The role of diffusion weighted sequences in evaluation the musculoskeletal tumors in pediatrics age group.

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Aims and objectives

Over the past two decades MRI has proven to be a valuable diagnostic tool in oncology. However, using conventional MRI sequences, difficulty in differentiating benign from malignant lesions may arise when they share certain morphologic and contrast enhancement characteristics. In these cases DWI might be of value in tumor assessment, as it has the ability to provide tissue contrast based on molecular diffusion (Vermoolen et al., 2012).

However, few studies have been performed on utility of diffusion sequences and ADC in the musculoskeletal system, especially in pediatrics with sometimes conflicting results, making its role less well understood.

Our aim was to evaluate the signal characteristics of DWIs of musculoskeletal tumors in pediatrics and their corresponding ADC values and assess their ability to differentiate between benign and malignant lesions and maybe in the future limit the proportion of patients with benign disease who undergo biopsy.

Also to aid in the follow up of tumors.
Methods and materials

Patients

From December 2012 to March 2013 we prospectively included 27 children with clinical/radiological suspicion of a bone/soft tissue lesion, or already diagnosed and under follow up. The setting was the radiology department in National Cancer Institute. 5 patients were imaged in Children's Cancer Hospital.

Exclusion criteria were;

- Cases with negative follow up (clear operative bed, fat necrosis... etc).
- Cases with lesions having a diameter less than 2 cm.
- Cases with metal prosthesis due to marked artifact.

MRI Imaging protocol

Imaging was performed on a 1.5T superconducting MR system (Achieva XR, MRI Philips, Netherlands) with a 33-66mT/m maximum gradient capability using the most optimal surface coil to accommodate each lesion either body coil or phase arrayed torso coil (16 channels). §§The MR imaging protocol included the conventional TI, T2, STIR and diffusion weighted echoplanar imaging (EPI) and contrast enhanced T1W images.

DWIs were obtained before contrast medium injection. They were acquired in the axial plane by combining a single shot spin-echo EPI sequence and additional motion probing gradient (MPG) pulses. §§ Fat suppression was added to DW EPI. The b values used in this study were 0, 50, 400, 800s/mm2.

Imaging performed in Children's Cancer Hospital was also done on a 1.5T superconducting MR system (Magneto vision, Siemens Erlangen, Germany) with a 25mT/m maximum gradient capability. Almost the same parameters were used in different pulse sequences. The b values included were 50, 400 and 800s/mm2.

Quantitative Image Analysis
The ADC and exponential ADC images were automatically generated on the operating console using. A ROI with a diameter not less than 0.5cm and not exceeding 1.5cm was placed on the solid, enhancing and most restricted region whenever possible.

**Histopathological Correlation**

14 cases were biopsied in the radiology department and sent for histopathological assessment.

**Statistical Analysis**

To compare the mean ADC between the malignant and benign tumors and effect of therapy student t-test was used.

<table>
<thead>
<tr>
<th></th>
<th>FSE T1W</th>
<th>FSE T2W</th>
<th>FSE STIR</th>
<th>DW EPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echo time(ms)</td>
<td>15</td>
<td>110</td>
<td>20</td>
<td>100</td>
</tr>
<tr>
<td>Repitition time(ms)</td>
<td>500</td>
<td>3000-5000</td>
<td>3500-5000</td>
<td>1300</td>
</tr>
<tr>
<td>Echo train length</td>
<td>4</td>
<td>23</td>
<td>16</td>
<td>-</td>
</tr>
<tr>
<td>Inversion time(ms)</td>
<td>-</td>
<td>-</td>
<td>160</td>
<td>-</td>
</tr>
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<td>No of sections</td>
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<td>25</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Section thickness(mm)</td>
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<td>4-7</td>
</tr>
<tr>
<td>Distance factor(gap)</td>
<td>0.7</td>
<td>0.7</td>
<td>0.7</td>
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</tr>
<tr>
<td>Field of view(mm)</td>
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<td>250-400</td>
<td>250-400</td>
<td>250-400</td>
</tr>
<tr>
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<td>300x256</td>
<td>300x256</td>
<td>256x256</td>
<td>128x129</td>
</tr>
<tr>
<td>Number of signal average NSA</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Bandwidth(Hz/pixel)</td>
<td>31</td>
<td>31</td>
<td>31</td>
<td>41</td>
</tr>
</tbody>
</table>

**Table 1. MRI parameters**
Results

Thirty two patients were included in this study, 13 females and 19 males.

