Contrast-enhanced color Doppler sonography of parotid gland tumors

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Abstract The objective of the present study is to assess the potential of color Doppler sonography in imaging tumors of the parotid gland enhanced by application of ultrasound contrast agents. To this end 26 patients with tumors of the parotid gland were investigated. The color Doppler signal areas before and after administration of Doppler signal-enhancing agent (Levovist, Schering, Germany) were determined by means of computer-assisted analysis, and the relevant parameters were evaluated. The tumors can be classified as follows: 11 pleomorphic adenomas, 8 adenolymphomas and two squamous cell carcinomas of the parotid gland, two lymph nodes, one adenoma, one neurinoma of the facial nerve and one non-Hodgkin's lymphoma. Before the administration of Doppler signal-enhancing agent, the adenolymphomas showed a significantly stronger Doppler signal area as compared to the pleomorphic adenomas. The maximum color Doppler signal area after administration of Doppler signal-enhancing agent showed no difference within both groups. If one considers the relative change in the Doppler signal area before and after applying enhancing agent, however, a significantly stronger enhancement of perfusion (increase in Doppler signal area) is noted within pleomorphic adenomas. The changes in the Doppler signal area after administration of signal-enhancing agent show a different course depending on the histology of the investigated tumors.

Keywords Color Doppler sonography · Signal-enhancing agent · Parotid gland tumor · Pleomorphic adenoma

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Introduction

For many years B-mode sonography next to magnetic resonance imaging and computed tomography has served as an important diagnostic modality for imaging tumor masses in the parotid gland [6, 16]. A number of sonomorphologic criteria have been developed to differentiate tumors of the parotid gland. Regions with a homogeneous echo signal structure and a lobular form tend to indicate a pleomorphic adenoma, while mutiple non-echoic regions indicate an adenolymphoma. An indistinct tumor border in the ultrasound image points toward a potentially malignant alteration. In many cases malignant transformations can show a smooth boundary, though, so that differentiation ultimately remains uncertain [4]. The most accurate diagnostic tool, of course, is ultrasound-guided fine-needle aspiration, which already represents an invasive procedure. Visualizing tumorous structures within the parotid gland not only provides diagnostic information but also gives insight into local features such as growth and invasiveness. This, of course, is of great clinical relevance in the case of malignant tumors.

With the introduction of Doppler sonography a further diagnostic tool for imaging and assessment of tumor vascularization within tumor masses has become available [1, 2, 10, 14]. The option of using Doppler signal-enhancing agents to achieve improved visualization of tumor vascularization has provided new possibilities for characterizing masses, as for example in the parotid gland. In the present study we endeavor to analyze to what extent color Doppler sonographic parameters undergo time-dependent changes after administration of Doppler signal-enhancing agent and to determine whether these changes are typical of certain types of parotid gland tumors.

Subjects and methods

Patients and histology

Twenty-six patients with tumors of the parotid gland were examined preoperatively. The patients were between 19 and 88 years of

age, with a mean age of 52.9 years. The patient group comprised 12 women and 14 men.

Preoperative sonographic evaluation and the later evaluation of the results were performed without knowledge of the histologic status. The postoperative pathohistologic evaluation yielded the following diagnoses: pleomorphic adenoma (11 cases), adenolymphoma (8 cases), lymph node (2 cases), squamous cell carcinoma of the parotid gland (2 cases), one adenoma of the parotid gland, one neurinoma of the facial nerve and one non-Hodgkin's lymphoma.

Sonography

The tumor-afflicted parotid gland was preoperatively subjected to a standardized examination procedure comprising B-mode sonography, color Doppler sonography and contrast-enhanced color Doppler sonography. The B-mode and color Doppler sonographic findings were documented before and after administration of contrast agent on digital storage discs and videotape. Quantitative evaluation of the acquired color Doppler signals was performed with a computer-assisted image processing system.

B-mode sonography

All investigations were carried out using the Siemens Sonoline Elegra ultrasound modality (Siemens Medical Engineering Group, Erlangen, Germany). A 7.5 MHz linear phased-array transducer (7.5; L40) was implemented. Settings were as follows: power transmission of 100%, line density ZD 3, imaging depth 3 cm, focus position 1.5 cm, color scale from –7 to +7 cm/s, image scan rate (B/s) (images per second) in dependence on the size of the selected color Doppler window, enhancement 14–20 dB and mechanical index 0.6.

Color Doppler sonography

The following parameters were applied: pulse repetition frequency (PRF) 868 Hz, filter F9, color Doppler enhancement 70 dB. color Doppler frequency CF 5.14 MHz and line density ZD 4.

Doppler signal-enhancing agent Levovist

Levovist from the Schering company (Berlin, Germany) served as Doppler signal enhancer agent, and 4 g Levovist was dissolved in 8 ml aqua dest. and injected intravenously in the patient within 10 s.

