Diagnosis of parotid gland tumours with Contrast-Enhanced Ultrasound: a systematic review and meta-analysis

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Abstract

Aim: Contrast-enhanced ultrasound (CEUS) appears to be a promising application for the diagnosis of parotid gland tumours. We aimed to systematically review and meta-analyse the ability of CEUS in distinguishing benign from malignant parotid gland tumours. Material and methods: PubMed was searched for relevant studies. Data on area under time intensity curve (AUC) in arbitrary unit (AU), and mean transit time (MTT) in seconds (sec) were analysed using the Cochrane Review Manager Software. Results: Nine studies met the eligibility criteria comprising a total number of 498 parotid gland tumours (benign, number (n)=423; malignant, n=75). Descriptive evaluation of parotid gland tumours following CEUS administration showed overlap characteristics in benign and malignancies. Two publications assessed AUC and MTT in 72 and 60 parotid gland tumours, respectively. AUC was significantly lower in benign compared to malignant tumours following contrast administration (AUC, mean difference (MD) -266.77 AU, 95% confidence intervals (CI) -433.22, -100.33, p=0.002). No significant different in MTT between benign and malignant tumours (p=0.12). Heterogeneity was statistically significant in AUC (p=0.04) and MTT (p<0.00001). Conclusion: Descriptive evaluation of parotid gland tumours showed overlap CEUS characteristics. Perfusion related CEUS parameters analysis is promising in differentiating benign parotid tumours from malignancies. Keywords: Contrast-enhanced ultrasound; parotid gland; tumour

Introduction

Parotid gland is the most common site of salivary gland tumours [1]. Differentiating malignant from benign parotid gland tumours is critical for surgical planning [2,3]. Ultrasound-guided fine-needle aspiration cytology and ultrasound-guided core biopsy are considered the reference standard for pre-operative diagnosis and are suggested to be performed in patients with suspected malignancy [4-6].

Ultrasound is inexpensive, safe and widely available for the assessment of parotid gland masses. However, sonographic characteristics of benign and malignant parotid tumours in conventional ultrasound may overlap and may be inconclusive, showing high sensitivity for diagnosing but low specificity for differentiating salivary gland lesions [4,7–9]. Salivary glands have a complex vasculature [10,11], and malignancies usually show high vascularisation pattern [12]. The use of contrast-enhanced ultrasound (CEUS) has been recommended by the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) for the assessment of salivary gland tumours which appears to be promising application in differentiation between benign and malignant parotid gland tumours [4,13]. Micro-bubbles consist of very small gas bubbles, range 1 to 5 μm on average, coated with a layer of phospholipid or galactose allowing them to pass through capillaries exploited for the visualisation of the vascularisation of tumours non-invasively.
Studies that assessed the ability of CEUS in diagnosing parotid gland tumours reported different findings to whether it is possible to characterise benign tumours and differentiate them from malignant tumours. Two studies done by Klotz et al (2013 and 2014) reported that CEUS has the potential to differentiate between benign and malignant parotid gland tumours pre-operatively based on perfusion characteristics [12,19]. In contrast, Badea et al (2013) and Mansour et al (2017) concluded that CEUS showed no significant differences in circulatory beds with poor predictive value in diagnosing benign and malignant parotid tumours [20,21]. Available data on the role of CEUS in diagnosing malignant parotid showed a wide range in sensitivity (46.2-92.3%) and specificity (81-98.2%) [7,11,21]. Therefore, the aim of the present study was to systematically review and meta-analyse the ability of contrast-enhanced ultrasound in distinguishing between benign and malignant parotid tumours.

