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Potential of ultrasound diagnosis for parotid tumors: Analysis of qualitative and quantitative parameters

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OBJECTIVE: Histology of parotid tumors determines the extent of surgery. The aim was to test ultrasound (US) contrast enhancer-kinetics to identify histologic entities, possibly being superior to qualitative morphological parameters.

STUDY DESIGN: In a cross-sectional assessment of ultrasound diagnosis, the subjective US-classification was compared with contrast analysis with histology as gold standard.

SUBJECTS AND METHODS: A total of 64 male and 61 female patients with a mean age of 54 years were included, with 13 malignant tumors. These were classified with US morphology, then time-dependent contrast medium analysis.

RESULTS: A total of 92.8% of tumors were classified correctly as malignant or benign. The sensitivity, specificity, positive- and negative-predictive values were 66.7%, 86.3%, 60.6%, and 89.1% for differentiating Warthin tumors, but only 46.2%, 98.2%, 75%, and 94% for malignant lesions. Contrast parameters yielded significant parameters for benign tumors, not for malignant entities.

CONCLUSION: Although contrast medium analysis provided statistical criteria, these, however, do not possess the ability to improve the diagnostic prediction of tumor histology. Neither the morphologic classification nor contrast medium analysis was able to identify a malignant lesion sufficiently.

The histology and site of tumors of the parotid gland determine the extent of surgery (extracapsular dissection; superficial, complete, or radical parotidectomy).[1] Ultrasound (US) together with magnetic resonance imaging (MRI) is currently the technique of choice for investigating tumorous changes of the parotid gland.[2-5]

Use of high-resolution ultrasound transducers and color Doppler sonography allow measurement and demonstration of very small changes in location, size, and perfusion pattern within gland tissues. There are numerous reports of qualitative sonomorphologic criteria (presence of distal reflection phenomena, margin definition, and vessel distribution) that suggest a possible differentiation between histologic tumor types. Regions with a homogeneous echotexture and a lobular form are supposed to indicate a pleomorphic adenoma, whereas multiple anechoic zones are supposed to be characteristic of a Warthin tumor.[3,5,6]

Indistinguishable margins and inhomogeneous echogenicity are indicative for malignant lesions. With the use of US contrast enhancement, the sensitivity for visualizing tumor vascular architecture has increased, thus serving as an additional potential criterion in the assessment of benign and malignant parotid gland tumors. With respect to the published studies, there appears to be consent that the current imaging options of B-scan, color-codes, and enhanced US enable the identification of numerous parotid lesions.

The diagnostic impact of the US examination, however, depends to a great extent on the experience of the investigator to evaluate and assess the sonomorphologic results.[6-9]

Finding objective, ie, investigator-independent, parameters for tumor evaluation is the aim of modern computer-assisted methods in tumor assessment. In studies with the use of MRI, analysis of contrast agent kinetics has improved the predictive power for the most frequent tumors of the parotid gland.[1,2]

The principle of the measurement is the behavior of echo-contrast within histologically different tumors over time interval from wash-in through storage and disappearance of contrast agent. The aim of this study was to test the diagnostic potential of enhanced US with contrast medium kinetic analysis in the histologic evaluation and classification of different histologic types of parotid tumors for the first time in a large group of patients.

METHODS

One hundred twenty-five consecutive patients were examined in the US laboratory after referral with the clinical diagnosis of a solid tumorous space occupying lesions of the parotid gland.

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Patients were excluded when the parotid mass was not located within the gland, no surgery conducted, the patient reported of prior surgery in the tumor area, or the patient denied participation in the study. During the study period from end of 2004 to 2006, 125 (65.7%) of 190 patients with initial parotid gland tumor were finally included in the study.

The studies were carried out by two experienced US users (certified instructors for head and neck US by the German society of ultrasound in medicine) with a high-end device (Siemens Sonoline Elegra Advanced, Malvern, PA) with a high-resolution linear transducer (7.5L40).

In the first part of the study, tumors were measured in three dimensions and qualitatively classified according to the following sonographic criteria (*indicates malignancy): distal phenomenon (distal enhancement/dwindling); sonographic margin definition (sharp, regular, indistinguishable,* irregular*); echogenicity (homogeneous, inhomogeneous,* echo-poor, echo-rich, anechoic); perfusion pattern in power mode (peripheral, central, diffuse).

