

## Pleomorphic Adenoma Versus Warthin Tumor of the Parotid Gland: Diagnostic Value of CT Perfusion Imaging and Its Pathologic Explanation

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### ABSTRACT

**AIM:** To investigate the value of CT perfusion (CTP) imaging in the differentiation of pleomorphic adenoma and warthin tumor deriving singly from the parotid gland, and to explain its pathological basis.

**METHODS:** CTP was successfully performed in 29 patients with parotid tumors whose diagnoses were confirmed by surgery or biopsy. Data were postprocessed by using the Philips EBW workstation and analyzed using a dynamic analysis module. Postprocessing-generated a tissue time-density curve (TDC) and maps showed blood flow (BF), blood volume (BV), time-to-peak (TTP) and peak enhancement index (PEI). Independent-sample test and receiver operating characteristic (ROC) curves were used to analyze the difference and diagnostic efficacies of all perfusion data between the tumors. HE dyeing pathological section of all tumors was obtained after operation.

**RESULTS:** Perfusion maps of all tumors were successfully obtained. TDC of pleomorphic adenomas mainly showed a gradually ascension, and warthin tumours showed a fast ascent followed by a fast descent. The BF, BV, PEI and TTP values were statistically significant different between the pleomorphic adenomas and warthin tumors ( $p < 0.01$ ). ROC demonstrated that BF, BV and PEI, except for TTP, had actual significant differences between these two tumor types. Warthin tumors contains rich capillary network, and with a high cellularity-stromal grade. With regard to pleomorphic adenomas,

it had less angiogenesis, but abundant muciform and chondroid tissue.

**CONCLUSIONS:** CTP could provide TDC and perfusion data, which is feasible to differentiate pleomorphic adenomas from Warthin tumors, and could reflect tumors histopathological feature.

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**Key words:** Partiod gland; Pleomorphic adenoma; Warthin tumor; CT perfusion

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### INTRODUCTION

Parotid tumor is the most common type of salivary gland tumor, and 75-80% of them are benign<sup>[1]</sup>. Pleomorphic adenomas (PAs) and Warthin tumors (WTs) are the two most common types of the parotid tumors, and the incidence of WTs has gradually increased in recent years<sup>[1, 2]</sup>. Although, they are both benign, the biological behavior and surgical plan are absolute different. PA can grow larger or become malignant due to a delayed excision, and it would recur easily after surgery. At present, resection of tumor tissue or part parotid tissue is mostly selected for PA and tumorectomy for WT. With view to the patients prognosis and the required treatment, pre-operation knowledge of the tumor types would be of outstanding important. To our knowledge, they always present as painless, slow-growing lumps and there are no specific manifestations in laboratory and traditional maging examinations. Even though, previous studies showed that multiple lesions, smoking and elderly male are helpful to suggest WT, there are still many overlapping features are confusing

and difficult to diagnosis and clarify before operation<sup>[3-5]</sup>. Fine needle aspiration (FNA) is considered to be gold standard for parotid tumors diagnosis, but has some limitations, even under optimum conditions and may be associated with poor levels of diagnostic accuracy<sup>[6]</sup>. In addition, a meta-analysis study<sup>[7]</sup> showed the actual sensitivity for parotid tumors diagnosis by using FNA was estimated to be low (only 71%). The false positive rates of FNA in PA and WT which were reported to be 9% and 8%, and the variegated cytomorphology of these tumors may lead to an error in interpretation<sup>[8]</sup>. Pre-operation imaging examination may be a better approach to identify these tumors.

Recently, multi-slice CT (MSCT) has been increasingly used for examination prior to parotidectomy.

