ADC-corrected SUV derived from voxel-based SUV-ADC scatter plots in $^{18}$FDG-PET/MR hybrid imaging

Poster No.: C-0875
Congress: ECR 2017
Type: Scientific Exhibit
Authors: R. Kamei, Y. Watanabe, K. Sagiyama, S. Kawanami, S. hong, H. Honda; Fukuoka/JP
Keywords: Image registration, Cancer, Imaging sequences, PET-MR, PET, MR-Diffusion/Perfusion, Molecular imaging, Musculoskeletal soft tissue, Oncology
DOI: 10.1594/ecr2017/C-0875

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Aims and objectives

Background

The combined use of $^{18}$FDG-PET and apparent diffusion coefficient (ADC) has recently been investigated in efforts to improve the diagnostic accuracy of methods relying on SUVmax, SUVpeak, ADCmean, and ADCminimum for the assessment of malignancy, and its usefulness has been reported for some types of tumors [1, 2]. However, these parameters represent only specific areas within the tumor, and the heterogeneity of the whole tumor were not taken into account in the previous studies. Though SUV is a powerful tool in discriminating malignant lesions from their benign counterparts [3, 4], it omits the information on cell density. Therefore, depending solely on SUV may lead to misclassifying malignant lesions as benign when they have sparse distribution of cells.

A hybrid PET/MR system has recently become available, which enables the acquisition of $^{18}$FDG-PET and DWI simultaneously, and precise image coregistration, and could potentially provide direct voxel-by-voxel comparison of glucose metabolism and cell density, represented by SUV and ADC, respectively. We hypothesized that the correction of the SUV using the simultaneously obtained ADC values could facilitate the diagnosis and treatment response evaluation of tumors. We considered soft-tissue tumors as suitable subjects for this method, with their variety in tissue structure and cell population [5, 6].

Objectives

The purpose of this study was to investigate the usefulness of a newly-developed parameter derived from voxel-based SUV-ADC scatter plots in the evaluation of soft-tissue tumor malignancy and treatment effect with a hybrid PET/MR system.
Methods and materials

Subjects

We retrospectively included 35 patients with soft-tissue tumor (25 high-grade and 10 low-grade tumors, classified according to the WHO Classification of Soft Tissue and Bone [6]) who underwent PET/MR examination with the Ingenuity TF PET/MR system (Philips Healthcare, Cleveland, OH) from October 2014 to March 2016. Patient demographics are shown in Fig. 1 on page 5. Follow-up PET/MR imaging after treatment was available for 8 out of 35 cases with malignant lesions, who received either chemotherapy, chemoradiotherapy, or heavy particle radiotherapy.

PET/MR Imaging

The subjects were administered 4.0 MBq/kg of $^{18}$FDG and underwent PET/CT as part of a clinical routine, and then PET/MR imaging was initiated approximately 2 hours after the administration of $^{18}$FDG. Participants underwent PET imaging with the sampling time of 5 minutes per station. Images were reconstructed with $2^3$ mm voxels using 3D ordered subset expectation maximization (3D-OSEM) and time of flight (TOF). Among the obtained images, PET, FST2WI, and DWI were used for the analysis. Parameters for the MR part of the examination are shown in Table 1.

Table 1. Parameters for magnetic resonance sequences

<table>
<thead>
<tr>
<th>Parameter</th>
<th>FST2WI</th>
<th>Zoomed DWI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repetition time (ms)</td>
<td>5000</td>
<td>2500-6000</td>
</tr>
<tr>
<td>Echo time (ms)</td>
<td>75</td>
<td>43-57</td>
</tr>
<tr>
<td>In-plane resolution (mm)</td>
<td>0.29-0.60</td>
<td>0.80-1.60</td>
</tr>
<tr>
<td>Slice thickness (mm)</td>
<td>5 or 6</td>
<td>5 or 6</td>
</tr>
</tbody>
</table>

*obtained through spatially-selective radiofrequency excitation pulses

Image Processing

The construction of a scatter plot from the PET and MR data involved image registration, reslicing, tumor contouring, and resolution matching. The ADCs and SUVs within the whole tumor ROIs were recorded along with the X-Y coordinates in a voxel-wise manner, and scatter plots of SUV/ADC vs. ADC were generated for each tumor. The details of the image processing are presented in Fig. 2 on page 5.
Parameters Derived from the Scatter Plots

Firstly, the regression line was generated from the scatter plot of SUV/ADC vs. ADC. When there was a statistically significant linear corellation in SUV/ADC and ADC, a new parameter named computed-SUV (cSUV) was calculated by using the SUV/ADC value on the regression line where ADC was $0.5 \times 10^{-6}$ mm$^2$/s. A representative plot is shown in Fig. 3 on page 6. The 'conventional' parameters of tumor volume, SUVpeak and ADCminimum were also obtained.

