

## Ultrasound Contrast Media in the Study of Salivary Gland Tumors

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**Abstract.** *Background:* The aims of the present study were: to assess standard ultrasound and color-Doppler patterns for the study and characterization of salivary gland tumors; to define the improvement in the color-Doppler ultrasound image after injection of a signal amplifier (Levovist); to compare morphological and vascular aspects of the neoplasm with data obtained during postoperative histopathological analysis. *Materials and Methods:* We used color-Doppler ultrasound before and after injection of the contrast medium to study 56 patients (32 males and 24 females) between the ages of 28 and 77 years old, presenting nodular pathology of the salivary glands. Only patients with less than optimal results of the basic color-Doppler examination (grade of vascularization 0-1) were included in the study. The data were then compared with the final histological results. *Results:* According to B-mode ultrasonography, all neoplasms were hypoechoic; 8 showed irregular margins and, of these, 6 were carcinomas. We did not obtain significant data regarding size and echostructure. In 10 cases, we observed the presence of multiple locoregional formations in the lymph nodes. Patients were selected on the basis of unsatisfactory color-Doppler examination results; following injection of the contrast medium, we were able to visualize an increased number of vascular signals in 40 out of 56 patients, compared to the basic examination. This enabled us to better assess the vascular map of the neoplasms, as well as more easily trace the vascular blood flow and perform a better extrapolation of the quantitative and semi-quantitative data. This study demonstrated the importance of the vascular pattern, which is

predictive of a malignant lesion when it is high-grade with multiple vascular poles and irregular vascular distribution. Furthermore, certain semi-quantitative parameters proved to be important, particularly the velocity of the systolic peak (SP), the cut-off of which was approximately 25 cm/s. The resistance index (RI) and pulsatility index (PI) did not prove significant and showed overlapping values. *Conclusion:* We observed that the contrast medium was useful in characterizing lesions of the salivary glands by allowing for a more precise vascular map of the lesions, as well as greater diagnostic accuracy in tracing the vascular blood flow and calculating quantitative and semi-quantitative data.

Salivary gland tumors are rare lesions, representing 1% of all neoplasms (1). Approximately 80% of these lesions involve the parotid gland and in 80% of the cases the tumors are benign in nature (2).

*Pleomorphic adenomas* represent the most frequent benign neoplasms (24-71%) (3, 4); in most cases, they are localized on the surface of the gland and are generally slow-growing. Histologically, these tumors consist of epithelial, myoepithelial and mesenchymal tissue (1). Malignant degeneration is possible in 5% of the cases (5). *Cystadenolymphomas* (Warthin's tumors) are the second most frequent benign tumors of the salivary glands. They, too, grow slowly and can be multifocal and/or bilateral (10-15%); they are common in young subjects (2). *Mucoepidermoid carcinomas* are the most frequent malignant tumors of the salivary glands (80-90%) (6), generally occurring in adult patients (7). *Adenoidocystic carcinomas* are rarer tumors (2%) (6); they are not generally encapsulated and have a strong tendency for vascular invasion (8). *Adenocarcinomas and squamous cell carcinomas* are rare forms of primitive malignant tumors, without any significant characteristics differentiating them from mucoepidermoid carcinomas (8).

Ultrasonography has a principal role in the diagnosis of pathologies of the salivary glands, given that this procedure provides a high-resolution image, is easy to perform, non-

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*Key Words:* Doppler ultrasound, ultrasound contrast media, salivary gland tumor.

Table I. Nodules of the salivary glands studied using B-mode and color-Doppler ultrasound before and after injection of US contrast medium (Levovist). Ecographic results were evaluated by comparison with to the histological findings.

