Peer Review File

Article information: http://dx.doi.org/10.21037/gs-20-837

Reviewer A

I read the work with pleasure. The differentiation of parotid gland neoplasms at the preoperative stage is indeed a current topic in otolaryngology. Therefore, the topic of this study is interesting and actual. Due to the small number of tumors, apart from PA and WT, it is difficult to conclude on the value of ARFI-sonoelastography in all types of parotid gland tumors. Undoubtedly, this topic requires further research on larger groups of patients. In my opinion, it is a very well written research paper in all respects. Without a doubt, I recommend this work for publication in GS. I have only one comment:

Comment A1: Line 161: repetition of information contained in lines 105-106. It is enough to leave the link to Table 1.

Reply A1: Thank you for the comment. We revised the manuscript according to your recommendation, removed the repeated text passages and inserted a link to Table 1 (line 161). Table 1 was adapted to present the data sufficiently.

Changes in the text: Line 161, Table 1 (revised).

Reviewer B

It is really well structured and written paper, I only would like to add a few comments:

Comment B1: Once you start using PG (for parotid gland), you should keep using the PG acronym.

Reply B1: Thank you for the comment. We revised the manuscript and used the acronym "PG"

after its introduction in the further manuscript text.

Changes in the text: PG is introduced as an acronym in line 53 and replaces the term "parotid gland" in the further text.

Comment B2: Could you describe your diagnostic protocol for PG masses? Other imaging techniques than US, FNA…

Reply B2: Thank you very much for your question.

In our department, every patient receives a detailed interview and clinical examination first. When a mass is detected, supposed or other pathological processes have to be excluded requiring imaging, we always conduct an ultrasound examination primarily. We perform these examinations ourselves in the department, including the entire head and neck region and salivary glands. These examinations always include color-Doppler imaging and, when applicable, elastography. In parotid gland masses, this ultrasound examination is supplemented by MRI scans in selected cases: in particular if the lesion extends medially of the mandible and is therefore not completely visible when performing a transcutaneous ultrasound, or if major vessels seem to be affected in large lesions, or if nerve or skull base infiltration is suspected. We use CT scans in cases in which we consider an infiltration of bony structures, including the skull base. In addition, CT scans of the thorax and brain are performed in malignant lesions to detect metastasis.

We do not perform routine biopsies of parotid gland neoplasms, and we do not perform FNA. If biopsies are taken, we prefer core needle biopsies (CNB), as these have been reported to deliver more reliable results (PMID: 32813401), which is also congruent with our experience. From our perspective, nearly every parotid gland mass requires surgical management. In times before the SARS-CoV pandemic, every patient with a parotid lesion received an urgent appointment for surgery; biopsies were taken only in selected cases, especially in multimorbid patients who are at risk when performing the operation in general anesthesia. However, SARS-

CoV and limited surgical capacities forced us to take preoperative biopsies more often in order to structure the surgical management due to its urgency.

We hope that our explanations address your question appropriately.

Changes in the text: None; please also see Reply B4, which addresses these aspects concerning imaging (lines 259-271).

Comment B3: Did you try to find the relationship between the mass and the facial nerve? It could be helpful and relevant for the clinicians.

Reply B3: Thank you very much for mentioning this important aspect.

Ultrasound cannot depict the facial nerve appropriately, even not when performing sonoelastography, which is why this question is not addressed in the present manuscript. However, other reports investigated this topic before (e.g. PMID: 31179604), and our group published an article about the use of ultrasound for the preoperative analysis of the relationship between parotid gland lesions and the facial nerve (PMID: 32487325). Although the nerve is not visible in routine ultrasound examinations itself, it is helpful to determine the minimal distance between the parotideomasseteric fascia and the superficial capsule of the tumor. The mean value for this distance was 1.3 mm for tumors located in the superficial and 4.6 mm for tumors located in the deep lobe. When the cutoff value was set at 2.6 mm, the result of this study was that the sensitivity and specificity of ultrasound were 89.6 and 88.4%, respectively, to distinguish between superficial and deep lobe neoplasms. These data can assist the surgeon preoperatively whether to expect the facial nerve superficial of or under the mass within the parotid gland.

We hope that our comment is sufficient to answer your question, and we revised the manuscript accordingly.

Changes in the text: We modified the manuscript and added a sentence, explaining that sonoelastography does not give information about the relation of the lesion to the facial nerve

(line 126-127): "As ultrasound cannot depict the facial nerve appropriately, we did not address the spatial relationship between the tumors and the nerve in this study."

Comment B4: Could you discuss a little bit further which are the benefits (and disadvantages) of each imaging technique (MRI, CT, US...)?

Reply B4: Thank you very much for this question.