Material and methods

Search strategy and study selection

The study was carried out in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (no Ethics Approval or Institutional Review Board Approval is required for this study). A systematic search of PubMed was conducted to retrieve all articles evaluating differential diagnosis of parotid tumours using CEUS (until June 2020). Search keywords included: Oral lesion OR salivary gland lesion OR salivary neoplasm OR salivary cancer OR salivary carcinoma OR salivary tumour OR salivary mass OR salivary lesion OR parotid gland lesion OR parotid lesion OR parotid neoplasm OR parotid cancer OR parotid carcinoma OR parotid tumour OR parotid mass AND contrast enhanced ultrasound OR CEUS OR Microbubbles ultrasound were used for searching in title and abstract. Searches were restricted to ‘humans’ and ‘adults +19’ and ‘English’. Pre-specified inclusion criteria were used to prevent bias; an original, peer-reviewed published paper that involved evaluation of parotid gland tumours using CEUS, and histology and/or cytology results was used as the reference standard. Review studies, letter to editor, unpublished materials, studies evaluated salivary gland tumours with absent information/data on parotid gland tumours, abstracts and case studies were excluded. The reference lists of studies for evaluation were searched manually for additional relevant studies. The searches were carried out by two independent researchers.

Data acquisition and quality assessment

From the included studies two independent researchers extracted the following data: first author and publication year, primary aim, study design, number of parotid tumour (benign/malignant), reference standard, contrast agent, tumour characteristics on CEUS images, data provided in publications on CEUS parameters and study findings were extracted. Benign and malignant parotid tumours were classified according to the World Health Organisation histological classification [22,23]. Non-benign/malignant parotid tumours were excluded from the total number of tumours, including neurofibroma, chronic sialadenitis, Sjögren’s syndrome, lipoma, granulomatous lymphadenopathy, non-Hodgkin’s lymphoma, inflammatory lymph node and cystic lesions. Studies provided parameters of CEUS in mean and standard deviation, and compared data of benign and malignant parotid tumour were included in meta-analysis. Values stated within the text on area under the time intensity curve (AUC) in the arbitrary unit (AU) and mean transit time (MTT) in seconds (sec) following CEUS administration for the assessment of defined parotid tumour (i.e. benign or malignant) were used for analysis. AUC and MTT were decided on as they were the only CEUS parameters used to compare benign and malignant parotid tumours available throughout the articles. Data of non-defined parotid tumour or overall data including both benign and malignant tumours and values of non-classified tumours were not used for analysis. If data on a specific tumour (e.g. pleomorphic adenomas) and overall data of more than one tumour were provided, the data of the overall tumours was used for analysis. If values of each benign tumour were provided instead of the overall value of all benign tumours, data from each benign tumour was used for comparison with the provided overall data of malignant tumours and the total number of malignant tumours was distributed to the benign groups. Quality assessment of the included studies was assessed using 14 criteria from the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) [24]. Each of the following criteria was equal to one point: clearly described selection criteria, subjects recruited are representative of patients in clinical practice, available of clinical information of recruited subjects, used reference standard that correctly classify the target condition, reference standard is independent of CEUS, same reference standard was used for all patients, all samples collected from subject verified using the reference standard of diagnosis, methods of performing reference standard is described, CEUS imaging protocol is described, length of contrast inflow being tracked, blinding of assessment, blinding of personnel and participant, complete outcome data, and explanation of subject withdrawals if present.
Data analysis

As this review included studies of benign and malignant parotid tumours, descriptive and data evaluation of benign and malignant parotid tumours were used to characterise parotid tumours and allow for comparison. For meta-analysis, studies compared CEUS parameters between benign and malignant tumours were grouped according to endpoints (AUC and MTT). The results of continuous data on AUC and MTT are expressed as mean difference (MD) with 95% confidence intervals (CIs). Data from each endpoint were analysed as forest plots using the Cochrane Review Manager software (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Since heterogeneity was expected between study protocols (type of tumour, region of interest and time considered for analysis following contrast administration) random-effect models were used. Studies were weighted by sample size and statistical significance was set at p<0.05.