At the end of the examination, the user decided on a suspected US diagnosis. The mass was first classified as a malignant or a benign lesion. For benign tumors, the tumor was then further classified as pleomorphic adenoma, Warthin tumor, or "other benign" space-occupying lesion.

The second part of the study consisted of setting up and using contrast medium–assisted perfusion analysis of the tumor with the use of AXIUS ACQ 6 software (Siemens Medical, USA). This is an ultrasound-device integrated function for contrast medium–assisted vessel and tissue visualization. Visualization of the time-dependent changes in pixel intensity allowed evaluation of the perfusion status and quantitation of tissue perfusion (Fig 1). The wash-in and wash-out data were collected for selected regions of interest (ROIs) of the tumor. The data were displayed graphically as intensity values against time (Fig 2).

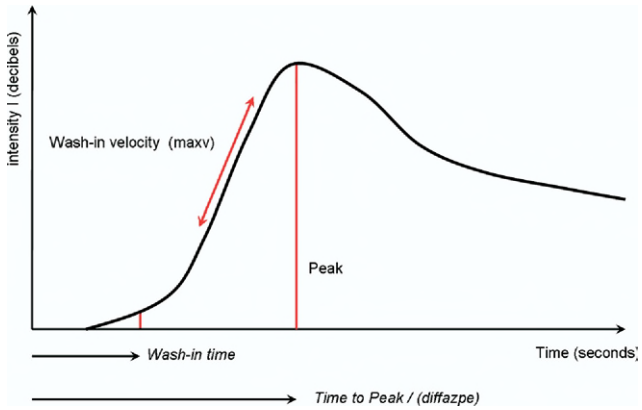

Figure 1 Definition of contrast agent kinetic parameters, scheme of a time-intensity curve after contrast agent injection. Wash-in time (s): time in seconds after start of recording in which the intensity increases to 10% of the maximum increase in intensity compared with baseline. Wash-in velocity (maxv) (dB/s): rate of increase in contrast enhancer in decibels per seconds. Peak (dB): The peak decibel (dB) intensity value compared with the baseline. Time to peak (s): time in seconds from start of recording to peak intensity.

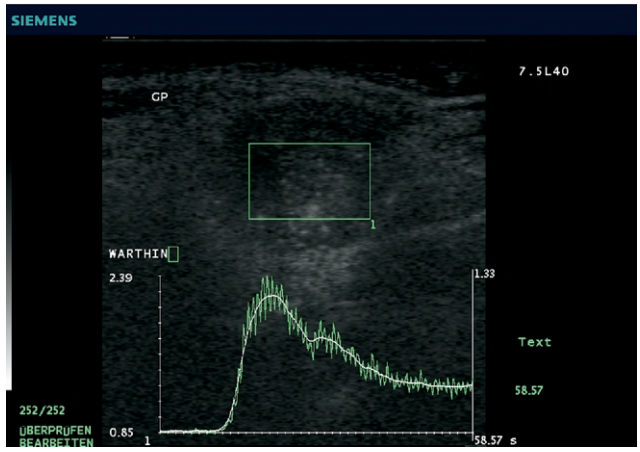

Figure 2 Warthin tumors after placing of the region of interest (ROI) within area of the lesion. In the lower half is the corresponding wash-in curve demonstrated. On the x-axis the time after contrast agent application against signal enhancement in decibels (y-axis).

Once contrast harmonic imaging mode was switched on, the following constant settings were chosen: subsampling rate 8, maximum frame rate, 3% broadcast strength. SonoVue (Bracco/Altana Pharma, Konstanz, Germany), a sulphur-hexafluoride-containing aequeos suspension of phospholipid microbubbles was injected [1 to 5] $\times$ 10^8/mL as a bolus, followed by 10 mL of saline solution. Digital documentation of the ultrasound investigations started immediately before and continued for up to 90 seconds after contrast enhancer injection (252 individual images). The image data were saved and evaluated offline with the software packet AXIUS ACQ 6.

All patients then underwent surgical treatment the next day, and the tumor was processed histologically. The study was approved by the Research Ethics Committee (IRB), and all patients gave written informed consent.

