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Diagnostic Value of Superb Microvascular Imaging in Parotid Tumors

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Background: The aim of this study was to evaluate the clinical diagnostic value of superb microvascular imaging (SMI) in assessing vascular distribution, vascularity, and vessel morphology of parotid tumors (PTs).

Material/Methods: PT patients confirmed by postoperative histopathological detection and who underwent color Doppler flow imaging (CDFI), microvascular imaging (MVI), and SMI examination were recruited. PTs were classified into 3 groups: pleomorphic adenoma (PA), Warthin tumor (WT), and malignant PT (MT). The tumor vascular distribution, vascularity, and vessel morphology recorded by CDFI, MVI, and SMI were compared among PA, WT, and MT group. PT diagnosis was performed using histopathological detection. Fisher's exact test was used to compare the diagnostic sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), and accuracy between SMI and MVI examination in PTs.

Results: We enrolled 198 PTs consisting of 114 PAs, 56 WTs, and 28 MTs into our study. CDFI examination found no significant differences in vascular distribution and vascularity among the PA, WT, and WT groups. SMI examination found significant differences in vascular distribution and vascularity among the 3 groups. MVI found significant differences in vessel morphology, including uneven distribution of blood flow, arborization, and irregular blood flow among the PA, WT, and MT groups. SMI found significant differences in arborization and irregular blood flow, but none of the differences in uneven distribution of blood flow among the 3 groups were significant. The diagnostic sensitivity, specificity, and accuracy of SMI and MVI in PTs showed no significant differences.

Conclusions: SMI more accurately evaluated the vascular distribution and vascularity of PTs than CDFI. SMI might be a potential non-invasive diagnostic method for PTs in clinical practice.

MeSH Keywords: Diagnosis • Diagnostic Imaging • Parotid Neoplasms

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Background

Parotid tumors (PT) account for 80% of salivary gland tumors in clinical practice [1,2], of which 80–85% are benign tumors and 15–20% are malignant tumors (MT). Benign tumors consist of pleomorphic adenomas (PA) and Warthin tumors (WT), and malignant tumors consist of mucoepidermoid carcinoma, adenoid cystic carcinoma, and acinar cell carcinoma [3,4]. There are great differences in treatment and long-term prognosis among PA, WT, and MT patients. Patients with PA or WT commonly undergo superficial parotidectomy/total parotidectomy and preservation of facial nerves. Malignant evolution occurs in 2–25% of untreated PA patients, and 50% of PA patients who undergo parotidectomy have cancer relapse [5–8]. Malignant evolution is occurred in less than 1% WT patients, and less than 2% of patients who underwent parotidectomy have tumor relapse [5,9,10]. MT patients are usually treated with total parotidectomy (with postoperative chemo/radiotherapy), which can result in complete facial paralysis if the facial nerve needs to be resected along with the parotid lobes. PTs are characterized by heterogeneity, and there is a lack of specific clinical manifestations among different subtypes of PTs. Therefore, it is difficult to precisely diagnose different pathological types of PTs before surgery through non-invasive imaging methods.

Color Doppler flow imaging (CDFI) is the most commonly used examination for detecting blood flow signals in PTs. Contrast-enhanced ultrasound microvascular imaging (MVI) has high sensitivity in detection of microvascular perfusion, which can improve the diagnostic accuracy of solid tumors [11–13], but it is cost-expensive and time-consuming. Superb microvascular imaging (SMI) is a new ultrasound technology that can detect the signals of low-velocity blood flow without contrast enhancement in breast, thyroid, liver, and kidney tumors, which is economical and time-saving [14–19].

In this study, the vascular distribution, vascularity and vessel morphology of PTs were detected by SMI and were compared with that of MVI to assess the diagnostic value of SMI. Our work may provide the theoretical foundation for non-invasive, ultrasonic diagnosis of PTs.

Material and Methods

Ethics

This study was approved by the Ethics Committee of Tianjin Medical University Cancer Institute and Hospital (No. bc2019095). All patients provided signed informed consent.