Results

The initial search yielded 1,397 records; nine relevant publications were identified from the PubMed database and from the reference list of relevant publications comprising a total number of 498 parotid tumours (benign, n=423; malignant, n=75). A flow chart of article retrieval and selection is presented in figure 1, and a summary of the data extracted from included studies is shown in table I.

CEUS of parotid tumours

CEUS pattern in benign parotid tumours showed homogeneous and inhomogeneous contrast uptake [20]. Pleomorphic adenoma showed a trend to higher marginal perfusion and absence of central enhancement, whereas, Warthin tumours showed homogeneous central enhancement and small nodular peripheral defects [7,15,17]. Myoepithelial demonstrated weak contrast enhancement [17] and rapid contrast inflow with uniform enhancement and central area resemble necrosis with no contrast uptake were reported in basal cell adenoma [15]. On the other hand, malignancies demonstrated chaotic/inhomogeneous contrast uptake pattern, areas of necrosis and hyper-vascularity with rapid contrast enhancement of peripheral vessels [15,17,20]. It was also reported that organised vessel formation combined by slight enhancement on CEUS appeared in malignant tumours [17]. CEUS identified hypervascularised Warthin tumours with a 100% sensitivity, 93% specificity and 80% positive predictive value. The sensitivity of malignant tumours is 100%, but specificity and positive predictive value decrease to 83% and 50%, respectively [17].

Two studies done by Klotz in 2013 and 2014 demonstrated that specific CEUS parameters can characterise benign and malignant parotid tumours [12,19]. Klotz et al, (2013) reported that malignant tumours had high CEUS perfusion compared to benign showing significantly higher MTT and AUC (MTT: malignant, 17.94±1.62 sec vs benign, 14.86±0.65 sec, p<0.05; AUC: malignant, 584.9±143 AU vs benign, 400.62±53.85 AU; p<0.05) [12]. High AUC in malignancies compared to benign tumours was also reported by Klotz (2014) (AUC: malignant, 528.6±183.3 AU vs benign, 174.4±52.9 AU; p<0.05) [19]. Longer normalised time to peak (nTP) and normalised mean transit time (nMTT) has been reported in carcinomas compared to Warthin tumour (nTP: carcinoma, 1.03±0.08 s vs Warthin, 0.74±0.074 s, p<0.03; nMTT, carcinoma, 1.06±0.05 s vs Warthin, 0.62±0.12 s, p<0.02) [17]. Other CEUS parameters including peak enhancement (PE), wash-in-rate (WiR) and wash-in perfusion index (WiPI) were also significantly higher for malignant lesions than for benign tumours (PE: malignant, 155.3±69.5 dB vs benign, 38.2±9.0 dB; p<0.05; WiR: malignant, 24.1±6.8 AU vs benign, 9.2±2.5 AU; p<0.05; WiPI: malignant, 53.3±15.8 AU vs benign, 24.8±5.9 AU; p<0.05) [19]. However, there were no differences between benign and malignant parotid tumours evaluated by CEUS parameters, including time to peak, wash-in velocity, wash-in time, contrast persistence and maximum contrast signal increase [7,12,20]. Similarly, assessment of the increase in colour Doppler signal post-
Table I. Summary of included studies in chronological order

