Role of Conventional and Diffusion Weighted MRI in the Evaluation of Pediatric Musculoskeletal Tumors

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Abstract

Background: Soft tissue masses usually represent a diagnostic dilemma, since there is a large and heterogeneous group of lesions than can manifest as such in children, including both neoplastic and non neoplastic lesions.

Purpose: To evaluate the signal characteristics of conventional and diffusion weighted MRI sequences of musculoskeletal tumors in pediatric patients and their corresponding ADC measurements and their ability to differentiate between benign and malignant lesions and their response to therapy.

Material and Methods: From July 2012 to March 2014 twenty three children with soft tissue tumors 15 malignant (8 denovo and 7 cases received treatment) and 8 benign were assessed by conventional and diffusion MR images. Diffusion was carried out by single shot SE-EPI sequence using 0, 500 and 1000. ADC was automatically generated on the operating console.

Results: The mean ADC of benign tumors was 1.4 X 10⁻³ mm²/s. While that of malignant tumors was 0.9 X 10⁻³ mm²/s, p value < 0.001. However overlap still exists. ROC analysis produced a cut off value >1.1 X 10⁻³ mm²/s has 100% specificity and 87.5% sensitivity. The mean ADC of tumors that had received treatment was 1.8 X 10⁻³ mm²/s which was proved to be significantly different from that of de novo malignant tumors.

Conclusion: DWI and ADC can assist in evaluation of musculoskeletal tumors in conjunction with conventional sequences but do not have high accuracy. They may be used as markers to assess tumor response. Further dedicated study of a bigger sample is recommended to confirm our results, especially concerning follow-up of tumors and the use of perfusion insensitive ADC.

Key Words: Magnetic resonance imaging (MRI) – Musculoskeletal tumors – Diffusion weighted imaging (DWI) – ADC value.

Introduction

SOFT tissue masses usually represent a diagnostic dilemma, since there is a large and heterogeneous group of lesions than can manifest as such in children, including both neoplastic and non neoplastic lesions.

Although in some cases the clinical history and physical examination findings will be sufficient to determine the cause, in a large number of cases further evaluation with imaging is required-first to establish whether the palpable lump represents a true mass; second to help make a more specific etiologic diagnosis; and finally, to assess the extent of the lesion [1].

With conventional MR imaging sometimes it is difficult to differentiate benign from malignant soft tissue lesions as most soft-tissue masses have been considered to lack characteristic features that would allow differentiation between benign and malignant lesions [2].

It has been noted that diffusion-weighted MR imaging play a role in this differentiation by showing significantly increased true diffusion in benign masses compared with malignant lesions [3].

MRI have been used in the evaluation of therapeutic effects on soft tissue tumor, however assessment is commonly achieved by comparing tumor size and contrast enhancement before and after completion of therapeutic intervention.

It would be advantageous to evaluate early response to a particular treatment at the early stage of therapeutic intervention, thus enabling unnece-
sary treatment to be avoided and optimizing individual management. Detection of early changes within the tumor during treatment is of great value because intra-tumoral changes such as vascular shutdown and consequent increase in the necrotic tumor fraction can precede morphological changes [4].

DWI can be used to monitor the reduction in both perfusion and diffusion changes in the extent of necrosis following therapy. DWI has several potential advantages over other methods: It is non-invasive, does not use ionizing radiation and requires no administration of contrast medium. It has also a shorter examination time than other techniques with an easily reproducible technique that enables close follow-up of cancer treatment [4].

Patients and Methods

The setting was the Radiology Department in National Cancer Institute where cases are referred from pediatric oncology clinic for evaluation of palpable soft tissue mass. From July 2012 to March 2014 we prospectively included 23 patients (11 males and 12 females), their ages range from (6 months to 18 years).

Inclusion criteria:
- Pediatric age group (1 day to 18 years).
- Patients with clinical findings suggestive of a soft tissue mass or already diagnosed and under follow-up.
- Soft tissue masses has solid portions suitable for Region of Interest (ROI) analysis.