Patients

We enrolled 182 patients (198 parotid gland tumors) who underwent parotidectomy from September 2016 to August 2018 in our hospital. The inclusion criteria were: (1) lesions in parotid gland were detected; (2) the clinical, ultrasonic, and pathological data of the patients were recorded; (3) PA, WT, and MT were confirmed by postoperative histopathological detection; and (4) patients did not receive treatment before admission. The exclusion criteria were: (1) patients did not receive surgical treatment; (2) patients with parotid cystic neoplasm; (3) missing data on SMI or MVI images.

Imaging

All sonographic scanning was operated by 2 experienced radiologists using an Aplio 500 device (Toshiba Medical Systems, Tokyo, Japan) and a PLT-805AT high-frequency probe at 7.0~12.0 MHz.

All patients underwent ultrasound examination within 3 days before surgery, including 2-dimensional (2D) ultrasound, CDFI, MVI, and SMI. SMI images included gray-scale mode (mSMI) and color mode (color, cSMI). The patients were in supine position to expose the entire parotid and submandibular gland area. The location, lesion size, boundary, shape, and internal echoes of tumors were recorded by 2D ultrasound. CDFI, cSMI, and mSMI were used to detect the signals of blood flow, and the color gain was adjusted to detect signals of small vessels. The speed scale of SMI was 0.8–1.2 cm/s. The sampling frame contained the tumor and its surrounding 1-cm area. During imaging scanning, tumors should not be pressurized, and patients should breathe calmly and avoid swallowing. Based on the tumor localization detected by 2D ultrasound, the SMI software was used to scan tumors from multiple angles and sections. The images of the tumor section with the largest diameter and the most abundant blood flow were saved; the vascular distribution, vascularity, and vessel morphology of tumors were recorded using cSMI and mSMI modes.

The definition of vascular distribution, vascularity, and vessel morphology

The vascular distribution in PTs was classified as avascular type with absent blood flow signals being found in tumors, central type with blood flow signals being found in tumors, peripheral type with blood flow signals being found in the periphery of tumors, and mixed type with blood flow signals being found in both periphery and center of tumors.

The vascularity of tumors were graded by Adler's method [14], which includes Grade 0 (absence of blood flow signals), Grade 1 (small blood flow with 1–2 shape of dot or line blood flow

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signals), Grade 2 (medium blood flow with 3–4 dotted blood flow signals/1 linear signal throughout the tumor), and Grade 3 (abundant blood flow with more than 5 dotted low-flow signals or 2 linear signals, and blood flow is tortuously and unevenly distributed).

Vessel morphology consisted of: (1) unevenly distributed blood flow signal; (2) arborization-like blood flow; and (3) irregularly distributed blood flow, such as the abnormal branching of blood flow with no branch, vascular malformations, uneven thickness, and tortuously distributed blood flow [5].

MVI examination

We injected 2.4 ml SonoVue microbubbles (Bracco company) into the patients' elbow superficial vein, then 5.0 ml normal saline was injected. The targeted longitudinal tumor section was observed for more than 3 min. For patients with multiple target lesions, if the lesions could not be simultaneously displayed in the same section, we waited 6–10 min after angiography until the contrast agent completely disappeared before performing the next lesion examination.

Statistical analysis

SPSS 23.0 software (IBM, Corporation, Armonk, NY) was used for statistical analysis. The chi-square test was used to calculate differences in vascular distribution, vascularity, and vessel morphology among the 3 groups. $P<0.05$ was considered as significant difference.

Based on conventional ultrasound characteristics, tumors with clear boundary, regular morphology, and arborization of blood flow distribution were diagnosed as benign PTs, while tumors with unclear boundary, irregular morphology, abnormal branching, and tortuous blood flow were diagnosed as malignant tumors. Histopathology was the criterion standard for assessing diagnostic sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), and accuracy of malignant tumors examined by CDFI, SMI, and MVI. Fisher's exact test was used to compare the diagnostic sensitivity, specificity, NPV, PPV, and accuracy between SMI and MVI in PTs.

