, provides an indication of the tissue's elasticity. Using ARFI, we have recently demonstrated that healthy parotid glands exhibit lower tissue elasticity compared to healthy submandibular glands.¹¹

In this study, we evaluate normal salivary parenchyma, healthy lymph nodes of the parotid gland and tumours of the parotid gland via ultrasound, colour Doppler ultrasound and virtual touch quantification elastography. By using various well-tried but above all novel ultrasound techniques, the aim of this work is to develop baseline ranges and/or guideline values for more accurate diagnosis and differentiation of masses of the parotid glands and to examine the added value in the diagnostic application in clinical practice.

Methods and materials

Study design and study population

This prospective study was performed at the Department of Otorhinolaryngology, Head and Neck Surgery, Grosshadern Medical Center, Munich, Germany. Healthy volunteers and patients with masses of the parotid glands were enrolled by the employees of the Department of Otorhinolaryngology between July 2016 and May 2017 and underwent a routine ultrasound examination. The study was approved by the local ethics committee and informed consent was obtained from all patients.

Ultrasound imaging

A single physician examined all patients following the same protocol using an Acuson S3000 ultrasound system (Medical Systems, Erlangen, Germany). The measurements were performed using a 9 MHz linear array transducer. The examination consisted of a conventional B-scan followed by colour-coded duplex

sonography. The colour gain mode was employed only to the extent necessary to avoid obscuring artefacts. Additionally, automatic image gain optimization was performed. For elastography analysis, elastography ARFI software was used to measure the velocity of shear waves. “Virtual Touch TM Tissue Quantification” allows for the tracking of a shear wave within the region of interest (ROI) as it travels perpendicularly to the transmitted longitudinal push pulse. Subsequently, “Time to Peak analysis” allows for the computation of a numerical value of the shear wave velocity obtained over the ROI and expressed in meters per second (m/s). The stiffer the tissue, the higher the shear wave velocity.¹² Thus, the measurements provide quantitative information about tissue elasticity. For ARFI measurements, the transducer had only light contact to the skin surface and ample coupling gel was used to avoid pre-compression.

The ultrasound device features a high-performance processor and provides output documentation as dynamic image sequences in cine mode by a digital frame buffer. The examination of each healthy volunteer or patient began with two-dimensional ultrasound of the parenchyma of the gland. If a lymph node or a tumour was visible, the B-mode was performed on the mass. Afterwards, colour Doppler examination was performed and the vascular density determined as poor (0), little (1) moderate (2) or high (3) was measured for the parenchyma and if present for the lymph node and tumour. For elastography analysis, elastography ARFI software was used to measure the velocity of shear waves. Five 5×5 mm ROIs were randomly chosen in each parotid gland within the parenchyma and if present in the lymph node or tumour to measure the shear wave velocity with VTQ. Overflow measurements above the 8.4 m/s threshold were displayed as a non-numeric value of “XXX” by the software. For the numerical statistics, the size was assumed to be 8.5 m/s for all “XXX” values. In addition, a separate evaluation of the proportion of non-numerical results and an evaluation excluding the “XXX” values were analyzed.

Inclusion criteria

The study encompasses patients with tumours located in the parotid gland as well as a control group of healthy volunteers.

Exclusion criteria

There were no exclusion criteria because the elastography measurement is considered to be a safe standard ultrasound technique.

Data and statistical analysis

Data analysis from digitally stored video sequence data sets was performed using a statistical software package (SigmaStat for Windows, Jandel Scientific, Erkrath, Germany). After testing for normality of data (Shapiro–Wilk test), either the *t*-test (two groups) or the one-way ANOVA test (more than two groups) was used for the estimation of stochastic probability in intergroup comparisons. Mean values and standard deviations are given. *p*-values < 0.05 were considered significant.

Results

Study population

The values of a total of 102 glandulae parotideae were measured. There were 47 female (46.08%) and 55 male (53.92%) study participants with an age range of 17–79 years (mean age 51.9 years). 14 healthy lymph nodes from these volunteers and 51 parotid tumours were analyzed. The histopathological differentiation performed after surgery revealed 44 benign (86%) and 7 malignant (14%) lesions consisting of 17 PA tumours, 21 WTs, 6 other benign tumours (2 lymphangioma, 1 basal cell adenoma, 1 haemangioma, 1 lipoma and 1 cystadenoma) and 7 malignant tumours (1 acinic cell carcinoma low grade, 1 mucoepidermoid carcinoma high grade, 1 small cell carcinoma, 2 metastasis of squamous cell carcinoma, 1 marginal cell lymphoma and 1 adenoid cystic carcinoma) (Tables 1 and 2).

