นิพนธ์ต้นฉบับ • Original Article

การวัดค่า Apparent Diffusion Coefficient โดยใช้เทคนิค Diffusion-Weighted MR imaging เพื่อวินิจฉัยแยกเนื้องอกธรรมดาและเนื้องอกร้ายในเนื้อเยื่ออ่อนของร่างกาย

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The Measurement of Apparent Diffusion Coefficient using Diffusion-Weighted MR Imaging in Differentiation between Benign and Malignant Musculoskeletal Soft Tissue Tumors

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วัตถุประสงค์: เพื่อหาค่า Apparent Diffusion Coefficient (ADC) ของเนื้องอกในเนื้อเยื่ออ่อนแต่ละชนิดของร่างกาย และเพื่อศึกษาค่า ADC value ที่ใช้แยกระหว่างเนื้องอกธรรมดา และเนื้องอกร้ายในเนื้อเยื่ออ่อนของร่างกาย

วิธีการศึกษา: เป็นการศึกษาเชิงพรรณนาโดยเก็บรวบรวมข้อมูลแบบย้อนหลัง ในผู้ป่วยที่มีเนื้องอกในเนื้อเยื่ออ่อนของร่างกายที่ยังไม่ได้รับการรักษา จำนวนทั้งหมด 21 เนื้องอก โดยมี 11 เนื้องอกธรรมดา และ 10 เนื้องอกร้าย ที่ได้รับการตรวจด้วยเทคนิค diffusion-weighted magnetic resonance imaging ในโรงพยาบาลศรีนครินทร์ ระหว่างเดือนธันวาคม 2556 ถึง สิงหาคม 2558 ทำการวัดค่า ADC และนำมาวิเคราะห์ทางสถิติ

ผลการศึกษา: ค่าเฉลี่ย ADC ของเนื้องอกร้าย (1.075 ± 0.392 x $10^{-3}$$mm^2$/s) มีค่าต่ำกว่าเนื้องอกธรรมดา (1.594 ± 0.494 x $10^{-3}$$mm^2$/s) อย่างมีนัยสำคัญทางสถิติ ($p < 0.05$) ในกลุ่ม non-myxoid tumors ค่าเฉลี่ย ADC ของเนื้อร้ายลดลง (0.937 ± 0.247 x $10^{-3}$$mm^2$/s) และมีค่าต่ำกว่าเนื้องอกธรรมดา (1.597 ± 0.413 x $10^{-3}$$mm^2$/s) อย่างมีนัยสำคัญทางสถิติเช่นกัน ($p < 0.05$) ค่าจุดแบ่ง ADC value ที่ 1.316 x $10^{-3}$$mm^2$/s สามารถช่วยแยกวินิจฉัยเนื้องอกธรรมดา และเนื้องอกร้ายได้โดยมีค่าความไว 82% และค่าความจำเพาะ 90%

สรุป: ค่าเฉลี่ย ADC ของเนื้องอกร้ายมีค่าต่ำกว่าเนื้องอกธรรมดาอย่างมีนัยสำคัญทางสถิติ และค่าจุดแบ่ง ADC value

Objective: The objective of this study were to assess the Apparent Diffusion Coefficient (ADC) values in benign and malignant musculoskeletal soft tissue tumors and determine the ADC threshold for discriminating the benign from the malignant lesions.

Materials and Methods: From December 2013 to August 2015, the retrospective descriptive study was performed in the 21 non-treated musculoskeletal soft tissue tumors with proven pathology (11 benign and 10 malignant tumors) in Srinagarind hospital by using diffusion-weighted magnetic resonance images with b-values of 0 and 600s/mm^2. The ADC values were obtained by consensus of two musculoskeletal radiologists. The mean ADC values in each group of benign, malignant, benign non-myxoid and malignant non-myxoid tumors were calculated. The receiver operating characteristic (ROC) analysis was used to determine the threshold ADC value for discriminating malignant from benign tumors.

