RESEARCH ARTICLE

Differentiation between solitary fibrous tumors and schwannomas of the head and neck: an apparent diffusion coefficient histogram analysis

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Objectives: We sought to elucidate the differences between solitary fibrous tumors (SFTs) and schwannomas in the head and neck by apparent diffusion coefficient (ADC) histogram analyses.

Methods: Our study included 5 patients with SFT and 18 patients with schwannoma in the head and neck region for whom pre-operative ADC images were obtained using either 1.5 or 3.0T MRI system with two b-values. An ADC image that showed the tumor at the largest major diameter was selected for each patient, and a region of interest was set circumscribing the tumor. The histogram distributions of ADC values within the region of interest were compared between SFTs and schwannomas with respect to the mean, standard deviation, median, skewness, kurtosis, and percentile.

Results: The mean and the median ADC values were significantly higher for schwannomas than in SFTs ($p = 0.007$ in both). Skewness and kurtosis of ADC histograms were significantly lower for schwannomas than for SFTs ($p = 0.002$ and 0.005 , respectively). ADC values differed greatest between the two tumor groups at the 90th percentile, and were significantly higher for schwannomas than for SFTs ($p = 0.005$). On receiver operating characteristic curve analysis, the area under the curve for kurtosis, skewness, and the 90th percentile ADC values was 0.92, 0.90, and 0.90, respectively.

Conclusions: Our study suggests that skewness on ADC histograms may be the most useful diagnostic factor, followed by kurtosis and the 90th percentile ADC values, for differentiation between SFTs and schwannomas.

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Keywords: solitary fibrous tumor; schwannoma; apparent diffusion coefficient; histogram analysis; head and neck

Introduction

Solitary fibrous tumors (SFTs) are rare spindle-cell neoplasms originating from mesenchymal tissue. SFTs most commonly occur in the pleura, but can arise in

several regions of the body, including the head and neck. According to the WHO 2013 classification of soft tissue and bone tumors, SFTs are categorized as fibroblastic tumors with rarely metastasizing borderline malignancy, and are now considered to be the same entity as hemangiopericytoma, except for those in the central nervous system.^{1,2} SFTs with high mitotic cell counts are

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classified as malignant SFT, and approximately 10% of SFTs exhibit malignant behaviors developing local and distant recurrence.^{2,3}

On the other hand, schwannoma is a benign peripheral nerve sheath tumor. It is derived from the myelinating cells of the peripheral nervous system and is almost entirely composed of Schwann cells. Most schwannomas originate from peripheral, cranial, or autonomic nerves in the body.⁴ Approximately 25–45% of schwannomas originate from the cranial nerve and are located in the head.⁵

The MRI findings of schwannoma are well-established. Schwannomas often present as ovoid to fusiform in shape, with smooth and sharply circumscribed tumor margins. Schwannomas typically vary in signal intensity on T_1 weighted images, ranging from low to high, and they show higher intensity than muscle on T_2 weighted images (T_2 WI). Small tumors commonly demonstrate dense uniform enhancement on contrast-enhanced MRI, but intramural non-enhanced cysts are often present in large lesions.^{6,7}

SFTs can share similar MRI characteristics with schwannomas, such as ovoid lesion with heterogeneous hyperintensity on T_2 WI, strong heterogeneous enhancement due to histopathological degeneration on contrast-enhanced images, and mild diffusion reduction on diffusion-weighted images.⁸ Therefore, differentiation between SFT and schwannoma has been challenging using conventional MRI techniques. A more accurate diagnostic method for these tumors has been desired for determining appropriate treatment.

Apparent diffusion coefficient (ADC) values have been used as a diagnostic indicator for several tumors. ADC values of biological tissues are determined by numerous factors, and a significant inverse correlation was reported between ADC values and tumor cellularity of histological specimens in different neoplasms.^{9–12} A similar inverse correlation was also found between the ADC value and Ki 67 expression.¹³ Some previous studies have reported the conventional MRI findings and ADC values of schwannoma or SFT.^{5,6} To our knowledge, however, there are no reports using ADC histogram analysis for differentiation of SFTs and schwannomas.

