

Preoperative Multiparametric Ultrasound and Fine Needle Aspiration Cytology evaluation of parotid gland tumors: which is the best technique?

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Abstract

Aims: To evaluate the pre-surgical diagnostic value of Multiparametric Ultrasound (MPUS) and Fine Needle Aspiration Cytology (FNAC) in differentiating parotid gland tumors, comparing the results with histology. **Materials and methods:** The study enrolled 84 patients with parotid gland lesions surgically treated in a single tertiary center and evaluated by MPUS. Each patient underwent FNAC. Histological examination was considered the gold standard. **Results:** Histology identified 62 benign tumors and 22 malignancies. In the differential diagnosis between malignant and benign lesions, B-mode Ultrasound (US), Color-Doppler US, Contrast-Enhanced US (CEUS), Elastography (USE) and FNAC showed the following values of sensitivity: 82%, 81%, 86%, 77%, 73% respectively; specificity: 97%, 61%, 95%, 71%, 97% respectively; PPV: 90%, 43%, 86%, 50%, 89% respectively; NPV: 93%, 90%, 95%, 88%, 91% respectively; and accuracy: 89%, 71%, 90%, 78%, 84% respectively. **Conclusions:** CEUS proved to be a valid and accurate method for identifying malignant tumors of parotid gland; the combination of B-mode US with CEUS showed similar diagnostic accuracy, but better sensitivity than CEUS taken alone. USE did not improve the diagnostic performance of the B-mode US, alone or in association with CEUS; however, it revealed the highest diagnostic accuracy in the differentiation between benign lesions. FNAC demonstrated lower values in comparison with CEUS and with USE. Therefore, according to our study, MPUS could be proposed as a valid alternative to FNAC.

Keywords: Multiparametric Ultrasound (MPUS); parotid gland tumors; Fine Needle Aspiration Cytology (FNAC)

Introduction

Parotid neoplasms are the most frequent salivary gland tumors; 60% of them are benign and are mainly located in the superficial lobe (76% of cases), while

malignant lesions usually involve the deep lobe or both lobes. Tumor location, extension and correct preoperative characterization play a crucial role in deciding the proper treatment [1-4].

Surgical treatment of parotid tumors ranges from extracapsular dissection to total parotidectomy with or without neck dissection [5-11]. Characterization of parotid tumors is relevant in planning surgery and in predicting possible complications or recurrences. Imaging techniques such as Ultrasound (US), Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) are frequently used for the evaluation of parotid lesions, although none of them can guarantee an accurate differ-

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ential diagnosis between benign lesions and malignancies [1]. The sensitivity and specificity of Fine Needle Aspiration Cytology (FNAC) varies according to lesion location and size, and the pathologist's experience. Furthermore, FNAC may be non-diagnostic, and the patients need a second FNAC to achieve a diagnosis [12,13]. Therefore, to date, the gold standard in the diagnosis of salivary gland neoplasms remains surgical excision followed by histopathology.

Recently, some authors have focused on US coupled with various innovative techniques, under the name of Multiparametric Ultrasound (MPUS) [14]. These techniques, such as Contrast-Enhanced Ultrasound (CEUS) and Ultrasound-Elastography (USE), are used to increase the effectiveness and the accuracy of B-mode US in the differential diagnosis of parotid masses and decrease the need for invasive techniques [1,2].

The aim of our study was to evaluate the diagnostic accuracy of MPUS, with CEUS and USE, and of FNAC in differentiating parotid gland tumors, comparing the results with post-surgical histology.

Materials and methods

Eighty-four consecutive patients (36 female and 48 male patients, age range = 20-78 years, mean age = 49 years) with parotid neoplasms presented to the Otolaryngology and Maxillofacial Surgery Departments of our University Hospital between September 2018 and October 2020 were included in the study. All subjects provided written informed consent. The research was conducted in accordance with the ethical guidelines of the Helsinki Declaration and the Internal Review Board of our University Hospital approved it.

Patients were studied preoperatively using B-mode US, Color-Doppler US, CEUS, USE and FNAC. Subsequently, patients were treated surgically with extracapsular dissection or superficial parotidectomy in cases of suspected benign tumor and total parotidectomy in case of presumed malignancy (with or without lymph node dissection according to histological subtype and tumor extension). The surgical samples were analyzed by an anatomic-pathologist and histopathology results compared to the above-mentioned diagnostic techniques.