Histologic Processing

Immediately after surgery, the prepared parotid tumor samples were embedded in paraffin analogous to the US orientation. The pathologist was blinded for the sonographic result. Sections were stained with hematoxylin and eosin and inspected and reported by experienced diagnostic pathologists. For demonstration of the vascular supply, representative sections were also stained with the endothelial cell marker CD34 (Immunothech, Marseille, France).

To recognize possible correlations of perfusion behavior of the tumor and vascular characteristics, the vessel thickness and size distribution were determined. Five regions were chosen and inspected at 100 times magnification (1 mm^2). For evaluation of the vessel distribution, the numbers of microvessels ($<$1 mm diameter), macrovessels, and total vessels per mm^2 were calculated.

Statistical Evaluation

For statistical analysis, the accuracy of US was calculated with the use of sensitivity, specificity, predictive values

(positive/PPV, negative/NPV), and the Youden Index (sensitivity + specificity – 1) as test parameters for evaluating the diagnostic power, with exact confidence intervals calculated according to Clopper and Pearson. The maximum Youden index was to determine the best cutoff-point to discriminate between tumors. This is the point where the differentiating ability of the parameter of interest is optimized. Fisher's exact test was used to assess the statistical significance of the relationship between qualitative sonomorphologic parameters and malignancy of parotid tumors/type of tumor. The Wilcoxon-Mann-Whitney-U-Test was used to compare the distribution of quantitative parameters among different kinds of tumors. Quantitative parameters were further evaluated by ROC (receiver operator characteristics) analysis. Analyses were carried out using the statistical program "R" ("*R & R*" of the Statistics Department of the University of Auckland) with the additional package "rocr."

RESULTS

Qualitative Sonographic and Histological Classification of Malignant Parotid Tumors

The study group comprised 125 patients (female, 61 [48.8%] and male, 64 [51.2%]) with tumors of the parotid gland. The mean age was 53.9 years (standard deviation, [SD] 16.8), patients with benign tumors had a mean age of 53.9 years (SD, 16.7), and the group of patients with malignant lesions had a mean age of 62.4 years (SD, 16.2). Benign tumors were found in 56 male and 56 female patients, whereas 5 (38.4%) female and 8 (61.5%) male patients presented with malignant gland tumors.

With respect to histologic findings, Warthin tumors (n = 30) and pleomorphic adenomas (n = 51) were the largest groups. Patients in the study group had 13 malignant tumors and a further 31 benign tumors of various histologic types. No patient in the group had a bilateral or multilocular tumor. The mean tumor size was 18.8 mm (6.9 to 53.5 mm).

In the noncontrast enhanced study, taking into account all subjective sonomorphologic characteristics, 6 of the 13 space-occupying lesions were correctly classified as malignant. In 116 (92.8%) patients, a parotid gland tumor was correctly classified by US as being benign/malignant with incorrect diagnoses in nine (7.2%) cases. In seven cases, a malignant space-occupying lesion was falsely diagnosed as benign. The sensitivity and specificity of the tests with 95% confidence intervals (CI) according to Clopper and Pearson was 46.2% (CI, 19% to 75%) and 98.2% (CI, 94% to 100%) with a Youden Index of 0.44 (Table 1). Predictive values were: PPV 75% (CI, 35% to 97%) and NPV 94% (CI, 88% to 98%), respectively.

On separate analysis of the individual sonographic criteria, no association between the occurrence of the variables considered (distal echo phenomenon, margin, echogenicity, and perfusion pattern) and malignant/benign lesions was observed, thus no statistically significant classification rule could be established. Qualitative differentiation between pleomorphic adenomas and Warthin tumors as most frequent benign parotid tumors.

Table 1
Sonographic comparison of ultrasound and histology in different parotid gland lesions

	Histology		
Sonography	Benign	Malignant	Total
Benign	110	7	117
Malignant	2	6	8
Total	112	13	125

Histologic results in the study group found 30 Warthin tumors and 51 pleomorphic adenomas. Thirty-three Warthin tumors were diagnosed, of which 20 were in fact this type of tumor. Pleomorphic adenomas were correctly identified in 46 of 51 cases by US. The sensitivity and specificity of US were 90.2% (CI, 79% to 97%) and 70.3% (CI, 59% to 80%); PPV 68% (CI, 55% to 79%), NPV 91% (CI, 81% to 97%); (Youden Index: 0.60) for diagnosis of pleomorphic adenomas, and 66.7% (CI, 47% to 83%) and 86.3% (CI, 78% to 93%); PPV of 61% (CI, 42% to 77%), NPV 89% (CI, 81% to 95%); (Youden Index: 0.53) for diagnosis of a Warthin tumor. The presence of a distal acoustic enhancement was significantly more frequent in pleomorphic adenomas (*P* value, 0.0425) and was the only reliable parameter (expected misclassification 51.2%). The combination of multiple criteria resulted in no improvement of the possible prediction of tumor type.