Anamnestic data			B-mode Ultrasound			ECPD	LEVOVIST					Histology
No.	Gender	Location	mm	Margins Ly	Lymph nodes mm	Vascular grade	Increase	Vascular poles	RI	PI	SP	
1	M	Right parotid	28x17	Regular	10	1	2	0	1	2.3	36	Pleomorphic adenoma
2	M	Left parotid	5x3	Regular	10	1	1	1	0.8	1.7	18	Pleomorphic adenoma
3	M	Left parotid	15x8	Regular	-	0	1	1	0.8	2	20	Pleomorphic adenoma
4	F	Right parotid	30x17	Regular	-	1	3	multiple	0.9	3	36	Moderately-differentiated adenoma
5	M	Right parotid	20x12	Regular	-	1	2	2	0.8	2.8	28	Granulomatous lymphadenopathy
6	M	Right parotid	40x22	Regular	-	-	1	2	0.8	2.7	36	Pleomorphic adenoma
7	M	Left parotid	28x23	Regular	20	1	2	multiple	0.8	1.6	35	Carcinoma
8	F	Left parotid	30x16	Regular	-	1	3	multiple	0.9	2.6	26	Warthin's tumor
9	F	Right parotid	50x20	Regular	-	0	1	0	0.7	1.4	18	Lymphoma
10	F	Left parotid	27x16	Regular	10	0	2	2	0.9	2.6	18	Warthin's tumor
11	M	Right parotid	40x26	Regular	-	0	1	2	0.9	2	14	Pleomorphic adenoma
12	M	Left parotid	33x14	Regular	-	1	2	0	0.7	1.3	9	Pleomorphic adenoma
13	M	Left parotid	30x17	Regular	0.7	1	2	multiple	0.7	1.2	40	Pleomorphic adenoma
14	M	Left parotid	33x20	Regular	-	1	2	multiple	0.8	1.8	18	Warthin's tumor
15	M	Left submandibular	16x8	Regular	-	0	0	0	0.8	1.2	20	Chronic sialoadenitis
16	M	Right parotid	21x12	Regular	-	1	2	multiple	0.7	1.1	19	Pleomorphic adenoma
17	F	Left parotid	34x20	Regular	-	0	2	multiple	0.5	0.9	15	Basal cell adenoma
18	F	Right parotid	17x12	Regular	-	0	2	multiple	0.6	0.9	10	Pleomorphic adenoma
19	M	Right parotid	23x19	Regular	19	0	2	multiple	0.7	1.4	36	High-grade mucoepidermoid-ca
20	M	Right parotid	23x8	Regular	-	0	0	multiple	0.7	1.6	16	Nodular hyperplasia
21	M	Right parotid	19x17	Regular	-	1	1	1	0.7	1.2	18	Pleomorphic adenoma
22	M	Left parotid	30x15	Regular	12	1	2	multiple	0.8	1.6	20	Warthin's tumor
23	F	Left parotid	11x4	Regular	0.7	0	0	0	0.9	1	18	Nodular hyperplasia
24	F	Left submandibular	17x13	Regular	10	0	1	1	0.8	1.9	17	Pleomorphic adenoma
25	F	Right parotid	12x5	Regular	10	1	1	0	0.7	1.2	20	Warthin's tumor
26	F	Right submandibular	35x20	Regular	-	0	1	2	0.8	1.6	20	Pleomorphic adenoma
27	F	Right parotid	32x27	Regular	22	0	2	multiple	0.8	1.5	40	Carcinoma
28	F	Right parotid	33x18	Regular	-	1	1	2	0.8	1.6	40	Pleomorphic adenoma
29	M	Right parotid	17x13	Regular	10	1	2	0	1	2.0	36	Pleomorphic adenoma
30	M	Right parotid	28x23	Regular	10	1	1	1	0.8	1.7	16	Pleomorphic adenoma
31	F	Right parotid	30x16	Regular	-	0	1	1	0.8	2	20	Pleomorphic adenoma

