**Diffusion magnetic resonance imaging and PET-CT as prognostic factors to neoadjuvant therapy response in rectal cancer: preliminary results**

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Aims and objectives

Local recurrences in rectal cancer can occur in up to 50% of patients with T3 or node positive lesions [1]. In order to decrease the rates of local recurrence, neoadjuvant treatment (radiotherapy with or without chemotherapy, CRT) is generally recommended for patients with T3 or higher and/or N+ rectal cancers. Neoadjuvant CRT allows downsizing and downstaging of the tumor, leading to improved resectability and local control [2,3]. Neoadjuvant CRT is usually followed by total mesorectal excision, although recently in some cases considered clinically and radiologically as complete responders a "wait and see" strategy has been proposed [4]. Unfortunately, in locally advanced rectal cancer neoadjuvant therapy results are variable: 9%-25% of patients show complete pathologic response, while 54%-75% of patients show downstaging of tumor and others show no response [5]. Therefore, prognostic factors to predict the efficacy of neoadjuvant CRT are needed to tailor treatment to each patient. However, these prognostic factors should be easily assessed in routine clinical practice. Magnetic Resonance Imaging (MRI) with diffusion-weighted sequences (DWI) is able to calculate Apparent Diffusion Coefficient (ADC) maps and values that provide an in vivo quantification of water diffusion correlated to tissue cellularity and integrity of cellular membranes. DWI provides informations about the random (Brownian) motion of water molecules in tissues. Different studies using 1.5T MR systems demonstrated that pretreatment ADC could be a predictor of the response to neoadjuvant CRT in locally advanced rectal cancer [6-13]. PET/CT has also been proposed as a tool to predict and/or evaluate response to neoadjuvant rectal cancer treatment [14-16]. The identification of patients that may or may not respond to neoadjuvant CRT regimens using MRI with DWI sequences and/or PET already during initial staging could help in differentiating the treatment in patients that are expected not to respond. The purpose of our work is to assess if Apparent Diffusion Coefficients of DWI sequences and Standard Uptake Values (SUV) of 18FDG-PET-CT, assessed before the beginning of neoadjuvant therapy, correlate with tumor response (Dworak grade, 0-4) at histopathologic analysis.
Methods and materials

A total of 20 patients with primary locally advanced rectal carcinoma (>\(=\)T3 and/or >\(=\)N1 according to MRI at staging) underwent rectal MRI (1.5 Tesla) before neoadjuvant CRT; MR imaging included the following sequences: T2 frFSE in the 3 orthogonal planes (4mm slice thickness, 0mm gap), T2 frFSE (3mm slice thickness, 0mm gap) in an axial plane respect to the tumor and DWI (4mm slice thickness, 0mm gap) b1000 in the axial plane. 13/20 patients also underwent PET-CT as part of the initial staging. PET-CT included: non enhanced CT, PET acquisition and contrast enhanced CT in portal phase.

Tumor ADCs and SUVs were calculated and compared with histopathologic results of surgical resection. To obtain the ADC value a single region of interest (ROI) was manually drawn on the ADC map in the axial image were the tumor was more evident. SUV was calculated trying to pick the highest SUV (SUV max) of the lesion.
Results

Of the 20 patients with rectal cancer included in the study 17 had adenocarcinomas and 3 had mucinous adenocarcinoma.

Eight patients were considered responders (Figure 1, 2 and 3) to neoadjuvant therapy (Dworak >2) and 12 were considered non responders (Dworak </=2) (Figure 4, 5 and 6).

The mean ADC resulted 0.713E-03mm2/sec in responders and 1.14E-03mm2/sec in non responders.

Standard deviation of ADC values in this series of patients were 0.382E-003 for responders and 0.220E-003 for non responders.

The ADC values resulted significantly different between responders and non responders (P=0.0074, Student t test).

Excluding the 3 patients with mucinous tumors the difference further improved (P=0.0036); the mean ADC resulted 0.636E-003 (SD 0.3737E-003) in responders and 1.049E-003 (SD 0.071E-03) in non responders.

In Figure 7 the ROC curve represents the sensitivity and specificity of ADC, also represented in Table 1.

In Figure 8 the ROC curve represents the sensitivity and specificity of ADC excluding mucinous tumors from statistical analysis, also represented in Table 2.

It has to be noted that only calculating ADC with a ROI that included the whole tumor in the slice were the tumor had the bigger dimensions a significant result was obtained.
No significant difference was observed between the SUV of responders and non respondents. In fact, the mean SUV resulted 7.3 (SD 2.51) in responders and 10.2 (SD 5.34) in non responders.
Fig. 1: MR and PET CT of responder patient: MR pre neoadjuvant therapy (CHT+RT): T3, N1.

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**Fig. 2:** MR DWI of responder patient (same as figure 1): MR DWI ADC 0.766E-03. pTNM: T0, N0, Dworak 4

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**Fig. 3:** ADC of responder patient (same as figure 2): MR DWI ADC 0.766E-03. pTNM: T0, N0, Dworak 4

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Fig. 4: MR and PET ceCT of non responder patient: MR pre neoadjuvant therapy (CHT +RT): T3, N1

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Fig. 5: MR DWI of non responder patient (same as figure 4): MR DWI ADC 1.14E-03. pTNM: T3, N1, V1, Dworak 2

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Fig. 6: ADC of non responder patient (same as figure 5): MR DWI ADC 1.14E-03. pTNM: T3, N1, V1, Dworak 2

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Fig. 7: ROC curve, responders (Dworak >2), including all tumors

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**Table 1:** Area under the ROC curve (AUC) including all tumors

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**Fig. 8:** ROC curve, responders (Dworak >2), excluding mucinous tumors

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<table>
<thead>
<tr>
<th>Area under the ROC curve (AUC)</th>
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<tr>
<td>Standard Error&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.109</td>
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<tr>
<td>95% Confidence interval&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.649 to 0.989</td>
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<tr>
<td>z statistic</td>
<td>3.609</td>
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<td>Significance level P (Area=0.5)</td>
<td>0.0003</td>
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</tbody>
</table>

<sup>a</sup> DeLong et al., 1988

<sup>b</sup> Binomial exact
Table 2: Area under the ROC curve (AUC) excluding mucinous tumors

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Conclusion

Our data indicate that low pre-therapy ADC values in rectal carcinoma may correlate with good response to neoadjuvant therapy.

It is important to notice that excluding patients with mucinous tumors the statistical difference of ADC in predicting responders and non responders improves.

The DWI sequence can be easily added to a rectal cancer MR protocol and may allow to predict the probability of neoadjuvant treatment effectiveness.

In the future, the use of DWI in the staging of rectal cancer may help in defining patients that will likely respond and those that will not.

PET SUV values before neadjuvant therapy did not help in the definition of patients that will respond from those that will not. Although good results have been reported with PET CT response prediction performing PET CT before and after neadjuvant therapy [15,16], PET CT has been used in research settings and in our opinion in current clinical practice there is no routine indication in the staging of rectal cancer.
References