Colour Doppler investigation

The vascularization of the tissue (parenchyma, lymph node, or tumour) was investigated and defined as 0 (no vascularization), 1 (minimal vascularization), 2 (moderate vascularization), or 3 (high vascularization). The average vascularization value was 0.5 for parenchyma, 0.25 for lymph nodes, 1.0 for PAs, 1.5 for WTs, 1.3 for all benign tumours and 1.86 for malignant tumours. Consequently, significantly higher

Table 1 Study population

Tumour	Number (n)	♀	♂	Benign tumours	Total tumours
Pleomorphic adenoma	17	10 (59%)	7 (41%)	39%	33%
Warthin tumour	21	2 (10%)	19 (90%)	48%	41%
Lymphangioma	2	2 (100%)	–	5%	4%
Basalzell adenoma	1	1 (100%)	–	2%	2%
Cystadenoma	1	–	1 (100%)	2%	2%
Lipoma	1	–	1 (100%)	2%	2%
Haemangioma	1	1 (100%)	–	2%	2%

Benign tumour types of the study population.

Table 2 Study population

Tumour	Number (n)	♀	♂	Malignant tumours	% of all tumours
Acinic cell carcinoma (low grade)	1	—	1 (100%)	14.2%	2%
Mucoepidermoid carcinoma (high grade)	1	1 (100%)	—	14.2%	2%
Adenoid-cystic carcinoma	1	1 (100%)	—	14.2%	2%
Marginal cell lymphoma	1	1 (100%)	—	14.2%	2%
Metastasis of squamous cell carcinoma	2	—	2 (100%)	29%	4%
Small cell carcinoma	1	—	1 (100%)	14.2%	2%

Malignant tumour types of the study population.

vascularization occurred in tumours in comparison to the parenchyma or the lymph nodes ($p < 0.01$). Malignant tumours showed significant higher perfusion in comparison to PA ($p < 0.05$) and higher although not significant perfusion in comparison to WTs. WTs were better perfused than PA but not significantly $p = 0.06$ (Table 3).

Virtual Touch Q shear wave velocity of parenchyma, lymph nodes and tumours in user defined ROI

After picking 5 ROIs in the examined tissue, mean values and standard deviation of the shear wave velocity were calculated with an average of 3.43 ± 1.04 m/s for the parenchyma of the parotid gland and 3.39 ± 1.18 m/s for the 14 lymph nodes of healthy volunteers. In total, the SWV was 6.35 ± 2.14 for all benign tumours and 6.24 ± 2.91 m/s for the malignant tumours. The average SWV was 6.64 ± 1.96 m/s for PA and 6.51 ± 2.02 m/s for WT. The average shear wave velocity of all tumours showed statistically significant higher values in comparison to the parenchyma of the parotid glands and the healthy lymph nodes ($p < 0.001$). Dividing the tumours in the subgroups (all benign, malignant, PA, WT and other benign) demonstrated, the same statistically significant higher values of each tumour group in comparison to the parenchyma and the lymph nodes

($p < 0.001$). Among the tumour groups, no statistically significant differences were measured (Figure 1a–d).

The highest measurable SWV of our measurement device was 8.4 m/s, and multiple times the SWV was higher than this limit of 8.4 m/s, in which case the value showed “XXX” as a result. An overflow value greater than 8.4 m/s was measured in 2% of parenchyma, 7% of the lymph nodes, 65% of WT, 64% of other benign tumours, 68% in the PA group and 57% of malignant tumours. In total, 64% of all benign tumours showed a high value (Table 4). Excluding the non-numeric “XXX” values, the average of the shear wave velocity was 2.53 ± 1.35 m/s for all benign tumours and 3.22 ± 1.52 m/s for the malignant tumours. The average SWV for PA was 2.66 ± 1.22 m/s and 2.69 ± 1.58 m/s for WT. The malignant tumour group was stiffer in comparison to the benign tumour group but not by a statistically significant amount ($p = 0.06$).

Discussion

Not only because of its delicate location in the facial area and the direct contact to the facial nerve but also because there are infinitely many different tumour entities, the treatment of mass lesions in the parotid gland poses a great challenge. There are not only malignant and benign tumour types, but also benign tumours like the PA that can become malignant as well as different types within the same tumour group.¹³ Histopathologically, different tumours in the same group behave differently and the transition between benign and malignant tumours is fluid; e.g. azinus cell carcinoma is not easily distinguishable from a benign tumour. Furthermore, the histology of individual PA generally differs from that of other PA. On the basis of this unusual constitution, it is not only difficult for the pathologist to make a correct diagnosis but also difficult for the clinically diagnosing doctor to make a pre-operative tumour classification via ultrasound.

