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**Advanced magnetic resonance imaging findings in salivary gland tumors**

Gökçe E *et al.* Advanced MRI findings in SGTs

## **Abstract**

Salivary gland tumors (SGTs) make up a small portion (approximately 5%) of all head and neck tumors. Most of them are located in the parotid glands, while they are less frequently located in the submandibular glands, minor salivary glands or sublingual gland. The incidence of malignant or benign tumors (BTs) in the salivary glands varies according to the salivary gland from which they originate. While most of those detected in the parotid gland tend to be benign, the incidence of malignancy increases in other glands. The use of magnetic resonance imaging (MRI) in the diagnosis of SGTs is increasing every day. While conventional sequences provide sufficient data on the presence, localization, extent and number of the tumor, they are insufficient for tumor specification. With the widespread use of advanced techniques such as diffusion-weighted imaging, semi-quantitative and quantitative perfusion MRI, studies and data have been published on the differentiation of malignant or BTs and the specificity of their subtypes. With diffusion MRI, differentiation can be made by utilizing the cellularity and microstructural properties of tumors. For example, SGTs such as high cellular Warthin's tumor or lymphoma on diffusion MRI have been reported to have significantly lower apparent diffusion values than other tumors. Contrast uptake and wash-out levels of tumors can be detected with semi-quantitative perfusion MRI. For example, it is reported that almost all of the pleomorphic adenomas show an increasing enhancement time-intensity curve and do not wash-out. On quantitative perfusion MRI studies using perfusion parameters such as  $K_{trans}$ ,  $K_{ep}$ , and  $V_e$ , it is reported that Warthin's tumors can show higher  $K_{ep}$  and lower  $V_e$  values than other tumors. In this study, the contribution of advanced MRI to the diagnosis and differential diagnosis of SGTs will be reviewed.

**Key Words:** Salivary gland tumors; Magnetic resonance imaging; Diffusion-weighted imaging; Dynamic contrast-enhanced imaging; Perfusion-weighted magnetic resonance imaging

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**Core Tip:** Conventional magnetic resonance imaging (MRI) provides more data than other radiological modalities in determining the extent of tumor extension and evaluating its relationship with vascular and neural structures in salivary gland tumors (SGTs). Advanced MRI techniques, which have been increasingly used in the radiological evaluation of SGTs in recent years, contribute to obtaining more information about the nature of the lesion compared to conventional sequences. Different features such as cellularity, microstructural features and vascularity of tumors can be evaluated by diffusion MRI or perfusion MRI techniques, and they can contribute to the differentiation of benign or malignant tumors.

## **INTRODUCTION**

Salivary gland tumors (SGTs) account for approximately 3%-5% of all head and neck tumors<sup>[1-3]</sup>. The majority of SGTs occur in the parotid glands, followed by those arising from the submandibular glands, minor salivary glands, and sublingual glands<sup>[3-6]</sup>. While the majority of those developing from the parotid glands are benign, the incidence of malignancy increases in tumors in other glands. In SGTs for which operation is planned, it is essential to determine the preoperative characterization of the tumor, its number, location (localization in the superficial or deep lobe for the parotid gland), extension to the surrounding tissues and lymphatic involvement<sup>[7]</sup>. The most effective radiological method in operative planning is magnetic resonance imaging (MRI). Conventional sequences may be insufficient to characterize SGTs. For this reason, in recent years, it has been tried to characterize tumors with advanced MRI applications [diffusion-weighted imaging (DWI) MRI, dynamic contrast-enhanced (semi-quantitative) MRI, perfusion (quantitative) MRI, diffusion tensor imaging (DTI), MR spectroscopy (MRS) *etc.*]<sup>[1-7]</sup>. In this review, it is aimed to evaluate the imaging findings detected in advanced MRI applications of SGTs.

## DWI

DWI is an imaging method that detects the motion of water molecules and allows calculation with the apparent diffusion coefficient (ADC). DWI, which can determine the cellularity and microstructural properties of tissues, can contribute to the differentiation of tumors<sup>[8]</sup>. When the studies on SGT were reviewed, some studies stated that the ADC values of malignant and benign tumors (BTs) were significantly different<sup>[9-16]</sup>, while in some studies no significant difference was found<sup>[17,18]</sup>, but in most of these studies, it was reported that ADC values were more effective in separating subgroups [pleomorphic adenomas (PMAs), Warthin's tumors (WTs) and lymphoma]. In the literature, mean ADC values of malignant SGTs are  $(0.8-1.53) \times 10^{-3} \text{ mm}^2/\text{s}$  that of benign SGTs is  $(1.04-1.72) \times 10^{-3} \text{ mm}^2/\text{sec}$  reported in the range<sup>[16-21]</sup>. Although ADC values overlap in some SGTs due to the nature of the components they contain, we can generalize the mean ADC values of SGTs as malignant lymphomas < WTs < carcinomatous malignant tumors (MTs) < PMAs.

## SEMI-QUANTITATIVE DYNAMIC CONTRAST-ENHANCED MRI

Dynamic contrast-enhanced (DCE) MRI in tumoral lesions is the acquisition of multiple T1-weighted images (T1WI) within a few minutes following contrast material administration to monitor contrast agent uptake and wash-out. On DCE MRI, the time intensity curve (TIC) is obtained in connection with the signal changes that occur with the passage of the contrast material through the tissues and the wash-out processes from the tissues. Slope, signal intensity (SI) peak, time to peak (Tpeak), enhancement ratio and wash-out ratio (WR) values can be obtained semi-quantitatively from the TIC curve. In the literature, different TIC patterns have been defined based on the Tpeak and wash-out values of SGTs<sup>[14,22-27]</sup>. The most preferred TIC patterns were those described by Yabuuchi *et al*<sup>[24]</sup>. Tumor cellularity and vascularity are correlated with TIC patterns. Tpeak is related to the microvessel number and tends to be short when the microvessel count is high. Wash-out is dependent on the cellularity and stromal grade,

with cellular tumors being wash-out more rapidly<sup>[3,24]</sup>. When we evaluate the TIC patterns of SGTs, in general, PMAs tend to demonstrate progressive enhancement due to low microvessel content and cellularity-stromal grade. WTs and lymphomas show rapid enhancement and wash-out because of their high microvessel content and cellularity-stromal grade. MTs show rapid enhancement and wash-out due to high microvessel count and lower cellularity-stromal grade, but they tend to have a lower and slower wash-out compared to WTs<sup>[3]</sup>. TIC analysis can reveal physiological characterizations of different tissues using the blood flow properties of SGTs<sup>[26,28]</sup>. Despite overlapping TIC patterns in some SGTs, semi-quantitative DCE MRI is an imaging modality that can help differentiate subtypes of SGTs.