Analysis

The settings remained unchanged during the investigation of all patients. The video documentation of the color Doppler signals, which began at the time of contrast agent application, was evaluated by computer-assisted analysis using the computer program Cap-Image, version 6.02 (Dr. Zeintl, Heidelberg, Germany).

The individual measurements were performed at intervals of 10 s over a total period of 4 min. The video image was frozen each time when the maximum Doppler signal area in the systole was attained; the color Doppler signals were marked and then evaluated. Overall, 4 min of video documentation of color Doppler signals could be evaluated in each patient, with the first measured value corresponding to the color Doppler signal prior to contrast agent administration. At first the circumference of the tumor mass was manually outlined on the black-and-white monitor for calculation of the basic tumor area.

In the subsequent measurements of the color Doppler signals this area represented the "region of interest" (ROI) for reference purposes. Only color Doppler signals located within this area were marked and evaluated. All color Doppler signals originating from outside this marked reference area were designated as extratumoral color Doppler signals. Manual delineation of the color Doppler signal area with subsequent gray-scale acquisition served for quantitative analysis.

Statistics

Statistical analysis was performed with the SPSS 7.5.2 program module for Windows and SAS 6.12. The Wilcoxon-U-test method was used for non-parametric and independent samples. Statistical significance was assumed at a level of $P < 0.05$.

Applied parameters

To enable a comparison of parameters between patients, each Doppler signal area was calculated as a percentage value relative to the previously determined total Doppler signal area. The applied parameters are described in Table 1 and Fig. 1.

Table 1 Applied parameters

DMIN	Percent contribution of the color Doppler signal area to the total tumor area before injection of contrast agent
DMAX	Percent contribution of the maximum color Doppler signal area after injection of contrast agent
TMAX	Period of time between contrast agent injection and appearance of the maximum color Doppler signal area
DFACTOR	Relative enhancement of the color Doppler signal area after contrast agent injection, quotient of DMAX/DMIN
M2X1	Gradient of the color Doppler signal plot up to the point of inflection
M2X2	Negative gradient of the regression curve (y= min (M2X1) + max (log 10(x)– log 10)(M2X2) + intercept

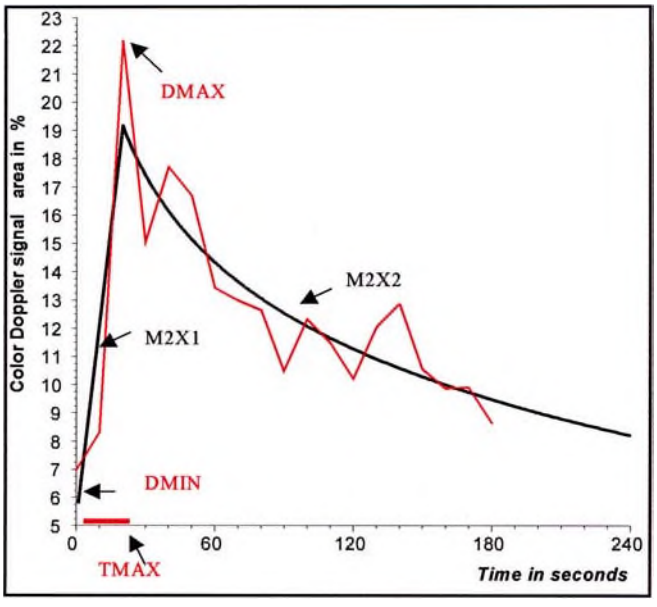

Fig. 1 Course of color Doppler signal curve after administration of signal-enhancing agent together with the following parameters. (*DMIN* initial magnitude of the signal area, *DMAX* maximum signal area, *TMAX* time after which maximum signal area is reached, *M2X1* ascent of linear regression curve, *M2X2* decline of linear regression curve)