Ideally, the role of imaging for pre-operative tumour diagnosis should not be limited to merely determining the location and extent of the mass but would preferably be also able to effectively determine the tissue type and, in particular, reliably assess whether the mass is benign or malignant. Numerous approaches have, therefore, been used to attempt to predict the nature of the tumour

Table 3 Vascularisation of the different tumour types

Comparison of vascularisation	p-value	Significant
Benign/malignant tumour	0.1040	X
Pleomorphic adenoma/malignant tumour	0.0205	✓
Pleomorphic adenoma/Warthin tumour	0.0631	X
Pleomorphic adenoma/parenchyma	0.0004	✓
Pleomorphic adenoma/lymph node	0.0108	✓
Warthin tumour/malignant tumour	0.3683	X
Warthin tumour/parenchyma	0.0001	✓
Warthin tumour/lymph node	0.0001	✓
Malign tumour/parenchyma	0.0001	✓
Malignant tumour/lymph node	0.0001	✓
Parenchyma/lymph node	0.2015	X

Statistically significant higher vascularization occurred in tumours in comparison to the parenchyma or the lymph nodes ($p < 0.01$). Malignant tumours showed statistically significant higher perfusion in comparison to pleomorphic adenoma ($p < 0.05$) and higher but not significant perfusion in comparison to Warthin tumours.

Figure 1 Average shear wave velocities of the region of interest. No statistically significant differences in the average shear wave velocities of the different tumour groups were measured (a, b). The average shear wave velocity of all tumours was higher than those of the parenchyma of the parotid glands and the healthy lymph nodes by a statistically significant value ($p < 0.001$) (c, d). Similarly, when dividing the tumours into subgroups (all benign, malignant, PA, WT, other benign), parenchyma and the lymph nodes also showed statistically significant lower values in comparison to other tumour groups ($p < 0.001$) (data not shown). PA, pleomorphic adenomas; WT, warthin tumour.

by defining imaging characteristics via ultrasound, MRI and CT with limited success.^{14,15}

In recent years, sonoelastography has proven to be an important diagnostic tool in assessing the stiffness or elasticity of various tissues. For example, there have been promising results in the diagnosis of breast cancer, thyroid cancer and liver fibrosis.^{16,17} As malignant tissue is generally stiffer than benign tissue,¹⁷ efforts have been made to apply elastography in the differential diagnosis of salivary gland tumours.

Elastography consists of strain elastography and shear wave elastography. Conventional strain elastography evaluates stiffness of the target area as a direct

correlation of manual compression, thus introducing substantial interobserver variability.¹⁸ In an effort to find a more objective and reproducible diagnostic, ARFI elastography has been introduced, in which tissue is mechanically excited by a transducer with short duration acoustic pulses that propagate in a perpendicular direction. ARFI allows for qualitative and quantitative assessment of the lesion's stiffness by estimating tissue displacement or measuring the shear wave propagation speed.

In 2010, Dumitriu et al used compression elastography to examine salivary gland lesions. They did not find differences between PA and malignant tumours.¹

Table 4 Amount of “XXX” values

Group	<i>n</i> total	XXX	% of XXX of total values
Pleomorphic adenoma	85	58	68%
Warthin tumour	105	68	65%
Benign tumours	220	140	64%
Malignant tumours	35	20	57%
Parenchyma	510	9	2%
Lymph node	60	4	7%

Overflow values per tumour type. The maximum measurable SWV in the examination was 8.5 m/s. However, multiple times the SWV was higher than 8.5 m/s, and the overflow value “XXX” was displayed with the following frequency by tumour type: 2% in parenchyma, 7% in the lymph nodes, 65% in WT, 64% in other benign tumours, 68% in the PA group and 57% in the malignant tumours. All benign tumours together showed overflow values above 8.5 m/s in 64% of the measurements.