<table>
<thead>
<tr>
<th>Reference (Author/year)</th>
<th>Primary aim</th>
<th>No. of tumours (B/M)</th>
<th>Reference standard</th>
<th>Contrast agent</th>
<th>ROI</th>
<th>Time used in analysis</th>
<th>Findings</th>
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<tbody>
<tr>
<td>Steinhart 2003 [27]</td>
<td>To assess the potential of CDU in imaging tumours of the parotid gland using CEUS application</td>
<td>22 (20/2)</td>
<td>Histopathology</td>
<td>Levovist</td>
<td>Doppler signal within the tumour</td>
<td>NA</td>
<td>Doppler signal area before and after applying CA administration showed a stronger enhancement of perfusion PA compared to AL.</td>
</tr>
<tr>
<td>Gallipoli 2005 [25]</td>
<td>To characterise of salivary gland tumours, including parotid tumours, using conventional ultrasound and CEUS for and to compare morphological and vascular aspects of the neoplasm with histopathology</td>
<td>41 (35/6)</td>
<td>Histopathology</td>
<td>Levovist</td>
<td>whole tumour</td>
<td>NA</td>
<td>CEUS improve visualisation of tumours vascular, however, it did not yield important information for the characterisation of parotid tumours</td>
</tr>
<tr>
<td>Bozzato 2007 [7]</td>
<td>To test the diagnostic potential of CEUS to differentiate between types of parotid tumours</td>
<td>125 (112/13)</td>
<td>Histopathology</td>
<td>SonoVue</td>
<td>Area within the tumour decided by the user</td>
<td>90 sec</td>
<td>CEUS allowed better visualisation of the vascular distribution. PA showed presence of distal echo enhancement and a trend to higher marginal perfusion, whereas, possess higher blood supply compared to other tumours, WT and showed marked central perfusion trend. However, the wash-in and wash-out parameters of CA did not improve the diagnostic accuracy of parotid tumours.</td>
</tr>
<tr>
<td>Fischer 2010 [15]</td>
<td>To differentiate parotid tumours with the visualisation of contrast medium inflow in tumours.</td>
<td>22 (20/2)</td>
<td>Histopathology</td>
<td>SonoVue</td>
<td>Vascularised area within tumour</td>
<td>60 sec</td>
<td>Standardised analysis of CEUS inflow curves has the potential to differentiate parotid tumours. BT including PA, WT and BCA showed absent of central enhancement, small nodular peripheral defects and homogeneous enhancement of the center and hypervascularity with rapid contrast inflow and nearly uniform enhancement and Central area resemble necrosis with no contrast uptake, respectively. MT showed Central area of necrosis with rapid contrast enhancement of peripheral vessels</td>
</tr>
<tr>
<td>Knopf 2012 [17]</td>
<td>To characterise parotid gland tumours using multimodal ultrasound, including CEUS</td>
<td>27 (22/5)</td>
<td>Histopathology</td>
<td>SonoVue</td>
<td>Area within tumour and surrounding parotid tissue decided by the user</td>
<td>NA</td>
<td>CEUS differentiates tumours that are hypervascularised in the CDU mode. BT including PA, MYO and WT showed poor perfusion, weak and hyperperfusion in CEUS, respectively. MT showed Chaotic vessel formation with increased enhancement with CEUS or with organized vessel formation combined by slight enhancement on CEUS.</td>
</tr>
<tr>
<td>Reference (Author/year)</td>
<td>Primary aim</td>
<td>No. of tumours (B/M)</td>
<td>Reference standard</td>
<td>Contrast agent</td>
<td>ROI</td>
<td>Time used in analysis</td>
<td>Findings</td>
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<td>Badea 2013 [20]</td>
<td>To evaluate multimodal ultrasound approach for parotid tumours discrimination in a noninvasive manner</td>
<td>20 (12/8)</td>
<td>Histopathology</td>
<td>SonoVue</td>
<td>Whole tumour</td>
<td>120 sec</td>
<td>CEUS of parotid tumours did not reveal significant differences between benign and malignant circulatory bed. PA showed homogeneous and inhomogeneous CEUS uptake pattern. MT showed inhomogeneous CEUS uptake pattern with areas of necrosis and hypervascularity</td>
</tr>
<tr>
<td>Klotz 2013 [12]</td>
<td>To investigate CEUS as a diagnostic tool for quantitative assessment of microcirculation in different parotid gland tumours</td>
<td>39 (32/7)</td>
<td>Histopathology</td>
<td>SonoVue</td>
<td>At the centre of the tumour tissue and surrounding parotid tissues</td>
<td>90 sec (first 30 sec)</td>
<td>CEUS seems to be a quantitative and independent method for the assessment of malign and benign parotid gland tumours. BT including PL and WT showed less CEUS perfusion compared to MT</td>
</tr>
<tr>
<td>Klotz 2014 [19]</td>
<td>To evaluate CEUS quantitative parameters to distinguish between benign and malignant parotid tumours</td>
<td>33 (24/9)</td>
<td>Histopathology</td>
<td>SonoVue</td>
<td>Area within the tumour decided by the user</td>
<td>90 sec (first 30 sec)</td>
<td>CEUS quantitative analysis provides important information of perfusion characteristics of benign and malignant parotid gland tumours</td>
</tr>
<tr>
<td>Mansour 2017 [21]</td>
<td>To evaluate the diagnostic pathway of parotid gland lesions using multimodal ultrasound, including CEUS</td>
<td>177 (154/23)</td>
<td>Histopathology</td>
<td>SonoVue</td>
<td>Area within the tumour and surrounding parotid tissue decided by the user</td>
<td>NA</td>
<td>CEUS may demonstrate beneficial assessment of lesion micro and macro-vascularization, but not able to predict tumours entity.</td>
</tr>
</tbody>
</table>