B-mode US and Color-Doppler US

US evaluation was performed using a "high-end" machine (Canon Medical Systems Aplio 500, i800 US system, formerly Toshiba Medical Systems, Otawara, Japan) and a 5-14 MHz linear probe by a single radiologist with 15 years of experience in CEUS and 10 years in USE.

The patients were placed in supine position, with a pillow placed under the shoulders, to obtain neck hyperex-

ension. Bilateral axial and sagittal images were acquired. The size, the shape, the margins of the lesions and the vascularization with Color-Doppler US were recorded.

The following patterns were considered at the evaluation with baseline ultrasound: 1) suspected malignant lesions: nodular appearance, irregular or frankly infiltrating margins, heterogeneous hypoechoic structure, calcifications and hypo-anechoic necrotic-hemorrhagic internal areas, associated regional lymphadenopathy [1,15]; 2) pleomorphic adenoma: homogeneous, lobulated, hypoechoic structure with posterior wall enhancement, with or without calcifications, poor vascularization [1,16]; 3) Warthin's tumor: oval, hypoechoic mass, capsulated with anechoic and hypervascularized areas [1,17,18].

In the evaluation with Color-Doppler US, the following patterns were considered: Type 1 - marked and irregular intralesional blood flow; Type 2 - homogeneous flow or mild and peripheral vascularization. Type 1 pattern was considered more typical of malignant lesions, while Type 2 of benign ones.

We also tried to identify a specific pattern of vascularization in order to distinguish between benign lesions as follows: marked and homogeneous vascularization for Warthin's tumor while mild and peripheral flow for pleomorphic adenoma [19-21].

USE

USE was performed using a semi-quantitative quasi-static technique by the same experienced radiologist.

The patients were asked not to move and rhythmic compressions were performed for 3-4 seconds in order to allow the acquisition of data. Then, the operator performed the examination using longitudinal scans and checking a quality indicator in real time; a colorimetric scale on the screen indicated the correspondence between hard and soft areas, respectively shown with blue and red colors and subsequently, the operator placed two regions of interest (ROI), one in the nodule and another one in the adjacent gland tissue. The USE software then calculated the strain ratio [22-26].

CEUS

A medical history was collected for each patient, aiming to exclude contraindications for the US contrast medium administration [27-30].

CEUS was performed after intravenous administration of 2.4 mL of contrast medium (SonoVue™, Bracco, Milan, Italy) followed by 10 ml of isotonic saline solution. The CEUS study was carried out for at least two minutes, using low mechanical index (MI 0.05-0.07). The procedure was recorded digitally on AVI files in order to perform a qualitative analysis.

After CEUS examination, lesions were divided in two categories (type 0-1), using a classification system that

originates from the studies by Wei et al [30] and from David et al [2].

For CEUS, the following patterns were considered: Type 0 – a) homogeneous enhancement of the lesion; b) heterogeneous enhancement but with defined margins; c) no enhancement and iso-enhancement; Type 1: heterogeneous enhancement of the tumor with poorly defined margins. Type 0 pattern was considered more typical of benign lesions, while Type 1 of malignant ones.

All patients underwent Fine Needle Aspiration Cytology (FNAC), surgery and histopathological examination.

Statistical analysis

Statistical analysis was carried out by calculating, for each method, sensitivity, specificity, positive and negative predictive value and area under the ROC curve. The ROC curve and the Youden test were used to identify the optimal strain ratio cut-off to discriminate between benign and malignant lesions and, within benign lesions, between pleomorphic adenomas and Warthin’s tumors. The comparison between the performances of the various US methods was performed by comparing the areas under the ROC curves (AUC) through the Bonferroni test. The analysis was performed using the STATA 15 statistical package.

Results

Post-operative histopathology analysis revealed benign tumors in 62 patients (73.8%) and malignant tumors in 22 patients (26.2%). The average size of the evaluated lesions was 25 mm, with a range between 3 mm and 55 mm.

Histological results were as follows: Warthin’s tumor 33.3% (n=28), pleomorphic adenoma 19% (n=16), acinic cell carcinoma 7.1% (n=6), primary squamous cell

carcinoma 7.1% (n=6), non-specific inflammation 7.1% (n=6), benign vascular tumor 4.8% (n=4), non-Hodgkin type B lymphoma 4.8% (n=4), metastasis from squamous cell carcinoma 2.4% (n=2), carcinoma ex-pleomorphic adenoma 2.4% (n=2), poorly differentiated carcinoma 2.4% (n=2), mucoepidermoid carcinoma 2.4% (n=2), lymphoepithelial cysts 2.4% (n=2), oncocytoma (2.4% (n=2), ductal cyst 1.2% (n=1), papillary oncocytic cystadenoma 1.2% (n=1).