Ultrasound has numerous advantages: it is fast, cost-effective, radiation free, and a precise real time imaging modality available nearly everywhere. The examination can be performed by treating surgeon, even during the operation. This is particularly helpful to locate lesions when these are difficult to palpate and the gland does not have to be fully resected. Secondly, the determination of the minimal distance between the parotideomasseteric fascia and the superficial capsule of the tumor allows a preoperative estimation whether the facial nerve has to be expected laterally or medially of the tumor. Ultrasound of the neck also enables an assessment of the cervical lymph nodes, which usefully complements the overall picture. The main disadvantage of ultrasound is that bony structures, as the mandible, limit the field of view - tumors extending medially of the mandible cannot be fully depicted. Further, deep lobe tumors or those that are in close contact with the skull base are difficult to evaluate using ultrasound.

In these selected cases, MRI and CT scans can give valuable information und supplement the results from ultrasound examinations. CT scans are important to illustrate bony infiltrations (mandible, skull base) or distant metastasis, in particular regarding the lung. MRI, in contrast, is the technique of choice to evaluate soft tissue infiltration (nerves, dura, parapharyngeal space). In the majority of cases, however, ultrasound provides sufficient information to plan the surgical procedure without the need for additional imaging.

We hope that these comments can answer your question appropriately. Your comment prompted us to revise the discussion chapter, and we added a paragraph to shortly discuss the

advantages and disadvantages of ultrasound and the mentioned imaging techniques. **Changes in the text:** A paragraph was added to the discussion chapter (line 259-271).

Reviewer C

The authors' conclusion is that a reliable identification and differentiation of parotid gland tumors as well as clinical treatment decisions cannot be made with the sole use of ARFI-sonoelastography.

Comment C1: So, what lessons does this paper teach us?

Reply 1: Thank you very much for this question.

Sonoelastographic measurements are established to evaluate neoplasms of different organs, and the technique can supply additional information in breast, liver, prostate and thyroid lesions. For those, elastography has been proven to deliver reliable results in differentiating benign from malignant masses when defined examination protocols and techniques are used. Regarding parotid gland lesions, the question whether sonoelastography can be a reliable option to differentiate between benign and malignant lesions has remained a matter of controversy.

The largest meta-analysis that addressed this open question to date (PMID: 29992386**)** concluded that the varying elastographic techniques performed in former studies complicate the comparison of the different study results, impeding a proper conclusion. However, the mentioned article summarized the most important aspects that have to be considered for further evaluations.

In our present study, we respected these criteria: firstly, we focused on parotid gland lesions only and did not include submandibular gland tumors (lines 104-106). Secondly, we exclusively applied the most recent quantitative measurement techniques and omitted qualitative ones (lines

137-149). Thirdly, we performed the examinations using two different high-end ultrasound devices to evaluate out whether variations were limited to a single system (lines 115-118). Fourthly, we conducted all examinations according to a strictly defined protocol in an identical way in each patient (lines 118-126). In addition, the measurement results did not supplement the results of other ultrasound techniques as color-Doppler, contrast enhanced ultrasound or other imaging techniques but were analyzed separately as an individual parameter, to minimize any kind of confounding.
Considering all these aspects, we can clearly conclude that a reliable differentiation or identification of parotid gland tumors was not possible with this ultrasound technique on its own (lines 317-319; 357-360; 363-365; 368-370). This has not been investigated in this context before.

It would have been desirable for everyone to report on a new diagnostic option to reliably distinguish different parotid gland tumor entities from one another. We are aware that our results and conclusion may be interpreted as a "negative result", but we think that the present article adds valuable information for clinicians and future studies about the identification and differentiation of parotid gland lesions preoperatively.
We hope that our comments can answer your question appropriately.
Changes to the text: None.

Comment C2: And the distinction between benign and malignant tumors is the most important in differentiating parotid tumors, and there is no discussion about this.

Reply C2: Thank you very much for this comment.
We fully agree with your statement that the differentiation between benign and malign tumors is the most crucial aspect. The importance of this question is reflected by the ongoing and bustling efforts to develop and assess new methods in salivary gland imaging. Although

progress has been achieved in the last years, an all-embracing technique has not yet been successfully established.

Our goal in the present study was to evaluate whether quantitative sonoelastography might be helpful to answer this question. In general, it was not possible to distinguish benign from malignant lesions (lines 192-198). Subsequently, we tested whether pleomorphic adenomas were responsible for this inability, and the answer was no (lines 199-209). In addition, pleomorphic adenomas could not be differentiated from malignant lesions by using shear wave velocities (lines 217-219). These results are addressed and discussed later in the text (lines 317-319; 321-352), but your comment prompted us to discuss this aspect more thoroughly. We therefore revised and supplemented the manuscript in the discussion section, adding a further explanation why this differentiation was not possible (lines 357-360), and hope that our comments address your comment appropriately.

Changes in the text: (lines 357-360), added: "The differentiation between benign and malignant lesions in general was moreover complicated by the fact that the considerable number of different tumor entities showed large spreads of shear wave velocity values, impeding the establishment of clear cut-off-values in our study (Table 2)."