Contrast agent kinetics in parotid tumors. Warthin tumors showed significant differences in computer-assisted contrast agent kinetic analysis, with a shorter time to contrast agent maximum (*P* value time to peak: 0.019) and a higher wash-in velocity (*P* value for wash-in velocity: <0.01). The "cutoff-points" were determined as <12.63 s for time to peak and >3.49 dB/s for wash-in velocity (Table 2).

Analogous evaluations for pleomorphic adenomas identified the statistical parameter wash-in velocity (*P* value <0.01), with an optimal cutoff-point of <2.5 dB/s for pleomorphic adenomas on ROC analysis. For malignant tumors, no statistically significant parameters could be identified on contrast agent kinetic analysis.

In all patients, administration of US contrast enhancer allowed better visualization of the vascular distribution and angioarchitecture, but it did not change the suspected diagnosis in any case. Warthin tumors had a trend to possess a higher blood supply, but it was not possible to validate this aspect as statistically significant. Comparison of sonographic perfusion patterns with immunohistological vessel distribution and vessel diameter resulted in no significant correlation. Moreover, there was no association between vessel distribution or vessel diameter and contrast medium kinetics.

Table 2
Comparison of contrast enhanced kinetics in Warthin tumors and other (benign and malignant) lesions (*P* value of Wilcoxon test)

Variable	Tumor	N	Median	Mean	SD	Minimum	Maximum	*P* value
Wash-in time (s)	Other	82	14.41	15.43	6.06	4.52	39.75	
	Warthin	28	14.19	15.09	4.21	5.99	24.77	0.7758
Peak (dB)	Other	82	27.68	28.85	10.07	13.61	58.55	
	Warthin	28	23.67	25.52	7.06	14.57	45.34	0.1365
Time to peak (s)	Other	82	11.70	13.42	7.04	4.59	40.83	
	Warthin	28	9.63	10.44	4.37	5.50	28.44	0.0193
Wash-in velocity (dB/s)	Other	82	2.19	2.66	1.89	0.40	11.15	
	Warthin	27	4.10	3.93	1.91	0.43	8.54	0.0015

S, seconds; *dB*, decibels; *dB/s*, decibels per second; *SD*, standard deviation.

DISCUSSION

As a result of technical developments, there has been a significant improvement over the past few years in preoperative diagnosis of malignant potential or type of tumor in the parotid gland using noninvasive imaging techniques such as MRI and US. The aim of diagnosis is not only to localize the tumor, but also to predict as accurately as possible the histology. The more precise this presurgical evaluation, the more appropriately the nature and extent of the procedure may be planned, with a consequent reduction in morbidity.[9]

In addition to the aforementioned imaging methods, fine needle aspiration should be noted. As this diagnostic method is not an imaging modality itself with variable reported diagnostic precision (sensitivity, 64% to 93%; specificity, 93% to 98%), it was currently excluded from discussion.[10]

In the current literature, the attempt to assign sonomorphologic characteristics to histologically different tumor types has led to variable predictive accuracy for individual tumor types in the past.