### **QUANTITATIVE DCE PERFUSION MRI**

On DCE MRI, in addition to semi-quantitative examination with TIC parameters, quantitative perfusion MRI can be performed. In the literature, <sup>1</sup>perfusion parameters such as Ktrans [volume transfer constant between blood plasma and extracellular extravascular space (EES)], Kep (flux rate constant between the EES and plasma), and Ve (EES fractional volume) have been studied in SGTs on quantitative DCE perfusion MRI<sup>[29]</sup>. In the literature, the Ktrans values of PMAs were found to be lower than the Ktrans values of other SGTs. However, while some studies stated that the Ktrans values of PMAs differ significantly from those of other SGTs<sup>[29,30]</sup>, some studies could not detect a significant difference<sup>[31]</sup>. In studies in the literature, Kep values were found to be lowest in PMAs and highest in WTs. In some studies<sup>[29,31]</sup>, the Kep values of PMAs, WTs and MTs differed significantly, while in some studies only the Kep values of WTs differed significantly from the other SGTs<sup>[30]</sup>. In the literature, it was found that mean Ve values of WTs were significantly lower than the Ve values of other SGTs<sup>[29-31]</sup>.

### **<sup>1</sup>*Dynamic susceptibility contrast perfusion-weighted MRI***

Dynamic susceptibility contrast (DSC) perfusion-weighted MRI <sup>2</sup>measures signal loss during passage of a non-invasive contrast bolus through a tumor and can be performed

using the bolus tracking technique that follows the first passage of contrast material through a capillary bed. DSC perfusion-weighted MRI is increasingly used as a diagnostic and research tool and to assess the extent of capillaries and microvasculature, mostly in central nervous system tumors. DSC perfusion-weighted MRI contributes to the assessment of tumor angiogenesis as the degree of signal loss depends on the volume of the intravascular space within a tumor and the concentration of injected contrast material in the blood<sup>[32]</sup>. There is a limited number of studies in the literature that have performed DSC perfusion-weighted MRI for SGTs and differing results have been obtained. In the study of Abdel Razek and Mukherji<sup>[33]</sup> on parotid tumors, it was reported that the mean DSC % values of both MTs and all BTs as well as PMAs, WTs and MTs were significantly different. Park *et al*<sup>[32]</sup> found that WTs tended to have higher DSC % values than malignant parotid tumors, although there was no significant difference. The parameters used in the evaluation of SGTs on some advanced MRI techniques are shown in Table 1.

#### *Pseudo/pulsed continuous arterial spin labeling*

Arterial spin labeling (ASL) provides measurement of tumor blood flow (TBF) using the magnetization of protons in arterial blood as an intrinsic tracer without the use of contrast material<sup>[34,35]</sup>. High vascularity, increased tumor blood volume, arterio-venous shunt formation, altered capillary transit time and increased the capillary permeability may lead to high TBF values in MTs. There is a limited number of studies in the literature that have performed ASL perfusion-weighted MRI for SGTs<sup>[35]</sup>. Razek<sup>[35]</sup> reported that TBF values of malignant SGTs were significantly higher than benign SGTs.

#### **DTI**

DTI provides the ability to distinguish between different tissue compartments at the cellular level, with different matrices that reflect the micromovement of water molecules. The most common DTI metrics used are fractional anisotropy (FA) and mean



diffusivity (MD). MD is the average diffusivity along three orthogonal planes in the x, y, z directions of the tensor, equal to the mean of the three eigenvalues and equal to the ADC value. As the cellularity of the tumor increases, the MD value decreases. FA indicates the level of directionality of tissue microstructure in water diffusion and correlates with structural tissue orientations. FA correlates linearly with tumor cellularity and grade of malignancy. Abdel Razek *et al*<sup>[33]</sup> found a significant difference between the MD values of malignant and benign SGTs. At the same time, significant differences were found between the FA values of MTs and BTs in DTI studies performed for SGTs<sup>[20]</sup>. WTs, which are rich in lymphoid content and have high anisotropy, have the highest FA levels among benign SGTs<sup>[20,33]</sup>.

### **DIFFUSION KURTOSIS IMAGING**

Diffusion kurtosis imaging (DKI) is a complex method that uses the non-Gaussian movement of water molecules in tissues. The MR images are obtained based on the diffusion and microstructural features resulting from the organization of water molecules. A minimum of three  $b$  values are required on the DKI<sup>[36]</sup>. In the literature, some authors reported that DKI is useful in defining benign and malign SGTs, while some authors reported that no significant difference was found in distinguishing BTs and MTs. However, some of these authors reported that DKI parameters [ADC ( $D_{app}$ ) and apparent kurtosis coefficient ( $K_{app}$ )] differ significantly in PMAs compared to other SGTs<sup>[30,37]</sup>.

### **INTRAVOXEL INCOHERENT MOTION MRI**

Intravoxel incoherent motion (IVIM) provides both true molecular diffusion and motion of water molecules in the capillary network can be estimated with a single diffusion-weighted acquisition technique. Microvascular volume fraction ( $f$ ), pure diffusion coefficient ( $D$ ), and perfusion-related incoherent microcirculation ( $D^*$ ) parameters are used on IVIM. Single-shot spin-echo echo-planar imaging with multiple  $b$  values usually ranging from 0-800 s/mm<sup>2</sup> is used to generate IVIM MRI. Sumi and



Nakamura<sup>[26]</sup> reported that WT<sub>s</sub> had significantly higher  $f$  values than PMAs. In addition, Sumi and Nakamura<sup>[26]</sup> reported that  $D$  and  $D^*$  values contribute to the differentiation of WT<sub>s</sub>, PMAs, and MT<sub>s</sub>, and even the use of these parameters together provides 100% diagnostic accuracy.