Results: The mean ADC value of malignant soft tissue tumors (1.075 ± 0.392x$10^{-3}$$mm^2$/s) was significantly lower than that of benign soft tissue tumors (1.594±0.494x$10^{-3}$$mm^2$/s) with a $p \leq 0.05$. The mean ADC value of malignant non-myxoid soft tissue tumors lowered to 0.937±0.247x$10^{-3}$$mm^2$/s and was significantly lower than that of benign non-myxoid soft tissue tumors (1.597±0.413x$10^{-3}$$mm^2$/s)

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ที่ 1.316x10^{-3}mm^2/s สามารถช่วยแยกวินิจฉัยเนื้องอกธรรมดา และเนื้องอกร้ายได้

$p < 0.05$. ROC analysis showed a threshold ADC value at 1.316x10^{-3}mm^2/s, used for discriminating benign from malignant soft tissue tumors with 82% sensitivity, 90% specificity and AUC of 0.8636.

Conclusion: The mean ADC value of malignant soft tissue tumors was significantly lower than that of benign soft tissue tumors. A threshold ADC value of 1.316x10^{-3}mm^2/s. is recommended for differentiating benign and malignant musculoskeletal soft tissue tumors.

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Introduction

The conventional MR imaging in soft tissue tumors have important roles in the diagnosis, staging of diseases and treatment monitoring based on the differences in signals of hydrogen atoms (H) in water molecule H_2O in various tissues. The other MR technique: functional MR imaging focus in Diffusion-weighted imaging (DWI) is a technique that reflects the Brownian motion of water molecules in the cellular level of various tissues, which derives from transport of water protons through the cell membranes[1]. Many factors may affect the Brownian motion such as the cell size, cellular density, intercellular spaces and nature of the extracellular matrix[2]. The apparent diffusion coefficient (ADC) is a quantitative measurement of the Brownian motion in each tissue which is inversely proportional to the degree of restricted diffusion of the water molecule. By the pathological knowledge, in general, the malignant soft tissue tumors have larger cell size, more cellularity and less intercellular spaces than the benign tumors, resulting in more restricted diffusion of the water protons in the malignant tumors[3]. At present, the DWI has been used to help distinguish benign and malignant soft tissue tumors. There are several previous studies shown that variability and overlapping of the ADC values between benign and malignant tumors. However there have been no final conclusive results and never been studied in Thailand. In our study, the main objection was to assess the ADC values in benign and malignant musculoskeletal soft tissue tumors. A secondary objection was to determine the threshold ADC values for discriminating benign from malignant tumors.

Materials and Methods

Patients

From December 2013 to August 2015, the 21 musculoskeletal soft tissue masses in 20 patients were retrospectively reviewed by using the Picture Archiving and Communications System. The study was approved by the Ethics Committee for Human Research at Khon Kaen University. All tumors were proven histologically. There were 11 benign tumors and 10 malignant tumors. In the benign tumors, there were myositis ossifican (n=1), plexiform neurofibroma (n=1), schwannoma (n=5), hemangioma (n=2), parachordoma (n=1) and myxoid leiomyoma (n=1). The malignant tumors, there were one lesion in each small round cell tumor, desmoplastic small round cell tumor, malignant round cell tumor, metastatic adenocarcinoma, pleomorphic leiomyosarcoma, unspecified sarcoma, and myxoid leiomyosarcoma. There were three for synovial sarcoma. We also subclassified the groups of tumors based on myxoid material within the masses (Table 1).

MRI protocols

3T MR scanner (Phillips Achieva; Philips, Best, the Netherlands) and 1.5T MR scanner (MAGNETOM Aera; Siemens, Erlangen, Germany) were performed by using our institute soft tissue protocol. DWI was acquired in an axial plane using a single shot, spin-echo type, echo-planar imaging sequence with fat suppression technique with b-values of 0 and 600 s/mm^2. The ADC maps were automatically computed using the operating console with the following equation[1]:

$$ADC = \sum_{i=0}^{n} \frac{-ln[Si/S0]}{bi}$$

*b*i= diffusion gradient value, *S*0= signal intensity of the first image, and *S*i = signal intensity of the *i* th image.

Image analysis

The ADC measurement was performed in consensus by two musculoskeletal radiologists who were blinded to the pathological diagnosis. The three circular region of interest (ROI)s were placed over the tumor on the different non-consecutive slices. The diameters of ROI were varied depending on tumor size by adjusting approximately one-fourth of cross sectional diameter of the tumor and placing on the most possible restricted diffusion areas (Fig 1, 2). The ADC value was calculated by the automated software from the user-prescribed ROIs and reported as $x10^{-3}$ mm^2/s.