The mean ADC of the 10 newly diagnosed malignant tumors was $0.97 \times 10^{-3}$ mm$^2$/s $\pm 0.6$. After excluding the myxolipomatous tumor it lowered to $0.8 \times 10^{-3}$ mm$^2$/s $\pm 0.28$.

<table>
<thead>
<tr>
<th>Case no</th>
<th>Sex</th>
<th>Age</th>
<th>Site</th>
<th>Pathology</th>
<th>Diffusion signal</th>
<th>ADC in most restricted/solid area ($\times 10^{-3}$ mm$^2$/s)</th>
<th>ADC without lipomatous tumor ($\times 10^{-3}$ mm$^2$/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Female</td>
<td>9</td>
<td>Left lower leg</td>
<td>Osteosarcoma</td>
<td>Mixed</td>
<td>0.75</td>
<td>0.75</td>
</tr>
<tr>
<td>2</td>
<td>Female</td>
<td>15</td>
<td>Left thigh</td>
<td>Osteosarcoma</td>
<td>Mixed</td>
<td>1.37</td>
<td>1.37</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>13</td>
<td>Left thigh</td>
<td>Osteosarcoma</td>
<td>Low</td>
<td>0.97</td>
<td>0.97</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>13</td>
<td>Right lower leg</td>
<td>Osteosarcoma</td>
<td>Mixed</td>
<td>0.84</td>
<td>0.84</td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>18</td>
<td>Left thigh</td>
<td>Myxoliposarcoma</td>
<td>High</td>
<td>2.52</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Male</td>
<td>2</td>
<td>Right thigh</td>
<td>RMS</td>
<td>Mixed</td>
<td>0.77</td>
<td>0.77</td>
</tr>
<tr>
<td>7</td>
<td>Male</td>
<td>18</td>
<td>Pelvis</td>
<td>Ewing sarcoma</td>
<td>High</td>
<td>0.72</td>
<td>0.72</td>
</tr>
<tr>
<td>8</td>
<td>Male</td>
<td>11</td>
<td>Right forearm</td>
<td>Ewing sarcoma</td>
<td>High</td>
<td>0.55</td>
<td>0.55</td>
</tr>
<tr>
<td>9</td>
<td>Female</td>
<td>16</td>
<td>Left thigh</td>
<td>Ewing sarcoma</td>
<td>Mixed</td>
<td>0.45</td>
<td>0.45</td>
</tr>
<tr>
<td>10</td>
<td>Male</td>
<td>18</td>
<td>Right scapula</td>
<td>Ewing sarcoma</td>
<td>High</td>
<td>0.75</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Table 2. Diffusion signal and ADC values of malignant tumors before taking treatment.
The mean ADC of the 14 tumors under treatment was $1.86 \times 10^{-3}$ mm$^2$/s $\pm 0.43$. This proved to be significantly different from the mean ADC value of malignant tumors that were not yet treated showing a $P$ value $=0.001$.