Statistical Analysis

Tumor volume, SUVpeak, ADCminimum, and cSUV were compared between high-grade and low/intermediate-grade groups via Mann-Whitney U-test. Receiver operating characteristic (ROC) analysis was performed, and cutoff values were determined via the Youden index [7] to calculate the sensitivity, specificity, and accuracy of each parameter for differentiating high-grade tumors from low/intermediate-grade tumors. Histopathologic diagnoses were used as the reference standard.

For the 8 cases where follow-up study was available, the difference (%change) of SUVpeak and cSUV between pre- and post-treatment were examined, and was compared with clinical outcomes based on the RECIST 1.1 criteria [8].

All statistical analysis was performed using JMP Pro (version 11.0.0, SAS Institute Inc., Cary, NC) and $P < 0.05$ was considered statistically significant.
Subjects:  M/F = 19/16 (aged 13 - 84)

<table>
<thead>
<tr>
<th>High grade: n=25</th>
<th>Low / intermediate grade: n=10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteosarcoma: 6</td>
<td>Giant cell tumor: 3</td>
</tr>
<tr>
<td>Pleomorphic sarcoma: 4</td>
<td>Schwannoma: 2</td>
</tr>
<tr>
<td>Liposarcoma: 4</td>
<td>Atypical lipomatous tumor: 1</td>
</tr>
<tr>
<td>Myxofibrosarcoma: 3</td>
<td>Osteochondroma: 1</td>
</tr>
<tr>
<td>MPNST: 2</td>
<td>Neurofibroma: 1</td>
</tr>
<tr>
<td>Leiomyosarcoma: 2</td>
<td>Hemangioma: 1</td>
</tr>
<tr>
<td>Synovial sarcoma: 1</td>
<td>Osteomyelitis: 1</td>
</tr>
<tr>
<td>Clear cell sarcoma: 1</td>
<td></td>
</tr>
<tr>
<td>Chondrosarcoma: 1</td>
<td></td>
</tr>
<tr>
<td>Malignant epithelioid tumor: 1</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 1: Description of the 35 cases included in the study sample.
Fig. 2: The procedures for constructing scatter plots from PET and MR data.

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**Fig. 3:** A plot of SUV/ADC vs. ADC. cSUV is defined as the Y-intercept of regression line where ADC shows $0.5 \times 10^{-6}$ mm$^2$/s.

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Results

Comparisons of each measurement between high-grade and low/intermediate-grade tumors are shown in Fig. 4 on page 10 and Fig. 5 on page 10. The mean tumor volumes, SUVpeak, and ADCminimum did not show significant difference depending on the tumor grades.

As indicated by the scatter plots, all lesions showed significant negative correlation between SUV/ADC and ADC values. cSUV tended to be higher in high-grade tumors (5.0 ± 3.2), but the difference was not significant (3.3 ± 3.5, \( P = 0.07 \)).

**ROC Analysis**

The diagnostic performance of each parameter for differentiating high-grade tumors from low or intermediate-grade tumors via ROC analysis is listed in Table 2.

Table 2. ROC analysis of each parameter in tumor grading.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AUC</th>
<th>P</th>
<th>cutoff</th>
<th>sensitivity</th>
<th>specificity</th>
<th>accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conventional Parameters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor volume (mm(^3))</td>
<td>0.62</td>
<td>0.27</td>
<td>&gt;79.6</td>
<td>52.0%</td>
<td>80.0%</td>
<td>60.0%</td>
</tr>
<tr>
<td>SUVpeak</td>
<td>0.71</td>
<td>0.07</td>
<td>&gt;3.29</td>
<td>80.0%</td>
<td>70.0%</td>
<td>77.1%</td>
</tr>
<tr>
<td>ADC minimum (x10(^{-3})mm(^2)/s)</td>
<td>0.51</td>
<td>0.92</td>
<td>&lt;0.61</td>
<td>88.0%</td>
<td>40.0%</td>
<td>62.9%</td>
</tr>
<tr>
<td><strong>New Parameter</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cSUV</td>
<td>0.70</td>
<td>0.08</td>
<td>&gt;2.7</td>
<td>76.0%</td>
<td>70.0%</td>
<td>74.3%</td>
</tr>
</tbody>
</table>

Although cSUV demonstrated an AUC comparable to SUVpeak, statistical significance was not observed. Fig. 6 on page 11 and Fig. 7 on page 12 show representative cases of high-grade and low-grade tumors.