No.	Anamnestic data		mm	B-mode Ultrasound		Lymph nodes mm	ECPD Vascular grade	Increase	LEVOVIST			Histology
	Gender	Location		Margins	Ly				Vascular poles	RI	PI	
32	F	Left parotid	50x20	Regular	-	1	3	multiple	0.9	2.0	36	Moderately-differentiated adenoma
33	F	Left parotid	27x16	Regular	-	1	2	2	0.8	2.8	28	Granulomatous lymphadenopathy
34	F	Left submandibular	40x26	Regular	-	1	1	2	0.8	2.7	36	Pleomorphic adenoma
35	M	Right parotid	33x14	Regular	-	1	2	0	0.7	1.3	9	Pleomorphic adenoma
36	M	Right submandibular	30x17	Regular	0.7	1	2	multiple	0.7	1.2	40	Pleomorphic adenoma
37	M	Right parotid	33x20	Regular	-	1	2	multiple	0.8	1.8	18	Warthin's tumor
38	M	Right parotid	16x8	Regular	-	1	1	0	0.8	1.4	17	Chronic sialoadenitis
39	M	Left parotid	23x8	Regular	-	1	2	multiple	0.7	1.1	19	Pleomorphic adenoma
40	M	Right parotid	19x17	Regular	-	0	2	multiple	0.5	0.9	15	Basal cell adenoma
41	M	Right parotid	30x15	Regular	-	0	2	multiple	0.6	0.9	10	Pleomorphic adenoma
42	F	Right parotid	11x4	Regular	23	1	2	multiple	0.8	1.6	35	Carcinoma
43	M	Left parotid	17x13	Regular	-	1	3	multiple	0.9	2.6	26	Warthin's tumor
44	F	Left parotid	12x5	Regular	-	0	1	0	0.7	1.4	18	Lipoma
45	F	Right parotid	35x20	Regular	10	0	2	2	0.9	2.6	18	Warthin's tumor
46	M	Left parotid	32x27	Regular	-	0	1	2	0.9	2	14	Pleomorphic adenoma
47	M	Right parotid	33x18	Regular	-	1	1	1	0.7	1.2	18	Pleomorphic adenoma
48	M	Left parotid	20x12	Regular	12	1	2	multiple	0.8	1.6	20	Warthin's tumor
49	F	Left parotid	40x22	Regular	0.7	0	0	0	0.9	1.3	19	Nodular hyperplasia
50	F	Left parotid	28x23	Regular	20	0	2	multiple	0.8	1.5	40	Carcinoma
51	F	Right parotid	23x19	Regular	-	1	1	2	0.8	1.6	40	Pleomorphic adenoma
52	M	Left parotid	23x8	Regular	19	0	2	multiple	0.7	1.4	36	High-grade mucoepidermoid-ca
53	F	Left parotid	19x17	Regular	-	0	0	multiple	0.7	1.6	17	Nodular hyperplasia
54	F	Left parotid	23x19	Regular	10	0	1	1	0.8	1.9	17	Pleomorphic adenoma
55	M	Left submandibular	35x20	Regular	10	1	1	0	0.6	1.1	20	Warthin's tumor
56	M	Left parotid	17x13	Regular	-	0	1	2	0.8	1.6	20	Pleomorphic adenoma

RI: resistance index; PI: pulsality index; SP: systolic peak velocity (cm/s)

invasive and cost-effective, and echographical equipment is readily available. This method allows for an accurate evaluation of the parotid and submandibular glands with easy identification, localization and morpho-volumetric evaluation of focal lesions.

Furthermore, ultrasonography allows for the assessment of extracapsular extension (9) as well as the presence of locoregional lymphadenomegaly; in addition, it represents

an important instrument on which to base cytological examination of non-palpable nodular lesions.

Moreover, malignant tumors are characterized by the development of autonomous blood vessels that are irregularly distributed on the periphery and inside the lesions; this type of vascularization, which is recognized as a distinctive sign of malignancy (angiogenesis), represents an important parameter for characterizing nodules of the salivary glands.