Dual or three phases enhanced examination has been currently the primarily method for the assessment of the parotid tumors<sup>[3,4,9]</sup>. Based on previous literatures<sup>[9-11]</sup>, it is known that washout time (or washout ratio) of contrast agents in the tumors could provide many valuable physiopathology information and help to differential diagnosis among of parotid gland lesions. Between PAs and WTs, quickly expurgation of contrast material was unique for WTs, and a delayed enhancement for PAs, but the results were not accepted completely. In our previous study<sup>[3]</sup>, some WTs also present delayed enhancement. Dual phases enhanced CT, the time and measurement points selection was very important and was not easy to seize. In addition, the delayed imaging would increase the radiation doses or reduce the temporal resolution. Furthermore, conventional CT enhanced scanning can not reveal absolute quantification of perfusion changes in parotid tumors. Compared with dual phases enhanced CT, CTP is not only can provide time density curves (TDCs) that show the dynamic change of blood supply, but also can multiple perfusion parameter values. Previous CTP pilot studies have reported the feasibility of the study in head and neck imaging and provided normal as well as pathologic perfusion values<sup>[7,12]</sup>.

The aim of this study is to examine the feasibility of CTP imaging in differentiating between PAs and WTs by using TDCs features and perfusion values analysis, and to explain its pathological basis.

## MATERIALS AND METHODS

### Patients

The experimental protocol was approved by the Ethical Committee, the First People's Hospital of Foshan City, China. After being informed of the experimental protocol and purpose of this study, written informed consents were obtained from all patients. 32 patients were suffered from single mass of parotid gland and underwent CTP examination. Of these, because of movement and adverse drug reaction, 3 cases were excluded. The rest 29 cases were received CTP of parotid gland successfully, and all the tumors were confirmed by surgery or biopsy. Of 29 cases, 2 cases were parotid carcinoma, 1 case was neurilemmoma and 1 case was basal cell adenoma (BCA), these 4 cases were also excluded. In addition, another 2 WTs cases were excluded because of false teeth resulting in obvious metal artifact. At last, 23 cases were included in next study for CTP imaging analysis (13 males and 10 females; aged 49.5; range, 20-80 years). All these cases clinically presented single painless slow-growing lumps in the anterior inferior part of the auricular lobule for 2 months to 3.5 years. All patients underwent surgical resection of the parotid masses after a mean of 4.5±2.8 days after the CT survey.

### CT perfusion imaging protocol

CT perfusion scans were performed using a 256-slice CT scanner

(Brilliance iCT; Philips Medical Systems, Best, The Netherlands). After routine plain scan, all patients underwent MSCT perfusion imaging. The plane of focus was suitable for triggering the scans (full view of the parotid gland). A bolus of 20 mL physiological saline, followed by 50 mL contrast agent Iopamidol (300 mg I/mL) and 20-30 mL physiological saline was intravenously injected at a flow rate of 5 mL/s into the right median cubital vein using a high pressure syringe. Immediately after contrast agent injection, dynamic volume scan was performed with the scan parameters: tube voltage 100 kv, tube current 120 mAs, slice thickness 5 mm, matrix 512×512 cm. Arterial phase scans started 11-35 seconds and venous phase scans are initiated 35-60 seconds with 5 second scan duration. Fifteen volume datasets comprising 375 images were acquired. The collected data were post-processed at the Philips EBW4.3 workstation.

### Post-processing of CTP imaging and data analysis

Post-processing was performed by using Philips Perfusion software. The external carotid artery (common carotid artery or internal carotid artery as candidate) ipsilateral to the tumor at the level of observation was taken as the input data. Regions of interest were placed in the region without visible vessels, calcified, necrotic or cystic tissue as possible, and the size of the region of interest (ROI) was about 30-40 mm<sup>2</sup>. Enhanced region should be selected as possible when the lesions were not enhanced uniformly. TDCs of the ROI were plotted by dynamic analysis module and perfusion parameters including BF, BV, TTP and PEI were automatically generated. Parameter maps were displayed as color-coded images.

### Pathological examination

The tumor specimens of all patients were fixed with 4% formaldehyde, routinely dehydrated, embedded with paraffin, sliced into 5µm-thick sections, stained with hematoxylin-eosin and observed under optical microscope for cell morphology and composition. Pathological diagnosis was made by two physicians who had abundant clinical experience by consensus.