For differentiating between benign and malignant tumors using B-scan, the data show accuracy, sensitivity, and specificity of 57% to 96%, 62% to 84%, and 88% to 96%, respectively.[3,5,11,12] The resulting sensitivity of 46.2% in our group (n = 13) was lower than that of other groups. The low proportion and the small number of patients with malignancy investigated meant in statistical terms that a few false-negative or false-positive cases would lead to a large change in the accuracy. In five tumors with a false-negative benign diagnosis, the maximum diameter was less than 25 mm, and in six of the malignancies said to be benign, no unclear margin distinction could be observed. In one case of a large carcinoma ex pleomorphic adenoma, the irregular margin in the deep part of the gland could not be delineated. Moreover, assessment of a sharp margin in small and deeply situated parotid tumors was frequently difficult. The two pleomorphic adenomas falsely classified as malignant showed irregularities of the margin and an echoinhomogeneous texture. Echoinhomogenicity and margin distinction were not reliable criteria for diagnosing malignancy. The qualitative improvement of color Doppler sonography over the past few years has demonstrated that many space-occupying lesions have an inhomogeneous angioarchitecture. Considering the vessel distribution of lymph nodes, central hilar perfusion can be attributed to inflammatory lymphadenopathy; a hypothetical characteristic vessel pattern for various tumors of the parotid gland remains controversial.[1] In our collective of 125 patients this assumption of a specific angioarchitecture, vessel distribution or a typical color Doppler pattern could not be confirmed in this study.

Evaluation of contrast agent kinetics in our study population did not show any association between malignancy and any specific objective dynamic wash-in parameter. The failure to find a perfusion pattern or angioarchitecture typical for malignancy may be again due to the small number of malignant and histologic variable tumors.

In our collective, pleomorphic adenoma showed a statistically significant increase in the presence of distal echo enhancement and a trend to higher marginal perfusion. Warthin tumors, on the other hand, showed a marked central perfusion trend. These findings confirm partially the observations by other authors.[1,4-6,8] We could also confirm that the use of contrast medium improved the visualization of intratumoral vessel architecture in all cases without indicating specific patterns.[7] Conceivably, this result may be due to the uncharacteristic distribution of micro- and macro-vessels both in benign and malignant tumors in our patient group confirmed by immunohistologic evaluation. The reported sensitivity of US to identify a Warthin tumor ranges from 33%[13] to 93.3%.[12] In our group, sonographic classification of a Warthin tumor (sensitivity, 66.7%; specificity, 86.3%) is in agreement with the results of Zajkowski et al,[14] who investigated a group of 28 patients with benign tumors without having to distinguish malignant tumors. Testing contrast medium kinetic parameters showed that the variables' time to peak and wash-in velocity were statistically significant parameters for identification of Warthin tumors. Similarly, Warthin tumors were also identified with analysis of contrast agent kinetic criteria by Yabuuchi et al[2] in MRI. Previously reported data on diagnosis of pleomorphic adenomas show a sensitivity of 55%[14] to 82%,[5] and a speci-

ficity of 73%[14] to 86%. In this study, the sensitivity was 90.2% and specificity was 70.3%. With the use of contrast medium kinetic characteristics, the variable "wash-in time" (sensitivity, 67.4%; specificity, 65.2%) was significant for classification of pleomorphic adenomas but is not able to serve as a reliable parameter. The histologically heterogeneous appearance of pleomorphic adenomas may explain the absence of further characteristic perfusion patterns or a typical angioarchitecture.

We were able to confirm that high resolution B-mode and color Doppler US offer a certain degree of accuracy in the diagnosis of parotid tumors. Even though several sonomorphologic characteristics appear to be typical for Warthin tumors and pleomorphic adenomas, no reliable distinct sonomorphologic criteria have been defined that enable the histologic tumor type and, in particular, a malignancy to be identified. We were able to demonstrate that contrast agent kinetic analysis in Warthin tumors and pleomorphic adenomas of the parotid gland offers now new statistically significant investigator-independent variables. These results corresponded with results from other authors and imaging methods.[2] Alternative developments that concentrate on the ultrasonographic tissue analysis of the gland structure in previously published studies have shown more promising results on histologic tumor typing.[15-17] However, expansion of the diagnostic accuracy to differentiate between benign and malignant parotid tumors could not be observed in the present study in the small number of malignant space-occupying lesions.

CONCLUSION

The results of this study show that despite new contrast medium parameters that were identified, the diagnostic accuracy of ultrasound could not be increased to a point rendering histologic verification unnecessary. Neither the morphologic classification nor contrast medium analyses are currently able to identify malignant lesion sufficiently or enable a reliable subtype-discrimination of benign parotid gland tumors.

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Alessandro Bozzato, study design, manuscript preparation; **Johannes Zenk**, study design; **Holger Greess**, data collection; **Joachim Hornung**, manuscript preparation; **Frank Gottwald**, data collection; **Christina Rabe**, statistics, manuscript preparation; **Heinrich Iro**, study design.

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