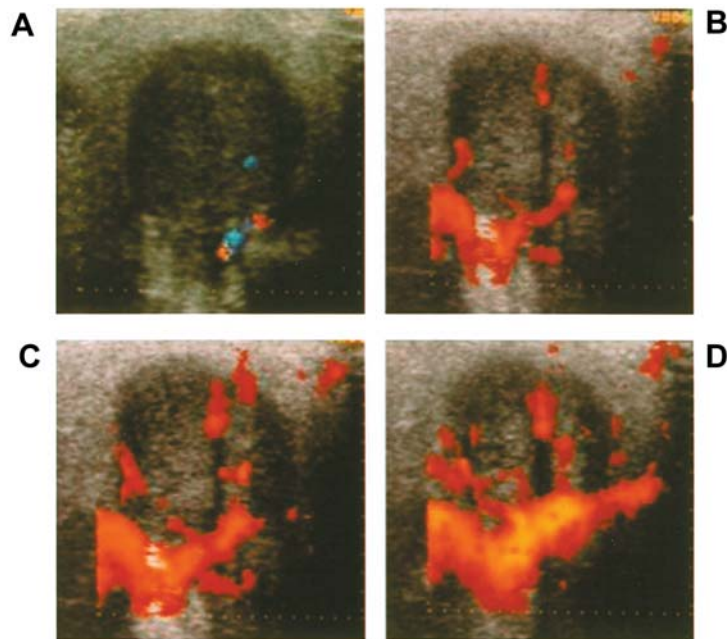


Figure 1. *Pleomorphic adenoma. A) Basic color-Doppler: only two small peripheral vascular poles. B-C-D) Echo-color-Doppler 30, 60 and 90 seconds after injection of Levovist: considerable progressive increase in vascular signals, which were for the most part localized peripherally.*

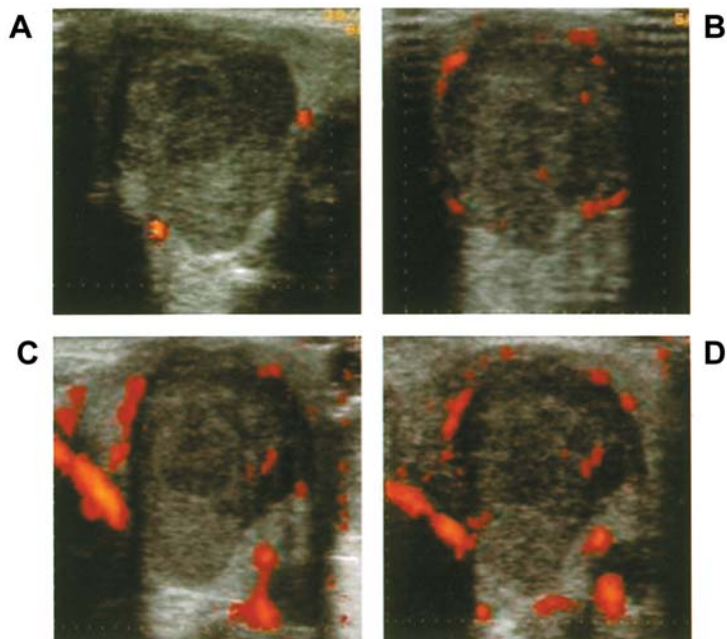


Figure 2. *Moderately-differentiated adenocarcinoma. A) Basic color-Doppler: shows single vascular pole. B-C-D) Echo-color-Doppler 30, 60 and 90 seconds after injection of Levovist: marked progressive increase in both intralésional and perilesional vascular signals.*

Color-Doppler ultrasound provides important information regarding the characteristics of tumor vascularization; this method facilitates evaluation of the grade and location of vascularization and the possible presence of arteriovenous shunts which are responsible for the condition of

pathological blood flow with increased velocity and relatively low resistance (10).

However, despite technological advances, it is not always possible to assess these parameters with basic color-Doppler examination. The aim of our study was to evaluate the

diagnostic advantage that using contrast medium can have, in characterizing the salivary glands tumors when the results of the basic color-Doppler examination are less than optimal.

## Materials and Methods

From June 2002 to December 2003, at the National Tumor Institute in Naples, Italy, we studied 56 patients (32 males and 24 females), ranging in age between 28 and 77 years (Table I), with nodular pathology of the salivary glands; 24 of the cases involved the left parotid gland, 26 the right parotid gland, 4 the left submandibular gland and 2 the right submandibular gland.

Ultrasound was performed using an Aloka 2000 with 7.5/10 MHz convex probes, before and after slow continuous intravenous infusion of Levovist (1 ml/s); doses of Levovist at a concentration of 300 mg/ml were used (11, 12). The ultrasound machine was set with PRF and filters to detect slow flows. When injected intravenously, Levovist causes a dose-dependent and reproducible increase in back-scatter; the result is an amplification of the Doppler signal of about 10-20 dB.