Differentiation between malignant and benign lesions

B-mode US showed 62 of 64 benign tumors and 20 of 22 histologically proven malignant lesions.

Color-Doppler US evaluation detected benign neoplasm in 42 cases, 4 of which were malignant and 38 were benign at histology, and malignant lesions in 42 cases (Type 1), 18 of which were malignant and 24 benign at histology.

CEUS highlighted 60 benign cases (type 0 pattern) of 64 resulted being benign at histology and 18 malignant lesions (type 1 pattern) out of 22 malignant tumors at histology.

USE detected 45 of 64 benign lesions and 17 of 22 malignant ones.

Cytology (FNAC) identified 60 of 64 benign tumors and revealed 16 of 22 malignant cases.

The results of sensibility, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy in the differential diagnosis between malignant and benign lesions of the techniques taken alone and in combination are summarized in Table I.

Diagnostic differentiation of benign lesions

The same methods were used to differentiate between Warthin’s tumor 33.3% (n=28) and pleomorphic adenoma 19% (n=16). Our results showed that CEUS had a

Table I. Performance of the ultrasound techniques in the differentiation between parotid gland benign and malignant lesions.

	Se (%)	Sp (%)	PPV (%)	NPV (%)	Ac (%)
B-mode US	82	97	90	93	89
Color-Doppler US	81	61	43	90	71
CEUS	86	95	86	95	90
USE	77	71	50	88	78
FNAC	73	97	89	91	84
B-mode US + CEUS	95	54	63	88	86
B-mode US + USE	78	80	46	84	72
Color-Doppler US + CEUS	83	76	58	91	82
Color-Doppler US + USE	78	69	46	88	75
USE + CEUS	86	69	50	90	78

US, Ultrasound; Color-Doppler US, Color-Doppler Ultrasound; CEUS, Contrast-Enhanced Ultrasound; USE, Ultrasound-Elastography; FNAC, Fine Needle Aspiration Cytology; SE, Sensibility; Sp, Specificity; PPV, Predictive Positive Value; NPV, Negative Predictive Value; Ac, Accuracy.

Table II. Performace of the ultrasound methods in the differentiation between pleomorphic adenoma and Warthin's tumor

	Se (%)	Sp (%)	PPV (%)	NPV (%)	Ac (%)
B-mode US	76	78	64	86	78
Color-Doppler US	60	85	69	80	71
CEUS	81	87	74	86	80
USE	93	81	69	96	85
FNAC	57	96	79	71	76
B-mode US + CEUS	72	82	64	87	76
B-mode US + USE	70	76	50	88	73
Color-Doppler US + CEUS	95	37	63	88	66
Color-Doppler US + USE	60	77	57	80	68
USE + CEUS	83	85	68	86	82

US, Ultrasound; Color-Doppler US, Color-Doppler Ultrasound; CEUS, Contrast-Enhanced Ultrasound; USE, US-Elastography; FNAC, Fine Needle Aspiration Cytology; SE, Sensibility; Sp, Specificity; PPV, Predictive Positive Value; NPV, Negative Predictive Value; Ac, Accuracy.

slightly higher diagnostic accuracy (80%) compared to B-mode US alone, which had a diagnostic accuracy of 78%.

USE's accuracy, as well as specificity, increased with lesion diameter: it was lower in lesions ≤ 1 cm and increased progressively in lesions between 1.1 cm and 1.9 cm and in lesions ≥ 2 cm (ROC areas: 30% ≤ 1 cm; 45% 1.1-1.9 cm; 53% ≥ 2 cm; specificity: 60% ≤ 1 cm; 90% 1.1-1.9 cm; 97% ≥ 2 cm).

Regarding USE, the Youden test identified the cut-off of 2.5 as the value that optimized the ability of the method to discriminate between pleomorphic adenoma and Warthin's tumor, with values lower than 2.5 more associated with Warthin's tumor. In this case, the USE's accuracy was higher compared to CEUS and B-mode US (85% against 80% and 78%, respectively).

All the statistical results are summarized in Table II. It is worth nothing that USE resulted being the most effective technique for the differentiation of pleomorphic adenoma from Warthin's tumor.

In figures 1-3 are illustrated significant cases from our database.