<table>
<thead>
<tr>
<th>Case no</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Site</th>
<th>Pathology</th>
<th>Diffusion signal</th>
<th>ADC in most restricted/solid area ($\times 10^{-3}$ mm$^2$/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>13</td>
<td>Right lower leg</td>
<td>OS</td>
<td>Mixed</td>
<td>2.3</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>18</td>
<td>Left thigh</td>
<td>OS</td>
<td>Low</td>
<td>2.43</td>
</tr>
<tr>
<td>3</td>
<td>Female</td>
<td>16</td>
<td>Left thigh</td>
<td>OS</td>
<td>Low</td>
<td>2.03</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>15</td>
<td>Left thigh</td>
<td>OS</td>
<td>Low</td>
<td>1.85</td>
</tr>
<tr>
<td>5</td>
<td>Female</td>
<td>11</td>
<td>Right thigh</td>
<td>OS</td>
<td>Low</td>
<td>1.88</td>
</tr>
<tr>
<td>6</td>
<td>Female</td>
<td>18</td>
<td>Left thigh</td>
<td>OS</td>
<td>Low</td>
<td>2.31</td>
</tr>
<tr>
<td>7</td>
<td>Male</td>
<td>2</td>
<td>Left thigh</td>
<td>RMS</td>
<td>High</td>
<td>0.99</td>
</tr>
<tr>
<td>8</td>
<td>Male</td>
<td>8</td>
<td>Right pelvis</td>
<td>RMS</td>
<td>Mixed</td>
<td>1.54</td>
</tr>
<tr>
<td>9</td>
<td>Female</td>
<td>13</td>
<td>Left thigh</td>
<td>ES</td>
<td>Low</td>
<td>2.16</td>
</tr>
<tr>
<td>10</td>
<td>Female</td>
<td>6</td>
<td>Right lower leg</td>
<td>ES</td>
<td>Mixed</td>
<td>1.85</td>
</tr>
<tr>
<td>11</td>
<td>Male</td>
<td>15</td>
<td>Left thigh</td>
<td>Soft Tissue Sarcoma</td>
<td>Low</td>
<td>2.21</td>
</tr>
<tr>
<td>12</td>
<td>Female</td>
<td>18</td>
<td>Right axilla</td>
<td>Fibromatosis</td>
<td>Mixed</td>
<td>1.65</td>
</tr>
<tr>
<td>13</td>
<td>Male</td>
<td>18</td>
<td>Right arm</td>
<td>Fibromatosis</td>
<td>Low</td>
<td>1.73</td>
</tr>
<tr>
<td>14</td>
<td>Male</td>
<td>17</td>
<td>Right thigh</td>
<td>Synovial Sarcoma</td>
<td>High</td>
<td>1.14</td>
</tr>
</tbody>
</table>

Table 3. Diffusion signal and ADC values in tumors that received CTH/RTH.
The mean ADC of the 8 benign tumors was $1.74 \times 10^3 \text{ mm}^2/\text{s} \pm 0.62$. There was a significant difference between the latter and the mean ADC value of de novo malignant tumors with a $P$ value=0.014.

<table>
<thead>
<tr>
<th>Case no</th>
<th>Sex</th>
<th>Age (yrs)</th>
<th>Site</th>
<th>Pathology</th>
<th>Diffusion signal</th>
<th>ADC in most restricted/solid part ($\times 10^3 \text{ mm}^2/\text{s}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Female</td>
<td>6</td>
<td>Left thigh</td>
<td>Haemangiom</td>
<td>Low</td>
<td>1.82</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>10</td>
<td>Left arm</td>
<td>Haemangiom</td>
<td>Low</td>
<td>1.27</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Osteochondroma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Female</td>
<td>14</td>
<td>Right thigh</td>
<td>Cartilage cap</td>
<td>High</td>
<td>2.21</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low</td>
<td>1.58</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>15</td>
<td>Left arm</td>
<td>Osteochondroma</td>
<td>Low</td>
<td>1.4</td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>6</td>
<td>Left thigh</td>
<td>Bone cyst</td>
<td>Mixed</td>
<td>2.67</td>
</tr>
<tr>
<td>6</td>
<td>Female</td>
<td>18</td>
<td>Left thigh</td>
<td>Non ossifying fibroma</td>
<td>Low</td>
<td>2.37</td>
</tr>
<tr>
<td>7</td>
<td>Male</td>
<td>18</td>
<td>Left thigh</td>
<td>Neuroma</td>
<td>High</td>
<td>1.74</td>
</tr>
<tr>
<td>8</td>
<td>Female</td>
<td>13</td>
<td>Right hand</td>
<td>Fibromatosis</td>
<td>Mixed</td>
<td>0.62</td>
</tr>
</tbody>
</table>

Table 4. Diffusion signal and ADC values of benign tumors.

ROC analysis produced cut off values 1.1 with a 89% specificity and 80% sensitivity and a cut off value 1.4 with a 78% specificity and 90% sensitivity. They were not ideal and cannot be used as a reliable independent diagnostic test. The mean ADC of tumors that had received treatment was $1.86 \times 10^3 \text{ mm}^2/\text{s} \pm 0.43$ which proved to be significantly different from that of de novo malignant tumors, $P$ value= 0.001.
Fig. 1: Pie chart demonstrating gender distribution.

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Fig. 2: Pie chart demonstrating the different tumor pathologies.

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**Fig. 3:** ROC curve of ADC values of benign and de novo malignant tumors.