### Statistical analysis

SPSS13.0 (SPSS Inc., Chicago, IL) software was used for statistical analysis. All data (including BV, TTP and PEI) were expressed as mean±SD. Independent samples t-test was used for comparing all CTP parameters involved between PAs and WTs. A level of  $p < 0.05$  was considered statistically significant. ROCs were used to estimate the diagnostic efficacies of perfusion data in the identification of these tumors. ROC area was also calculated for each variable, and the optimal threshold for a variable was determined from its ROC analysis by evaluating the sensitivity and specificity.

## RESULTS

Of the 32 cases, a total of 9 cases were excluded because of reasons depicted above, and the remaining 23 cases were enrolled in this study. Pathology confirmed that these 23 cases included 14 WTs cases and 9 PAs cases. Under the microscope, WTs mainly contained two layers of acidophilic cell epithelium with abundant lymphoid tissue. Glandular formations with cystic or papillary cystic structure were present. Tumors interstitial compartment contained much proliferative lymphoid tissue, and lymphoid follicles are always found. Under low magnification, glandular tubes seemed to be inserted in the lymphoid tissue; many different-sized vessels were observed inside and outside the tumor cell membrane and in the lymphoid tissue (Figure 1A). PAs were mainly composed of

glandular epithelial cells and myoepithelial cells. Parts of epithelium presented with strip-shaped or tubiform structure, epithelial cells with various morphologies and visible glandular structure were arranged in multiple layers. Muciform and chondroid tissue was abundant, but vascular formations were deficient (Figure 1B).

On visual assessment, the TDCs of parotid tumors in this study were divided into three types (Figure 2). Type I TDC presented fast enhancement and fast washout, Type II TDC presented fast enhancement and slow decrease, and type III TDC presented gradual enhancement and without apparent washout. In this work, 12 of 14 WT cases ( about 85. 7%) showed type I TDC, and the rest 2 cases had type II TDC. The majorities ( 8 cases) of PAs presented type III TDC, except for 1 PA cases showed Type I TDC. It demonstrated that type I and type III were mostly a characterized of the WTs and PAs respectively. The perfusion parameters maps were all evaluated at the same time. Table 1 showed the results for BF, BV, PEI and TTP in these two types parotid tumors. The BF, BV and PEI values from the standardized ROIs through the WTs were significantly higher ( $p < 0. 01$ ) when compared with the mean perfusion parameters of PAs, while the TTP values were significantly lower ( $p < 0. 01$ ) (Figures 3 and 4).

Table 2 reveals the ROC areas, thresholds and diagnostic efficacy of perfusion parameters for identifying histopathology between WTs and PAs. The BF, BV and PEI had real significant differences (95% CI not including 0. 5), except for TTP, with the ROC areas 0. Compared with PEI, the BF and BV had a higher diagnostic efficacy (Figure 5).

## DISCUSSION

Accurate preoperative predictions of the histopathologic characteristics of parotid tumors are useful for surgical planning and

for predicting prognosis. However, it is still difficult to diagnose parotid tumors without surgical biopsy. Fine-needle aspiration cytology is a common diagnostic tool used for parotid gland tumors; however, its usefulness in differentiating the malignancies in these tumors is challenged because of its low accuracy and sensitivity, especially for benign lesions<sup>[7, 8]</sup>. Perfusion imaging is a novel functional CT technique that is used to study the blood flow perfusion in lesions. CTP imaging is a dynamic scan of the selected layer after intravenous injection of contrast agent. The measured signal density is the increased CT value after injection of contrast agent, so the change in contrast agent concentration in the tissue can be reflected. Therefore, CTP can reflect the blood flow within tissue directly, truly and reliably<sup>[9, 12, 13]</sup>.