The utility of ADC histogram analysis assessing the heterogeneity of diffusion in the tumor has been confirmed for several tumors.¹⁴ The prognosis of SFTs highly depend on the initial treatment, and total resection is associated with a longer progression-free survival.¹⁵ Conventional MRI findings are often not sufficient to differentiate SFT from other benign tumors. The purpose of this study was to clarify differential diagnostic information for SFTs and schwannomas in the head and neck by means of ADC histogram analyses.

Methods and materials

Study ethics

This retrospective study was approved by our institutional review board and informed consent was waived.

Subjects

Initially, 10 patients with SFT and 22 patients with schwannoma of the head and neck region pathologically diagnosed at Mita hospital between January 2011 and May 2017 were consecutively recruited after a medical record search. All were Japanese patients living in Japan. Histological diagnosis was performed by expert pathologists at our institution. From these 32 patients, we excluded 5 SFT and 4 schwannoma patients who had not undergone diffusion-weighted MRI pre-operatively. Finally, a total of 23 cases (5 SFTs and 18 schwannomas) were enrolled in our analysis.

MR imaging

ADC images were retrieved from the picture archiving and communication system of Mita hospital. 2 of 5 cases with SFT and 9 of 22 cases with schwannoma underwent pre-operative MRI at the referring hospitals, as Mita hospital is a tertiary medical center. Therefore, MR image acquisition parameters are provided on a case-by-case basis in Table 1. In summary, all diffusion-weighted images were obtained with either 1.5 or 3.0 T. ADC images were calculated with two b-values: 0 and 1000 s mm⁻² in 21 cases, 0 and 800 s/mm² in 1 case, 500 and 1000 s mm⁻² in 1 case. Slice thickness was of 4–6 mm, and field of view was of 220 to 350 mm with reconstruction matrices of 100 × 72 to 256 × 256.

Image analysis

We used image data processing software (ImageJ 1.48, National Institute of Health, Bethesda, MA, <http://imagej.nih.gov/ij>) for the image data analysis. On a trans-axial ADC image where the tumor was largest, a region of interest (ROI) was carefully drawn by an experienced radiologist such that the ROI outlined the periphery of the tumor, and then a histogram was made for each ROI (Figures 1–3). The distribution of the ADC values within the ROI was assessed with typical histogram metrics, including the mean, standard deviation, median, skewness, and kurtosis values, using ImageJ. We also calculated the ADC at each 10th percentile of each tumor. The percentile ADC values were averaged across SFTs and schwannomas, respectively, and the differences between these two tumor groups were calculated.

Statistical comparisons

We used statistical software (R 3.3.2, The R Foundation for Statistical Computing, Vienna, Austria, <https://cran.r-project.org/>) for data analysis. Wilcoxon's rank sum test with Bonferroni correction was used to assess differences between SFTs and schwannomas. The receiver operating characteristic (ROC) analysis was used to estimate the diagnostic performance of the skewness, kurtosis, mean, median, and the 90th percentile of the ADC value.