Discussion

B-mode US, used routinely in clinical practice, allows the identification and location of parotid lesions and the depiction of their inner structure. However, a more accurate and detailed representation of the blood flow patterns, in particular a quantitative analysis of micro-vascular perfusion, of the different lesions can be achieved with CEUS [2,14,27].

There is still limited evidence on the use of CEUS in the parotid gland neoplasms. In the latest edition of the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) guidelines, no clinical

recommendation was possible, even though they recognized a research role [29]. Nevertheless, recent studies showed a promising perspective of CEUS. Wei et al in 2013 defined the usefulness of CEUS in the evaluation of micro-vascularization of the lesion according to the morphological and distribution characteristics of the vascular pattern. The results of this study showed that benign lesions present mainly with widespread homogeneous enhancement with clearly defined margins or no enhancement and iso-enhancement, while malignant tumors mainly show heterogeneous enhancement with poorly defined margins [30].

USE provides information about the elasticity/rigidity patterns of gland tissues, which correlate with the composition and structural organization of macromolecules [31,32]. Currently, it may have a role in differentiating the most common benign parotid lesions. USE also has a role in differentiating between benign and malignant parotids tumors.

Elastographic technique has already been evaluated for the characterization of the head-neck lesions, with different results. Bathia et al [33] have reported that USE does not allow to differentiate the tumors, since areas that show the same stiffness can be found in lesions that present a different histology. Dumitriu et al [16] reported the absence of any elastographic pattern that could define the malignant or benign nature of a lesion, observing little benefits in differentiating parotid tumors, particularly regarding the quantitative values of the pleomorphic adenoma which presented similar results to malignant tumors. In particular, the authors observed an intra-lesional variability of rigidity, which may be high in the pleomorphic adenoma due to the heterogeneity of the tissue, concluding that USE in the parotid gland is not a valid tool to exclude malignancy. Contrarily, a meta-analysis from 2016 evaluated the results of 9 studies without publica-

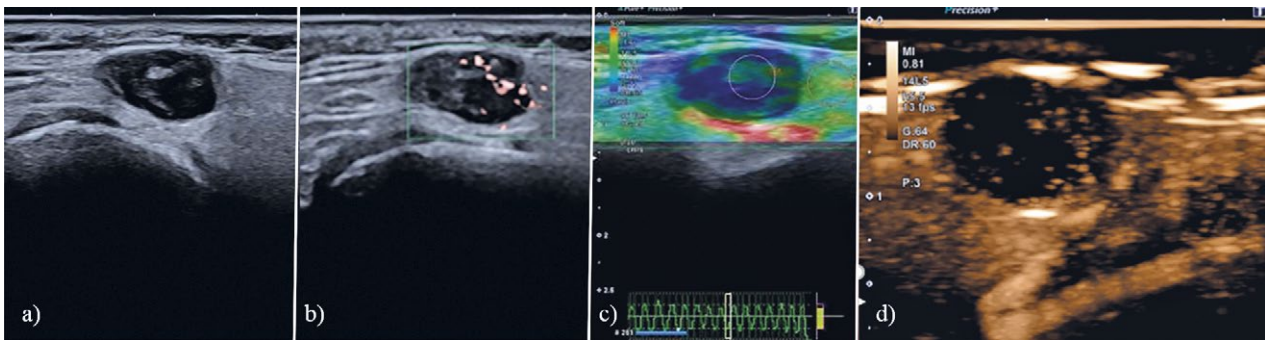


Fig 1. Parotid gland hypoechoic lesion, oval-shaped, with well defined margins and poor vascularization at Color-Doppler US (a,b). The lesion appeared moderately stiff at USE (SR 3.40); c) and showed slight enhancement at CEUS (d). Histology showed pleomorphic adenoma.

