Ultrasonography techniques in the preoperative diagnosis of parotid gland tumors – an updated review of the literature

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Abstract
Preoperative diagnosis of parotid tumors plays a crucial role in selecting and planning the surgical treatment. Ultrasound (US) with its modern techniques can contribute to the differential diagnosis of parotid tumors. This paper aims to achieve a comprehensive review of the ultrasound techniques used in the differential diagnosis of parotid tumors, based on the latest literature data. Considering that most parotid gland tumors are located in the superficial lobe, US is frequently the first imaging technique used for the diagnosis of parotid tumors. Sonoelastography can provide additional data on the elasticity of parotid tumors, but there is an overlap between malignant and benign parotid tumors parameters. Contrast-enhanced ultrasound adds value to conventional ultrasound and allows a more complete characterization of parotid tumors. Many authors have reported promising results using contrast-enhanced ultrasound in the differential diagnosis of parotid tumors. Multiparametric ultrasound with a careful and systematic approach usually allows an accurate differential diagnosis of parotid tumors.

Keywords: ultrasound; elastography; contrast-enhanced ultrasound (CEUS); diagnosis; parotid gland tumors

Introduction
Salivary glands tumors account for 2 to 6% of all head and neck tumors. Among these, 70-80% are located in the parotid glands, 70-80% are benign and 20-30% are malignant. Parotid tumors have a wide histological variety, the pleomorphic adenoma (PMA) being the most common benign tumor (60-80%), followed by the Warthin tumor (WT) (15-30%). Mucoepidermoid carcinoma is the most encountered malignant tumor of the parotid glands (30%) [1-4].

Benign parotid tumors are frequently located in the superficial lobe, being well delimited, mobile, do not modify the covering skin and have a firm-elastic consistency. Signs and symptoms such as: pain, rapid growth, invasion of surrounding tissues, ulceration of the overlying skin, facial nerve palsy, otalgia, cervical adenopathy and weight loss should raise malignancy suspicion. One third of malignant tumors have a clinical behavior similar to benign tumors [2,3].

Imaging investigations play an essential role in the preoperative differential diagnosis of parotid gland tumors providing information about the specific tumor localization in the gland and the relationships with surrounding structures. The preoperative differentiation between benign and malignant lesions and the knowledge of the histological type of the parotid tumors is extremely important for the surgical planning: malignant tumors require extensive surgery in accordance with oncological principles, while in the case of benign tumors less invasive surgical treatment is performed, which may differ depending on the tumor histological type [5].
Ultrasonography techniques in the preoperative diagnosis of parotid gland tumors

Currently, cross-sectional imaging investigations, including modern US techniques, are routinely used and studied for the differential diagnosis of parotid tumors, with promising results published in literature. There are a few papers published focused on the evaluation of US techniques used in the differential diagnosis of parotid tumors. This paper aims to achieve an updated, objective and comprehensive review of the US techniques used in the diagnosis of parotid tumors based on the latest literature data.

Diagnostic value of ultrasound techniques (US)

Current US techniques can contribute to the differential diagnosis of parotid lesions. In 80-90% of cases tumors are localized in the superficial lobe [6-8]. Usually US is the initial method of choice for parotid tumors diagnosis, due to a large number of advantages (low-cost, accessible, non-invasive and non-irradiating technique). The diagnostic accuracy is very high for the differentiation between tumors and other glandular pathologies such as cystic, infectious or inflammatory lesions. US can make the differential diagnosis between benign and malignant tumors, can locate the intra- or extra-glandular lesions and is very helpful for the guidance of fine needle aspiration biopsy (FNAB). The technique presents a series of limitations such as: dependence of the operator, lack of standardized sections, low specificity in assessment of parotid tumors histological type, difficulty in evaluating tumors located in the deep parotid lobe or posterior to bone structures [1,5,7-14].