Exclusion criteria:
- Patient over 18 years.
- Patient who has one or more of the absolute or relative MRI contraindications i.e. patient with one or more of the following:
  - Electronically, magnetically and mechanically activated implants.
  - Metallic splinters in the eye.
  - Ferromagnetic haemostatic clips in the Central Nervous System (CNS).
  - Cochlear implants.
  - Insulin pumps and nerve stimulators.
  - Lead wires or similar wires.
  - Prosthetic heart valves (in high fields, if dehiscence is suspected).
  - Haemostatic clips (body).

Patient preparation:
- For the patient needed anesthesia, fasting for four hours before the scan is acquired.

Technique:
1- Conventional Contrast Enhanced MRI:
All patients were evaluated by CEMRI technique using 1.5 tesla superconducting MR imager (MRI Philips, Netherlands).

All the cases were examined in supine position with the most optimal surface coil to accommodate each lesion either body coil or phase arrayed torso coil (16 channels) using the following sequences:
- Axial and coronal T₁ WI (500/15ms) TR/TE spin echo.
- Axial and coronal T₂ WI (4540/110ms) TR/TE spin echo.
- Coronal STIR WI (4500/20ms) TR/TE spin echo.
- 5mm thickness and 256 X 256 matrix size.
- After intravenous administration of gadolinium-DTPA (0.3mg/kg), contrast enhanced axial, sagittal and coronal T₁ WIs are obtained.

The lesions were evaluated in CEMRI commenting on:
- The number of the lesions.
- Signal behavior.
- Heterogeneity (presence of intratumoral hemorrhagic or necrotic components).
- Enhancement degree and pattern.

2- MR diffusion imaging:
Axial DW imaging was performed by using a single shot T₂-weighted echo planar spin echo sequence with the following parameters 1300/100, diffusion gradient encoding in three (x, y, z) orthogonal directions; b-values of 0, 500, 1000s/mm²; field of view 25-40cm; matrix size 128 X 128; slice thickness 4-7mm; section gap 0mm and one signal acquired. At each b value, x, y and z single-direction DW images and a baseline image (b-0 s/mm²) were acquired; combined ([x-y-z]/3) DW imaging was calculated and performed automatically by the MR instrument.
10 sections with 50 images were obtained at each b-value in 13 seconds (10 images of combined [(x-y-z)/3] DW imaging, 10 images of the baseline image and 10 images each of the x-, y- and z-direction DW images). Therefore each DW imaging study yielded a total of 200 images.

All DW imaging data were transferred to a computer workstation for determination of the signal intensity and ADC. Each image used for the creation of the ADC map was obtained with one signal acquired.

The ADC was measured by manually placing regions of interest in tumor regions on the ADC map. In patients with contrast enhanced tumors, regions of interest were placed at the site of enhanced lesions on contrast enhanced T\(_1\)-weighted MR images. In patients with weakly enhancing or non enhancing tumors, regions of interest were chosen after indentifying the tumor area as an area of hyperintensity on STIR images.

Necrotic components were differentiated on contrast enhanced T\(_1\) weighted images as the interior of enhanced lesions.

Hemorrhagic lesions were differentiated on unenhanced T\(_1\)-weighted MR images as areas of hyperintensity.

We compared the ADC maps and other MR images carefully and placed the regions of interest only in the solid tumor components. We excluded cystic, necrotic and hemorrhagic tumor areas. We chose regions of interest as central as possible within the tumor area at random and averaged the ADC of each tumor.

Histopathological correlation:

All cases were biopsied and sent for histopathological assessment. In the case of hemangioma clinical and radiological assessment was sufficient.

Statistical analysis:

Analysis of data was done using SPSS (statistical program for social science) as follows.

Description of quantitative variables as mean, median and range.

Description of qualitative variables as number and percentage.

Chi-square test was used to compare qualitative variables.