Statistical Analysis

The mean and standard deviation of the ADC values of malignant and benign soft tissue tumors were calculated. Two-sample t test with equal variances were used for the difference of mean ADC value between the comparison groups: all benign and all malignant tumors; benign and malignant non-myxoid tumors. The p-value < 0.05 was considered to indicate statistically significant difference. The receiver operating characteristic (ROC) analysis were constructed to determine the threshold ADC value used to discriminating malignant from benign soft tissue tumors, with calculation of sensitivity, specificity and area under the curve (AUC).

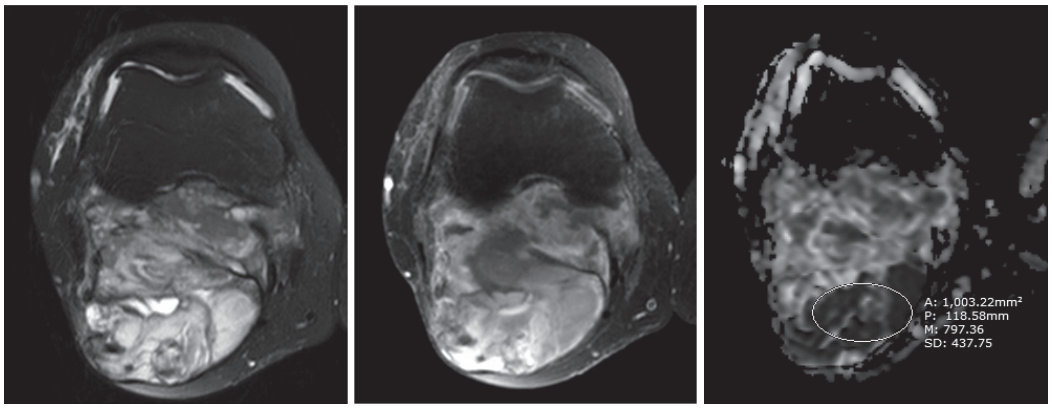

Figure 1 A 49-year-old woman with synovial sarcoma at right knee, A: Axial fat-suppressed T2-weighted image shows a heterogeneous mixed iso and hypersignal mass. B: Axial fat-suppressed contrast-enhanced T1-weighted image shows a heterogeneous enhancement of the mass. C: Axial ADC map shows low signal intensity of the restricted diffusion area in the mass. The ROI was placed over the tumor and was adjusted about one-fourth of the tumor size by avoiding the region of cystic or necrotic portions in the mass, with the ADC values of $0.797\times10^{-3}mm^2/s$.

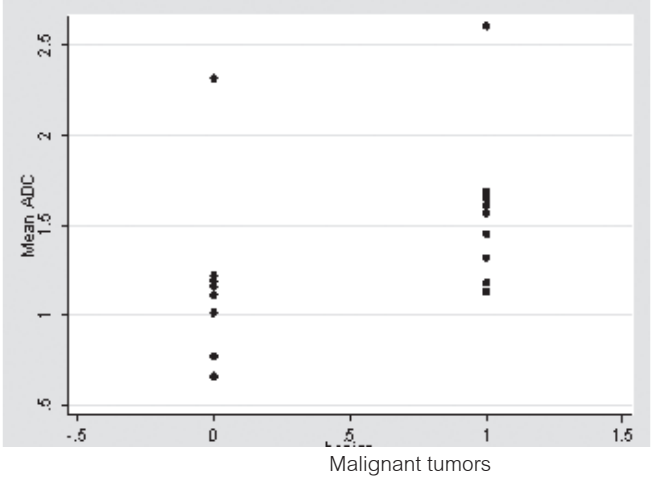

Figure 2 Scatterplot of ADC values of all benign and malignant tumors.

Results

Among the total of 21 soft tissue masses, 10 were malignant and 11were benign tumors. The ADC values of all benign and malignant soft tissue tumors are summarized (Table 1).

The mean ADC value of the benign tumors was 1.594 ± 0.494 x $10^{-3}mm^2/s$ and of the malignant tumors was 1.075 ± 0.392 x $10^{-3}mm^2/s$. The highest ADC value of malignant tumors was found in the myxoid leiomyosarcoma (2.316 x $10^{-3}mm^2/s$) and higher than that of some benign tumors. This report showed that the mean ADC value of malignant tumors was significantly lower p-value than that of benign tumors (Table 2).