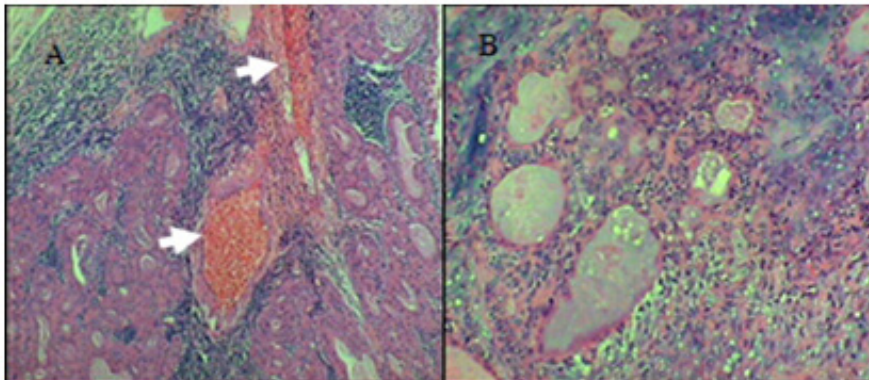
**Table 1** The average values of CT perfusion of parameters.

Diseases	BV (mL 100g-1)	BF (mL 100g-1min-1)	TTP (s)	PEI (Hu)
Pleomorphic Adenoma	21.67 ± 2.07	19.85 ± 2.87	40.09 ± 2.91	33.29 ± 10.35
Warthin Tumor	31.61 ± 7.76**	114.81 ± 36.63**	12.43 ± 3.86**	59.32 ± 9.63**

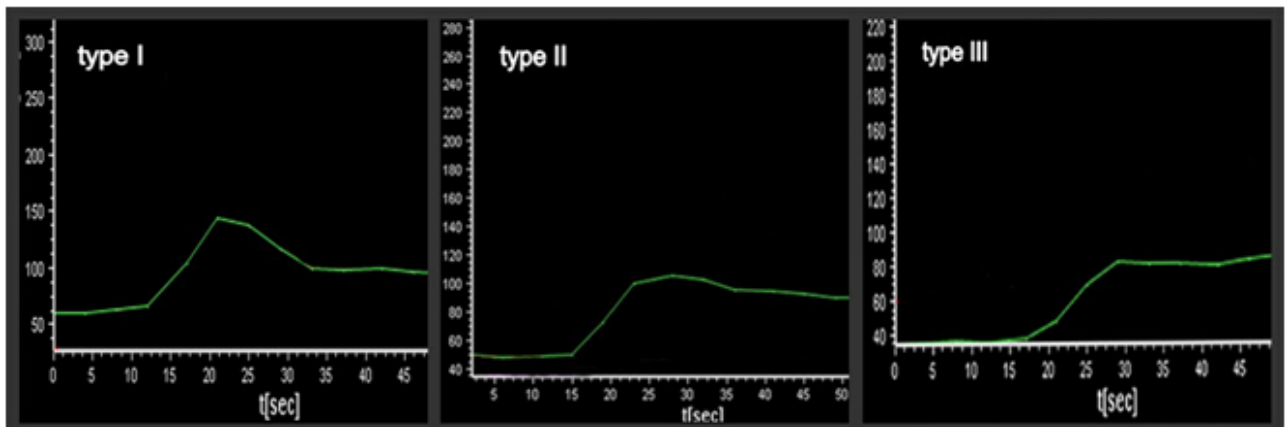
BV: blood volume; BF: blood flow; TTP: time-to-peak; PEI: peak enhancement index; \*\*  $p < 0.01$ .