Results

Basic characteristics of patients

Among the 182 patients, there were 96 males and 86 females; the mean age was 50.17 years (range, 7–77 years). The size of the PTs ranged from 0.8 cm to 8.2 cm, with an average of 2.96±1.12 cm. The 198 PTs confirmed by postoperative histopathological examinations consisted of 170 benign tumors (114 PA and 56 WT) and 28 MTs (8 adenoid cystic carcinomas, 6 mucoepidermoid carcinomas, 6 acinar cell carcinomas, 5 carcinoma ex pleomorphic adenoma, 2 squamous cell carcinomas, and 1 basal cell adenocarcinoma).

Comparison of basic tumor characteristics among the 3 groups by CDFI data

As Table 1 shows, the mean ages of patients in the PA, WT, and MT groups were 45.76 years, 58.77 years, and 47.82 years, respectively. There were 114, 56, and 28 tumors in the PA, WT, and MT groups, respectively. The tumor localization and morphology were preliminarily assessed by CDFI examination. In the PA group, 81 tumors had regular morphology, 97 tumors had clear boundary, and 65 tumors had homogenous internal echoes. In the WT group, 42 tumors had regular morphology, 47 tumors had clear boundary, and 23 tumors had homogenous internal echoes. In the MT group, 6 tumors had regular morphology, 5 tumors had clear boundary, and 11 tumors had homogenous internal echoes. We found significant differences in regular morphology and clear boundary among the PA, WT, and MT groups, but there were no significant differences in homogenous internal echoes among the 3 groups.

Difference in vascular distribution and vascularity among the 3 groups by SMI and CDFI detection

CDFI examination did not show any significant differences in vascular distribution (Table 2) and vascularity (Table 3) among the PA, WT, and MT groups ($P>0.05$). However, SMI examination showed significant differences in vascular distribution (Table 2) and vascularity (Table 3) among the 3 groups ($P<0.05$). SMI detection showed that 70.1% of PAs were peripheral or mixed types, 71.4% of WTs were central and mixed types, and 67.8% of MTs were central or mixed types (Table 2). SMI detection found that 67.6% of PAs were Grade 0 and Grade 1, 73.3% of WTs were Grade 2 and Grade 3, and 67.9% of MTs were Grade 2 and Grade 3 (Table 3).

Comparison of vascularity and vessel morphology in PTs as detected by SMI and MVI

SMI found that 19 tumors were Grade 0, 68 tumors were Grade 1, 52 tumors were Grade 2, and 59 tumors were Grade 3 (Table 4). MVI showed that 6 tumors were Grade 0, 73 tumors were Grade 1, 54 tumors were Grade 2, and 65 tumors were Grade 3. The positive rate of Grade 1, Grade 2, and Grade 3 as detected by MVI was higher than that by SMI (36.9% *vs.* 34.3%, 27.3% *vs.* 26.3%, and 32.8% *vs.* 29.8%, respectively), but the differences were not significant ($P<0.01$).

As Table 5 shows, 77.2% of PAs, 84.9% of WTs, and 96% of MTs had uneven distribution, and the differences among

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Table 1. The basic characteristic of PA, WT and MT groups.

Parameter	PA	WT	MT	χ^2 value	*P*-value
Patient					
No. of patients	105	49	28		
Mean age (years)	45.76±15.47	58.77±9.54	47.82±16.44		0.000
Gender (male/female)	40/65	38/11	18/10	22.635	0.000
Lesion					
No. of lesions	114	56	28		0.000
Mean size (cm)	2.68±1.00	3.21±0.94	3.37±1.25		
Feature of gray-scale					
Regular morphology					
With	81	42	6	27.717	0.000
Without	33	14	22		
Clear boundary					
With	97	47	5	57.714	0.000
Without	17	9	23		
Homogenous internal echoes					
With	65	23	11	5.317	0.070
Without	49	33	17		

PT – parotid tumor; PA – pleomorphic adenoma; WT – Warthin tumor; MT – malignant tumors.

Table 2. Comparison of vascular distribution among three groups by CDFI and SMI.