### **PROTON MRS**

Metabolite concentration in tissues and organs is measured in Proton MRS (1H-MRS) and used to characterize metabolic changes associated with tumors. Proton MRS in neoplasms uses a diagnostic algorithm based predominantly on the detection of high levels of choline compounds. Choline is an indicator of cellular proliferation and cell membrane transformation<sup>[38]</sup>. A limited number of studies have been conducted in the literature with MRS in SGT<sub>s</sub><sup>[39]</sup>. King *et al*<sup>[39]</sup> reported that Cho/Cr ratios were significantly different between PMAs and WT<sub>s</sub>, and between BT<sub>s</sub> and MT<sub>s</sub>.

### **SGTS**

According to the 4<sup>th</sup> edition of the World Health Organization (WHO)'s head and neck tumors classification published in 2017, SGT<sub>s</sub> are classified as MT<sub>s</sub>, BT<sub>s</sub>, non-neoplastic epithelial lesions, benign soft tissue lesions and haematolymphoid tumors<sup>[40]</sup>. WHO's head and neck tumors classification version 4 is given in Table 2. Despite efforts to simplify this classification, there are still more than 30 entities. MT<sub>s</sub> were divided into 20, BT<sub>s</sub> 11, non-neoplastic epithelial lesions 4, benign soft tissue lesions 3 subgroups. Two new entities have been added to this classification: Secretory carcinoma [known as mammary analogue secretory carcinoma (MASC)] and sclerosing polycystic adenosis to non-neoplastic epithelial lesions<sup>[41]</sup>.

### **SALIVARY GLAND BTS**

#### ***Pleomorphic adenoma (benign mixed tumor)***

Pleomorphic adenoma is the most frequently observed SGT. Great majority of them are located in the parotid gland, and about 80%-90% is found on the surface of the gland<sup>[42]</sup>.

<sup>44]</sup>. PMAs are slowly growing, painless masses observed in 30-60 years of age and more frequently in women (ratio 2:1)<sup>[43,44]</sup>. Multicentricity of PMAs is less than 1%<sup>[43]</sup>. At cellular level, morphological diversity characterized by a mixture of both epithelial and mesenchymal components is a characteristic feature of PMAs<sup>[44,45]</sup>. Ratio of these components varies greatly in PMAs, and MRI features vary based on the distribution of these components<sup>[44,46]</sup>. Stromal components in PMAs could <sup>14</sup> be myxomatous, chondromatous, lipomatous, hyalinized, fibrous, calcified, or osseous, myxoid stroma being the <sup>12</sup> most frequent (94.2%)<sup>[44,45]</sup>. Tsushima *et al*<sup>[47]</sup> mentioned that high intensity signals on T2WI represented myxoid histology. Classical appearance on T2WI of MRI is generally well bordered, microlobule contoured masses with prominently high signal confined by hypointense fibrous capsule<sup>[10,44,46-48]</sup>. Zaghi *et al*<sup>[49]</sup> evaluated the diagnostic efficiency of conventional MRI in differentiating PMAs using five different criteria. They found that masses with <sup>12</sup> bright T2 signal, sharp borders, heterogeneous nodular enhancement, lobulated contours and a T2 dark rim were predictive of PMAs with a sensitivity of 43.9% and a specificity of 95%. Cellular variants of PMAs featured intermediate SI on T2WI due to their epithelial components, while the ones with fibrous stroma were hypointense. PMAs with hypointense signals on T2WI could represent malignancy, but the presence of complete capsule and lobulated contour are good indications of PMAs<sup>[44]</sup>. Cystic degeneration was observed in 29%-40% of parotid gland PMAs<sup>[50]</sup>. Due to their heterogeneous composition of epithelial, myoepithelial and stromal cells with fluid areas within epithelial glandular regions, PMAs have unrestricted diffusion and high ADC values. ADC values of PMAs were reported to vary between 0.66 and  $2.86 \times 10^{-3} \text{ mm}^2/\text{s}$ <sup>[19-21,51]</sup>, while  $\text{ADC}_{\text{mean}}$  values varied from 1.35 to  $2.15 \times 10^{-3} \text{ mm}^2/\text{s}$ <sup>[10,11,13-15,19-21,51-53]</sup>. Cellular variants of PMAs could have lower ADC values in the range of  $(1.0-1.3) \times 10^{-3} \text{ mm}^2/\text{s}$ <sup>[44,54]</sup>. Average Dapp value of  $(1.525 \pm 0.396) \times 10^{-3} \text{ mm}^2/\text{s}$  and average Kapp value of  $0.394 \pm 0.172$  were reported for PMAs on DKI<sup>[37]</sup>. Huang *et al*<sup>[30]</sup> reported the mean *D* value as  $1.81 \times 10^{-3} \text{ mm}^2/\text{s}$  and the *K* value as 0.51 on DKI. Zheng *et al*<sup>[52]</sup> reported that a great majority of PMAs featured type A TIC pattern (persistent and *Tpeak* > 120 s) because of unbroken capillary endothelial

cells and more complex nature of stroma in tumor (Figure 1). They also mentioned slow flow of contrast medium into extracellular space. However, cellular variants of PMAs showed atypical gradual wash-out pattern on DCE MR due to their high epithelium content and low myxoid stroma<sup>[52]</sup>. Frequency of this atypical pattern in all PMA TIC patterns was reported to be about 17%-18%<sup>[24,44,55]</sup>.

