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Perfusion characteristics of parotid gland tumors evaluated by contrast-enhanced ultrasound

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ABSTRACT

Purpose: Contrast enhanced ultrasound (CE-US) is a promising imaging modality for non-invasive analysis of parotid gland lesions because their vascularisation differs from normal gland tissue. This clinical study should further investigate CE-US as a diagnostic tool for parotid gland tumors.
Materials and methods: 39 patients underwent CE-US measurements after intravenous application of a contrast agent (*SonoVue*, Bracco, Italy) before surgical tumor resection. Time–intensity curves gradients were calculated and parameters of intratumoral microcirculation were analysed. The vascularisation parameters were compared among the different tumor entities as defined per definitive histological diagnosis.
Results: Histological analyses revealed 17 pleomorphic adenoma, 15 cystadenolymphoma and 7 malignoma. A significant difference of area below intensity time curve (AUC) and mean transit time (MTT) was measured in the malignant lesions compared to benign tumors ($p < 0.05$). A significant difference of AUC and maximum of signal increase (ΔSI_{max}) for pleomorphic adenoma versus cystadenolymphoma was found ($p < 0.05$).
Conclusion: CE-US seems to be a quantitative and independent method for the assessment of malign and benign parotid gland tumors. Further studies and clinical experience will have to validate this method as a reliable diagnostic tool that facilitates preoperative planning.

1. Introduction

Tumors of the salivary glands are rare with an incidence of <3% of all tumors and about 5% of all head and neck neoplasms. They include a variety of different types of histology [8,12,14]. Recent studies reported an increased incidence of malignant parotid gland tumors during the last decades [16]. In approximately 75% of salivary gland neoplasms, the lesions are located in the parotid glands, which are the largest salivary glands [8]. Mainly, benign lesions are located in the parotid gland, but about 20% of the parotid gland tumors are malignant lesions, such as primary malignoma or metastases [8,14]. Differential diagnosis is very difficult because of the diversity of histological entities, but might be very important in order to provide the indication for surgery. Furthermore, neoplasms of the salivary glands may become malignant during growth [8]. Preoperative classification of the histological tumor type affects the surgical procedure and the postoperative morbidity of patients and may possibly predict or avoid the risk of harming the facial nerve during surgery [18].

B-mode ultrasound is a common technique in the diagnostic pathway of salivary gland lesions. High resolution images, the lack of radiation exposure and the widespread availability characterizes ultrasound as the diagnostic gold standard for the imaging of salivary glands [12]. But the reliable prediction of histological entity and preoperative assessments are lacking.

In recent years, contrast-enhanced ultrasound (CE-US) has been established as a valid diagnostic tool that allows a quantitative analysis of microvascular perfusion in solid tumor tissue [6,19]. Different studies have significantly improved the reliability of diagnosis by CE-US [3,17,19]. CE-US yields measurable and reproductive perfusion kinetics after intravenous injection of the ultrasound contrast agent consisting of microbubbles. These contrast agents are primarily excreted through the respiratory tract, enabling their application also in cases of severe impairment of renal function

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[3,4]. Further studies have validated CE-US as a diagnostic tool for monitoring vascular changes in salivary gland tissue [11,17].

The purpose of our current study was to evaluate CE-US for quantitative assessment of microcirculation in the tissue of different parotid gland lesions, trying to achieve a classification into different benign and malignant neoplasms. Since among the two most common benign tumor entities, pleomorphic adenoma has greater a greater tendency toward malignant transformation in the long-term course than cystadenolymphoma, the differential diagnosis between these two entities would also provide clinically useful information.

2. Patients and methods

The study protocol was approved by the ethics committee of the University of Munich and all patients gave oral and written informed consent. 39 adult patients with parotid gland tumors were included in the study. Patients were excluded when the tumor was not located within the gland, when no surgery was conducted or when patients reported about prior surgery in the tumor area or denied participation in the study and in case of severe organic disease or known intolerance to a component of the contrast agent. During the study period from 2009 to 2012, 39 of 55 consecutive patients with clinical suspicion of parotid gland neoplasms were included into the study.

All ultrasound measurements were accomplished by an experienced radiologist with a high-end device (Siemens ACUSON S2000; Siemens Healthcare, Erlangen, Germany) using a linear multifrequence transducer (9 MHz, S2000; Siemens Healthcare, Erlangen, Germany). For CE-US imaging the Cadence™ contrast pulse sequencing (CPS) technology as a real-time tissue harmonic imaging was used. First, B-mode imaging of tumors in longitudinal and transverse direction was performed for measurement of tumor size. After this, color-coded imaging was used to identify the supplying artery and the draining vein to optimally adjust the transducer for the following contrast enhanced ultrasound measurement. Examinations were performed with low mechanical index (MI = 0.09) to avoid destruction of microbubbles. Frame rate during CE-US measurements was between 23 and 29 frames per second, depending on the penetration depth.