**Table 2** ROC area, thresholds, sensitivities and specificities for distinguishing between PAs and WTs.

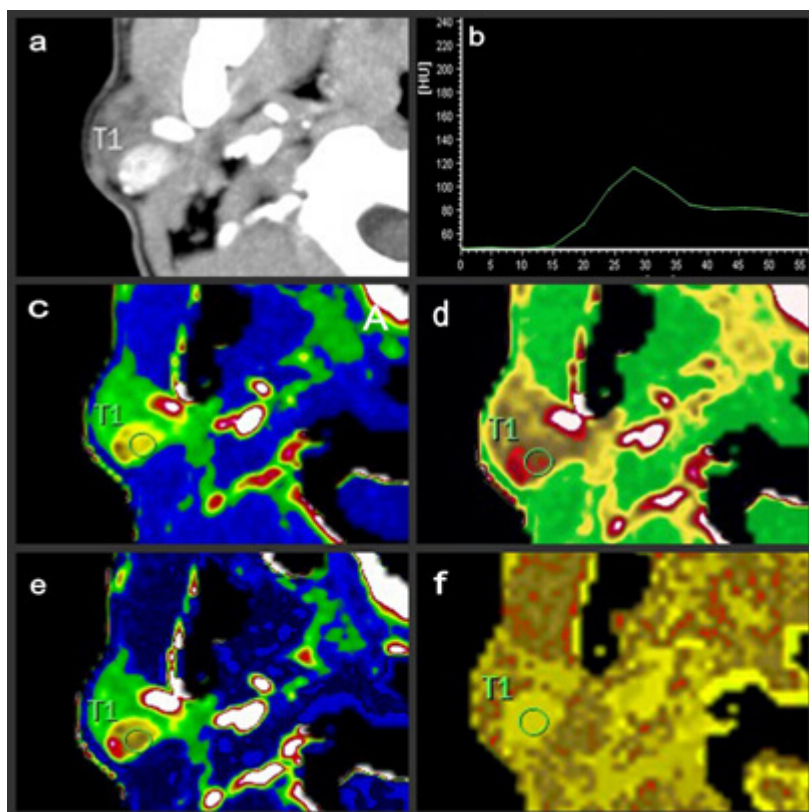
Groups	BV (mL 100g-1)	BF (mL 100g-1min-1)	TTP (s)	PEI (Hu)
ROC area	0.992	1.00	0.00	0.976
Thersholds	20.66	48.67	-----	50.40
Sensitivities	100%	100%	-----	85.7%
Specificities	88.9%	100%	-----	100%



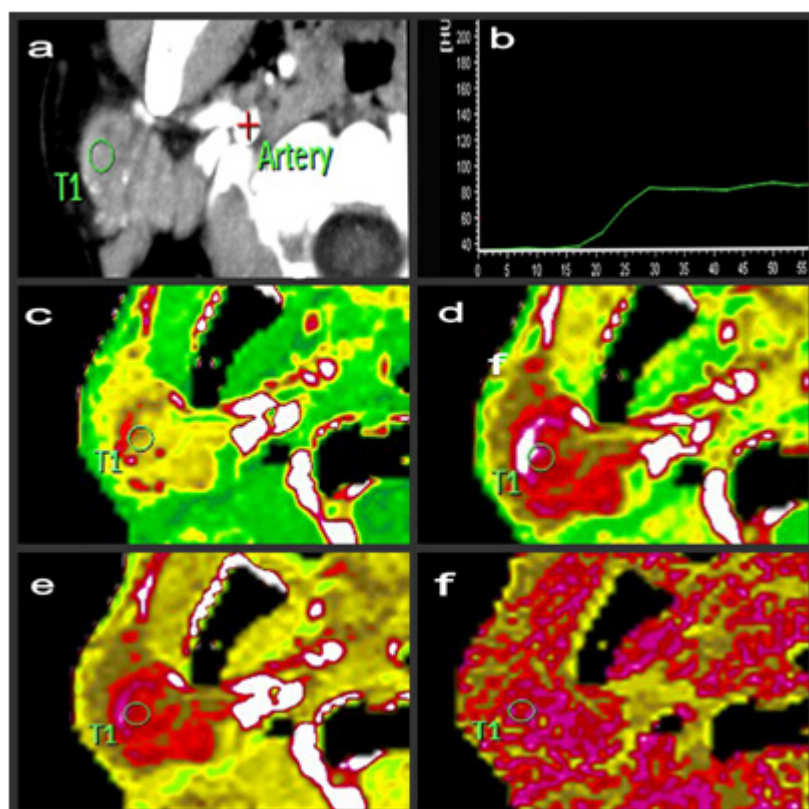
**Figure 1** Pathohistological features of WT and PA of parotid gland (hematoxylin-eosin staining, ×200). (A) WT is composed of acidophilic cell epithelium and abundant lymphoid interstitial substance. Glandular tubule-like structure and abundant expanded blood capillaries are observed (arrows). (B) PA is composed of glandular epithelium and myoepithelial cells. Epithelial cells are arranged in multiple layers and exhibit different morphologies. There is abundant mucoid and chondroid interstitial substance in the tumor tissue, but vascular structure is rarely observed.