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Fig. 4: Case 1. An 18 year old male diagnosed with Ewing sarcoma of the right thigh. Metastatic deposits are seen in the pelvic bones and proximal femora.

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Fig. 5: Case 1. The lesions are bright in DWI and isotense in ADC map. They measure 0.72.

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Fig. 6: Case 2. An 18 year old male having a myxoliposarcoma of the left thigh. The mass has hyperintense streaks in T1WI denoting its fatty component and has a bright T2 signal denoting its myxoid content. It has a bright signal in DWI which turns dark in EADC denoting its facilitated diffusion. ADC measures 2.5.

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**Fig. 7:** Case 3. A 16 year old female diagnosed with osteosarcoma of the left femur and receiving treatment. A soft tissue mass is seen surrounding the entire of the left femur.

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**Fig. 8:** Case 3. It shows mixed signal in DWI. ADC measures 2. The relatively high ADC could be attributed to post therapeutic changes.

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**Fig. 9:** Case 4. A 15 year old female diagnosed with high grade osteosarcoma in her left femur (telangiectatic osteosarcoma). The mass shows haemorrhagic areas in T1WI and bright cystic areas in T2WI.

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Fig. 10: Case 4. DWIs show a high signal which increases with increasing the B value, proving its restriction. EADC is heterogenous where brighter areas represent more restriction. ADC measures 1.5.
Fig. 11: Case 4. The ADC value decreased when we eliminated the effect of tumor vascularity by applying high B values. This is called PIADC (perfusion insensitive apparent diffusion coefficient) or TDC (true diffusion coefficient).

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Fig. 12: Case 5. Left knee simple bone cyst in an 18 year old female. The lesion is hypotense in T1WI with a rim enhancement. It is hyperintense in T2WI.

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**Fig. 13:** Case 5. The bright signal of the lesion in DWI diminishes with increase in B value. This is the T2 shine through phenomena which is demolished in EADC. ADC measures 2.4.

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**Fig. 14:** Case 6. Stump neuroma in an 18 year old male following left side above knee amputation. A nodule along the sciatic nerve elicits high diffusion signal. The ADC measures 1.4.

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Fig. 15: Case 7. Fibromatosis in a 13 year old girl. A thenar mass with peripheral enhancement and central breaking down.

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Fig. 16: Case 7. In DWI as we increase the B value the cystic part shows signal attenuation while the solid part becomes brighter. The ADC measures 0.6 by placing the ROI on the solid part.

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Conclusion

We found that there is a statistically significant difference between ADC values of benign and malignant soft tissue and bone tumors, however, caution must be taken because overlap exists in some tumors such as the cases of fibromatosis, myxoliposarcoma and telangiectatic osteosarcoma affecting its clinical application.

Thus DWI can assist in evaluation of musculoskeletal tumors in conjunction with conventional sequences, but cannot be used independently.

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 (Koh & Collins, 2007). In our study all the benign cystic lesions showed a high signal intensity that sometimes persisted with high b values (b800) due to the "T2 shine through" effect simulating more aggressive tumors with true restriction. This false impression was corrected in the exponential and ADC images. Thus EADC & ADC proved to be much more accurate in judging lesions.

In this work the mean ADC value was $1.5 \times 10^{-3}$ mm$^2$/s in a case of aggressive telangiectatic osteosarcoma mimicking that of benign lesions. This can be explained by the cystic component of the osteosarcoma and marked vascularization which facilitate diffusion. Perfusion insensitive ADC was calculated by applying the high b values only(400 and 800) as stated by Padhani et al., 2012 and gave smaller figures ranging from 1 to $1.8 \times 10^{-3}$ mm$^2$/s for ADC which was still high compared to other malignant tumors.

Thus the true diffusion coefficient may play an important role in improved characterization of musculoskeletal tumors and improved evaluation of tumor response to therapy. (Van Rijswijk et al., 2002).

DWI and ADC may be used as markers to assess tumor response.

Limitations in our study were wide spectrum of pathologies, small size of the random sample chosen and the lack of some of the musculoskeletal tumors, which make it difficult to generalize our results on the whole population.
Further dedicated study done on a bigger sample is recommended to confirm our results, especially concerning post-treatment follow up of tumors and the use of perfusion insensitive ADC.
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