Vascular distribution		PA	WT	MT	χ^2 value	*P*-value
CDFI	Avascular type	39/34.2%	8/14.3%	7/25.0%	11.033	0.087
	Peripheral type	36/31.6%	16/28.6%	8/28.6%		
	Central type	28/24.6%	21/37.5%	8/28.6%		
	Mixed type	11/9.6%	11/19.6%	5/17.9%		
SMI	Avascular type	13/11.4%	3/5.4%	3/10.7%	14.670	0.023
	Peripheral type	51/44.7%	13/23.2%	6/21.5%		
	Central type	21/18.4%	19/33.9%	9/32.1%		
	Mixed type	29/25.4%	21/37.5%	10/35.7%		

PA – pleomorphic adenoma; WT – Warthin tumor; MT – malignant tumors; CDFI – color Doppler flow imaging; SMI – superb microvascular imaging.

3 groups were not significant. Arborization was present in 18.8% of PAs, 32.0% of MTs, and 49.1% of WTs. Abnormal branching of blood flow was present in 20.8% of PAs, 28.3% of MTs, and 64.0% of WTs. SMI examination showed that tortuous blood flow in vessel morphology was present in 11.9% of PAs, 20.8% of WTs, and 60% of MTs, and the differences among the 3 groups not significant.

MVI examination found uneven distribution in 79.6% of PAs, 91.1% of WTs, and 96.4% of MTs; arborization was found in 22.2% of PAs, 32% of MTs, and 53.5% of WTs; abnormal branching of blood flow was found in 15.7% of PAs, 19.6% of MTs, and 53.6% of WTs; and tortuous blood flow in vessel morphology was found in 7.4% of PAs, 16.1% of WTs, and 50% of MTs, the differences among 3 groups were not significant (Table 5).

The diagnostic efficacy of SMI and MVI examinations

CDFI examination found that 152 tumors were diagnosed as benign PTs and 46 tumors were malignant PTs; the diagnostic

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Table 3. Comparison of vascularity based on Adler's method among three groups by CDFI and SMI.

Grade		PA	WT	MT	χ^2 value	*P*-value
CDFI	0	39/34.2%	8/14.3%	7/25.0%	12.458	0.052
	1	40/35.1%	18/32.1%	8/28.6%		
	2	23/20.2%	16/28.6%	7/25.0%		
	3	12/10.5%	14/25.0%	6/21.4%		
SMI	0	13/11.4%	3/5.4%	3/10.7%	16.239	0.013
	1	50/43.9%	12/21.4%	6/21.4%		
	2	27/23.7%	17/30.4%	8/28.6%		
	3	24/21.1%	24/42.9%	11/39.3%		

PA – pleomorphic adenoma; WT – Warthin tumor; MT – malignant tumors. CDFI – color Doppler flow imaging; SMI – superb microvascular imaging.

Table 4. Comparison of vascularity based on Adler's method of PTs by SMI and MVI.

MVI	SMI				Total
	Grade 0	Grade 1	Grade 2	Grade 3	
Grade 0	6	0	0	0	6 (3.0%)
Grade 1	13	54	6	0	73 (36.9%)
Grade 2	0	10	39	5	54 (27.3%)
Grade 3	0	4	7	54	65 (32.8%)
Total	19 (9.6%)	68 (34.3%)	52 (26.3%)	59 (29.8%)	198

PT – parotid tumors; SMI – superb microvascular imaging; MVI – microvascular imaging.

sensitivity was 71.4% (20/28), the specificity was 78.8% (134/170), and the accuracy was 77.8% (154/198) (Table 6). SMI examination found that 159 tumors were benign and 39 tumors were malignant PTs; the diagnostic sensitivity, specificity, and accuracy were 82.1%, 93.5% and 89.4%, respectively. MVI examination found that 163 tumors were diagnosed as benign PTs and 35 tumors were malignant PTs; the diagnostic sensitivity, specificity, and accuracy were 89.3%, 94.1%, and 93.4%, respectively. The diagnostic accuracies of SMI and MVI examinations were obviously higher than that of CDFI examination. The diagnostic accuracy of SMI was similar to that of MVI, and there were no significant differences between SMI and MVI in diagnostic sensitivity, specificity, PPV, NPV, or accuracy in PTs.