CE-US measurement was performed 24 or 48 h before surgery. For evaluation of contrast agent flow, the contrast agent *SonoVue* (Bracco Diagnostics, Milano, Italy) was used. *SonoVue*, a second generation contrast agent, is a stabilized microbubble preparation containing sulphur hexafluoride (SF_6), an echogenic and poorly soluble gas. These microbubbles are stabilized in an aqueous dispersion by a monolayer of phospholipids. Mean particle size ranges between 2 and 3 μm and particles remain in the intravascular space. An intravenous bolus injection, 2 ml of the described contrast agent, was injected into the cubital vein, followed by 10 ml of a saline solution (0.9%; B.Braun AG, Melsungen, Germany), as it was the defined standard dosage by our experienced radiologist. After many years of experience at our ultrasound center, this dosage provides valid and standardized measurements.

Imaging was recorded on digital cine clips, starting shortly after the injection and continuing for up to 90 s. All ultrasound data was analyzed after the examination, using the DICOM raw data on the ultrasound machine as a workstation (Siemens Healthcare, Erlangen, Germany). For comparison, two measurements were calculated for each studied tumor and a region of interest (ROI) was marked in each parotid gland tumor (standardized in the center of the solid tumor tissue). Both measurements were averaged to avoid invalid parameters in the partially inhomogeneous tumor tissue. The area of the ROI depended on the size of the tumor with a ROI-size difference of not more than 20% between individual patients. Other ROIs were drawn in the supplying artery, in the draining vein and in the surrounding parotid gland tissue. Time intensity curve analyses were calculated after the examination using the integrated SIEMEMS workstation on the ultrasound machine (Contrast Dynamics Software; Siemens Healthcare, Erlangen, Germany) and then transferred into a spread sheet table (Excel 2010; Microsoft, Redmond, WA, USA). Further analysis was performed in a blinded manner, the scientists having no knowledge of clinical or histological data.

Table 1
Overview of benign and malignant neoplasms included into the study.

Benign lesions	malignant lesions
Pleomorphic adenoma ($n = 17$)	Adenoidcystic carcinoma ($n = 2$)
Cystadenolymphoma ($n = 15$)	Poorly differentiated carcinoma ($n = 3$)
	Acinic cell carcinoma ($n = 2$)

The first 30 s following the achievement of microbubbles in the supplying artery were used for further analysis. Each time intensity curve was normalized for precontrast baseline signal intensity (SI). Area under time intensity curve (AUC) in arbitrary units (AU), maximum in signal increase ($\triangle SI_{max}$) in decibel (dB), rate of SI increase from baseline to initial peak (RSI) in decibels per second (dB/s), time to initial peak (TP) in seconds (s) and mean transit time (MTT) in seconds (s) were calculated.

All patients underwent a surgical treatment and each parotid gland tumor was processed histologically including immunohistochemistry when necessary. Hereafter, parotid gland tumors were divided in two groups, malignant and benign tumors. For further analysis, benign tumors were splitted into two subgroups: pleomorphic adenoma and cystadenolymphoma.

2.1. Statistical analysis

All measurements are shown as mean ± standard error of the mean (SEM). Statistical analysis of the data sheets were performed using the non-parametric Mann–Whitney rank sum test for inter group comparison. To analyze the variability of a parameter in the same individual the Wilcoxon signed rank test was used. p-values < 0.05 were considered to indicate a statistically significant difference. All analyses were performed with SigmaStat software (version 3.5; Systat Software Inc.).

3. Results

3.1. Patients

Thirty-nine patients with parotid gland tumors, undergoing CE-US measurement, subsequent resection of the tumor and histological analysis, were included into the study. Patient age ranged from 22 to 93 years with a mean age of 58.7 ± 3.34 years (mean ± SEM). Patients with malignant lesions had a mean of 67.1 ± 9.3 years. Patients with benign tumors had a mean age of 56.9 ± 3.5 years. There was no statistically significant difference ($p = 0.165$).

There were seven primary malignant tumors of the parotid gland. The remaining 32 patients had benign tumors of the parotid gland, including 17 pleomorphic adenoma and 15 cystadenolymphoma (Warthin tumor) (Table 1).

3.2. Contrast-enhanced ultrasound

CE-US parameters were quantified from the calculated time intensity curves corresponding to the parotid gland tumor area (Fig. 1). Time intensity curves were normalized for precontrast baseline of signal intensity.