AL: adenolymphoma; B/M: benign/malignant; BCA: basal cell adenoma; BT: benign tumour; CA: contrast agent; CDU: color Doppler ultrasound; CEUS: contrast-enhanced ultrasound; MT: malignant tumour; MYO: myoepithelioma; PA: pleomorphic adenoma; ROI: region of interest; sec: second; WT: Warthin tumour.
CEUS administration did not yield important information for the characterisation of parotid tumours based on optical-visual scale [25].

**AUC**

Two publications [12,19] assessed the AUC of CEUS in 72 parotid tumours (benign, n=56 and malignant, n=16). AUC was significantly lower in benign compared to malignant tumours following contrast administration (AUC, mean difference (MD) -266.77 AU, 95% confidence intervals (CI) -433.22, -100.33, p=0.002, fig 2). Heterogeneity was statistically significant in AUC (p=0.04; I²=76%, fig 2).

**MTT**

MTT following CEUS administration was assessed in two publications [12,17] in 60 parotid tumours (benign, n=48 and malignant, n=12). There was no significant difference in MTT between benign and malignant tumours (p=0.12, fig 3). Heterogeneity was statistically significant in MTT (p=0.00001; I²=97%, fig 3).

**Quality**

The median (range) quality score of the included publications is 9 (range 7-11). Among the 9 included publications, all 9 studies recruited subjects representative of patients in clinical practice, used reference standards that correctly classify the target condition, used a reference standard that is independent of CEUS. The same reference standard was used for all patients, all samples collected from subjects were verified using the reference standard of diagnosis, and described CEUS imaging protocols and provided complete outcome data; 6 clearly described the subjects selection criteria; 5 tracked the length of the contrast inflow; 5 reported blinding of assessment, personnel and participants; 2 provided clinical information of recruited subjects; 1 described the method of performing the reference standard test and no study reported subject withdrawals. Studies included in the meta-analysis showed no publication bias or relationship between quality score and AUC (-0.44, p=0.55) or MTT (0.86, p=0.06).

**Discussion**

The aim of this study was to determine the ability of CEUS to differentiate between benign and malignant parotid tumours. Our analysis has shown that AUC is significantly lower in benign tumours compared to malignancies post-contrast. However, MTT showed no significant difference in parotid tumours following contrast administration. Our analysis has highlighted the limited amount of research carried out to date, suggesting further work is required investigating CEUS parameters to differentiate between benign and malignant parotid tumours.