**Figure 2** The TDC types of CT perfusion of WTs and PAs.



**Figure 3** (a) A 67-year-old female patient with a single WT arised from the superficial lobe of the left parotid gland. (b) TDC of the tumor; (c) BF; (d) BV; (e) PEI; (d) TTP. TDC showed fast fill in and washout. Note the more elevated BF, BV, PEI ( red and brown yellow colour) and low TTP(light yellow), with the naked eye.



**Figure 4** (a) A 35-year-old male patient with a single PA arised from the superficial lobe of the right parotid gland. (b) TDC of the tumor; (c) BF; (d) BV; (e) PEI; (d) TTP. TDC showed fast fill in and washout. Note the more elevated BF, BV, PEI and TTP (red and brown yellow colour),with the naked eye.

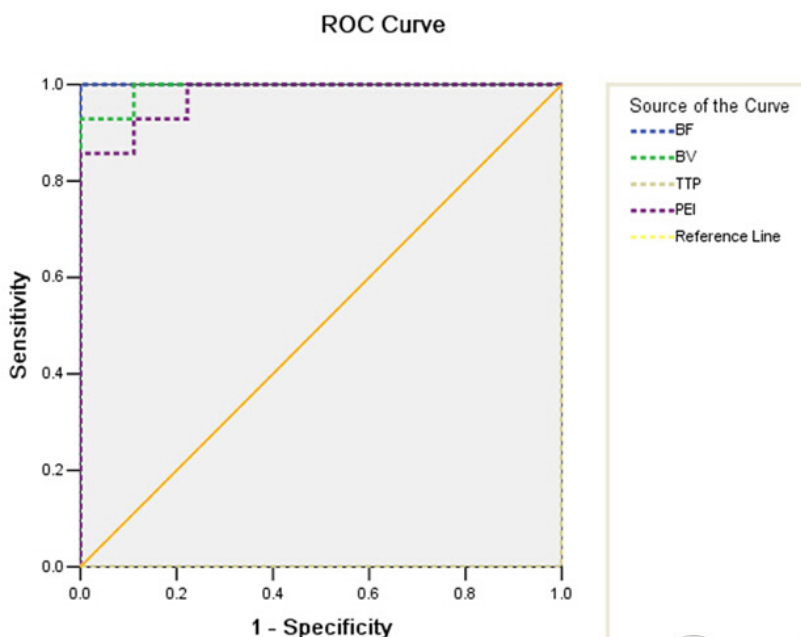


Figure 5 Sensitivity and specificity ROC curves of perfusion parameters for WTs and PAs differential diagnosis.