Table 1 The image acquisition data of SFT and schwannoma

	Case no	Age	Sex	Vendor	Model name	Field strength (T)	TR (ms)	TE (ms)	Thickness/gap (mm)	In-plane resolution (mm)	b value ($s\text{ mm}^{-2}$)
SFT	1	56	F	Philips	Achieva	1.5	3123	74	4/0.4	1.37×1.37	0/1000
	2	77	M	Philips	Achieva	1.5	3126	74	4/0.4	1.37×1.37	0/1000
	3	35	F	Philips	Achieva	3	8000	70	5/0.5	1.74×1.74	0/1000
	4	33	F	Siemens	Trio	3	6323	73	5/1	1.17×1.17	0/1000
	5	43	F	Siemens	Verio	3	5000	89	5/0.5	1.72×1.72	0/1000
Schwannoma	1	20	M	Philips	Achieva	3	6000	72	5/0.5	0.90×0.90	0/1000
	2	47	M	Philips	Achieva	3	8000	70	4/0.4	1.74×1.74	0/1000
	3	39	F	Philips	Achieva	3	8000	70	4/0.4	1.74×1.74	0/1000
	4	48	F	Philips	Achieva	3	8000	70	4/0.4	1.74×1.74	0/1000
	5	36	F	Philips	Achieva	3	8000	70	4/0.4	1.74×1.74	0/1000
	6	50	F	Philips	Achieva	3	8000	70	5/0.5	1.74×1.74	0/1000
	7	54	F	Siemens	Verio	3	1,4300	70	5/0.5	1.37×1.37	0/800
	8	39	M	Siemens	Avanto	1.5	9900	78	6/0.6	1.17×1.17	0/1000
	9	53	F	Philips	Achieva	3	4849	106	6/0.6	0.90×0.90	0/1000
	10	87	F	Siemens	Spectra	3	8000	65	5/0.5	3.0×3.0	0/1000
	11	56	M	Siemens	Skyra	3	9800	53	5/0.5	0.83×0.83	500/1000
	12	49	M	Philips	Achieva	3	8000	70	5/0.5	1.74×1.74	0/1000
	13	49	F	Philips	Achieva	3	8000	70	4/0.4	1.74×1.74	0/1000
	14	39	F	Siemens	Verio	3	1,3900	72	4.5/0.9	1.33×1.33	0/1000
	15	78	F	Siemens	Spectra	3	8000	65	5/0.5	1.40×1.40	0/1000
	16	34	M	Philips	Achieva	3	8000	70	5/0.5	1.74×1.74	0/1000
	17	38	M	Philips	Achieva	3	8000	70	5/0.5	1.74×1.74	0/1000
	18	39	F	Siemens	Avanto	1.5	5000	82	5/0.5	1.17×1.17	0/1000

SFT, solitary fibrous tumor; TE, echo time; TR, repetition time.

Histopathological study

Histopathological diagnosis was performed by expert pathologists at our institution for all 23 cases. Because SFT corresponds to intermediate malignancy, the cellularity, the numbers of mitoses (per 10 high power microscopic fields), and the immunohistological staining of CD34 antigen were evaluated in all SFTs. The Ki67 labeling index was additionally obtained in four SFTs and P53 protein overexpression by immunohistochemical staining in three SFTs, respectively.

Results

The results of the ADC histogram values are summarized in Table 2. The mean and median values of ADC were significantly higher for schwannomas than for SFTs ($p = 0.007$ in both). Skewness and kurtosis of ADC values were significantly lower for schwannomas than for SFTs ($p = 0.002$ and $p = 0.005$, respectively). Negative skewness in some schwannomas suggested a left-skewed distribution, *i.e.* with the peak located at relatively high ADC values. The higher kurtosis of SFTs suggested a relatively centered distribution of ADC values around the peak. The 90th percentile of the ADC values differed greatest between the two tumor groups (Figure 4) and was significantly higher in schwannomas

than in SFTs ($p = 0.005$). We performed ROC curve analysis for the mean, standard deviation of the mean, median, skewness, kurtosis, and the 90th percentile of the ADC value. And the results showed that the area under the curve (AUC) of the skewness, kurtosis, and the 90th percentile of the ADC value was 0.92, 0.90, and 0.90, respectively (Figure 5). The AUC of both the mean and median of the ADC values was 0.89.