In the case of exclusion of the myxoid containing-tumors, the mean ADC value of malignant non-myxoid tumors lowered to 0.9376 ± 0.2474 x $10^{-3}mm^2/s$. While, the mean ADC value of benign non-myxoid tumors was not affected. The mean ADC value of malignant non-myxoid tumors was significantly lower than that of benign non-myxoid tumors with a p-value of <0.05 (Table 3).

The scatterplot of the ADC values of all benign and malignant tumors is demonstrated (Fig 2). The ADC values of all benign tumors ranged from 1.131 x $10^{-3}mm^2/s$ to 2.607 x $10^{-3}mm^2/s$ and the ADC values of all malignant tumors ranged from 0.656 x $10^{-3}mm^2/s$ to 2.316 x $10^{-3}mm^2/s$. The ADC values of some benign tumors overlapped the ADC values of the malignant tumors.

ROC analysis showed a threshold ADC value at 1.316 x $10^{-3}mm^2/s$ for discriminating benign from malignant tumors with a sensitivity of 82%, a specificity of 90% and AUC of 0.8636 (Fig 3).

Table 1 Summary of histological diagnosis and the ADC values of benign and malignant soft tissue tumors.

Benign tumors		Malignant tumors	
Non-myxoid tumors (n=10)	Average ADC*	Non-myxoid tumors (n=9)	Average ADC*
Myositis ossifican	1.180	Small round cell tumor	0.770
Plexiform NF	1.450	Desmoplastic small round cell tumor	1.013
Schwannoma	2.607	Malignant round cell tumor	0.661
Schwannoma	1.665	Synovial sarcoma	1.190
Schwannoma	1.689	Unspecified sarcoma	1.218
Schwannoma	1.665	Metastatic adenocarcinoma	1.114
Schwannoma	1.131	Synovial sarcoma	0.656
Hemangioma	1.649	Pleomorphicleiomyosarcoma	1.158
Hemangioma	1.613	Synovial sarcoma	0.658
Parachordoma	1.316		
Myxoid tumor (n=1)		Myxoid tumor (n=1)	
Myxoid leiomyoma	1.570	Myxoidleiomyosarcoma	2.316

Average ADC= Apparent diffusion coefficient, * expressed in units of 10^{-3} mm^2/s.

Table 2 The mean ADC values of all benign and all malignant soft tissue tumors.

Soft tissue tumors	Mean ADC (x$10^{-3}mm^2/s$) ± SD
Benign (n=11)	1.594 ± 0.494
Malignant (n=10)	1.075 ± 0.392
p-value	0.0149 (<0.05)

Table 3 The mean ADC values of benign and malignant soft tissue tumors which were classified as myxoid and non-myxoid tumors.

Tumors	Mean ADC ($x10^{-3}mm^2/s$) ± SD		p-value
	Benign (n=11))	Malignant (n=10)	
Non-myxoid (n=19)	1.597±0.413	0.9376±0.2474	0.0007 (<0.05)
Myxoid (n=2)	1.570	2.3160	-

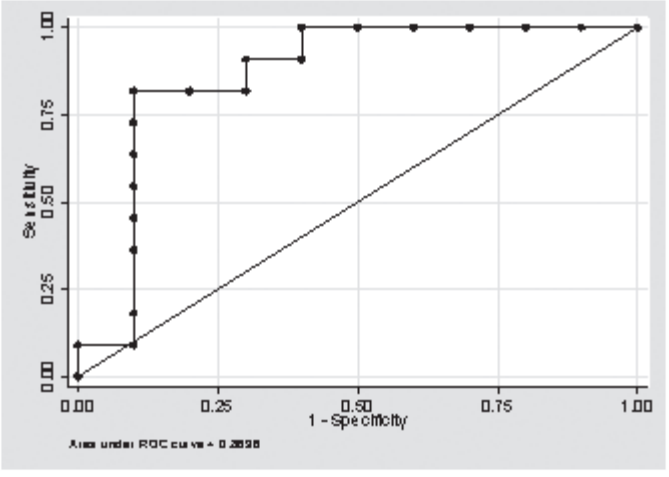

Figure 3 ROC curve of the ADC values for discrimination between benign and malignant soft tissue tumors.

