Is ADC value can be predictive factor and early marker of tumor's response to radiofrequency ablation therapy in patients with hepatocellular carcinoma?

Poster No.: C-2156
Congress: ECR 2011
Type: Scientific Exhibit
Keywords: MR-Diffusion/Perfusion, Ablation procedures, Neoplasia, Liver
DOI: 10.1594/ecr2011/C-2156

Any information contained in this pdf file is automatically generated from digital material submitted to EPOS by third parties in the form of scientific presentations. References to any names, marks, products, or services of third parties or hypertext links to third-party sites or information are provided solely as a convenience to you and do not in any way constitute or imply ECR's endorsement, sponsorship or recommendation of the third party, information, product or service. ECR is not responsible for the content of these pages and does not make any representations regarding the content or accuracy of material in this file.

As per copyright regulations, any unauthorised use of the material or parts thereof as well as commercial reproduction or multiple distribution by any traditional or electronically based reproduction/publication method is strictly prohibited.

You agree to defend, indemnify, and hold ECR harmless from and against any and all claims, damages, costs, and expenses, including attorneys' fees, arising from or related to your use of these pages.

Please note: Links to movies, ppt slideshows and any other multimedia files are not available in the pdf version of presentations.
www.myESR.org
Purpose

Yearly there are about 600 000 new cases of hepatocellular carcinoma (HCC) registered worldwide [1]. A surgical treatment may prolong survival time, but in less than half of the patients, advanced disease stage at the time of diagnosis is a cause of disqualification from the treatment. Image-guided percutaneous ablation is accepted therapy for nonsurgical patients [2]. The procedure is safe and generally well tolerated, with a mortality rate of 0.3% and a major complication rate of 2.2% in one of the largest series of 2320 patients with liver lesions [3].

Rapid progress of ablative techniques is followed by the necessity to search for new diagnostic methods reaching out to the standard morphological assessment of tumors response. Today ablative techniques' efficacy is evaluated by contrast-enhanced magnetic resonance imaging (MRI) and multiphase computed tomography (CT). However the evaluation of tumor response is sometimes difficult due to the presence of therapy-induced reactive changes, that can persist for few months [4,5] and may be the reason of diagnostic errors.

In the last decade a significant development of diffusion-weighted imaging (DWI) in detection and characterization of liver neoplasms has been observed [6,7]. Scientific studies have confirmed DWI usefulness in the assessment of treatment response in patients with hepatic neoplasm [8-12]. To our knowledge there is only one report on application of DWI in evaluation of RFA treatment outcome in patients with HCC [13].

The aim of our study is the assessment of the Apparent Diffusion Coefficients' (ADC) efficacy in evaluation of radio frequency ablation therapy (RFA) effects in patients with HCC and its ability of predicting the RFA therapy outcome.
Methods and Materials

39 patients (17 women and 22 men, age 25 to 83 years, median 65) with 67 HCC foci were included in this prospective study.

Inclusion criteria were /1/ presence of HCC focus greater than 10mm and smaller than 10cm in diameter, /2/ number of HCC lesions less than 5, /3/ good visibility of lesions in ultrasound, /4/ disqualification of patient from the surgical treatment and /5/ being scheduled for RFA therapy.

Exclusion criteria were /1/ presence of any contraindications to MR imaging, /2/ heavy artifacts in MR examination or /3/ withdraw of patient's consent for further research.

Patients were examined with 1.5 T MR system before RFA, during first 24 hours and 6 weeks after RFA therapy. Protocol included T1- and T2-weighted sequences and single shot echo-planar diffusion-weighted images with different b (b=0, 15, 30, 100, 300 and 500sec/mm$^2$).

MR images were evaluated by two independent radiologist blinded to RFA outcome and with at least 10 years of experience in field of abdominal radiology.

HCC foci were identified on T1, T2 and diffusion-weighted images. Subsequently ROI covering the whole focus was manually drawn on DWI maps and mean ADCs were automatically calculated with use of commercially available software Functool 4.5.3.

ADC value of HCC foci were measured in pre- and post-treatment images.

RFA was performed under ultrasound guidance by radiological-surgical team experienced in this procedure. A 200W generator with straight internally cooled single or cluster electrode was used.

All HCC foci were divided into two groups: responding and non-responding.