Morphostructural and volumetric characteristics were evaluated using B-mode ultrasonography; when color-Doppler ultrasound was used, we were able to assess the location and grade of the vascularization, the pulsatility index (PI), resistance index (RI) and systolic peak (SP) velocity. Finally, after injection of Levovist, we evaluated the grade of contrastographic increase.

The grade and increase of vascularization after Levovist injection (0=absent, 1=moderate, 2=considerable, 3=marked) were quantified using an optical-visual scale in relation to the quantity of color pixels visualized; the instrumental analyses were always performed by the same operator.

For all patients studied using Levovist, the results of their basic color-Doppler examination were less than optimal (grade of vascularization 0-1).

Finally, morphostructural and vascular aspects were correlated with postoperative histopathological findings.

## Results

In 26 cases, the histological diagnosis was pleomorphic adenoma (46.4%) (Figure 1A, B, C, D), in 10 cases Warthin's tumor (17.8%), in 8 cases carcinoma (14.3%), in 4 cases nodular hyperplasia (7.1%), in 2 cases lipoma (3.6%), in 2 cases basal cell adenoma (3.6%), in 2 cases chronic sialoadenitis (3.6%) and in 2 cases granulomatous lymphadenopathy (3.6%). The nodules studied measured from 5 to 50 mm in size.

B-mode ultrasonography revealed the significant presence of irregular margins in 8 cases (6 of which were carcinomas) and of multiple locoregional lymph nodes (larger than 18 mm in size) only in carcinomatous lesions.

All nodules yielded less-than-optimal results during the basic color-Doppler examination. After intravenous injection of Levovist, 40 out of 56 patients showed an increase in vascularization; 10 were grade 1 (25%), 26 grade 2 (65%) and 4 grade 3 (10%). Multiple vascular poles were revealed in 24 cases (43%).

The RI was between 0.5 and 1, the PI between 0.9 and 3.0, and the SP was between 9 and 40 cm/s (values >25 were observed in 20 patients, of which 8 were diagnosed with carcinoma). In the case of Warthin's tumors, we observed vascular signals only in the periphery of the lesions, also after Levovist injection.

## Discussion

Ultrasonography represents the most common method for examining nodular lesions of the salivary glands, especially when the size of these lesions does not make it possible to identify them during clinical examination (13). The presence of irregular margins and multiple lymphadenomegaly are indicative for a carcinoma. Nevertheless, there is often no difference in echographical characteristics between malignant and benign lesions (13). Furthermore, small-sized carcinomas (<2 cm) generally appear well-encapsulated with a homogenous echostructure.

The study of the qualitative and quantitative aspects of tumor vascularization with color-Doppler ultrasound allows for a more accurate characterization of the lesions.

A vascular pattern showing rich intra- and perilesional vascularization and multiple vascular poles, is significantly correlated with malignancy (14) (Figure 2B, C, D), as is high SP velocity and low blood flow resistance, which are probably due to the presence of intralesional arterovenous shunts (15, 16). A SP velocity of 25 cm/s represents the threshold value to differentiate benign salivary gland lesions from malignant ones (sensitivity of 72% and specificity of 88%) (16-19). Finally, the possibility of malignancy increases by one-third when there is an increase in vascular resistance (RI>0.8 and PI>1.8) (20). However, despite technological advances, it is still difficult to assess slow blood flows in small vessels, which are sometimes present in association with such lesions and, in these cases, the color- and power-Doppler examinations often yield unsatisfactory results (Figure 2A).

In our study, by using Levovist in patients whose basic color-Doppler examination results were unsatisfactory, we were able to achieve a clearer image of the tumor vessels in 40 out of 56 cases, which permitted us to better visualize a nodular vascular map as well as obtain better samples for studying blood flow. In particular, the SP velocity was significant (SP  $\geq$ 25 cm/s) in 20 subjects, of whom 8 were diagnosed with malignancies (40%); RI and PR, on the other hand, were not significant and revealed overlapping values.

## Conclusion

Although the use of contrast medium did not yield important information for the characterization of nodular lesions of the salivary glands, it did prove useful in increasing the vascular

signals, thereby increasing its diagnostic capacity in defining vascular maps and, furthermore, making it easier to trace blood flow patterns and extrapolate quantitative and semi-quantitative data, which could be significant in diagnosing the nature of the lesions.

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