Regarding Tpeak values of PMAs on DCE MRI, Tsushima *et al*<sup>[23]</sup> observed Tpeak was equal to or greater than 260 s while Sumi and Nakamura<sup>[26]</sup> found Tpeak values of 120 s or longer in 92.9% of the cases and less than 120 s in 7.1% of them. Similarly, Zheng *et al*<sup>[52]</sup> measured 120 s or over in 88.9% of the cases and less than 120 s in 11.1%. Tao *et al*<sup>[14]</sup>, on the other hand, found 58 s or longer Tpeak values in 82.0% of the cases whereas in 18% it was less than 58 s. For WR values of PMAs, Tsushima *et al*<sup>[23]</sup> reported no wash-out while Zheng *et al*<sup>[52]</sup> reported no wash-out in 88.9% of the patients and less than 30% WR in 11.1% of the cases. The literature contains a few studies on quantitative DCE perfusion MRI parameters (Ktrans, Kep and Ve) in SGTs. In these studies, mean Ktrans value of PMAs was  $(0.101 \pm 0.069)$  -  $(0.217 \pm 0.036)$ ; mean Kep values  $(0.245 \pm 0.160)$  -  $(0.567 \pm 0.048)$ ; mean and values were determined as  $(0.380 \pm 0.192)$  -  $(0.590 \pm 0.478)$ <sup>[3,7,30]</sup>.

### **Warthin's tumor**

Warthin's tumor is the second most commonly observed benign SGT<sup>[43,48]</sup>. It is mostly observed in middle-age or older men in the parotid gland or periparotid region and more commonly in the inferior pole of the parotid gland<sup>[56,57]</sup>. Smoking, autoimmune disease and radiation exposure were reported to increase WT risk<sup>[43,48,56]</sup>. About 20% of WTs tend to be bilateral and multicentric<sup>[43,56]</sup>. They generally have a spherical to ovoid shape of 2-4 cm diameter, and their surface is smooth. Warthin's tumor is basically an adenoma with mucoid or brown fluid filled cysts of variable number. The cysts are made of two layered papillary proliferations of oncocytic epithelium and supporting stroma made of an abundant follicle carrying lymphoid tissue. They may have focal hemorrhage and necrosis<sup>[57]</sup>. Transformation of WTs to malignancy is extremely rare

(0.3%)<sup>[43,56]</sup>. Intermediate or hypointense areas on short tau inversion recovery and T2WI, and hyperintense area on T1WI on MRI suggest WTs<sup>[48,57,58]</sup>. Solid WT components result in iso-intensity or hypo-intensity on T2WI because histopathologically WT is made of epithelial cells and lymphoid stroma with fibrovascular tissue<sup>[56]</sup>. About 30%-60% of WTs are partly or predominantly cystic<sup>[50,56,58]</sup>. WTs may resemble other less frequently observed benign lesions such as myoepitheliomas and basal cell adenomas (BCAs) which may also carry cystic components and tend to involve superficial lobe of parotid gland<sup>[48,59,60]</sup>. WTs were reported to have low ADC values (Figure 2) due to their epithelial and lymphoid stroma contents which have microscopic slit-like cysts containing proteinous fluid<sup>[56,57]</sup>. In different studies, ADC values of WTs ranged from  $(0.69-1.36) \times 10^{-3} \text{ mm}^2/\text{s}$  and  $\text{ADC}_{\text{mean}}$  was about  $(0.74-1.02) \times 10^{-3} \text{ mm}^2/\text{s}$ <sup>[10,11,13-15,17,19-21,52,53,56,57]</sup>. Only two studies in the literature reported  $\text{ADC}_{\text{mean}}$  values higher than  $1.0 \times 10^{-3} \text{ mm}^2/\text{s}$ , while others had lower values. A study reported that mean  $D_{\text{app}}$  and mean  $K_{\text{app}}$  values of WTs on DKI were  $(0.808 \pm 0.227) \times 10^{-3} \text{ mm}^2/\text{s}$  and  $0.999 \pm 0.228$ , respectively<sup>[37]</sup>. Huang *et al*<sup>[30]</sup> reported the mean  $D$  value of WTs as  $0.97 \times 10^{-3} \text{ mm}^2/\text{s}$  and the mean  $K$  value as 0.99 on DKI.

In terms of  $T_{\text{peak}}$  values of WT in studies on the literature dealing with DCE MRI, Tsushima *et al*<sup>[23]</sup> reported  $< 20 \text{ s}$ , Hisatomi *et al*<sup>[61]</sup> in the range of 30-45 s, Sumi and Nakamura<sup>[26]</sup>  $< 120 \text{ s}$ , while Tao *et al*<sup>[14]</sup> found that in 97.6% of the cases  $T_{\text{peak}}$  was less than 58 s and in 2.4% of the cases  $T_{\text{peak}}$  was equal to or greater than 58 s. For WR values of WTs, Hisatomi *et al*<sup>[61]</sup> mentioned that WR was prominent in the first 30 s after  $T_{\text{max}}$ . On the other hand, Sumi and Nakamura<sup>[26]</sup> found that WR ranged from 30%-70%, while Zheng *et al*<sup>[52]</sup> found WR values equal to or larger than 30%. Tao *et al*<sup>[14]</sup> found that WR values were 22.6% or over in 85.4% of the cases, less than 22.6% in 12.2% and no wash-out was observed in 2.4% of the cases. In the literature, quantitative DCE perfusion MRI values in WTs mean  $K_{\text{trans}}$  values  $0.105 \pm 0.064$  to  $0.464 \pm 0.036$ ; mean  $K_{\text{ep}}$  values  $0.729 \pm 0.112$  to  $2.299 \pm 1.312$ ; mean  $V_e$  values are reported in the range of  $0.1439 \pm 0.093$  to  $0.272 \pm 0.013$ <sup>[29-31]</sup>.

