Value of diffusion-weighted MRI in assessment of rectal tumor response to neoadjuvant chemoradiation therapy

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Purpose

Neoadjuvant chemoradiation therapy (CRT) improves resectability and patients outcomes in rectal cancer and currently is the standard treatment for locally advanced rectal cancer. The use of neoadjuvant CRT induces various rectal tumor responses: from complete pathological response, partial response with downsizing and downstaging of the primary tumor to poor tumor response. The degree of response of the tumor to neoadjuvant therapy may have prognostic significance and should be reported separately. Postchemoradiation MR imaging findings have moderate accuracy in assessment of tumor response in patients with rectal cancer due to limitations in the differentiation of residual tumor from surrounding fibrosis. Therefore, there is obvious need for development a noninvasive method for assessment of rectal tumor response after neoadjuvant CRT. While conventional MRI techniques only provide morphological information, diffusion-weighted MRI offers unique quantitative information reflecting tissue cellularity and potentially allows to measure disease response to treatment.

The purpose of this study was to evaluate the diagnostic value of diffusion-weighted imaging (DWI) for predicting tumor response to neoadjuvant chemoradiation therapy in patients with locally advanced rectal cancer with reference to histopathological findings.
Methods and Materials

Patients:

Thirty six patients (mean age 63.1 years; 21 men, 15 women) with histologically proved, locally advanced (T3 or T4 at pre-CRT MR imaging) non-mucinous rectal adenocarcinoma treated with neoadjuvant CRT and subsequent surgery.

MR technique:

- MRI examinations (DWI and T2 weighted imaging) were performed on 1.5-T MRI system (Magnetom Avanto, Siemens Medical Systems, Erlangen, Germany) in all patients before CRT and 8 weeks after completion of CRT.
- All patients underwent routine rectal MRI protocol.
- DWI was performed with two diffusion sensitivity values (0 and 800 s/mm²) using single shot echo-planar SE. The following acquisition parameters were used: TR of 4400 ms; TE of 76 ms; matrix size of 98x144; field of view of 320 mm; receiver bandwidth of 1736 Hz/pixel; number of excitation = 2; slice thickness = 4 mm; time of acquisition of 1.07 minute.

Image analysis:

Diffusion weighted images and ADC maps were obtained. The mean apparent diffusion coefficient (ADC) values were measured for three circular regions of interest (ROI) in the tumor area before and after CRT taking care to avoid areas of necrosis or fibrosis and to include areas of viable tumor as large as possible. Quantitative ADC maps were calculated on voxel-by-voxel basis using commercial workstation (Syngo, Siemens Medical Healthcare) for b=800 s/mm²[2]. The final ADC was calculated as the average of three values. We compared changes of apparent diffusion coefficients (ADC) before and after CRT dividing patients into three groups according histological postoperative staging: complete responders (TRG 0), incomplete responders (TRG 1 and TRG 2) and poor responders (TRG 3).

Standard of reference:

The tumor regression grade (TRG) served as a histopathological standard of reference. This is an alternative method to assess treatment response accomplished by grading histologic changes in the resected specimen that are caused by preoperative CRT. Areas of fibrotic changes after preoperative CRT contrast sharply with residual tumor.
and the adjacent normal bowel wall. Thus, tumor regression can range from a complete response with no viable tumor identified to no evidence of any treatment effect. We assessed TRG according to the CAP guidelines for Tumor Regression Grade adapted from Ryan et al. TRG was determined by the amount of viable tumor versus fibrosis, ranging from TRG 0 (total regression) when no viable tumor cells were detected, to TRG 3 (no regression) when fibrosis was almost completely absent, with minimal or no tumor kill and extensive residual tumor. TRG 1 (good regression) was defined as major regression of the tumor mass with single tumor cells or small groups of tumor cells and TRG 2 (moderate regression) was defined as residual tumor outgrown with fibrosis.
Results

Of the 36 patients, 11 patients were poor responders (TRG 3), 23 were intermediate responders (TRG 1 and 2) and 2 were complete responders (TRG0) (Table 1.).