Fisher exact probability test was used instead of chi-square test when the study group was <5.

Correlation coefficient test (r-test) was used to rank different variables against each other either positively or inversely.

Sensitivity representing the ability of the test to detect +ve cases, it was calculated by the following equation \{true +ve/true +ve + false –ve\}.

Specificity representing the ability of the test to exclude –ve cases, it was calculated by the following equation \{true –ve/true –ve + false +ve\}.

\*p\*-value >0.05 was considered insignificant.

\*p\*-value <0.05 was considered significant.

\*p\*-value <0.01 was considered highly significant.

Results

Twenty three patients were included in this study 11 males and 12 females. Their ages ranged from 6 months to 18 years.

The tumors included in this study were 15 cases with malignant tumors (8 cases are denovo and 7 cases received treatment) and 8 cases with benign tumors.

Table (1): Pathology and ADC of denovo malignant tumors.

<table>
<thead>
<tr>
<th>Histopathological diagnosis</th>
<th>ADC (10^{-3}) mm(^2)/s</th>
<th>ADC map</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabdomyosarcoma</td>
<td>1.1</td>
<td>Hypointense</td>
</tr>
<tr>
<td>Rabdomyosarcoma</td>
<td>1.1</td>
<td>Hypointense</td>
</tr>
<tr>
<td>Rabdomyosarcoma</td>
<td>0.8</td>
<td>Hypointense</td>
</tr>
<tr>
<td>Rabdomyosarcoma</td>
<td>0.8</td>
<td>Hypointense</td>
</tr>
<tr>
<td>Rabdomyosarcoma</td>
<td>0.6</td>
<td>Hypointense</td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td>0.9</td>
<td>Hypointense</td>
</tr>
<tr>
<td>NHL</td>
<td>0.4</td>
<td>Hypointense</td>
</tr>
<tr>
<td>Pelvic germ cell tumor</td>
<td>1.1</td>
<td>Hypointense</td>
</tr>
</tbody>
</table>

From the previous table we notice that most of the malignant tumors are below 1 \(10^{-3}\) mm\(^2\)/s. The mean ADC of the 8 tumors is 0.9 \(10^{-3}\) mm\(^2\)/s. Three cases showed ADC value 1.1 \(10^{-3}\) mm\(^2\)/s.
Fig. (1): 6 years old female with rabdomyosarcoma in the left forearm. A well defined soft tissue mass is noted occupying the whole medial aspect of the left forearm displaying isointense T₁ (A) And high T₂/STIR signal (B,C) With intense heterogeneous enhancement in the post contrast study (D). The calculated mean ADC value of the lesion is 0.8 X 10⁻³ mm²/s (E).

Fig. (2): 15 years old female with recurrent synovial sarcoma. A soft tissue mass is noted at the root of the neck and left side of the anterior chest wall. It is seen eliciting isointense T₁ (A) And high T₂/STIR signal (B,C) With intense enhancement in the post contrast study (D). The calculated mean ADC value of the lesion is 0.9 X 10⁻³ mm²/s (E).
Table (2): Pathology and ADC for malignant tumors that received treatment.

<table>
<thead>
<tr>
<th>Histopathological diagnosis</th>
<th>ADC ( (X 10^{-3} \text{mm}^2/\text{s}) )</th>
<th>ADC map</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabdomyosarcoma</td>
<td>1.5</td>
<td>Hyperintense</td>
</tr>
<tr>
<td>Rabdomyosarcoma</td>
<td>2.2</td>
<td>Hyperintense</td>
</tr>
<tr>
<td>Rabdomyosarcoma</td>
<td>1.5</td>
<td>Hyperintense</td>
</tr>
<tr>
<td>Rabdomyosarcoma</td>
<td>1.6</td>
<td>Hyperintense</td>
</tr>
<tr>
<td>Rabdomyosarcoma</td>
<td>2.8</td>
<td>Hyperintense</td>
</tr>
<tr>
<td>Soft tissue sarcoma</td>
<td>1.6</td>
<td>Hyperintense</td>
</tr>
<tr>
<td>Myxoid tumor</td>
<td>1.6</td>
<td>Hyperintense</td>
</tr>
</tbody>
</table>