In 2011, the same group did find a difference between malignant and benign tumours using a 4-class scoring method, but the differences between PA and WT and PA and malignant tumours were not statistically significant.¹⁹ Similarly, Bhatia reported that although the stiffness differences between salivary gland lesions were detectable, real-time elastography still had a poor ability to discriminate benign from malignant tumours.²⁰

Li et al performed a meta-analysis with nine studies to validate the performance of real-time elastography in 2016, where the performance of the elasticity score had a pooled sensitivity of 76% and a specificity of 73%.²¹ The group described that the study findings indicate that malignant lesions were commonly stiffer than benign ones, but there was still a substantial overlap between the elastographic properties of malignant and benign parotid lesions. The group themselves mentioned the limitations of their study to include its operator-dependent technique and the possibility that the external pressure applied on the neck or face may affect the values.

Zhou et al investigated ARFI technology and found that conventional strain elastography was not useful for evaluating major salivary gland masses. An ARFI elastography score greater than 3 achieved specificity of 81.3 and 62.5% of sensitivity in comparison of malignant and benign tumours. However, the difference between benign and malignant tumours was not statistically significant and three of eight malignant tumours were not identified.²² Mansour et al showed no statistically significant difference between PA and WT in sonoelastography with the compression technique. However, ARFI quantification determined different mean values for both entities.²³ Thus, previous studies suggest that ARFI might be an effective technique.

In our study, we measured 102 parenchyma and found a mean SWV of 3.43 ± 1.04 m/s. Matsuzuka measured 42 healthy parenchyma and found a SVW of 1.98 ± 0.73 m/s.²⁴ We measured 44 benign tumours with a mean SWV of 6.35 ± 2.14 m/s. Four malignant tumours in the Matsuzuka study showed in all cases a non-numeric value of “XXX” using the VTQ methods, whereas our results showed a mean SWV of 6.24 ± 2.91 m/s and in 57% a non-numeric value of “XXX”.

In his study population, 7 out of 11 benign tumours showed “XXX” values (63%) which is similar to our results which showed “XXX” measurements for 64% of the benign tumour group. The differences may be explained by the fact that the group of Matsuzuka used less or more transducer force, as Mantsopoulos found that the SWV is dependent on the applied transducer force, due to pre-compression of the tissue.²⁵ Furthermore, Hofauer et al reported variability among different investigators and a general low level of reproducibility of ARFI results of the parotid gland,²⁶ most likely due to differences in the applied transducer force that result in different pre-compression of the tissue, leading to different shear wave velocities.

We have tried to minimize these problems by performing all examinations by a single examiner who has applied as little pressure as possible to the ultrasound probe. Our study cohort is the largest to date using Virtual Touch Q for salivary gland masses. Our results clearly showed that a highly statistically significant difference exists between the stiffness of healthy parotid parenchyma in comparison to all kinds of tumours ($p < 0.001$). Healthy lymph nodes in the parenchyma were also less stiff than all kinds of tumours by clear statistical significance. This finding is clinically very important, because inexperienced investigators are often unable to distinguish between a lymph node and a tumour in the parotid gland, often resulting in patients undergoing unnecessary surgery. This technique can help provide proper diagnostics that are essential before performing substantial surgical intervention and help prevent unnecessary risky surgery in non-threatening cases.

SWV of benign tumours was lower in comparison to malignant tumours excluding the “XXX” values, but the result was not statistically significant ($p = 0.06$). PA were also stiffer than WT and less stiff than malignant tumours, both results are again not significant. The high degree of stiffness in PA could be related to the important fibrous component inside the tumour. Moreover, parotid tumours constitute a histologically diverse group of masses, some types having variable proportions of solid and cyst elements, which could lead to an intrinsic variation in SWV.²¹ Tumours showed

significantly higher vascularization in comparison to the parenchyma and the lymph nodes, and malignant tumours showed statistically significant higher vascularization in comparison to PA.

“XXX” values were measured in a high portion in the tumour groups up to 68% of all values, whereas the parenchyma and the lymph nodes had few “XXX” measurements. Elastography alone provides little distinction between benign and malign tumours or between PA and WT, while VTQ gave further information to characterize tumours pre-operatively especially for distinguishing tumours from lymph nodes. A limitation of the present study is that the number of malignancies included is small (14%); however, this matches to the 10–20% proportion of malignancies in parotid

glands. Nevertheless, the number should be expanded in further studies to improve statistical performance.

Conclusion

In conclusion, these preliminary results suggest that Virtual Touch Q can significantly improve the pre-operative determination of tumour and lymph nodes, which would be very beneficial to the patient treatment. Although the use of VTQ in our study was insufficient to clearly distinguish between malignant and benign tumours, our results suggest that larger and multicentre studies should be considered to further explore the potential value of Virtual Touch Q evaluation.

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