Grayscale and Doppler criteria

The following parameters can be assessed with the conventional B-mode US: axial diameter, borders, shape, acoustic enhancement, echotexture, echogenicity and the presence of anechoic areas. Doppler US provides additional information related to vascularization of parotid tumors [7,5,15]. On US, pleomorphic adenoma (PMA) typically presents well circumscribed margins, predominantly homogeneous echotexture, acoustic enhancement, internal focal calcifications (rarely), anechoic / cystic degeneration areas. A Warthin tumor (WT) usually has well-defined margins, internal cystic changes, hypoechoic internal septation, a more inhomogeneous structure and acoustic enhancement. Small, low-grade malignant tumors may appear well defined, homogeneous and hypoechoic, while large, high-grade malignant tumors present irregular, poorly defined margins, heterogeneous echotexture; extra-glandular spread and pathologic cervical adenopathy can be identified (fig 1, fig 2) [4,8,16,17].

On Doppler US, W Ts and malignancies have a rich capsular and/or internal vascularization. PMA shows reduced vascularization [4,8,16,17].

Fischer et al in 2010 describes a predominant distribution of the vessels in the periphery rather than in the center for PMA, compared to the WT, in which the overall tumor vascularization is much higher, without signifi-

Fig 1. a) Grayscale appearance for pleomorphic adenoma: well-defined margins, lobulated contour, acoustic enhancement, subcapsular location in the superficial lobe without capsular effraction; b) grayscale appearance for Warthin tumor: well defined lesion with necrotic areas; c) low-grade malignant lesion, well defined, irregular contour, calcification and perilesional round hypoechoic lymph node (histological proven as a collision tumor of acinic cell carcinoma and salivary duct carcinoma)

Fig 2. a) Illustration of malignant features identified in parotid tumors: a) infiltrative contour, inhomogeneous lesion; b) extracapsular spread (the arrow is showing the disruption of the parotid capsule)
cantages differences between the central and the peripheral part of the tumor (p<0.05) (fig 3) [16]

Rong et al (2014) was able to differentiate PMA from WT based on B-mode Doppler US characteristics [13]. Rzepakowska et al (2017) managed to differentiate PMA from WT [sensitivity (Se) 61.5%, specificity (Sp) 81.5%, accuracy 73.1%] as well as malignant tumors from benign lesions (Se 60%, Sp 95.2%, accuracy 90.3%) using B-mode and Doppler US [7].

Gerwel et al (2015) and Kovačević (2010) et al showed that an ill-defined margin is the most representative US parameter for malignant tumors (Sp 86%, Se 37.5%) while acoustic enhancement is a benign characteristic; simultaneous evaluation of all US parameters can increase the method sensitivity [18,19].

In the literature a diagnostic accuracy between 61.8-64.7%, a Se between 38.9-88% and a Sp between 67.4-90.1% were reported using only the conventional US parameters in differentiating malignant from benign parotid tumors [18,20,21].

Several authors propose that in cases of benign lesions confined to the superficial parotid lobe suggested by US and confirmed by the cytological result of FNAB, no further investigations are required [4,9,10,14].

Cheng et al (2019) showed that the US assessment of the minimum distance between the parotid fascia and the parotid tumor (MFTD) with a cutoff value of 2.4 mm can be used to differentiate the location of benign tumors in the parotid gland; distance of less than 2.4 mm correlates with the tumor localization in the superficial lobe of the parotid gland [22]. On the other hand, for a more precise and objective localization of tumors in the parotid glands with the help of the US, a schematic diagram based on marking the tumor location in relation to the external ear structures was proposed. The use of this diagram helps to standardize and organize the US preoperative report [23].

There is still a considerable overlap between benign and low-grade malignancies [8]. Therefore, differentiating among malignant and benign tumors based on B-mode and Doppler US is difficult and can lead to misdiagnosis. Zhang et al (2018) have showed that the diagnostic accuracy (96.1 vs 82.4%) of DWI-MRI was increased when ADC values were used in conjunction with US Doppler flow imaging features to differentiate parotid tumors compared to single usage of ADC values [24].