From the previous table we conclude that almost all the tumors have ADC values exceeding \(1 \times 10^{-3} \text{mm}^2/\text{s}\). The different figures are related to the amount of necrosis in each tumor which varies according to the number of CTH/RTH sessions received and the response of each individual to therapy. Their mean ADC is \(1.8 \times 10^{-3} \text{mm}^2/\text{s}\).

Table (3): Pathology and ADC for benign tumors.

<table>
<thead>
<tr>
<th>Histopathological diagnosis</th>
<th>ADC ( (X 10^{-3} \text{mm}^2/\text{s}) )</th>
<th>ADC map</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibromatosis</td>
<td>1.1</td>
<td>Mixed</td>
</tr>
<tr>
<td>Fibromatosis</td>
<td>1.4</td>
<td>Hyperintense</td>
</tr>
<tr>
<td>Fibromatosis</td>
<td>1.3</td>
<td>Hyperintense</td>
</tr>
<tr>
<td>Fibromatosis</td>
<td>1.4</td>
<td>Hyperintense</td>
</tr>
<tr>
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<td>1.4</td>
<td>Hyperintense</td>
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</tr>
<tr>
<td>Fibromatosis</td>
<td>1.4</td>
<td>Hyperintense</td>
</tr>
<tr>
<td>Hemangioma</td>
<td>1.8</td>
<td>Hyperintense</td>
</tr>
</tbody>
</table>

From the previous table we notice that all benign tumors show ADC that exceeds \(1 \times 10^{-3} \text{mm}^2/\text{s}\). The mean ADC of benign tumors is \(1.4 \times 10^{-3} \text{mm}^2/\text{s}\).
Fig. (4): 6 years old male with fibromatosis in the right thigh. A huge well defined oval shaped lesion is noted at the posteromedial aspect of the right thigh displaying mixed isointense and low T1 signal (A), mixed high and low T2/STIR signal (B, C) With intense heterogeneous enhancement in the post contrast study (D). The calculated mean ADC value of the lesion is $1.4 \times 10^{-3}$ mm$^2$/s (E).

### Table (4): Comparison between untreated malignant tumor and benign tumor regarding ADC value.

<table>
<thead>
<tr>
<th></th>
<th>Untreated malignant tumor</th>
<th>Untreated benign tumor</th>
<th>Independent t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean $\pm$ SD</td>
<td>Range</td>
<td>Mean $\pm$ SD</td>
</tr>
<tr>
<td>ADC</td>
<td>0.85$\pm$0.26</td>
<td>0.4-1.1</td>
<td>1.44$\pm$0.16</td>
</tr>
</tbody>
</table>

The above table showed that there is a significant difference between the ADC of benign tumors and de novo malignant tumors with a $p$-value <0.001.

Fig. (5): Difference between denovo malignant and benign tumors regarding the ADC value.

Fig. (6): ROC curve of ADC values of benign and de novo malignant tumors.

<table>
<thead>
<tr>
<th>Cut off point</th>
<th>AUC</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>$+PV$</th>
<th>$-PV$</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1.1</td>
<td>100.0</td>
<td>87.50</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
</tbody>
</table>
Discussion

Soft-tissue masses usually represent a diagnostic dilemma, since there is a large and heterogeneous group of lesions that can manifest as such in children, including both neoplastic and non neoplastic lesions.

Although in some cases the clinical history and physical examination findings will be sufficient to determine the cause, in a large number of cases further evaluation with imaging is required—first to establish whether the palpable lump represents a true mass; second to help make a more specific etiologic diagnosis; and finally, to assess the extent of the lesion [1].

With conventional MR imaging sometimes it is difficult to differentiate benign from malignant soft tissue lesions as most soft-tissue masses have been considered to lack characteristic features that would allow differentiation between benign and malignant lesions [2].