Previous studies<sup>[9-13]</sup> demonstrated that CTP imaging was usefulness to evaluate the vasclarity and to differential the tumors in the head and neck, including those of the salivary glands. TDC and perfusion parameters such as BV, BF and TTP were main indexes for analysis in CT perfusion. In this study, 29 of 32 cases were performed CTP of parotid gland successfully, accounting for 91%. It demonstrated that CTP was feasible for parotid lesion study, with a high success rate. The movement artefact caused by laryngeal motions was the most important reason for unsuccessful CTP<sup>[14]</sup>. Only 2 cases were excluded in this study because of swallowing not good control. In additional, previous study had revealed false teeth could affect the CTP results<sup>[10]</sup>. In this study, 2 cases with false teeth resulting in low quantify TDC, were also excluded. Therefore, before CT perfusion of parotid examination, it is very important to ask patients to take off false teeth and control swallowing ideally. Two-phases and three-phases enhanced CT was the main method for parotid tumors identify, for lesion differential between benign and malignant. The attenuation changes in tumors were related to its pathological feature. Compared with two-phases and three-phases enhancement, TDC reveals the lesion attenuation changes in multiple time points, and the perfusion parameters can be evaluated at the same time. There is evidence that TDC curves, BF, BV, TTP and PEI parameters can help objectively evaluate the microcirculation and tumor vessel formation and reflect the pathohistological characteristics of foci, and BF, BV and PEI can be used to effectively evaluate micro-vessel density and tumor angiogenesis<sup>[9, 12, 13]</sup>. Y Dong *et al*<sup>[10]</sup> and Bisdas S. *et al*<sup>[15]</sup> studies demonstrated that TDC pattern was very helpful for parotid tumor differential diagnosis. TCD findings in this study were classified into three types, type I TDC represented fast enhancement and fast washout, most of WTs showed this type. Type III TDC represented gradual enhancement without apparent washout for the majority of PAs. When compared with dual-phased enhanced CT, we assumed that Type I TDC was similar to early increase and fast decrease, and type III TDC were similar to delayed enhancement. The TDC findings features for WTs and PAs in this study strongly supported the previous opinions<sup>[9-13, 15]</sup>, but some differences were also depicted. Type II TDC for 2 WTs cases

observed in present work, showed fast enhancement and gradual washout, which was similar to type C TDC described by Y Dong *et al*<sup>[10]</sup>. In their study, it demonstrated that type C represented mostly basal cell adenomas (BCAs) and some malignant tumors, and no WTs case showed this TDC type. How to explain this different, more sample should be need in further study. Additionally, type I TDC were reported that was unique for WTs, but it was depicted in 1 PA case in current data. Another study<sup>[9]</sup> reported similar pattern, some PAs demonstrated early increase and then decreased in two-phase enhanced CT study of parotid tumors. Therefore, “unique” was not so correct. To our knowledge, type I TDC strongly suggest WTs cases, but not unique. A few PAs cases would have the same TDC pattern.

Pervious works involved in CTP studies on parotid tumors, differential diagnosis between the benign and malignant lesions by comparing the perfusion parameters. The absolut BF, BV, MTT and TTP were commonly evaluated for tumor identify. In mostly past researches<sup>[9, 10, 15, 16]</sup>, many different types of parotid tumor were usually contained as benign group to compared to malignant lesions. So far, few studies evaluated the distinction of various histological types of benign tumors by comparing perfusion paramaters. In this study, the BF, BV, TTP and PEI of WTs and PAs being to benign tumors were assessed successfully, and the differences between them were found. The values of these perfusion parameters were few overlap, and there was significantly higher values of BV, BF and PEI in WTs than that of PAs. Additionally, For TTP values of WTs was significantly lower, and no overlap was found. Our study revealed, as expected, significantly altered hemo-dynamic values between WTs and PAs. Higher values of BV, BF and PEI with lower TTP strongly suggest WTs. The current results strongly supported the previous work. However, the measured BF and BV values are slightly different from the values reported by Y Dong *et al*<sup>[10]</sup>, not identical software post-processing as well as the partial volume averaging in the ROI placement. Regarding to another study<sup>[17]</sup> on parotid CT perfusion, BF, BV, TTP and PEI values were nearly identical by using the same perfusion software and the similar approaches. we assumed that different perfusion software, different concentration of contrast agent and size of the standardized ROIs may account

for the different. Additionally, previous studies<sup>[10, 11]</sup> demonstrated the perfusion parameters value had large standard deviations that possibly indicating the wide intertumoral heterogeneity of examined lesion. However, it was not found in this work. The reason was not clear, we suspected that it was concerned with ROI selection, smaller size and local ROI sampling was used in our study. Therefore, our results suggest that ROI selection is a very important point that should be taken into account on CT perfusion researches.