Conventional US is a non-invasive examination with a facile and quick access for the clinicians, often being the first recommended for patients with parotid lesions. US completes the clinical exam, allowing in the majority of the cases a general evaluation of the parotid tumor and an overview in establishing the clinical final diagnosis. In addition, it has high Se and Sp for the differentiation from other non-neoplastic lesions of the parotid glands. US allows the characterization of malignant and benign tumors based on specific US criteria for each tumor entity, but has a low Se (38.9-88%) in the differential diagnosis of parotid tumors, due to an overlap between benign and low-grade malignant tumors, according to most literature data [5,8,15,16,18,20,21,25-28]. Mansour et al (2012) suggested in their study that vascular pattern and acoustic enhancement are the most significant parameters in differentiating PMA from WT, when using the US [29].

In addition to conventional US, modern techniques are currently available and allow the assessment of elasticity or other biomechanical tissue properties. These techniques are reunited under the name of multiparametric ultrasonography (MPUS), adding value to the conventional US and completing some of the disadvantages of the method. MPUS includes the ultrasound elastography (USE) with the two techniques- strain elastography (SE) and shear wave elastography (SWE) as well as the contrast-enhanced ultrasound (CEUS) [5,8,10,20,30-32].

Ultrasound elastography

Ultrasound elastography (USE) is a non-invasive technique that allows a quantitative or qualitative evaluation of the soft tissue elasticity.

Fig 3. Doppler US: a) pleomorphic adenoma with reduced vascularization; b) highly vascularized tumor (histological proven – a Warthin tumor) with capsular and internal vascularization; c) anarchic distribution of vessels in the case of a malignant lesion (histological proven – salivary duct carcinoma).
The use of USE in the differential diagnosis of parotid tumors is controversial. At present, the effectiveness of USE, as the only examination technique, is not proven in the differential diagnosis of parotid tumors. Many studies have shown that malignant tumors have higher stiffness values than benign ones and PMAs are in generally stiffer than WTs, but there is a large overlap between these findings [10,11,26,28,33].

USE brings new information on the characterization of parotid tumors, but nevertheless it has been shown that adding it to conventional US does not improve significantly the differential diagnosis between parotid tumors [29]. Initial results looking purely at USE techniques in the parotid glands diagnosis have been disappointing. Larger prospective studies are needed to determine the value of this investigation. USE recorded a pooled Se of 67%, a Sp of 64% and a diagnosis odds ratio of 8.00 in a meta-analysis [34] that evaluated the value of this investigation in the differential diagnosis of parotid tumors [9,26,34,35,36].

Dumitriu et al (2010) could not identify in their study a sonoelastographic pattern characteristic for the PMA [37]. Although the same authors found a statistically significant difference between the elastography scores of malignant tumors compared to benign lesions, the detailed analysis was not possible to establish a cutoff point for this scores, more likely due to the high stiffness of PMAs (fig 4) [38].

Mansour et al (2015) demonstrated that PMA presents significantly increased stiffness compared to monomorphic adenoma, malignant tumors or cystic lesions; however, this criterion has not been shown to be effective in differentiating between malignant and benign tumors [32].

On the other hand, many authors obtained promising results regarding the use of USE in the differential diagnosis of parotid tumors.

Mansour et al in 2012, using SWE with the mean ARFI velocity values, obtained a statistically significant difference (p<0.003) between PMA and WT (2.23±0.53 m/s vs 2.58±0.77 m/s) [29].

According to Bhatia et al (2012) the mean shear modulus of benign lesions was 18.3 kPa which overlapped considerably over malignant lesions (13.5 kPa). However, PMAs shown to be significantly stiffer compared with WTs (22.5 kPa versus 16.9 kPa) [28] (fig 5).

Wierzbicka et al (2013) used USE to differentiate benign from malignant parotid tumors. Malignant tumors had a mean stiffness of 146.6 kPa as opposed to benign tumors that had a mean stiffness of 88.7 kPa. The results were statistically significant (p <0.001) and the authors concluded that adding USE to US improves the differential diagnosis of parotid tumors [39].