Tumors were recognized as totally responding if in 6-weeks and 3-months MDCT control RFA treated ablative zones were unenhanced and larger than initial tumors and serum AFP level was not uprisng. In case of ambiguous radiological image or elevated laboratory results a follow-up examination was ordered (three cases).

Decision on completeness of RFA therapy was based on the consensus of two radiologist after prior clinical consultation. The radiologist were not involved later in ADCs measurement.
Tumors were recognized as non-responding if in MDCT in 6-weeks after RFA or in follow-up after 3-months (ambiguous cases) a nodular or irregular enhancements were visible in ablative zones [14,15].

Interobserver agreement in assessment of tumor ADC have been evaluated by means of the Spearman's rho statistics. Statistical analysis concerning difference in ACD values before and after RFA and difference in ADC values responding and non-responding lesions was performed accordingly with use of the Wilcoxon signed-rank test and the Mann-Whitney $U$ test. ROC analysis of sensitivity, specificity and accuracy of ADC values in tumor was performed. The $p$ value lower than 0.05 was considered significant. Statistical tests were performed with use of STATISTICA 8 (StatSoft Inc., Tulsa, OK, USA).

Study was approved by local Independent Bioethic Committee for Scientific Research. Patients gave their written consent to participate.
Results

Interobserver agreement

High interobserver agreement of ADCs values of liver tumors before RFA, in first 24 hours and 6 weeks post RFA has been stated ($r_s=0.81$, 0.76 and 0.85).

Impact of RFA therapy to tumors diffusibility

RFA therapy affects the diffusibility of HCC foci for all b values. ADC of hepatocellular carcinomas decreased significantly ($p<0.001$) in first 24 hours after RFA (ADC2) and after next 6 weeks (ADC3) increased significantly ($p<0.001$) above initial, pre-treatment values (figure 1 on page 9). Mean ADC1, ADC2 and ADC3 values for used b parameters were presented in table 1.

Differences between ADC values of responding and non-responding group

47 of all HCC foci were completely ablated (responding group) and 20 lesions had residual tumors (non-responding group).

Significant differences were observed between ADC values of responding and non-responding group. Residual tumors showed significantly higher pre-treatment diffusion in comparison to completely ablated lesions (table 2).

Initial, pretreatment mean ADC value of completely ablated HCC foci was $2.14 \times 10^{-3} \text{mm}^2/\text{sec}$ in comparison to $2.34 \times 10^{-3} \text{mm}^2/\text{sec}$ in residual tumors for $b=15 \text{ sec/mm}^2$ and $1.46 \times 10^{-3}$ and $1.71 \times 10^{-3} \text{mm}^2/\text{sec}$ for $b=500 \text{ sec/mm}^2$ respectively (figure 2 on page 9).

In first 24 hours post RFA treatment mean ADC value of completely ablated HCC's foci was significantly lower in comparison to residual tumors (table 2, figure 2 on page 9).

6 weeks after treatment mean ADC value of responding foci was significantly higher than non-responding lesions for all used $b$ parameter. Mean ADC value for $b=500 \text{ sec/mm}^2$ of residual tumors was $1.71 \times 10^{-3} \text{mm}^2/\text{sec}$ contrary to completely ablated tumors which mean ADC was $1.82 \times 10^{-3} \text{mm}^2/\text{sec}$ (figure 2 on page 9).
No significant difference were noted between ADC values of non-completely ablated HCC’s foci.

**Receiver operating characteristics (ROC) analysis of ADC values**

Efficacy of predicting RFA outcome basing on initial ADC values (expressed by area under ROC curve) before treatment were respectively 0.823 (b=15sec/mm$^2$) and 0.784 (b=500sec/mm$^2$) (figure 3 on page 10). The cut-off values of ADC discriminating responding from non-responding tumors was found at the level of 2.33x10$^{-3}$mm$^2$/sec (b=15sec/mm$^2$) and 1.55x10$^{-3}$mm$^2$/sec (b=500sec/mm$^2$) - table 3.

Efficacy of RFA therapy assessed on a basis of ADC values measured during the first 24 hours post RFA treatment (expressed by area under ROC curve) were respectively 0.949 (b=15sec/mm$^2$) and 0.871 (b=500sec/mm$^2$) (figure 4 on page 11). The cut-off values of ADC calculated one day after ablation discriminating responding from non-responding tumors was found at the level of 2.18x10$^{-3}$mm$^2$/sec (b=15sec/mm$^2$) and 1.48x10$^{-3}$mm$^2$/sec (b=500sec/mm$^2$) - table 3.