In this study, the tables of ROC curves analysis showed that the perfusion data, such as BF, BV and PEI all had high diagnostic values in the differentiation between WTs and PAs. The BF had best diagnostic efficiency, when the value was 48.67 ml. 100g-1. min-1, the sensitivity and specificities reach up to 100%. The BV and BF had higher diagnostic efficiency in differentiation of parotid tumor, was consistent with those reported in previous works<sup>[9, 10, 14, 15]</sup>. BV and BF reflecting neovascularity and angiogenic activity, were reported that had a highly correlation with pathology. On the contrary to the previous study, only the derived mean BF, BV values between WTs / PAs and malignant lesions, in our work, proved to be differentiating between WTs and PAs. Though, TTP of WTs was very lower than that of PAs, the ROC area was lower than 0.5. It demonstrated that no real significantly TTP between the two groups of tumors. The results are highly consistent with a previous study<sup>[17]</sup>. TTP is a hemodynamic parameter that may be highly dependent on the cardiovascular status of the patient, and thus, may be unsuitable for perfusion measurements. The current results showed that perfusion data was very useful for differentiation between WTs and PAs.

In consistency with the physiology, TDC and perfusion parameters were able to reflect blood flow dynamics of the neoplastic tissue. Vascular permeability, intravascular and extravascular spaces of the tumors are the most important factors for explanation of perfusion characteristics. Many studies<sup>[9, 18-20]</sup> described PAs as having low or intermediate degrees of vascularization. In contrast, majority of WTs are shown to have an intermediate or high level of vascularization. Our detailed pathologic study also confirmed the higher vascularity of WTs. Therefore, for WTs, higher values of BF and BV were observed. In addition, our data revealed that WTs consisted of acidophilic cell epithelium and abundant lymphoid tissue, with a high cellularity-stromal grade will retain less contrast material, this is in agreement with previous observations of wash-out curves and had a high washout ratio. With regard to PAs, muciform and chondroid tissue was abundant with more capacity of interstitial gap, result in more contrast material retain. Therefore, observations of gradual enhancement curves in this work were similar to previous reports.

CTP imagings is more widely available and offers a rapid and accurate quantification of the examined perfusion parameters, but accompanied with a radiation burden. Some technologies and softwares have been developed for significantly reducing the radiation dose<sup>[21, 22]</sup>. No radiation is superiority for MR performant. Previous studies involved in parotid tumor differentiation by using MR perfusion<sup>[23]</sup> and diffusion weighted imaging (DWI)<sup>[24]</sup> had been reported. Though, the characterization of different types parotid lesion were depicted, MRI is still limited widely used because of long scanning time, high expense and sensitive to motion etc. Additionally, a further study should to be need to compare the diagnostic efficiency of CTP imaging with that of DWI and MR perfusion, in order to establish a more superior diagnostic method. In this study, there were some limitations. First of all, radiation dose had a relatively high level, because of restriction on equipment performance. Secondly, a smaller number of trails in this study, the limited number of lesions did not

allow study on CTP features of different type of parotid tumors. The perfusion parameter values, especially for the diagnostic threshold value for differential should be amended in a large scale trial study.

In conclusion, this study demonstrated the CTP imaging can accurately reflect the pathohistological characteristics of tumors and provide valuable information for differential diagnosis between WTs and PAs. TDC curves and perfusion parameters, such as BF, BV, TTP and PEI showed the significantly difference between these two group parotid tumors.

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**Author Contributions:** Conceived and designed the experiments: Xu ZF and Pan AZ. Performed the experiments: Rong F and Yu T. Analyzed the data: Chen YY. Contributed reagents/materials/analysis tools: Gao Q and Zhou T. Wrote the paper: Xu ZF. We wish to thank Dr. Guo (Department of pathology, the first people's hospital of Foshan, China) for her help and support of this study.

## CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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