Cortcu et al evaluated the USE in discrimination of malignant and benign parotid tumors based on strain ratio (SR). Median SR value for benign tumors was 1.11
and 2.75 for malignant tumors, with a statistically significant p value. For the SR cutoff value of 2.1, the Se was 83.3%, Sp was 97%, positive predictive value- PPV was 83.3%, negative predictive value - NPV was 97%, and the diagnostic accuracy was 94% (fig 6) [11].

Klintworth et al (2012) showed that parotid tumors may have certain elastographic patterns: garland sign (reticular distribution of stiff tissue in the whole tumor) for malignant tumors, dense core sign (very stiff central zone with softer neighboring tissue) - characteristic of PMAs and half-half sign (a stiff area located in the superficial half of the lesion while the deeper part has a softer aspect) – for WT [40].

In a recent study, Cantisani et al showed that benign tumors had a mean elasticity contrast index (ECI) of 2.31 and malignant tumors had a mean value of 5.55. The ECI value >3.5 was the cutoff point for the differentiation of malignancies (90.5% diagnostic accuracy). The authors concluded that USE with ECI index improves US Se in discriminating parotid tumors [20].

Virtual touch imaging quantification (VTIQ) represents a two-dimensional new form of shear wave imaging which allows combining quantitative and relative stiffness imaging in a single screen. The investigation also allows the user to draw a two-dimensional region of interest (ROI). VTIQ includes several shear wave modes such as: velocity, quality, travel time, and displacement. VTIQ in combination with routine US techniques provides additional data useful in distinguishing benign from malignant parotid tumors [41,42].

Zengel et al (2017) using VTIQ showed that malignancies had much lower quality and the share wave velocity was higher than 6.8 m/s in comparison with benign lesions [41]. Using the same investigation, Liu et a. (2018) obtained higher values of share wave velocity for malignant tumors compared to benign ones; the cutoff value was 2,445 m/s with a Sp of 80% and a Se of 91.8% [31]. Altinbas et al (2017) looking for the diagnostic value of SE in parotid tumors differentiation presented the following results: mean elasticity score for benign tumors was 2.75±0.95, compared with malignant tumors score of 3.44±0.85; (p<0.034) [43]. Herman et al (2017) showed in their study that the coefficient of stiffness variability (CSV) which represents the ratio between the maximum and minimum stiffness values recorded with SWE is the strongest predictor of malignancy and allows parotid tumor differentiation between benignity and malignancy (p <0.0001) [27].

Regarding the modern US techniques, the use of elastography in the differential diagnosis of parotid tumors is still controversial due to the overlap between the parameters. An important overlap between the values of elasticity of PMA and malignant tumors was reported in the literature [10,38]. Moreover, adenolymphomas show a great variety of histological structure, which is reflected in the wide range of SWE elasticity modulus of these tumors reported by Huang et al (2018) [44]. However, most authors accept that, in general, malignant tumors are stiffer than benign lesions, and PMAs are stiffer than WTs, but this is not a strong enough criterion to allow the differentiation of parotid tumors [10,11,26,28]. Zhang et al (2019) in a meta-analysis presented a Sp of 67% and a Se of 64% recorded by USE for the differentiation of parotid tumors [34]. Many authors have investigated methods to improve USE diagnostic accuracy in differentiating parotid tumors. Thus, Mansour et al. (2019) [29] succeeded in differentiating PMA from WT using conventional US together with SWE. Cantisani et al (2017) [20] using a cutoff value >3.5 for the elasticity contrast index obtained significant results in differentiating malignant parotid tumors from benign lesions, with an accuracy of 90.5%.

Herman et al (2017) obtained encouraging results for differentiating parotid tumors with the help of a coefficient of stiffness variability (CSV) [27]. Cortcu et al (2018) managed to differentiate between malignancy and benignity using USE based on strain ratio cutoff value of 2.1 [11]. Encouraging results in the evaluation of parotid tumors with the help of USE have been obtained also by other authors [11,31,39], which shows that this investiga-
tion has a potential in differentiating parotid tumors that must be investigated by further studies. USE, especially SE is an operator-dependent investigation, which may explain the large variations between the results of the published studies.