Efficacy of RFA therapy assessed on a basis of ADC values measured 6 weeks after RFA treatment (expressed by area under ROC curve) were respectively 0.966 (b=15sec/mm$^2$) and 0.721 (b=500sec/mm$^2$) (figure 5 on page 12). The cut-off values of ADC calculated one day after ablation discriminating responding from non-responding tumors was found at the level of 2.46x10$^{-3}$mm$^2$/sec (b=15sec/mm$^2$) and 1.72x10$^{-3}$mm$^2$/sec (b=500sec/mm$^2$) - table 3.

**Table 1.** Impact of RFA therapy to ADC values of HCC’s foci for b=15sec/mm$^2$ (ADC1 - ADC before treatment, ADC2 - ADC during the first 24 hours after RFA therapy and ADC3 - 6 weeks after treatment).

<table>
<thead>
<tr>
<th>$b$ value [sec/mm$^2$]</th>
<th>Time of assessment</th>
<th>Mean ADC±SD [sec/mm$^2$] of all lesions (responding and non-responding)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>ADC1</td>
<td>2.20x10$^{-3}$±0.21x10$^{-3}$</td>
</tr>
<tr>
<td></td>
<td>ADC2</td>
<td>1.97x10$^{-3}$±0.15x10$^{-3}$</td>
</tr>
<tr>
<td></td>
<td>ADC3</td>
<td>2.56x10$^{-3}$±0.14x10$^{-3}$</td>
</tr>
<tr>
<td>$b$ value [sec/mm$^2$]</td>
<td>Time of assessment</td>
<td>Mean ADC±SD [sec/mm$^2$] of responding group</td>
</tr>
<tr>
<td>------------------------</td>
<td>--------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>15</td>
<td>ADC1</td>
<td>2,14±0,19x10$^{-3}$</td>
</tr>
<tr>
<td></td>
<td>ADC2</td>
<td>1,87±0,21x10$^{-3}$</td>
</tr>
<tr>
<td></td>
<td>ADC3</td>
<td>2,66±0,21x10$^{-3}$</td>
</tr>
<tr>
<td>30</td>
<td>ADC1</td>
<td>2,02±0,19x10$^{-3}$</td>
</tr>
<tr>
<td></td>
<td>ADC2</td>
<td>1,79±0,25x10$^{-3}$</td>
</tr>
<tr>
<td></td>
<td>ADC3</td>
<td>2,48±0,21x10$^{-3}$</td>
</tr>
<tr>
<td>100</td>
<td>ADC1</td>
<td>1,93±0,20x10$^{-3}$</td>
</tr>
<tr>
<td></td>
<td>ADC2</td>
<td>1,73±0,28x10$^{-3}$</td>
</tr>
<tr>
<td></td>
<td>ADC3</td>
<td>2,31±0,21x10$^{-3}$</td>
</tr>
</tbody>
</table>

Table 2. ADC values of all, responding and non-responding HCCs foci before treatment (ADC1), during the first 24 hours after RFA therapy (ADC2) and 6 weeks after treatment (ADC3) for different $b$ parameters.
Table 3. Thresholds of ADC values according to ROC curves and their efficiency.