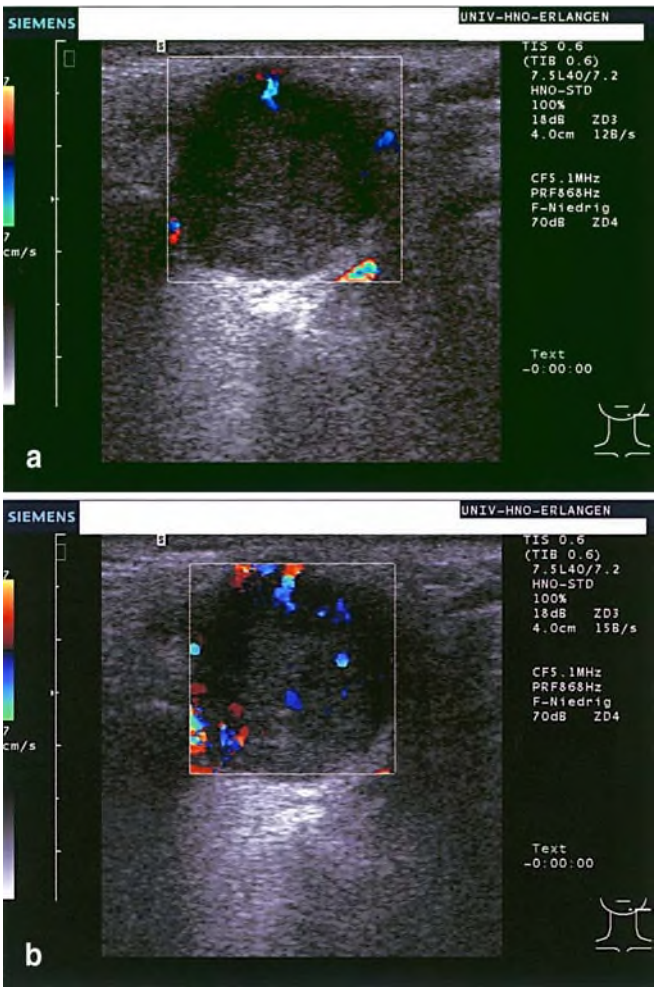

Fig. 2 **a** Color Doppler image of a pleomorphic adenoma of the parotid gland with low vascularization before application of signal-enhancing agent. **b** Maximum color Doppler signal of a pleomorphic adenoma after application of enhancing agent

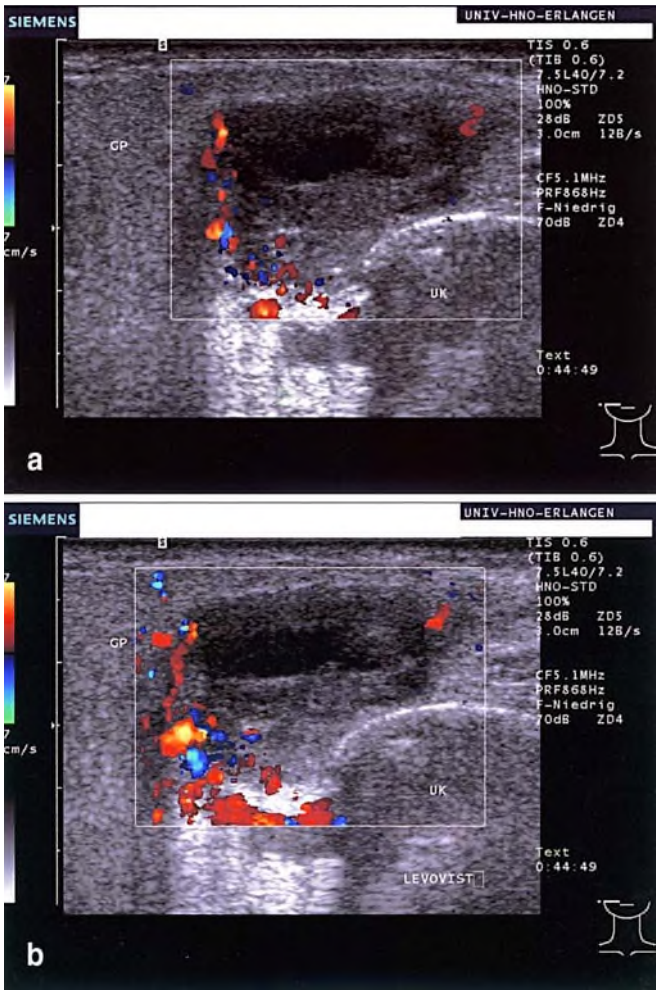

Fig. 3 **a** Pre-contrast examination of an adenolymphoma. **b** Maximum Color Doppler signal after application of signal-enhancing agent

Results

Comparison between adenolymphoma and pleomorphic adenoma

Prior to the administration of contrast agent, adenolymphomas showed a higher relative color Doppler signal area that was distinctly enhanced compared to that of pleomorphic adenomas (Figs. 2, 3). The maximum signal areas after injection of Doppler signal-enhancing agent did not differ significantly, however.

DMIN

In the case of adenolymphomas the color Doppler signal area prior to contrast agent injection was 7.64% (standard deviation: 3.45) and thus significantly higher than that of pleomorphic adenomas with a mean of 2.28% [standard deviation (s): 3.09], (P =0.005).

DMAX

After contrast agent administration, the color Doppler signal of adenolymphomas increased to 29.1% (s: 14.48) and that of adenomas to 26.4% (s: 26.1), (P =0.4).

TMAX

The color Doppler signal area of adenolymphomas reached its maximum value 61 s (s: 23) after contrast agent administration. That of pleomorphic adenomas reached its maximum after an average of 78 s (s: 54), (P =0.8).