Contrast-enhanced ultrasound

CEUS allows a quantitative analysis of the microvascular perfusion of tumoral tissue, representing a reproducible measurement of perfusion kinetics after intravenous administration of the contrast agent. It is a non-invasive investigation with all the advantages of conventional US. The contrast agent has a good safety profile, with a low risk of side effects, and can be administered even to patients with impaired renal function due to its elimination through the respiratory tract (sulphur hexafluoride gas). The standard CEUS protocol involves injecting 4.8 ml of contrast agent into a peripheral vein followed by dynamic monitoring of the contrast agent passage through the ROI for minimum 120 seconds. The conventional grayscale US images are displayed on the screen simultaneously with CEUS images. Quantitative parameters such as time-intensity curves (TIC) and enhancement patterns, but also a number of semi-quantitative parameters such as area under the curve (AUC), time to peak (TTP) and mean transit time (MTT) can be evaluated using CEUS investigation [8,10,25].

Wei et al (2013) assessed the morphologic and distribution features of micro-vascularity of the tumors and classified CEUS imaging into three types: type 1 - diffuse homogeneous enhancement; type 2 - heterogeneous enhancement with 3 subdivisions: a - more than 50% enhanced areas with well-defined margin, b - dotted or splattered vessels or less than 50% enhanced areas with well-defined margin and c - heterogeneous enhanced, lesions with ill-defined margin; and type 3 - no enhancement and iso-enhancement with 2 subtypes: a - no enhancement in lesions and b - iso-enhancement between lesions and surrounding tissues. The authors concluded that types 1 and 3 are representative for benign tumors and type 2, especially subtype c can suggest malignancy [45].

Many studies published in the literature have shown improved results with the use of CEUS for the differential diagnosis of parotid tumors (fig 7) [5,16,25,32].

Data from the literature show that the use of multimodal US to differentiate parotid tumors increased the Se of malignant tumors detection from 77% to 91% but decreased the Sp from 98% to 81% compared to conventional US [32].

Steinhart et al (2003) showed that using US contrast agents in combination with Doppler US, PMA recorded a significantly stronger perfusion enhancement with increased Doppler signal area. The authors concluded that the Doppler signal area can show different courses depending on tumor histology [46].

Fischer et a. (2010) were successful in differentiating PAM from WT based on the TTP parameter (26.8±11.1 versus 22.6±5.1 sec, p<0.05). Also, following the AUC analysis, the PMA registered much lower values compared to the WT [16].

According to Klotz et al (2013) malignant tumors register prolonged MTT (17.94±1.62 s versus 14.86±0.65 s; p<0.05) and AUC values (584.9±143 versus 400.62±53.85; p<0.05) compared to benign lesions. Regarding the benign tumors, WT showed higher AUC values than PMA (515.4±1.26 versus 285.82±36.44; p<0.05) [25].

Klotz et al (2014) using a new quantification software (Vuebox) for CEUS, were able to differentiate malignant tumors from benign ones (p<0.05) as well as WT from PMA (p<0.05) based on the following parameters: AUC - 528.6±183.3 vs. 174.4±52.9 – malign vs. benign and 302.8±36.2 – WT vs 65.6±13.8 – PMA, peak enhancement - 155.3±69.5 vs. 38.2±9.0 – malign vs. benign and 68.8±11.4 – WT vs 12.2±1.8 – PMA, wash-in-rate and wash-in perfusion index. On the other hand, they did not find significant differences for mean transit time (MTT) and rise time (RT) [47].

Küstermeyer et al (2016) using an innovative method of analysis the perfusion characteristics in 8 ROIs based on CEUS, obtained a significant difference between benign parotid tumors compared to malignant ones [48]. On the other hand, Badea et al (2013) could not find significant differences between the circulatory bed of benign and malignant tumors using CEUS investigation [12].