The histopathological findings of the five SFTs are summarized in Table 3. The cellularity was very high in one, high in three, and high with a partially low portion in one specimen. The largest number of mitoses per microscopic field was 6, 1, 9, 5, and 0, respectively in 5 specimens when counted in 10 microscopic fields magnifying the view by 400 times for each SFT specimen. The Ki67 index was 20, 10, 60, and 2%, respectively, but was not available for 1 SFT case. Pathological findings showed that the expression of CD34 antigen, an indicator of risk of malignancy, was strongly positive in 1, positive in 2, and negative in 2 cases of SFT. In one of two cases with negative CD34 expression, however, negative staining results might be false-negative because the specimen likely suffered degradation with protein denaturation by an acid used in decalcifying preparation to produce the histological specimen. P53 protein overexpression by immunohistochemical staining,

Figure 1 Representative images from SFT (Case 2). (a) Axial T_2 WI shows an elliptical-shaped mass with heterogeneous intensity occupying from the left parapharyngeal space to the medial portion of the left parotid gland (white arrow). (b) An ROI is drawn on a tumor on the trans-axial ADC image. (c) The histogram of the ADC values within the ROI shows higher kurtosis than a normal distribution and more positive skewness (right-skewed) than that of schwannoma. Count, total number of voxels; StdDev, standard deviation; Mode, mode value and the number in the parenthesis is the number of voxels; Bins, the number of bins; Min, minimal value of voxels; Max, maximum value of voxels. ADC, apparent diffusion coefficient; ROI, region of interest; SFT, solitary fibrous tumor; T_2 WI, T_2 weighted image.

another indicator for a risk of malignancy, was positive in one, partially positive in one, and negative in one case of SFT. Expression of P53 was not investigated in two SFT cases.

Discussion

Our results suggest that ADC histogram metrics are useful in differentiating SFTs from schwannomas. In

our study, compared with SFTs, schwannomas had higher mean and median ADC values, and lower skewness on ADC histograms. Therefore, schwannoma exhibits a slightly left-skewed ADC distribution with a higher peak compared with SFT on histograms. Tumor cellularity may explain these differences, *i.e.* the higher, left-skewed distribution of ADC can be attributable to the lower cellularity of schwannomas, compared with SFTs. Schwannomas had kurtosis values around

Figure 2 Representative images from schwannoma (Case 16). (a) An ovoid-shaped mass is observed in the left carotid space (white arrow) in the axial T_2 WI. (b) An ROI is drawn on the trans-axial ADC image. (c) The ADC histogram shows more negative skewness (left-skewed) and smaller kurtosis compared with those for SFT. ADC, apparent diffusion coefficient; ROI, region of interest; SFT, solitary fibrous tumor; T_2 WI, T_2 weighted image.

zero (mean: -0.11 , interquartile range: -0.37 to 0.29), suggesting that the ADC values follow a normal distribution, whereas, the higher kurtosis for SFTs suggests concentric ADC distribution around the peak, which may represent greater homogeneity. Among the ADC histogram values between the two tumors, the ROC curve analysis of the skewness gave the highest AUC values of up to 0.92 . Therefore, skewness may have the highest diagnostic performance in differentiating SFT from schwannoma, followed by kurtosis and the 90th percentile values (AUC = 0.90 in both), and mean and

median (AUC = 0.89 in both). From these data, therefore, we consider that ADC histogram comparison provides more robust diagnostic information than an average ADC value comparison.

SFTs are rare tumors with intermediate malignancy that can occur in numerous regions throughout the body. Schwannoma and cavernous hemangioma, the common benign lesions in the head and neck region, are usually included in the differential diagnosis of SFT. The radiological appearance of SFTs is not so specific enough to provide a definite diagnostic information. Schwannoma

Figure 3 Representative images from (a, b) SFT (Case 3) and (c, d) schwannoma (Case 7). (a) T_2 WI shows a comma-shaped mass with intermediate intensity occupying in the left parapharyngeal space (white arrow). (b) In the corresponding ADC histogram, kurtosis is higher than a normal distribution and skewness is more positive (right-skewed) than that of schwannoma. (c) T_2 WI shows a mass lesion at the left stylomastoid foramen (white arrow) with a heterogeneous intensity and ovoid-shape. (d) The corresponding ADC histogram shows more negative skewness (left-skewed) and smaller kurtosis compared with those for SFT. ADC, apparent diffusion coefficient; ROI, region of interest; SFT, solitary fibrous tumor; T_2 WI, T_2 weighted image.