### ***Oncocytoma***

Oncocytomas are well bordered, benign epithelial neoplasms of homogeneous solid structure consisting of mitochondria-rich oncocytes<sup>[48,60]</sup>. They constitute about 1% of parotid tumors, but about 80% of them are observed in the parotid gland<sup>[48,56,60]</sup>. They are commonly observed in people in their 60 s and 80 s, and are slightly more common in women. Because they have high cellularity and low free water content, conventional MRI findings of oncocytomas resemble those of WTs<sup>[62]</sup>. In addition, with their lower ADC content, fast enhancement and wash-out on dynamic MRI, findings of DWI and DCE MRI could overlap. However, oncocytomas usually have higher ADC values than WTs<sup>[56]</sup>. Oncocytomas were reported to have ADC values ranging from  $(0.8-1.16) \times 10^{-3} \text{ mm}^2/\text{s}$ <sup>[56,63]</sup>. Hisatomi *et al*<sup>[61]</sup> found that oncocytomas have similar contrasting dynamics to WT, and consequently, they cannot be differentiated from WTs using DCE MRI alone.

### ***BCA***

BCAs are made of basaloid cells carrying eosinophilic cytoplasm, and they have no clear cell borders. Their nuclei are round-to-oval. They have solid, trabecular, tubular and membranous distribution patterns. Although most tumors carry one of these patterns predominantly, some of them may have more than one pattern. Membranous BCAs have different biological characteristics from other BCA variants because they carry microfocal adenomas, incomplete capsules or no capsule. Besides, they may recur after operation and they have malignant transformation characteristics. Their frequency is higher after 50 years of age, and women have a slightly higher prevalence<sup>[51]</sup>. BCAs most frequently arise from the parotid gland and are more frequently located in the superficial lobe<sup>[31,51]</sup>. They tend to have clearly defined borders<sup>[3,31,51]</sup>. BCAs may have cystic or hemorrhagic components<sup>[51]</sup>. In MRI of BCAs, signal intensities on T1WIs are relatively low while on T2WIs intensity varies between hypointense to slightly intense. In studies in the literature, mean ADC values of BCAs were found to be  $(1.21 \pm 0.20)$ -

$(1.24 \pm 0.18)] \times 10^{-3} \text{ mm}^2/\text{s}$ <sup>[31,51]</sup>. On dynamic MRI, on the other hand, they feature rapid and prolonged enhancement<sup>[51]</sup>. Mukai *et al*<sup>[51]</sup> found that on DCE MRI, 12 of 14 BCAs (85.7%) had TIC patterns of either Tpeak > 120 s or Tpeak < 120 s and wash-out < 30%. Yabuuchi *et al*<sup>[31]</sup> reported Tpeak < 120 s and wash-out < 30% in 61.5% of BCAs in DCE MRI, and Tpeak > 120 s and no wash-out in 15.3% of them.

### ***Myoepithelioma***

Myoepitheliomas are responsible only for about 1%-1.5% of all salivary neoplasms. Their primary location is parotid gland (about 40%) but they may also appear on other salivary gland parts (about 21%)<sup>[59,64]</sup>. Differentiated myoepithelial cells in the form of spindle, plasmacytoid, epithelioid, or clear cells constitute most of myoepithelioma<sup>[59]</sup>. Myoepithelial cells were proposed to have contractile units helping to excrete glandular secretions. Myoepitheliomas need to be differentiated from parotid cyst, abscess, mucocele, schwannoma, leiomyoma, neurofibroma, rhabdomyosarcoma, smooth muscle neoplasms, extramedullary plasmacytoma, benign fibrous histiocytoma, PMA, mucoepidermoid carcinoma (MEC) and myoepithelial carcinoma<sup>[64]</sup>. They feature homogeneous isointense signal based on muscle tissue on T1WI and homogeneous isohyperintense signals on T2WI. In the majority of them (about 80%), hypointense capsule formation and homogeneous contrasting could be observed on T2WI and contrast-enhanced series<sup>[59]</sup>. ADC<sub>mean</sub> values of myoepithelioma in different studies varied from  $1.31 \pm 0.9$  to  $1.86 \pm 0.18$  (range 1.18-1.91)  $\times 10^{-3} \text{ mm}^2/\text{s}$ <sup>[19]</sup>.

### ***Schwannoma and neurofibroma***

Intraparotid neurofibromas or schwannomas could be associated with neurofibromatosis, but they may also arise sporadically<sup>[48]</sup>. Frequency of parotid tumors which originate in the facial nerve was estimated to be between 0.2%-1.55%<sup>[65]</sup>. A fusiform tumor appearance extending into intratemporal facial nerve canal could be a distinguishing feature in diagnosis. However, this appearance also resembles perineural extension of malignant neoplasms. Peripheral nerve sheath tumors could easily be

distinguished by their target and fascicular signs on MRI<sup>[48]</sup>. The target sign refers to the appearance of central T2 hypointensity and enhancement and peripheral T2 hyperintensity and non-enhancement<sup>[48,65]</sup>. The fascicular sign corresponds to multiple ring-like T2 hypointense foci within a relatively T2 hyperintense and enhancing background<sup>[48]</sup>. On DWI, neurofibromas were reported to have  $ADC_{mean}$  values in the range of  $(1.41-1.91) \times 10^{-3} \text{ mm}^2/\text{s}$ <sup>[13,17]</sup>.

### ***Lipoma or sialolipoma***

Lipomas are neoplasms consisting of mature adipose tissue. For salivary gland involvement, they may be intraglandular or extraglandular<sup>[48]</sup>. Lipomas have similar signal intensities to subcutaneous adipose tissue on T1WI and T2WI<sup>[66]</sup>. Fat-suppression is useful on MRI of salivary gland lipomas. These tumors may have septations when they surround vessels<sup>[48]</sup>. Some rare variants of lipomas with a biphasic pattern where serous tissue is diffusely scattered among fat is termed sialolipoma and their appearance closely resemble normal parotid tissue<sup>[48,67]</sup>. They are encapsulated but tend to be heterogeneous in appearance due to their soft salivary gland tissue and fat tissue<sup>[48]</sup>. DWI studies showed that lipomas had  $ADC_{mean}$  values of  $(0.09-0.62) \pm 0.21$  (range  $0.08-0.76$ )  $\times 10^{-3} \text{ mm}^2/\text{s}$ <sup>[19]</sup>.