Discussion

There are several studies, which have demonstrated the difference in the results of the ADC value to differentiate the benign from malignant soft tissue tumors.

Nakanishi et al[5] described that the ADC value of malignant soft tissue tumors were not significant different from benign soft tissue tumors and their ADC values were varied widely.

Maeda et al[6] compared the ADC values between 18 benign soft tissue tumors and 26 malignant soft tissue tumors. They found that the ADC values could not be used to differentiate between benign and malignant soft tissue tumors. However, when they compared the ADC values among myxoid and non-myxoid tumors, there was significantly different in the mean ADC value between them. Finally, they implied that myxoid content influences ADC value of both benign and malignant soft tissue tumors. In the our case of myoxid leiomyosarcoma, the average ADC value was rather high, which supported other studies that the mean ADC value of myxoid tumors was significantly higher than that of non-myxoid tumors.

Nagata et al[7] studied in large population (n=88). They categorized the soft tissue tumors based on the WHO Classification 2002 as benign (n=44), intermediate (n=8) and malignant (n=36) lesions. They demonstrated no significant difference in the mean ADC values among benign ($1.70 \pm 0.62 \times 10^{-3}mm^2/s$), intermediate ($1.30 \pm 0.37 \times 10^{-3}mm^2/s$), and malignant tumors ($1.19 \pm 0.58 \times 10^{-3}mm^2/s$). In case of tumor classification as myxoid and non-myxoid types, among non-myxoid tumors, they found that the mean ADC value of benign non-myxoid tumors (n=22, mean ADC=$1.31 \pm 0.46 \times 10^{-3}mm^2/s$) was significantly higher than that of malignant non-myxoid tumors (n=28, mean ADC=$0.94 \pm 0.25 \times 10^{-3}mm^2/s$). Thus they summarized that the ADC value might be useful for diagnosing the malignancy of non-myxoid soft tissue tumors. Similar to our study, we proved that the mean ADC value of malignant non-myxoid tumors was significant lower than that of benign non-myxoid tumors.

Razek et al[8] reported that the mean ADC value of malignant soft tissue tumors (1.0 ± 0.03 x $10^{-3}mm^2/s$) was significantly lower than that of the mean ADC value of benign soft-tissue tumors (1.54 ± 0.03 x $10^{-3}mm^2/s$). The threshold ADC value of 1.34 × $10^{-3}mm^2/s$ can be used for distinguish benign soft tissue tumors from malignant soft tissue tumors with a sensitivity of 94%, a specificity of 88%, and an overall accuracy of 91%.

The presented study found that the mean ADC value of all malignant soft tissue tumors was significantly lower than that of benign soft tissues tumors. The results are consistent with the previous studies by Razek et al[8]. The authors proved a threshold ADC value of 1.316 x 10^{-3} mm^2/s with a sensitivity of 82%, a specificity of 90% with a good accuracy for distinguish benign from malignant soft tissue tumors (AUC of 0.8636). There are no any malignant non-myxoid soft tissue tumor that have an ADC value higher than 1.300 x $10^{-3}mm^2/s$. There are two benign tumors that have ADC values, overlapping the malignant group; one is myositis ossifican (1.180 x $10^{-3}mm^2/s$) and another is schwannoma (1.131 x $10^{-3}mm^2/s$). However by a combination with the conventional MRI, these tumors are quite fit for diagnosis.

The limitations in presented study: the first, small size of the population and lack of variety of tumor types, which may not represent the whole population. The second, there is only one myxoid containing-tumor in each group of benign and malignant tumors causing nonequivalent population between the comparison groups. Therefore it seems the myxoid matrix not to affect the mean ADC values in both benign and malignant tumors. Future studies should be conducted in a large population and various tumor types especially the myxoid tumors that may affect the ADC values. The other causes may affect the ADC values should be investigated.

Conclusion

The mean ADC value of malignant soft tissue tumors was significantly lower than that of benign soft tissue tumors. A threshold ADC value of 1.316 x $10^{-3}mm^2/s$. is recommended for differentiating benign and malignant musculoskeletal soft tissue tumors.

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