often exhibits similar imaging findings with SFTs on conventional MR images, such as an ovoid lesion with heterogeneously hyperintense signals on T_2 WI, strong heterogeneous contrast enhancement with histological

degeneration on contrast-enhanced MRI, and mildly restricted diffusion on diffusion-weighted images.⁸

Liu et al reported eight patients with histologically proven SFT in the head and neck region, and

Table 2 Results of ADC histogram measurements

Histogram metric	SFT (IQR)	Schwannoma (IQR)	p value	AUC (95% CI)
Mean ($\times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$)	0.99 (0.96–1.39)	1.66 (1.39–1.85)	0.007	0.89 (0.67–1.00)
SD ($\times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$)	0.26 (0.16–0.28)	0.31 (0.26–0.37)	0.037	0.81 (0.63–0.99)
Median ($\times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$)	0.95 (0.90–1.39)	1.64 (1.32–1.87)	0.007	0.89 (0.67–1.00)
Skewness	0.91 (0.56–1.58)	0.14 (-0.19–0.49)	0.002	0.92 (0.81–1.00)
Kurtosis	3.46 (0.35–4.39)	-0.11 (-0.37–0.29)	0.005	0.90 (0.75–1.00)
90th percentile value ($\times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$)	1.33 (1.21–1.71)	2.16 (1.77–2.34)	0.005	0.90 (0.74–1.00)

ADC, apparent diffusion coefficient; AUC, area under the ROC curve; CI, confidence interval; IQR, interquartile range; ROC, receiver operating characteristic; SD, standard deviation.

Figure 4 Percentile ADC values of SFTs and schwannomas. The line graph shows percentile ADC values of SFTs (solid line) and schwannomas (dotted line). The standard deviation ranges are drawn at every 10%. The 90th percentile of the ADC values differs greatest between the two groups, with significantly higher values in schwannomas than in SFTs ($p = 0.005$). ADC, apparent diffusion coefficient; SFT, solitary fibrous tumor.

diffusion-weighted imaging was performed for five of them, though pre-operative diagnoses were hemangioma in three, pleomorphic adenoma in one, and schwannoma in one.⁸ In their study, the average ADC value for the five SFT patients was $1.157 \pm 0.3049 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$, which was slightly higher than that for our SFT

Figure 5 ROC curve analysis for top three histogram measures. The area under the curve for the skewness, kurtosis, and the 90th percentile of the ADC values are shown with 95% confidence intervals. ADC, apparent diffusion coefficient; AUC, area under the curve; ROC, Receiver operating characteristic.

patients ($0.99 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$, interquartile range: $0.96\text{--}1.39 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$). They also stated that the rapidly enhancing and slow washout pattern of time intensity curve may be an additional feature. In our study, we compared the ADC values of SFTs and schwannomas, and found that the mean and median ADC values of SFTs were significantly lower than those of schwannomas. The high cellularity on the histopathological examination of all five SFT specimens might be the cause of the low ADC values. However, we could not analyze the dynamic contrast-enhancement patterns of the lesions in this study, because dynamic contrast-enhanced MRI was not routinely performed throughout the referral and the referring hospitals. To enhance the strength of the retrospective nature, we focused on the ADC histogram analysis in this study for mathematical or statistical image difference between SFTs and schwannomas.

Recent MRI studies have reported the usefulness of ADC histogram analysis, especially regarding the skewness and kurtosis of ADC distribution in different tumors.^{14,16–18} ADC values depend on cellular integrity and density. Thus, a histogram analysis of ADC values can hopefully provide more sensitive diagnostic information than a simplified comparison of average ADC values because a histogram is less affected by outliers or noise. ADC histograms also can be evaluated by visual inspection of asymmetrical diversity and flatness, and occasionally dual peaks or two-component mixture normal distribution by their shape. As in the present study, the skewness of SFTs had a more positive (right-skewed) distribution and a higher peak (0.91) than that of schwannomas (0.14). This suggests that SFTs have lower ADC values than schwannomas. The averaged kurtosis was much higher in SFT (3.46) than in schwannoma (−0.11). Moreover, the ADC values of SFT had sharp peaks with a leptokurtic curve but schwannomas had milder peaks with a platykurtic curve. The ADC values of SFT may be more homogeneous or less variable than those of schwannomas, consistent with the abundant degeneration forms of schwannoma on histopathology.⁴