### ***Hemangioma***

Hemangiomas refer to vascular abnormalities involving increased proliferation and endothelial cell renewal. They are more common in childhood. About 60%-65% of hemangiomas are observed in the head and neck area, and 81%-85% of them are found in the parotid gland. Hemangiomas constitute 0.4%-0.6% of all tumors in the parotid gland and the ADC value of the hemangioma was found to be  $0.8 \times 10^{-3} \text{ mm}^2/\text{s}$ <sup>[68]</sup>. On MRI, they have homogeneously hyperintense appearance on T2WI and strong enhancement, but they are devoid of prominent flow. These tumors often affect the whole gland and could have additional lesions elsewhere in the head and neck or in other regions<sup>[48,68]</sup>.



## **SALIVARY GLAND MTS**

### ***MEC***

MEC refers to the most common salivary gland malignancy and 60% of these lesions involve the parotid gland. MEC develops in epithelium tissue of salivary gland ducts. It is made of mucus secreting cells, epidermoid cells and intermediate cells<sup>[46]</sup>. They may have low, intermediate or high-grade subtypes with different radiological appearances. Low grade tumors have smooth borders and cystic components containing mucin, and have hyperintense signals on T1WI and T2WI. High-grade tumors, on the other hand, are quite solid with undefined borders due to extension into neighboring structures. They often appear on T2WI as hypointense or isointense lesions due to their high cellularity<sup>[33]</sup>. ADC values of MECs on DWI is low in poorly differentiated lesions. ADC<sub>mean</sub> values of MECs on DWI studies were reported to vary from  $[(0.81 \pm 0.06)-(1.05 \pm 0.03)] \times 10^{-3} \text{ mm}^2/\text{s}$  [range  $(0.65-1.14) \times 10^{-3} \text{ mm}^2/\text{s}$ ]<sup>[13,19,20,69]</sup>. Zheng *et al*<sup>[52]</sup> reported Tpeak value of 120 s or lower for MECs on DCE MRI. WR of a case was reported to be less than 30% while that of another was 30% or over.

### ***Adenoid cystic carcinoma***

Adenoid cystic carcinoma (ACCa) is made of ductal epithelial and myoepithelial cells. It may be in solid, cribriform or tubular forms, cribriform being most common. It is more frequent in middle-aged or elderly patients. Perineural spreading and invasion capacity of ACCa is very high<sup>[46]</sup>. They can result in distant metastases and local invasions. ACCa is frequently observed as ill-defined masses with perineural spreading in imaging. ACCa has intermediate to low signal on T1WI and T2WI MRI. The parotid gland is the most common location for ACCa (about 25%), which often involves perineurium of cranial nerve VII during the diagnosis<sup>[46]</sup>. On DWI studies, ACCas were found to have ADC<sub>mean</sub> values varying from  $[(0.84 \pm 0.07)-(1.46 \pm 0.03)] \times 10^{-3} \text{ mm}^2/\text{s}$ <sup>[9,13,17,19,69]</sup>. Tsushima *et al*<sup>[23]</sup> detected PMA-like TIC pattern (Figure 3) in two ACCa cases using DCE MR (Tpeak > 260 s and no wash-out). It was suggested that this

pattern could be due to increased interstitial space of ACCa which contains extracellular mucin and low microvessel count<sup>[3,23]</sup>. Zheng *et al*<sup>[52]</sup> reported that one ACCa they studied had the TIC pattern most commonly observed in MTs (Type C,  $T_{peak} \leq 120$  s and  $WR < 30\%$ ).

### *Acinic cell carcinoma*

Acinic cell carcinoma is a low-grade malignant lesion, and about 90% of these lesions are located in the parotid gland<sup>[46]</sup>. Its characteristic feature is serous acinar differentiation and basophilic granules in cytoplasm<sup>[8]</sup>. No specific finding is observed in imaging, but most acinic cell carcinomas are homogeneously enhanced, well-bordered, slowly growing masses like other benign or low grade malignant lesions<sup>[33,46]</sup>. Most of the malignancies which were previously considered acinic cell carcinomas are now identified as MASCs<sup>[46]</sup>. Kashiwagi *et al*<sup>[70]</sup> revealed that acinic cell carcinomas tended to be solid while MASCs were predominantly cystic masses with solid papillary extensions. The authors mentioned that intermediate-high SI of acinic cell carcinomas on T1WI could help in differential diagnosis. DWI studies in the literature showed  $ADC_{mean}$  values from  $[(0.79 \pm 0.33)-(1.76 \pm 0.11)] \times 10^{-3} \text{ mm}^2/\text{s}$  for acinic cell carcinomas<sup>[69,70]</sup>. Zheng *et al*<sup>[52]</sup> studied three acinic cell carcinoma cases on DCE MRI and observed a  $T_{peak}$  value of 120 s or less.  $WR$  was over 30% in two cases and equal to or larger than 30% in the other.

### **MASC**

<sup>6</sup> MASC was first described in 2010 as a rare salivary carcinoma mimicking acinar cell carcinoma and was released to the <sup>6</sup> World Health Organization classification of head and neck tumors in 2017<sup>[71,72]</sup>. MASC has morphological and genetic similarities with secretory carcinoma of the breast. The majority of MASCs (approximately 70%-80%) are located in the parotid gland, while a smaller number are located in other minor salivary gland areas or major salivary gland glands<sup>[72,73]</sup>. MASCs are often tumors of “papillary and cystic” or “non-papillary and cystic” morphology. The cystic and solid components

of these tumors have high signal on T1WIs on MRI, more often in the cystic component. On contrast-enhanced MRI series, solid components may show different forms of enhancement (homogeneous, heterogeneous, or scarce)<sup>[72]</sup>. DWI has been applied in a limited number of cases in MASCs, and ADC values in the solid components of the tumor vary between  $(0.5-1.7) \times 10^{-3} \text{ mm}^2/\text{s}$ <sup>[70,72]</sup>.