**Evaluation of treatment effect**
Fig. 8 on page 13 shows the pre/post treatment changes in SUVpeak and cSUV. In patients with partial response (n = 5), one case showed an increase in SUVpeak, which could have erroneously led to a diagnosis of progression. On the other hand, all cases demonstrated decrease in cSUV. For patients with stable disease (n = 3), 2 cases showed decrease in SUV after treatment, whereas cSUV showed minimal changes compared with the pre-treatment values. By employing cSUV, the difference between the two groups become more discrete, although limited sample size prohibited further statistical analysis. Fig. 9 on page 14 demonstrates a case of partial responder in which cSUV provided a more precise evaluation of the clinical outcome compared with SUVpeak.
Conventional parameters

<table>
<thead>
<tr>
<th>Tumor volume</th>
<th>SUV peak</th>
<th>ADC minimum</th>
</tr>
</thead>
<tbody>
<tr>
<td>low/intermediate grade</td>
<td>high grade</td>
<td>P = 0.53</td>
</tr>
<tr>
<td>94.5 ± 141.8 vs. 129.6 ± 150.6 cm³</td>
<td>4.2 ± 3.7 vs. 6.3 ± 3.9</td>
<td>P = 0.96</td>
</tr>
<tr>
<td>low/intermediate grade</td>
<td>high grade</td>
<td>0.91 ± 0.38 vs. 0.92 ± 0.34 x 10⁻³ mm²/s</td>
</tr>
</tbody>
</table>

**Fig. 4:** Comparison of 'conventional parameters' between high-grade tumors and low/intermediate grade tumors.

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Fig. 5: Comparison of cSUV between high-grade tumors and low/intermediate grade lesions.

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**Fig. 6**: A case of synovial sarcoma (high-grade) in the knee (20s, female). Both SUVpeak and cSUV were above the cutoff value, suggesting the malignant nature of the lesion.

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Fig. 7: A case of Schwannoma (low-grade) arising from cervical spinal root (70s, male). SUVpeak of 3.3 led to a misclassification of the lesion as malignant, whereas cSUV showed an equivocal value of 2.7.

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Fig. 8: % changes of SUV and cSUV pre- and post-treatment.

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Fig. 9: A case of pleomorphic sarcoma before and after radiotherapy.

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Conclusion

Discussion

In general, a voxel with a low ADC value suggests an increased number of tumor cells. By dividing SUV by ADC, we attempted to incorporate the aspect of cell density into SUV. An arbitrary value of $\text{ADC} = 0.5 \times 10^{-6} \text{ mm}^2/\text{s}$ was selected for computing cSUV. It is a theoretical value of SUVpeak supposing that the tumor cells of interest are highly clustered as seen in lymphomas or small round cell tumors [9]. By correcting SUV using ADC, we intended to perform an assessment of biological features (i.e. glucose metabolism) of the tumors regardless of cell distribution.

Based on our results, cSUV implied its potential in differentiating high-grade from low/intermediate-grade tumors, being more accurate than the tumor size or ADCminimum, and comparable to SUVpeak. In addition, cSUV seemed to facilitate the assessment of treatment effect for the limited 8 cases. However, statistical significance was not observed. This warrants further study with a large number of patients.

The direct voxel-based comparison of functional images in this study is one of the unique ways to use the PET/MR system. Despite recent advances in image fusion software, it is still difficult to retrospectively generate well-matched fusion images using DWI and PET images acquired with different machines separately. Although we detected minor misregistrations due to small motions by patients in this study, these were easily corrected by a simple image registration with rigid transformation. In addition, the use of zoomed DWI [10] instead of conventional DWI could reduce the image distortion associated with conventional DWI.

Conclusion

We proposed a new diagnostic parameter derived from a voxel-based analysis of SUV and ADC with a PET/MR system, in the aim to improve the classification and treatment monitoring of soft tissue tumors. Despite some positive features, further investigation with a larger sample size is required to determine whether the observed gains are reliable.
Personal information

Contact information

Presenting author: Ryotaro Kamei, M.D.

Kyushu University Graduate School of Medical Sciences, Department of Clinical Radiology

E-mail: rkamei@med.kyushu-u.ac.jp
References