Table 2. shows the results of pretreatment T stage assessed with MRI (T) vs. posttreatment histopathological T stage (yT). There was no disease progression. After CRT, 2 of 36 patients (5.6%) were classified as complete responders. Both of them had T3 disease before CRT and showed yT0 after treatment. After CRT, 11 of 36 patients (30.6%) were classified as poor responders. Among them, 7 of 23 patients who had T3 tumor before CRT (30.4%) showed yT3, and 4 of 13 patients who had T4 tumor showed yT4 (30.7%) after CRT. Twenty three patents were classified as intermediate responders. Among them, from 14 patients who had T3 tumor before CRT, 9 showed yT1 and 5 showed yT2 after CRT and from 9 patients who had T4 tumor, 4 showed yT2 and 5 yT3 after treatment.

The mean ADC value before CRT in the complete responder group was $0.71 \pm 0.15 \times 10^{-3} \text{ mm}^2/\text{s}$ (ranging from $0.53$ to $0.94 \times 10^{-3} \text{ mm}^2/\text{s}$), in the incomplete responder group was $0.98 \pm 0.19 \times 10^{-3} \text{ mm}^2/\text{s}$ (ranging from $0.71$ to $1.13 \times 10^{-3} \text{ mm}^2/\text{s}$) and in the poor responder group $1.06 \pm 0.18 \times 10^{-3} \text{ mm}^2/\text{s}$ (ranging from $0.69$ to $1.24 \times 10^{-3} \text{ mm}^2/\text{s}$). In the group of complete responders, we found a significant increase of mean ADCs ($x 10^{-3} \text{ mm}^2/\text{s}$) ($p=0.002$) after CRT ($1.22 \pm 0.21 \times 10^{-3} \text{ mm}^2/\text{s}$), while in the groups of incomplete and poor responders there was no significant increase of mean ADCs ($1.28 \pm 0.24 \times 10^{-3} \text{ mm}^2/\text{s}$ and $1.13 \pm 0.23 \times 10^{-3} \text{ mm}^2/\text{s}$ respectively), although the increase of ADC values in incomplete responders group was observed (Table 3, Figure 1.).
<table>
<thead>
<tr>
<th>TRG</th>
<th>PATIENTS</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>No.</td>
</tr>
<tr>
<td>TRG 0 (total regression)</td>
<td>2</td>
</tr>
<tr>
<td>TRG 1 (good regression)</td>
<td>13</td>
</tr>
<tr>
<td>TRG 2 (moderate regression)</td>
<td>10</td>
</tr>
<tr>
<td>TRG 3 (no regression)</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>36</td>
</tr>
</tbody>
</table>

**Table 1**: TRG with respect to primary tumor in 36 patients with neoadjuvant CRT and surgery

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<table>
<thead>
<tr>
<th>T stage</th>
<th>yT0</th>
<th>yT1</th>
<th>yT2</th>
<th>yT3</th>
<th>yT4</th>
<th>Total</th>
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<tr>
<td>T3</td>
<td>2</td>
<td>9</td>
<td>5</td>
<td>7</td>
<td>0</td>
<td>23 (63,9%)</td>
</tr>
<tr>
<td>T4</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>5</td>
<td>4</td>
<td>13 (36,1%)</td>
</tr>
<tr>
<td>Total</td>
<td>2 (5,6%)</td>
<td>9 (25%)</td>
<td>9 (25%)</td>
<td>12 (33,3%)</td>
<td>4 (11,1%)</td>
<td>36 (100%)</td>
</tr>
</tbody>
</table>

**Table 2**: Pretreatment T stage assessed with MRI and posttreatment histopathological T stage (yT)
Table 3: PreCRT and postCRT mean ADC values for b=800 s/mm\(^2\) (value x 10\(^{-3}\) mm\(^2\)/s ± SD, * p

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**Fig. 1:** Box-and-whiskers plots comparing pretreatment and posttreatment mean ADC value in the complete responder group. Mean ADC value (line through box) before CRT is significantly lower than mean ADC value after the treatment.

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Conclusion

DWI MRI can improve identifying complete responders after CRT because the increase of mean tumor ADC values correlated with good response to CRT, but is not accurate enough for identifying incomplete and poor respond to CRT. DW MR imaging is a promising non-invasive technique which provides important information about therapeutic tumor response and could be accurately used for prediction of good response in patients with locally advanced rectal cancer who undergo CRT.
References

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