### ***Carcinoma ex pleomorphic adenoma***

Carcinoma ex pleomorphic adenoma arises in connection with a primary or repeating benign PMA. About 1.5% of pleomorphic adenoma cases develop carcinoma ex pleomorphic adenoma in five years, and 10% of them in 15 years. In this condition, a painless mass still for many years starts growing. They appear in MRI as masses with ill-defined borders extending into surrounding tissues, discontinuous hypointense rim and mediate to low heterogeneous SI on T2WI<sup>[74]</sup>. On DWI studies, carcinoma ex PMAs were reported to have  $\text{ADC}_{\text{mean}}$  values in the range of  $[(0.82 \pm 0.01)-(1.32 \pm 0.035)] \times 10^{-3} \text{ mm}^2/\text{s}$ <sup>[9,13,17]</sup>. Zheng *et al*<sup>[52]</sup> found that Tpeak of carcinoma ex PMA was 120 s or less while their WR was less than 30% on DCE MRI.

### ***Lymphoma***

Primary lymphoma of salivary glands is rare and in 75%-80% of the cases parotid gland is involved. Most commonly encountered Non-Hodgkin lymphoma types of salivary glands are extranodal marginal zone B-cell lymphoma in mucosa-associated lymphoid tissue (MALT), follicular B-cell lymphoma and diffuse large B-cell lymphoma. Follicular type and MALT lymphomas are low-grade lesions characterized by slow growth, which sometimes regress spontaneously. In cases with autoimmune conditions such as Sjogren's syndrome MALT lymphoma risk is 44 times higher. Parotid MALT lymphomas are mostly solid-cystic lesions which may have a solitary or diffused pattern. In non-MALT lymphomas, on the other hand, multiple or solitary homogeneous internal structure is more common. A diffuse large B-cell lymphoma is the most common high-grade lymphoma involving the parotid gland. Some of them

arise from an underlying low-grade lesion. They manifest themselves with an asymptomatic mass in the parotid gland which grows in a period of four to six months<sup>[75]</sup>. The ADC values of lymphomas on DWI were generally lower than other solitary tumors (Figure 4), which helps in their differential diagnosis. DWI studies found ADC<sub>mean</sub> values from 0.55 to 0.98 (range 0.4-1.21 × 10<sup>-3</sup> mm<sup>2</sup>/s) for parotid gland lymphomas<sup>[9,11-13,15,20,21,58,76]</sup>.

It has been known that malignant lymphomas have higher cellularity and less extracellular space than head and neck carcinomas<sup>[27,76]</sup>. Therefore, malignant lymphomas show rapid enhancing and wash-out TIC patterns<sup>[19,26,28]</sup>. Since TIC patterns of malignant lymphomas and WTs are similar, differentiation of WTs and malignant lymphomas cannot be done using DCE MRI alone<sup>[27]</sup>. However, T<sub>peak</sub> of lymphomas are somewhat longer and their WR is lower compared to WTs. In their study dealing with head and neck lymphomas, Asaumi *et al*<sup>[77]</sup> measured average maximum duration for lymphomas to reach contrast index as 78.5 ± 29.1 s. Tao *et al*<sup>[14]</sup>, on the other hand, found that in all of seven lymphomas they studied T<sub>peak</sub> was less than 58 s while WR was less than 22.6% in six of them (85.7%) but equal to or greater than 22.6% in one (14.3%). Wang *et al*<sup>[76]</sup> evaluated 20 MALToma cases and reported that parotid MALTomas were usually (94.1% of the patients) in early ascending type (*i.e.*, type I, with a T<sub>peak</sub> of less than 79.65 s and an initial slope of increase less than 0.807). They mentioned that T<sub>peak</sub> values could be used to distinguish between parotid tumor-like benign lymphoepithelial lesion (BLEL) and MALToma because T<sub>peak</sub> value was at least twice higher in tumor-like BLEL cases compared to MALToma cases<sup>[76]</sup>.

### ***Salivary duct carcinoma***

Salivary duct carcinoma (SDC) refers to tumors of different sizes characterized by duct structures which contain eosinophilic tumor cells. They often have a cribriform structure. SDC constitutes the most commonly encountered malignant component of carcinoma ex pleomorphic adenoma. Majority of SDCs originate from PMAs<sup>[78]</sup>. On DWI studies, ADC<sub>mean</sub> values of SDCs were reported to vary from 0.88 to 1.28 ± 0.16

[range  $(0.87-1.47) \times 10^{-3} \text{ mm}^2/\text{s}$ ]<sup>[26,27,30,31,79]</sup>. Motoori *et al*<sup>[79]</sup> reported that on DCE MRI 78% of SDCs appeared as type B ( $T_{\text{peak}} < 120 \text{ s}$  and  $\text{WR} < 30\%$ ), and 67% of had areas of type C TIC pattern ( $T_{\text{peak}} > 120 \text{ s}$ ) due to their abundant fibrotic tissue.

### <sup>13</sup> **Epithelial-myoepithelial carcinoma**

<sup>11</sup> Epithelial-myoepithelial carcinoma (EMC) is a rare subtype of malignant salivary gland tumor. Histopathologically, it consists of a biphasic array of inner lumen ductal cells and outer myoepithelial cells. On conventional MRI, EMCs are well-contoured, may contain mostly solid or cystic components, septa or multi-nodularity can be detected, solid components are isointense or hypointense on T1WIs, hyperintense or isointense on T2WIs, contrast-enhancement with different forms (homogeneous or heterogeneous; moderate, mild or none) can be seen as masses. On DWI studies, ADCmean values of EMCs were reported to vary from 0.96 to  $1.05 \pm 0.03$  [range  $(0.789-1.14) \times 10^{-3} \text{ mm}^2/\text{s}$ ]<sup>[80]</sup>.