Criteria for the diagnosis of benign and malignant parotid tumours have been suggested by David et al (2016) reporting that in benign tumours parotid gland demonstrated with clear delineation, lack of cervical lymphadenopathy, homogeneous vascularity and homogeneous distribution of the circulatory bed, whereas, malignancy are demonstrated with unclear delineation of the gland.
the presence of large cervical lymphadenopathy, inhomogeneous vascularization and uneven distribution of the circulatory bed [4]. However, overlap characteristics in benign and malignancies have been reported in which both types demonstrated hypervascularity with homogenous and inhomogeneous contrast enhancement [15,17,20]. Analysis of CEUS parameters including AUC, MTT, TP, PE, WiR and WiPI were significantly higher for malignant lesions than for benign tumours [12,17,19]. This may indicate that the use of computerised analysis of CEUS quantitative parameters is more reliable than descriptive evaluation in diagnosing parotid tumours.

Our systematic review has highlighted that there are a limited number of studies investigating the use of CEUS in benign and malignant parotid tumours. From the limited studies available, our meta-analysis of CEUS parameters showed significantly lower AUC in benign tumours compared to malignancies, but no difference in MTT between parotid tumours. These findings were similar in studies which investigated AUC and MTT following contrast administration in parotid tumours [19]. However, Klotz et al (2013) reported significantly longer MTT in malignant tumours compared to benign [12]. Knopf et al (2012) reported that Warthin tumours showed significantly shorter normalised mean transit time than in pleomorphic adenomas and carcinomas, but no significant difference between pleomorphic adenomas and carcinomas [17]. Studies which evaluated the differences in benign tumours with the analysis of CEUS parameters reported that AUC and intratumoral TP demonstrated a significant difference between pleomorphic adenomas and Warthin tumours [15]. Knopf et al (2012) reported that normalised TP and MTT also showed a significant difference in Warthin tumours compared to polymorphic [17]. This suggests that values of CEUS parameters in benign tumour differ depending on its type which affects the overall outcome of comparison between benign and malignant tumours; further studies investigating CEUS parameters of parotid tumours is required.

In addition to the variation in CEUS parameters values of benign tumours, heterogeneity in terms of selection of region of interest and the length in which contrast being tracked post-injection makes it difficult to compare results between studies (see tab I). Drown region of interest in areas within the tumour may have different measurable microcirculation [19], and may lead to wide variations between observers; therefore, the average of CEUS parameters from multiple areas within the tumours may be considered for analysis. Also, it is possible that the length in which contrast being tracked post-injection may play a role. For example, a significant difference in CEUS parameters between benign and malignant parotid tumours in studies used the first 30 seconds following the arrival of microbubbles in the supply artery for analysis [19,26]. However, no changes were seen in CEUS parameters in which the exploration was carried out continuously from the time of injection for about 120 seconds [20]. Also, different CEUS parameters and scales were used for comparison between parotid tumours throughout the studies which are considered as factors of heterogeneity. A greater number of homogenous studies considering these factors in clinical practice will help in developing a standardised imaging and analysis protocol to improve reproducibility and comparability of CEUS application in diagnosing parotid tumours.

There are a number of limitations to consider in this study. First, the small number of parotid tumours particularly the number of malignant tumours in the publications. Second, a significant statistical heterogeneity was observed in the meta-analyses; therefore, results should be interpreted with caution because of the heterogeneity between studies in terms of the type of parotid tumour, region of interest and time considered for analysis. Third, only one of the nine articles reported blinding of assessment and four reported blinding of personnel and participant, factors that can influence the reported outcomes. However, we found no significant correlation between study quality and effect size in this review.

**Conclusion**

Descriptive evaluation of parotid tumours following CEUS administration may be difficult due to the overlap in CEUS characteristics in benign and malignancies. The use of CEUS parameters including AUC, MTT, TP, PE, WiR and WiPI are promising quantitative parameters to differentiating a benign from a malignant parotid tumour. Data from studies investigating the role of CEUS in parotid tumours is very limited and we suggest that further research evaluating the CEUS quantitative to distinguish between benign and malignant tumours is required.

**Conflict of interest:** none

**References**

4. David E, Cantisani V, De Vincentis M, et al. Contrast-enhanced ultrasound in the evaluation of parotid gland le-