Discussion

Angiogenesis plays vital roles in cell growth, cell invasion, and cell metastasis of PTs. The vessel morphology and vascular distribution in benign and malignant PTs are distinct. The vascular characteristics are closely related to the malignant degree of PTs. However, conventional CDFI examination cannot assess the vascular characteristics of tumors.

Previous studies found that contrast-enhanced ultrasound MVI has high performance in detecting characteristics of tumor microvascular, such as vascular distribution, vascularity, and vessel morphology. However, the high cost and sensitization risk of contrast agents limit the clinical application of MVI. SMI is a new Doppler technique with high performance for detecting low-speed blood flow signals [20].

In the present study, we found that the tumor characteristics were distinct among the PA, WT, and MT groups. Most PAs and WTs presented expansive growth to squeeze the surrounding tissues. Most PAs (97/105) and WTs (47/49) had clear boundaries. MTs were characterized by aggressive growth with irregular morphology and unclear boundaries. With CDFI examination, there were no significant differences in homogenous internal echoes, vascular distribution, and vascularity among the PA, WT, and MT groups, and CDFI could not distinguish the

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Table 5. Comparison of vessel morphology of among three groups by SMI and MVI.

Vessel morphology	PA	WT	MT	χ^2 value	*P*-value
Vessels in tumor					
SMI	101	53	25		
MVI	108	56	28		
Uneven distribution					
SMI	78/77.2%	45/84.9%	24/96.0%	5.207	0.074
MVI	86/79.6%	51/91.1%	27/96.4%	7.067	0.029
Arborization					
SMI	19/18.8%	26/49.1%	8/32.0%	15.336	0.000
MVI	24/22.2%	30/53.5%	10/35.7%	16.667	0.000
Irregular Abnormal branching of blood flow					
SMI	21/20.8%	15/28.3%	16/64.0%	18.172	0.000
MVI	17/15.7%	11/19.6%	15/53.6%	16.549	0.000
Tortuous blood flow					
SMI	12/11.9%	11/20.8%	15/60.0%	27.758	0.000
MVI	8/7.4%	9/16.1%	14/50.0%	29.794	0.000

PT – parotid tumors; PA – pleomorphic adenoma; WT – Warthin tumor; MT – malignant tumors; SMI – superb microvascular imaging; MVI – microvascular imaging.

Table 6. The diagnostic efficacy of SMI and MVI examination.

Detection	Sensitivity	Specificity	Positive-prediction value	Negative-prediction value	Accuracy
CDFI	71.4% (20/28)	78.8% (134/170)	33.9% (20/56)	94.4% (134/142)	77.8% (154/198)
SMI	82.1% (23/28)	93.5% (154/170)	67.6% (23/39)	96.9% (154/159)	89.4% (177/198)
MVI	89.3% (25/28)	94.1% (160/170)	71.4% (25/35)	98.2% (160/163)	93.4% (185/198)
P-value	0.705	0.308	0.332	0.498	0.209

PT – parotid tumor; PA – pleomorphic adenoma; WT – Warthin tumor; MT – malignant tumors; CDFI – color Doppler flow imaging; SMI – superb microvascular imaging; MVI – microvascular imaging.

real signals of low-velocity blood flow from imaging noise. SMI showed that vascular distribution and vascularity were significantly different among the PA, WT, and MT groups.

The distinct vascular distribution and vascularity among the 3 groups might be the result of distinct histogeneses. Abundant blood flow is commonly distributed in PA abundant tumor cells, and absent/small blood flow is commonly distributed in PA with abundant stroma cells. In our study, under SMI examination, 70.1% of PAs were peripheral or mixed types and 67.6% of PAs had small and medium blood flow. WT originates from the parotid lymph node. The blood flow in WT is commonly characterized by arborization. Stimuli cause adenomatous hyperplasia of parotid lymph node with lymphoid cell infiltration and abundant blood flow [21]. Under SMI examination, 73.3% of WTs were central type and mixed type, and 71.4% of WTs had medium and abundant blood flow signals. A higher malignant degree in WTs was associated with more

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abundant blood flow signals. SMI showed that 67.8% of MTs were central and mixed type, and 67.9% had medium and abundant blood flow signals.