<table>
<thead>
<tr>
<th>b value [sec/mm²]</th>
<th>Time of assessment [sec/mm²]</th>
<th>Threshold ADC1</th>
<th>Sens.</th>
<th>Spec.</th>
<th>ACC</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>ADC1</td>
<td>2,33×10⁻³</td>
<td>0,70</td>
<td>0,87</td>
<td>0,82</td>
<td>0,823</td>
</tr>
<tr>
<td></td>
<td>ADC2</td>
<td>2,18×10⁻³</td>
<td>0,85</td>
<td>0,94</td>
<td>0,91</td>
<td>0,949</td>
</tr>
<tr>
<td></td>
<td>ADC3</td>
<td>2,46×10⁻³</td>
<td>0,94</td>
<td>1</td>
<td>0,96</td>
<td>0,966</td>
</tr>
<tr>
<td>30</td>
<td>ADC1</td>
<td>2,21×10⁻³</td>
<td>0,75</td>
<td>0,87</td>
<td>0,84</td>
<td>0,883</td>
</tr>
<tr>
<td></td>
<td>ADC2</td>
<td>2,03×10⁻³</td>
<td>0,90</td>
<td>0,94</td>
<td>0,93</td>
<td>0,935</td>
</tr>
<tr>
<td></td>
<td>ADC3</td>
<td>2,36×10⁻³</td>
<td>0,79</td>
<td>0,80</td>
<td>0,79</td>
<td>0,82</td>
</tr>
<tr>
<td>100</td>
<td>ADC1</td>
<td>2,12×10⁻³</td>
<td>0,60</td>
<td>0,87</td>
<td>0,79</td>
<td>0,786</td>
</tr>
<tr>
<td></td>
<td>ADC2</td>
<td>1,94×10⁻³</td>
<td>0,70</td>
<td>0,87</td>
<td>0,82</td>
<td>0,801</td>
</tr>
<tr>
<td></td>
<td>ADC3</td>
<td>2,19×10⁻³</td>
<td>0,81</td>
<td>0,55</td>
<td>0,73</td>
<td>0,719</td>
</tr>
<tr>
<td>300</td>
<td>ADC1</td>
<td>1,94×10⁻³</td>
<td>0,50</td>
<td>0,89</td>
<td>0,78</td>
<td>0,741</td>
</tr>
<tr>
<td></td>
<td>ADC2</td>
<td>1,93×10⁻³</td>
<td>0,35</td>
<td>0,96</td>
<td>0,78</td>
<td>0,752</td>
</tr>
<tr>
<td></td>
<td>ADC3</td>
<td>1,81×10⁻³</td>
<td>0,92</td>
<td>0,20</td>
<td>0,70</td>
<td>0,520</td>
</tr>
<tr>
<td>500</td>
<td>ADC1</td>
<td>1,55×10⁻³</td>
<td>0,75</td>
<td>0,75</td>
<td>0,75</td>
<td>0,784</td>
</tr>
<tr>
<td></td>
<td>ADC2</td>
<td>1,48×10⁻³</td>
<td>0,75</td>
<td>0,85</td>
<td>0,82</td>
<td>0,871</td>
</tr>
<tr>
<td></td>
<td>ADC3</td>
<td>1,72×10⁻³</td>
<td>0,83</td>
<td>0,70</td>
<td>0,79</td>
<td>0,721</td>
</tr>
</tbody>
</table>
**Fig. 0:** Figure 1. Box-and-whiskers plot: impact of RFA therapy to ADC values of HCC foci for $b=500\text{sec/mm}^2$ (ADC1 - ADC before treatment, ADC2 - ADC during the first 24 hours after RFA therapy, and ADC3 - 6 weeks after treatment).

© Department of Radiology, Medical University of Gdansk - Gdansk/PL
Fig. 0: Figure 2. Box-and-whiskers plot: Impact of RFA therapy to ADC values of completely ablated (c) and residual (r) HCC foci for b=500sec/mm² (ADC1 - ADC before treatment, ADC2 - ADC during the first 24 hours after RFA therapy, and ADC3 - 6 weeks after treatment). There were significant difference between ADC values of completely ablated HCC foci.

© Department of Radiology, Medical University of Gdansk - Gdansk/PL
Fig. 0: Figure 3. ROC curves: ADC values of HCC foci before treatment.

© Department of Radiology, Medical University of Gdansk - Gdansk/PL
**Fig. 0:** Figure 4. ROC curves: ADC values of HCC foci during the first 24 hours after RFA therapy.

© Department of Radiology, Medical University of Gdansk - Gdansk/PL
Fig. 0: Figure 5. ROC curves: ADC values of HCC foci 6 weeks after RFA therapy.

© Department of Radiology, Medical University of Gdansk - Gdansk/PL
Fig. 0: DWI (b=15sec/mm²) of a patient with single HCC focus before RFA treatment.

© Department of Radiology, Medical University of Gdansk - Gdansk/PL
**Fig. 0:** DWI (b=15sec/mm²) of the same patient as in figure 6. A residual HCC focus in 24 hours after RFA is visible.

© Department of Radiology, Medical University of Gdansk - Gdansk/PL
Fig. 0: CT in hepatic arterial phase of the same patient as in figure 6 and 7 in 6 weeks after RFA. A peripheral enhancement of residual lesion is visible.

© Department of Radiology, Medical University of Gdansk - Gdansk/PL
Conclusion

The ADC can be a predictive factor and early marker of HCC response to RFA therapy. ADC measurement on the first day after therapy may enable the second RFA session during one hospitalization in non-responders.
References