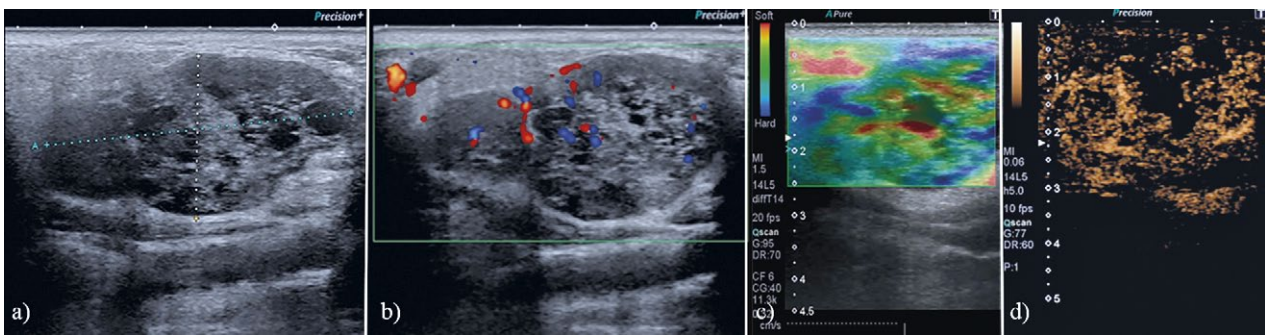


Fig 2. Well-defined parotid gland lesion, heterogeneous with some cystic areas (a), with peripheral and internal vascularization at Color-Doppler US evaluation (b). The lesion appeared mainly soft at USE, with stiff portions corresponding to the cystic areas (c). CEUS showed periferal perfusion (d). The lesion was histologically shown to be a Warthin’s tumor.

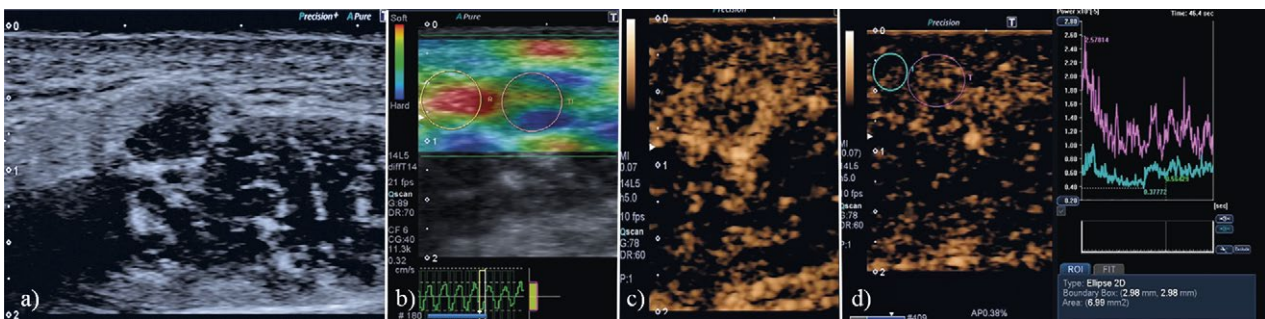


Fig 3. Parotid gland lesion, mostly hypoechoic with undefined margins (a) and increased stiffness at USE (SR 4.976; b). At CEUS evaluation the tumor showed rapid uptake of the contrast during the arterial phase, followed by a rapid wash-out at the end of the arterial phase. The enhancement curve is suggestive for malignancy (c,d). Histology showed acinic cell carcinoma.

tion bias regarding the use of this US method for the differentiation of 581 benign and malignant salivary gland lesions, highlighting good sensitivity and specificity values (76% and 73%, respectively). The results showed that malignant lesions were commonly harder than benign ones. The authors suggested USE in addition to the conventional US for the evaluation of the salivary gland tumors; however, the general accuracy of USE could not obviate the need for biopsy [34].

In the study by Klintworth et al, authors suggested the presence of some specific elastographic patterns useful in

the differentiation between parotid gland tumors. In our work, we did not take into account these patterns, limiting our evaluation to numerical elastographic values [23]. Other authors reported on the use of Shear Wave Elastography (SWE) also in this setting; however, we did not assess SWE effectiveness in our study and it is still under debate which is the best technique between USE or SWE. Mansour et al reported that SWE was better for discriminating parotid gland diseases such as Sjogren’s syndrome than to differentiate parotid gland lesions [24]; Hefman J et al suggested that SWE acceptably distin-

guished benign from malignant lesions on its own but did not bring additional value in the characterization of parotid gland tumors when used as an adjunct to regular US examination [35]. Zengel et al [25] and Liu et al [26] reported different results. In addition, a recent paper published by Jering et al [36] showed the importance of USE (especially SWE) in differentiating benign from malignant tumors, suggesting that the hard part of the lesion is larger in malignant tumors than in benign pleomorphic adenomas that usually have only a hard central area of increased stiffness.