Our study results were both consistent with and different from the results of previous studies. One study [22] found no significant differences in vascular distribution and vascularity among PA, WT, and MT, while another study [23] reported significant differences in vascularity between PA and WT, and did not find any significant differences in vascular distribution among PA, WT, and MT. Miao et al. [8] and Ryoo et al. [23] reported significant differences in vascular distribution and vascularity between PA and WT. Ryoo et al. [8] found that blood flow was absent in 73.7% of PAs, and most WTs were Grade 0 and Grade 3 with avascular type and central type under power Doppler sonography examination. SMI examination showed there was no blood flow in 68.4% of PAs, and most WTs were Grade 3 with central type and mixed type. The diagnostic accuracy of SMI combined with gray-scale ultrasound was obviously higher than that of Doppler sonography combined with gray-scale ultrasound in PAs and WTs. In our study, SMI showed that 11.4% of PAs had no blood flow, which was significantly lower than Ryoo reported, which might be due to possible selection bias and the different ultrasonic instrument parameters used. Ryoo used the speed scale to 2 cm/s, which might have caused loss of some blood flow signals at low velocity. We used speed scale less than 1.4 cm/s in the present study.

Compared with conventional CDFI, SMI detection had significantly better diagnostic sensitivity and accuracy of PT (71.4% *vs.* 82.1%, 77.8% *vs.* 89.4%). We analyzed the reasons for the significant increase in the diagnostic efficacy of SMI. CDFI showed that 31 tumors were Grade 0 and 15 tumors were Grade 1, but SMI showed that 11 tumors were Grade 2 and 5 tumors were Grade 3. CDFI showed that 11 benign tumors were diagnosed as Grade 1 and 6 benign tumors were diagnosed as Grade 2, and these tumors were detected as Grade 3 under SMI detection. Two malignant tumors with Grade 1 and 3 malignant tumors with Grade 2 were detected by CDFI, but were shown to be Grade 3 under SMI detection. Thirty-one tumors showed avascular type under CDFI detection, while 22 of 31 tumors were peripheral type, 6 tumors were central type and 3 tumors were mixed type in SMI examination. Ten tumors were detected as benign tumors with peripheral type in CDFI examination, and those 10 tumors were shown as mixed type in SMI examination. Six benign tumors displayed mixed type in CDFI examination but displayed central types in SMI examination. Among 5 malignant tumors, 1 was avascular type, 2 were peripheral type, and 2 were central type in CDFI examination, whereas SMI showed these 5 tumors were all mixed type. SMI could clearly and completely display the low-velocity blood flow inside of tumors.

We found significant differences among PAs, WTs, and MTs in arborization, abnormal branching of blood flow, and tortuous blood flow under both SMI and MVI examinations. A higher degree of tumor malignancy was associated with poorer pathological angiogenesis and more abnormal blood flow signals. Statistical data showed that the diagnostic sensitivity, specificity, and accuracy of MVI were slightly higher than that of SMI. MVI had higher sensitivity in blood flow signals than SMI, but SMI was better in clearly displaying vessel morphology (abnormal branching, tortuous blood flow). The limitation of MVI is requiring contrast agent and difficulty in scanning multiple lesions in the same section. However, the difference in diagnostic efficacy between SMI and MVI was not significant, and SMI has better safety and non-invasiveness, as well as being cheaper, and it might be a feasible, non-invasive method for PT diagnosis in clinical practice.

There are some limitations in our work. Firstly, the pathological types of MTs in this study were diverse, but the number of cases in each group was small, which limited the ability to study subgroups of MTs. Secondly, only patients with PAs, WTs, and MTs were enrolled into our study, and we did not include other rare benign tumors due to the small number of cases. Thirdly, vascular distribution under SMI and MVI examination was preliminarily studied, but time-intensity curves were not further analyzed.

Conclusions

Compared with CDFI, SMI can more effectively display vascular distribution, vascularity, and vessel morphology of PTs. The diagnostic efficacy of SMI in PTs was comparable to that of MVI. SMI might have a high application value in clinical diagnosis and decision-making for treatment. However, the application of SMI examination in blood flow detection of PTs is still in the preliminary stage in clinical practice, and research with larger sample size of PT patients are needed.

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