The CEUS parameters - TIC, TTP, MTT and AUC were successful in the differential diagnosis of parotid tumors [5,16,25]. Klotz et al (2013) showed in their study that MTT and AUC showed significantly higher values for malignant tumors compared to benign ones. The circulation of the contrast agent through abnormal and disordered vessel architecture of cancer lesions may explain these increased values; on the other hand, it seems that the reduced perfusion of benign tumors may occur due to the regular architecture of the vascular systems of these tumors [25]. Klotz et al (2014) [47] with the help of a new software and the parameters such as: AUC, PE, WiR, WiPI manage to differentiate malignant parotid tumors from benign ones with CEUS (fig 8).

The preoperative differential diagnosis of parotid tumors based on US investigations is challenging for clinicians due to the great histological variety of parotid tumors. According to the latest World Health Organization...
classification from 2017 [1], 20 malignant and 11 benign tumor histology are described, to which another 9 histological tumor types are added. The histological and US characteristics that overlap between many tumor entities, as well as the lack of clear guidelines for the differential diagnosis of parotid tumors contribute to the controversies of this topic. In cases of inconclusive results, additional investigations and/or a second imaging opinion could help establish the correct diagnosis.

The use of MPUS provides promising results for parotid tumors differential diagnosis. Data from the literature shows high Se of up to 91% and Sp by combining USE, CEUS and conventional US in differentiating parotid tumors; however, US still cannot replace the MRI scan [32,49]. Further studies are necessary in order to define the diagnostic value of the MPUS and to draw clear indications of the method in the current diagnosis of parotid tumors.

Based on the literature review [4-5,7-10,13,16-20,25,28,30-32,45], a guide for the US differential diagnosis of parotid tumors is proposed by our group and presented in fig 9.

**Fig 7.** Illustration of CEUS pattern in a histological proven Warthin tumor: peripheral inhomogeneous enhancement in the arterial phase (a) and intrallesional vascular septa and wash-out in the late phase (b); c) the enhancement curve of the lesion is suggestive for benign lesion.

**Fig 8.** CEUS appearance in a case with malignant parotid lesion: rapid tumoral uptake of the contrast during the arterial phase (a), followed by a rapid wash-out at the end of the arterial phase (b). The enhancement curve of the lesion is suggestive for malignancy, with similar pattern for the surrounding metastatic adenopathy (c).

**Fig 9.** US guide for the differential diagnosis of parotid gland tumors.


**Limitations**

This literature review is not without limitations. Many of the revised studies are retrospective, performed on small groups of patients. In these studies, there is no unity in the experience of radiologists or pathologists who have interpreted the investigation reports. The statistical methods used differ from one study to another. There are large variations between the US equipment and protocols. In some studies, there was an unequal distribution between the evaluated malignant and benign parotid tumors.

**Conclusions**

The most important statistically sustained conclusion of this review is that if the US of a parotid tumor located in the superficial lobe suggests benignity and the FNAB report confirms the diagnosis and succeeds in specifying the tumor histological type, no further investigations are necessary.

The preoperative differential diagnosis of parotid tumors is challenging and plays a crucial role in the choice of therapeutic strategy. Establishing a correct preoperative diagnosis with the US techniques requires a systematic and careful approach with the correlation of the clinical exam and the patient history. The experience of the US operator and the knowledge of the US limits are of great importance.

Ultrasonography adds important information to the clinical exam related to the tumor location and extension, has an important role in the differential diagnosis between benign and malignant lesions and guides the clinician for the need of further investigations and the therapy strategy.

The value of USE alone is not proven in the differential diagnosis of parotid tumors. However, the USE provides additional data on the elasticity of parotid tumors. Adding CEUS to conventional US increases the differential diagnosis accuracy of parotid tumors. MPUS allows the differential diagnosis of parotid tumors, but additional studies are required to validate the results. When the diagnosis of parotid tumors is inconclusive with the MPUS, MRI becomes mandatory.

**Conflict of interest:** none

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