It has been noted that diffusion-weighted MR imaging play a role in this differentiation by showing significantly increased true diffusion in benign masses compared with malignant lesions [3].

It would be advantageous to evaluate early response to a particular treatment at the early stage of therapeutic intervention, thus enabling unnecessary treatment to be avoided and optimizing individual management. Detection of early changes within the tumor during treatment is of great value because intra-tumoral changes such as vascular shutdown and consequent increase in the necrotic tumor fraction can precede morphological changes. DWI can be used to monitor the reduction in both perfusion and diffusion changes in the extent of necrosis following therapy. DWI has several potential advantages over other methods: It is non invasive, does not use ionizing radiation and requires no administration of contrast medium. It has also a shorter examination time than other techniques with an easily reproducible technique that enables close follow up of cancer treatment [4].

The potential value of diffusion in oncological imaging lies in the fact that it provides functional tissue information which can be combined with anatomical MR images to improve the specificity of lesion characterization. Certain tumor entities show typical features on multimodal diagnostic imaging in terms of localization, patterns of growth and signal characteristics. In many cases, however surgical biopsy is so far the only way to establish a diagnosis with confidence [5].

The aim of this study was to assess the role of diffusion weighted MRI in differentiation between benign and malignant soft tissue masses, to guide invasive diagnostic procedures and limit the proportion of patients with benign disease who undergo biopsy and in the follow-up of tumors. Also to assess its role in monitoring the response of the malignant masses to treatment. In this study the tumors are assessed qualitatively and quantitatively by the measurement of ADC values.

Because of its high contrast-to-noise ratio, lesions with restricted diffusion are usually easily recognized on diffusion weighted images [6]. This was shown in this study where all the lesions stood out, however the anatomy could not be well delineated. This is explained by the relatively low spatial resolution of the DWIs compared with conventional T1 or T2 weighted MR images [7].

Park et al., [8] argued that small lesions and those with a degree of diffusivity similar to surrounding normal tissue may not be distinguished on DWIs and ADC.

Neubauer et al., [9] speculated that partial volume effects may cause false low ADC measurements in small target lesions. Most recent recommendations of Padhani et al., [4] suggest a cut off value of 2 cm in minimum diameter of the lesion. This was applied in this study where all the lesions are more than 2 cm in diameter.

One of the pitfalls of visual assessment of DWI is that an area with a very long T2 relaxation time may remain high signal and be mistaken for restricted diffusion [6]. This false impression was corrected in the ADC image. Thus ADC proved to be much more accurate in judging lesions.

If ADC measurement is performed to differentiate tissues by their water diffusion characteristics exclusively, applying high maximum b-values may be preferable [7]. In this study b 1000 lead to adequate background suppression and damping of signal given by cystic necrosis in malignant lesions. This is also supported by Tang et al., [10] who described low b values to give high quality images with good SNR but it becomes highly affected by T2 shine through effect and perfusion leading to misjudgment of true diffusion in lesions.

In this study the highest observed ADC in malignant tumors was 1.1 X 10⁻³ mm²/s while the lowest ADC was 0.4 X 10⁻³ mm²/s. The mean ADC
value for malignant tumors was $0.9 \times 10^{-3} \text{mm}^2/\text{s}$.

This variation was explained by Humphries et al., 2007 who claimed it due to differences in tumor cellularity, extracellular stromal density and tortuosity. Also cellular size and cytoplasmic nuclear ratio plays a role [11]. Neubauer et al., (2012) produced very similar results to this study. In their work the lowest ADC was $0.4 \times 10^{-3} \text{mm}^2/\text{s}$ and the mean ADC value was $0.78 \pm 0.45 \times 10^{-3} \text{mm}^2/\text{s}$ [9].