### **Secondary malignancies of the salivary glands (metastases)**

Secondary malignancies of the salivary glands may develop either by distant metastasis or by direct infiltration of tumors from adjacent tissues. Secondary malignancies of the salivary glands may involve the parenchyma of the salivary glands or the intraglandular and/or periglandular lymph nodes. Secondary malignancies most commonly involve the parotid gland, followed by the sub-mandibular gland. Metastases in other salivary glands are less common. Metastases to the salivary glands most commonly arise from squamous cell carcinomas of the head and neck region and the upper aerodigestive tract<sup>[81,82]</sup> (Figure 5). Various hematopoietic and lymphoid malignancies, including lymphomas, but not as much as squamous cell carcinomas, constitute a significant portion of secondary malignancies of the salivary glands<sup>[81]</sup>. Metastases may originate less frequently from distant organs such as malignant melanoma, breast, lung, kidney, thyroid, pancreatobiliary, prostate, and bladder<sup>[81,82]</sup>.

### *Cystic lesions of parotid gland and its tumors which may have cystic component*

Parotid gland could have pure cystic benign lesions such as lymphoepithelial cysts, lymphangiomas, dermoid cysts, first branchial cleft cysts and mucocoele, but they could be BTs and MTs which contain cystic components of different size<sup>[50]</sup>. Kato *et al*<sup>[50]</sup> found cystic components of different size scattered over different areas which might have different T1 and T2 signal characteristics in 40% of PMAs, 60% of WTs, 67% of BCAs, 86% of SDCs, 80% of MECs, 75% of epithelial myoepithelial cell carcinomas, 50% of acinic cell carcinomas, 100% of carcinoma ex PMA, 100% of adenocarcinomas and 100% of ACCs. In order to avoid erroneous ADC measurements in tumors with cystic or necrotic components using DWI and in measurements to determine TIC pattern in DCI, ROIs should be placed in solid sections of the lesions<sup>[24,62,83]</sup>.

### **CONCLUSION**

In addition to the morphological data of conventional MRI, advanced MRI techniques allow us to obtain information about the cellularity, microstructural features or vascularity of tumors and thus to interpret the nature and subtypes of tumors. For example, while high cellular tumors such as WTs or lymphomas show low ADC values in diffusion MRI, they cause rapid contrast enhancement and significant wash-out in dynamic contrast MRI series. Except for their cellular variants, PMAs show high ADC values and an increasing TIC pattern in dynamic MR series. High cellular MTs show diffusion restrictions and WRs not as much as WTs or lymphomas. Quantitative perfusion MRI values (such as K<sub>trans</sub>, K<sub>ep</sub>, V<sub>e</sub>) can be measured in accordance with the structural features of the tumors. With the increase in data and studies on the nature and subtypes of SGTs in the literature, threshold values or acceptance intervals for quantitative measurements have begun to emerge, although there are overlaps.

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SIMILARITY INDEX

### PRIMARY SOURCES

- 1

Erkan Gökçe. "Multiparametric Magnetic Resonance Imaging for the Diagnosis and Differential Diagnosis of Parotid Gland Tumors", Journal of Magnetic Resonance Imaging, 2020  
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75 words — 1%
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[synapse.koreamed.org](https://synapse.koreamed.org)  
Internet

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- 3

[www.birpublications.org](https://www.birpublications.org)  
Internet

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[www.ajronline.org](https://www.ajronline.org)  
Internet

38 words — 1%
- 5

Daniel Thomas Ginat. "Imaging of Benign Neoplastic and Nonneoplastic Salivary Gland Tumors", Neuroimaging Clinics of North America, 2018  
Crossref

37 words — 1%
- 6

Ryo Kurokawa, Mariko Kurokawa, Akira Baba, Yoshiaki Ota, Toshio Moritani, Ashok Srinivasan. "Radiological features of head and neck mammary analogue secretory carcinoma: 11 new cases with a systematic review of 29 cases reported in 28 publications", Neuroradiology, 2021  
Crossref

27 words — < 1%
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[radiopaedia.org](https://radiopaedia.org)  
Internet



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[www.ncbi.nlm.nih.gov](http://www.ncbi.nlm.nih.gov)

Internet

20 words — < 1%

9

Ahmed Abdel Khalek Abdel Razek. "Multi-parametric MR imaging using pseudo-continuous arterial-spin labeling and diffusion-weighted MR imaging in differentiating subtypes of parotid tumors", Magnetic Resonance Imaging, 2019

Crossref

17 words — < 1%

10

Weiguo Cai, Dongyong Zhu, Sama Byanju, Jie Chen, Hanfei Zhang, Yanfang Wang, Meiyan Liao. "Magnetic resonance spectroscopy imaging in diagnosis of suspicious prostate cancer", Medicine, 2019

Crossref

16 words — < 1%

11

Douglas R. Gnepp, Alena Skalova, Silvana Di Palma, Roderick H.W. Simpson, Toshitaka Nagao, Elizabeth Ann Bilodeau. "Salivary Glands", Elsevier BV, 2021

Crossref

15 words — < 1%

12

Alexander T Kessler, Alok A Bhatt. "Review of the Major and Minor Salivary Glands, Part 2: Neoplasms and Tumor-like Lesions", Journal of Clinical Imaging Science, 2018

Crossref

14 words — < 1%

13

Guoliang Zhang, Rui Wang, Xueying Qiao, Jing Li. "Primary Epithelial-Myoepithelial Carcinoma of the Lung Presenting as Multiple Synchronous Lesions", The Annals of Thoracic Surgery, 2022

Crossref

12 words — < 1%

---

14 Hiroki Kato, Masaya Kawaguchi, Tomohiro Ando, Keisuke Mizuta, Mitsuhiro Aoki, Masayuki Matsuo. "Pleomorphic adenoma of salivary glands: common and uncommon CT and MR imaging features", Japanese Journal of Radiology, 2018 12 words — < 1%  
Crossref

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15 Paul M. Speight, A William Barrett. "Salivary gland tumours: diagnostic challenges and an update on the latest WHO classification", Diagnostic Histopathology, 2020 12 words — < 1%  
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16 [www.graduate-studies-in-cancer-research.org](http://www.graduate-studies-in-cancer-research.org) 12 words — < 1%  
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