Schwannoma is a peripheral nerve sheath tumor originating purely from Schwann cells. The pathological feature of schwannoma is the presence of different tissue components at variable proportions.^{4,19} These tumors have vascularization and sometimes aberrant or bizarre, but often exhibit degenerative features of acute and chronic thrombosis, hemorrhage, hyaline thickening of the ectatic vascular walls, necrosis, and lymphocytic infiltrates. The heterogeneity in the histogram of ADC values for schwannomas may reflect varying features described above.

On the other hand, ultrastructure of SFTs usually features fibroblastic-to-myofibroblastic differentiation, although a recent study has demonstrated that SFTs are more heterogeneous in their cellular composition than was previously thought, containing fibroblasts,

Table 3 Histopathological findings of SFT

	Case 1	Case 2	Case 3	Case 4	Case 5
Cellularity	Very high	High	High	High	High (partially low)
Mitoses	6	1	9	5	0
Ki67 index (%)	20%	10%	60%	N.A.	2%
Location	Parapharyngeal space	Parapharyngeal space	Parapharyngeal space	Maxillary sinus	Subcutaneous area of the neck
CD34 stain	Positive	Positive	Negative	Negative ^a	Strongly positive
P53 stain	Partially positive	Negative	Positive	NA	NA

NA, not available; SFT, solitary fibrous tumor.

Note: Mitoses are counted per 10 high power (400 × magnification) fields.

^aNegative CD34 staining results of case four might be false-negative because protein denaturation likely occurs during de-calcifying preparation of the maxillary bone.

myofibroblasts, endothelial cells, pericytes, and undifferentiated perivascular cells in varying proportions.^{4,20}

Although both tumors have heterogeneous and variable components, the higher kurtosis of SFTs (3.46) compared with schwannomas (0.11) may correspond with the differences in the degree of heterogeneity. This may provide supportive diagnostic information for conventional MRI.

Surgery is the treatment of choice for both tumors.^{21,22} However, observational strategies are often preferred when schwannoma is more likely, because it is a benign tumor. If SFT is more likely, surgical excision is the first choice. Favorable outcomes can be expected for patients who undergo complete surgical resection and have no malignant components. However, patients with positive surgical margins or whose tumors have a malignant component are at an increased risk for local recurrence. To plan the surgical approach, it is important to speculate the histopathological features pre-operatively, including the possibility of malignancy. Our results suggested that ADC values and histogram analysis are helpful to in differential diagnosis of SFT from schwannoma.

Our study has some limitations. Although there were statistical differences between SFTs and schwannomas in our ADC value metrics, the sample size was small, especially for SFTs. Second, MRI parameters including b-values and strength of the magnet were not identical

among patients because some cases underwent MRI examination at referring hospitals. ADC measurements reproducibility and repeatability should be adequately considered in these situations. At this point, Belli *et al* has reported a good agreement between the nominal and measured mean ADC, using a standardized phantom, on their multicenter quality assurance study with a total of 35 MR scanners with variable field strength (1, 1.5, and 3 T) from three vendors.²³ Habermann *et al* has also reported high correlation in ADC values ($r = 0.955$) of the human salivary glands between 1.5 and 3 T MR machines of different vendors.²⁴ We considered that these previous studies support the soundness of our study. In addition, we focused on the ADC histogram analysis as mathematical or statistical difference between SFTs and schwannomas. ADC histogram measures are considered to be less sensitive to an outlier voxel value or image noise.

In conclusion, we consider ADC histogram analysis of MRI would be useful in differentiating between SFT and schwannoma in the head and neck region, which will help in determining the treatment strategy.

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