Van Rijswijk et al., [3] argued that the most two important components of signal attenuation on diffusion weighted MR images in soft tissue tumors are diffusion of water molecules in the extracellular space and perfusion. Perfusion fractions of malignant tumors tend to be higher than that of the benign masses [12]. Therefore, perfusion contributes more to ADC of malignant tumors than it does in benign lesions. By excluding the perfusion effects on the ADC value which was more prominent in the malignant tumors, they calculated the true diffusion coefficient. A significant difference of the mean true diffusion coefficient of benign and malignant soft tissue tumors was then noted. The true diffusion coefficient may play an important role in improved characterization of musculoskeletal tumors and improved evaluation of tumor response to therapy [3].

In this study the mean ADC value for malignant tumors was $0.9 \times 10^{-3} \text{mm}^2/\text{s}$ which was expected because most malignant tumors in the study had increased cellular density and decreased extracellular matrix volume which impede free motion of water molecules [6]. Three cases showed ADC value of $1.1 \times 10^{-3} \text{mm}^2/\text{s}$. This is agreed with Humphries et al., [11] who stated that ADC values for pelvic rhabdomyosarcoma was $1 \times 10^{-3} \text{mm}^2/\text{s}$.

In this study benign tumors had a mean ADC of $1.4 \times 10^{-3} \text{mm}^2/\text{s}$ which proved significantly different from their malignant counterparts. The lowest ADC was $1.1 \times 10^{-3} \text{mm}^2/\text{s}$ and the highest ADC was $1.8 \times 10^{-3} \text{mm}^2/\text{s}$.

Nagata et al., [9] and Neubauer et al., [13] showed that there was significant difference between benign and malignant soft tissue tumors. We found that there is a statistically significant difference between both entities however it is not clinically significant due to overlap of some tumors such as some cases of fibromatosis and rhabdomyosarcoma which may not have affected our figures due to their small numbers in this study.

Based on ROC analysis in this study we obtained a cut off value of $>1.1 \times 10^{-3} \text{mm}^2/\text{s}$ with 100% specificity and 87.5% sensitivity and where there is highly significant difference between benign and malignant soft tissue tumors ($p<0.001$). This surpassed the results of Nagata et al., [9] who estimated an ADC cut off value threshold greater than $1.35 \times 10^{-3} \text{mm}^2/\text{s}$ with a 76.7% specificity and 76.3% sensitivity for differentiating benign from malignant lesions and Neuberger et al., [13] who estimated a cut off value of $\leq 1.03 \times 10^{-3} \text{mm}^2/\text{s}$ with 91% specificity and 90% sensitivity.

Tumors that received treatment (CTH or RTH) showed a mean ADC value of $1.8 \times 10^{-3} \text{mm}^2/\text{s}$ which was significantly higher than that of de novo malignant tumors ($0.9 \times 10^{-3} \text{mm}^2/\text{s}$).

In this study the technique used single shot SE-EPI showed adequate image quality, SNR and short acquisition time. It took 3 minutes and thus was technically feasible. Eddy currents, ghosting and distortion artifacts were reduced in this study by using half scan (half echo) and parallel imaging (SESE).

One of the challenges that must be faced to enable widespread adoption of ADC measurement in clinical practice is stabilization of study methods and reporting. Comparison of the results of this study with those of others was sometimes confusing due to differences in imaging sequences and differences in b-values.

The development of organ specific guidelines for DWI acquisition and ADC measurement and checklists for reporting of results may facilitate comparison of study results and contribute to the implementation of ADC measurement for tumor characterization in the clinical setting [7].

Limitations in this study were the small size of the random sample chosen and the lack of some of the soft tissue tumor pathologies which make it difficult to generalize the results of this study on the whole population.

Conclusion:

DWI and ADC can assist in evaluation of soft tissue tumors in conjunction with conventional sequences but do not have high accuracy. They may be used as markers to assess tumor response to treatment. Further dedicated study done on a bigger sample is recommended to confirm our results, especially concerning follow-up of tumors and the use of perfusion insensitive ADC.
References