In this study, we evaluated the diagnostic accuracy of MPUS with CEUS and USE in pre-surgical differentiation of parotid tumors comparing the results with B-mode US, Color-Doppler US and FNAC. MPUS evaluation seems the most promising approach to preoperative diagnosis of parotid neoplasms. In 2015, Mansour et al studied 202 patients with parotid lesions, documenting their clinical history, clinical examination, B-mode US, USE, Color-Doppler and CEUS. They concluded that there was a correlation between the micro- and the macro-vascularization of the lesions respectively evaluated with CEUS and Color-Doppler US, but the predictive value of each single technique was not so effective and a multiparametric assessment was required to increase the specificity and PPV in the diagnosis of malignant parotid lesions and the sensitivity in the differential diagnosis between pleomorphic adenomas and Warthin's tumors [37]. Another recent review confirmed that MPUS, specially if includes CEUS, enables the differential diagnosis of parotid tumors [1,20].

Concerning USE, in our study, a statistically significant difference in elasticity between benign and malignant tumors was identified. The ROC analysis showed that, for malignancy diagnosis, the cut-off value of SR is >3 . However, the method presented poor sensitivity (77%) and poor diagnostic accuracy (78%), mostly due to the presence of non-Hodgkin's lymphomas ($n=4$), which has elasticity similar to most benign parotid lesions.

Lesions studied with CEUS were classified into different types, similar to the study by Wei et al [30] and David et al [2], based on vascularization patterns. Subsequently, these patterns were compared with histological examination. This allowed us to create criteria for the assignment of a given pattern for malignant lesions and for benign lesions: type 0 pattern was more frequently associated with benign lesions and type 1 pattern with malignant ones.

Our study showed that CEUS has high diagnostic accuracy (90%), sensitivity (86%) and specificity (95%) and may be considered the optimal method for differentiating between benign and malignant lesions. These

results prove also the superiority of CEUS in terms of sensitivity, specificity and accuracy compared to standard methods, especially if compared to FNAC, still used today as the main exam in the patient's pre-operative planning. Indeed, FNAC was less accurate than B-mode US and CEUS, with a high percentage of non-diagnostic results and low sensitivity.

Among the various combined statistical evaluations, our results showed that the association of B-mode US with CEUS had the best performance, presenting with similar accuracy of CEUS taken alone, but with better sensitivity (95%).

Our results also confirmed that B-mode US is an important technique in the preoperative diagnosis, presenting high diagnostic accuracy (89%), in line with the literature [1,15,16,19,33,36,38]. However, being an operator-dependent examination, the results are linked to the execution by an experienced operator, especially in the study of the major salivary glands.

Color-Doppler US examination allowed us to evaluate the vascularization of the lesions, but it proved to be ineffective in discriminating benign from malignant tumors, showing a low diagnostic accuracy, thus resulting in a poor diagnostic value. This result may be due to the considerable overlap between Color-Doppler characteristics, especially between benign and low-grade malignant lesions, as recently confirmed by Knopf et al [39].

The elastographic method with cut-off SR >3 , presenting a diagnostic accuracy of 78%, appeared to be less performing than CEUS and of limited diagnostic value in differentiating malignant lesions from benign ones, in line with recent studies [1,16,33,40,41]. These results are probably due to the presence in the diagnostic sample of non-Hodgkin's lymphomas which have an elasticity comparable to that of benign parotid tumors.

Our results are in concordance with current literature that indicates that Warthin's tumor is the most common benign parotid tumor [42]. In the characterization between the two most common benign tumors, USE proved to be statistically superior to the other methods. USE showed diagnostic accuracy of 85%, much higher than that of B-mode US (78%) and CEUS (80%). Noteworthy, USE had an excellent reliability in differentiating Warthin's tumor from pleomorphic adenoma.

Our study has some limitations. Firstly, our results are based on a limited sample size; therefore, larger studies are required. Secondly, we relied on the accuracy of pathological diagnosis excluding patients who had not undergone surgery. Finally, we did not use SWE neither did we perform a comparison between MPUS and MRI [43].

Conclusions

Our results suggest that the combination of B-mode US and CEUS greatly improved the sensitivity of the CEUS performed individually and presented remarkable accuracy, with the potential to reduce the number of invasive procedures. USE may have a role in differentiating benign from malignant parotid tumors, but especially in differentiating Warthin's tumor from pleomorphic adenoma. FNAC demonstrated lower values in comparison with CEUS in the differentiation between malignant and benign neoplasms and with USE in the diagnostic differentiation of benign lesions.

Therefore, MPUS could be proposed as a valid alternative to FNAC; however, multicenter studies on a larger population, eventually including a comparison with MRI, are mandatory.

Conflict of interest: none

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