DFACTOR

This yielded a relative increase of color Doppler signal area after contrast agent administration of 4.0 for adenolymphomas and 24.7 for pleomorphic adenomas (P =0.05). The absence of regular circulation prior to contrast agent ap-

plication would result in division by zero. In these cases we gave DMIN the value 1. Altogether, this phenomenon was observed in three cases.

M2X1

The rate of enhancement following bolus injection gradient was 0.35%/s for adenolymphoma and 0.68%/s for pleomorphic adenoma. These values were thus not significantly different (P =0.904).

M2X2

The negative gradient of –23.8%/s during the washout phase was somewhat steeper in the case of adenolymphomas than for pleomorphic adenomas with a gradient of –16.7%/s (P =0.3).

Results for the remaining tumors

The values of DMIN were in the range of 0 to 11 for the remaining tumor types (lymph nodes, carcinoma, etc.). Equally, the values of DMAX and DFACTOR did not significantly differ from the values observed for pleomorphic adenomas and adenolymphomas. The parotid gland carcinomas initially showed a relatively small color Doppler signal area with an increase up to approximately 50% in one case. Results for all other factors such as TMAX, M2X1 and M2X2 all remained within the magnitude of those observed in adenolymphomas and pleomorphic adenomas.

Discussion

The regular B scan is a well-established tool in diagnosing diseases of salivary glands. In tumors located in the parotid gland it is of great interest to non-invasively acquire clinical information such as growth and invasiveness and to establish an accurate diagnosis prior to surgery. Before the benefits of sophisticated ultrasound workups were available, this was performed on a regular basis by correlating simple sonomorphological criteria such as the echo-free regions with specific histologies (adenolymphoma) [12].

Over the last few years color Doppler sonography has become a well-established part of ENT diagnostics, particularly in the framework of preoperative assessment of tumors and cervical lymph nodes [5, 15, 17, 18]. Since the implementation of color Doppler sonography data on color Doppler characteristics like the blood flow parameters “pulsation index” and “resistance index” have become available for various types of parotid tumor masses [2]. However, no unequivocal differences have been observed between the investigated tumor groups of adenolymphomans, pleomorphic adenomas and squamous cell carcinomas of the parotid gland. Other studies devoted to quantitative aspects of vascularization [10, 14] mostly found increased vascularization in malignant parotid tumors as compared to benign parotid tumors.

With contrast-enhanced color Doppler sonography one now has the means to assess microvascularization as a sensitive criterion for establishing a histological correlation. Ultrasound contrast agents are being successfully applied in the scope of differentiation of breast lesions [7, 8]. Further diagnostic aspects appear to emerge as far as differentiation of cervical lymph nodes is concerned, although it is still too early to speak of routine implementation [11, 13].

In the present study we have endeavored to determine so-called “dynamic” parameters as well. Especially in tumors whose vascularization can be detected only insufficiently, or not at all, by exclusively applied Doppler sonography the implementation of enhancing agent allows enhanced color signals to be acquired from which differentiated parameters can be derived. The results indicate that adenolymphomas exhibit a generally stronger basic vascularization compared to pleomorphic adenomas. This would be even more evident if all the cystic areas within the tumor could be excluded. Our results indicate that adenolymphomas appear to produce a higher microvessel density, which could be explained by the frequently observed histologically coherent chronic inflammation.

After administration of contrast agent the relative signal areas equilibrate and enhancement is significantly stronger in pleomorphic adenomas. Apparently, after injection of contrast agent, the finely structured vascular system of the pleomorphic adenoma can be better depicted as a color Doppler signal, whereas in the case of adenolymphomas only a small increase of signal intensity remains achievable.

Further parameters such as increase, decrease and maximum did not vary significantly. Due to the low number of cases analyzed a definite determination of malignancy prior to operation could not be established. Nevertheless, all dynamic parameters after contrast agent application (relative increase of DFACTOR) correlated with parameters obtained from regular color Doppler sonography (base perfusion) and therefore enabled accurate diagnosis by ultrasound. With a threshold value of 7% for DMIN basic perfusion, 6 out of 8 adenolymphomas and 8 out of 11 pleomorphic adenomas were diagnosed correctly. In order to increase sensitivity more factors such as DFACTOR will be added to the routine protocol. All results presented in this study only apply to the technical parameters described above. For optimal utilization of these features a more realistic real-time evaluation of all relevant factors will be needed. In view of current progress in ultrasound technology, these features will soon be available. For the time being visualization techniques like color Doppler sonography will remain inferior to ultrasound-guided fine-needle aspiration in diagnosis. It should be mentioned that the differentiation of benign tumors is of lesser importance than the examination of malignancies. Moreover, the applied technique of data analysis is too time-consuming. Thus, further efforts have to be focused on automated data analysis (already available in new sonography devices) and the goal of differentiating by this method.

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