FUNCTIONAL IMAGING OF PERITONEAL DISEASE IN OVARIAN CANCER: CHANGES IN APPARENT DIFFUSION COEFFICIENTS PREDICT BIOCHEMICAL RESPONSE TO CHEMOTHERAPY

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Introduction: Peritoneal dissemination is the hallmark of advanced ovarian cancer and its sensitivity to platinum-based chemotherapy determines patient management and disease prognosis. Standard treatment monitoring is biochemical (Ca125) but suffers from suboptimal accuracy early in the course of therapy.[1] Diffusion-Weighted Imaging (DWI) has shown promise in the early identification of therapy-induced changes in tumour cellularity of liver metastases before conventional markers of response become positive.[2] However, its value in response assessment of peritoneal carcinomatosis has not been reported. The purpose of this prospective study was to evaluate the Apparent Diffusion Coefficient (ADC) of whole disease burden as a surrogate biomarker of biochemical response in ovarian-related peritoneal carcinomatosis.

Method: Twenty females with metastatic ovarian or primary peritoneal cancer and at least one peritoneal lesion > 10 mm on CT/MRI were examined on a Siemens Avanto 1.5T scanner prior to and after the first and third cycle of platinum-based chemotherapy. Following administration of an antiperistaltic agent (hyoscine butylbromide 20 mg im), standard T1W and T2W imaging and free-breathing axial double spin-echo echo-planar DWI were performed in the abdomen (40 slices) and pelvis (50 slices) with SPAIR fat suppression (TR/TE=6300/69, 5 mm thickness, 5 averages, 128x128 matrix interpolated to 256x256, 380 mm FOV, Grappa = 2, three scan trace with b-values 0, 600, 900, 1050 s/mm^2). In-house software DiffusionView was employed to segment regions of interest on operator-determined peritoneal lesions and extract pixel-by-pixel ADC values (computed from mono-exponential fitting of all b-values). Mean and median ADCs at each timepoint were calculated for the entire tumour burden of each patient after summation of pixel ADCs from all individual lesions. The criterion for patient response was a >50% greatest reduction in Ca125 after the 3rd cycle of treatment.[3]

Results: A total of 36 lesions in 14 responding and 6 non-responding patients were evaluated. Twelve patients were chemonaïve and 8 had previous exposure to platinum-based regimens. Pretreatment mean and median ADC did not differ significantly between responders and non-responders [p=0.968 (mean) and p=0.904 (median), Mann Whitney U test]. Chemonaïve patients had significantly higher baseline ADC values than previously treated patients [118±22 vs 95±15 (x 10^{-5} mm^2/s) respectively, p=0.025, Mann Whitney U test]. After the first cycle of chemotherapy, responding patients demonstrated a significant increase in mean and median ADC [mean from 109±25 to 126±26 (x 10^{-5} mm^2/s); median from 106 to 124 (x 10^{-5} mm^2/s), p=0.001, Wilcoxon's signed ranks test] in contrast to non-responders [mean from 107±15 to 105±15 (x 10^{-5} mm^2/s); median from 103 to 101 (x 10^{-5} mm^2/s); p=0.60] (Figure 1). After the third cycle of treatment four responding patients were excluded from the analysis because of absence of residual measurable disease. Among the remaining evaluable patients sustained ADC increase compared to baseline values was observed in the responding group [mean from 110±25 to 138±28 (x 10^{-5} mm^2/s); median from 106 to 136 (x 10^{-5} mm^2/s), p=0.009, Wilcoxon's signed ranks test] but not in non-responders [mean from 107±15 to 106±20 (x 10^{-5} mm^2/s); median from 103 to 100 (x 10^{-5} mm^2/s); p=0.60]. There was a significant difference in percentage ADC change (defined as [(ADCpost-ADCpre)/ADCpre] x100) between responders and non-responders both after cycle 1 and 3 (Table). Receiver operating characteristic analysis for % ADC change after the 1st cycle demonstrated an area under curve AUC=0.933 (Figure 2). By setting specificity at 100% (in order to confidently distinguish all non-responding patients) a sensitivity of 64% was achieved at a threshold of 11% ADC increase.

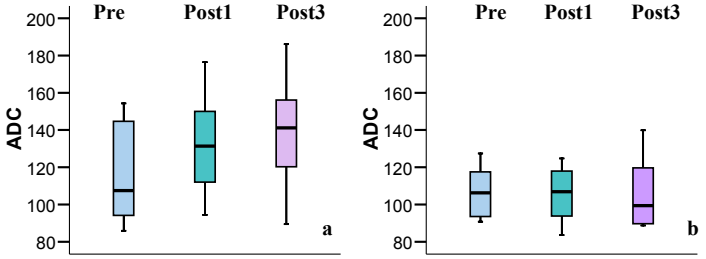

Figure 1. Box-and-whisker plots comparing mean ADC values (x 10^{-5} mm^2/s) at each timepoint between responders (a) and non-responders (b).

	% ADC mean (± SD)		% ADC median	
	Post1-preTx	**Post3-preTx***	**Post1-preTx**	**Post3-preTx***
R	17.46±23.47	22.85±29.51	18.94	24.50
NR	-1.31±4.44	-1.03±8.25	-1.09	-2.63
p	**0.002**	**0.012**	**0.016**	**0.016**

Percentage ADC change of mean and median ADCs after the 1st and 3rd cycle are compared between responders (R) and non-responders (NR) with the Mann Whitney U test. Statistical significance (p<0.05) is highlighted by bold typeface. (*): Analysis after exclusion of 4 patients without measurable residual disease.

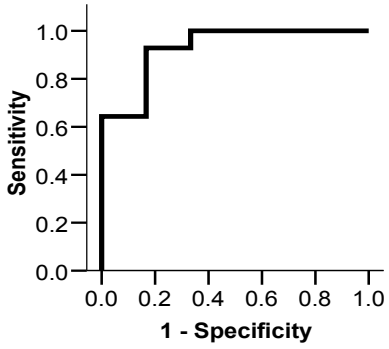

Figure 2. ROC curve for differentiating responders from non-responders with % ADC change after the 1st cycle.

Discussion & Conclusion: Pretreatment ADC values of peritoneal disease cannot predict chemosensitivity in metastatic ovarian cancer. An increase in mean/median ADC of the entire disease burden after the first cycle of chemotherapy indicates subsequent biochemical response. When a threshold of 11% ADC increase is used, response can be prospectively identified with 64% sensitivity and 100% specificity. Assessment of reproducibility is needed in order to test the robustness of the technique.

References: [1] Rocconi RP et al. *Gynecol Oncol*. 2009;114:242-245, [2] Koh DM et al. *Am. J Roentgenol*. 2007;188:1001-1008, [3] Rustin GJ et al. *J Clin Oncol*. 1996;14:1545-1551.

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