DIFFUSION-WEIGHTED MRI OF ADVANCED OVARIAN CANCER: EVALUATION OF THE VARIABILITY OF OVERALL DISEASE BURDEN ASSESSMENT METHODS

Jennifer C Wakefield[1,2], Stavroula Kyriazi[1], Jessica M Winfield[1], Veronica A Morgan[2], Sharon L Giles[2], David J Collins[1,2], and Nandita M deSouza[1,2]
[1]*Division of Radiotherapy and Imaging, The Institute of Cancer Research, Sutton, Surrey, United Kingdom,* [2]*Royal Marsden NHS Foundation Trust, Sutton, Surrey, United Kingdom*

TARGET AUDIENCE: Radiologists, Oncologists, Gynaecologists

BACKGROUND: Peritoneal and omental deposits are frequently non-measureable by standard morphological criteria (Response Evaluation Criteria In Solid Tumors (RECIST version 1.1)). Also, with the advent of new cytostatic and antiangiogenic chemotherapeutic agents, change in tumor size may occur late or not at all, making reliance on functional measures such as Apparent Diffusion Coefficient (ADC) valuable[1]. Previous studies have demonstrated that volumetric evaluation of tumors correlates better with histopathological tumor response than unidimensional tumor measurements[2, 3]. The RECIST working group has not currently incorporated volume based tumor assessment because there is a paucity of clinical data[4].

PURPOSE: To assess variability of tumor volumetry and ADC in ovarian cancer metastases and establish their value as response biomarkers.

METHODS: Tumor burden assessment was compared on an archived data set using three methods (1. Semi-automated (SA) region growing, which uses a seed Region Of Interest (ROI) chosen by the user and a multiplier. The seed region is grown to include all directly connected pixels that lie within the mean of the seed region plus or minus the multiplier times the standard deviation (std) of the seed region; 2. Manual (M) segmentation of Diffusion-Weighted Magnetic Resonance Imaging (DW-MRI) data; 3. RECIST measurements on CT). 16 females with advanced ovarian or primary peritoneal cancer underwent an MRI at baseline and after the third cycle of platinum-based chemotherapy on a Siemens Avanto 1.5 T scanner. Following administration of an antiperistaltic agent (hyoscine butylbromide 20 mg im), standard T1-weighted and T2-weighted imaging and free-breathing axial single-shot echo-planar DW-MRI were performed in the abdomen and pelvis. The protocol for this sequence was as follows: TR=6300ms (abdomen)/ 7900ms (pelvis); TE=69ms; 40 slices (abdomen)/ 50 slices (pelvis); 5 mm slice thickness; 5 averages; 128x128 matrix interpolated to 256x256; 380mm FOV; GRAPPA reduction factor 2; SPAIR fat suppression; three-scan trace; double spin echo; b-values 0, 600, 900, 1050 s/mm^2). Up to five measureable target lesions were analyzed per patient. Dedicated in-house software (Institute of Cancer Research) was used for image analysis. Conformal ROIs were drawn around target lesions on consecutive computed high b-value axial DW-MRI images (1050 s/mm^2) through the entire target lesion at baseline and after three cycles of chemotherapy. For the SA ROI method, the operator placed a seed within the target lesion, set the standard deviation of signal values to be included between two and three std and the SA ROIs were not subsequently edited. For the M ROI method, the operator manually drew around the periphery of the lesion on each axial image. Tumor volume and median ADCs were calculated for each target lesion from total pixel number and individual pixel values respectively within ROIs over multiple slices encompassing the entire lesion. CT scans at baseline and after three cycles of chemotherapy were assessed according to RECIST (version 1.1) criteria, by recording the longest diameter of the target lesions. Variability of the tumor burden assessment techniques were evaluated by calculating the Coefficient of Variation (CV) between the two baseline target lesion tumor burden measurements. A second radiologist assessed the tumor burden using an identical SA ROI growing method and the inter-observer variability was determined. The percentage change in tumor burden per patient and per lesion needed to indicate response was estimated using Receiver Operating Characteristic (ROC) curves, which compared percentage change in tumor volume and median ADC on a per patient and a per lesion basis to 50% reduction in CA125 post-three cycles of treatment as an indicator of response.

RESULTS: A total of 51 target lesions in 14 responding patients (44 lesions) and 2 non-responding patients (7 lesions) were evaluated (11 ovarian, 26 peritoneal and 14 omental target lesions).

	Volume						**Median ADC**					
	Per Lesion			**Per Patient**			**Per Lesion**			**Per Patient**		
	CV/ %	**95% C.I.**		**CV/ %**	**95% C.I.**		**CV/ %**	**95% C.I.**		**CV/ %**	**95% C.I.**	
Intra-observer Reproducibility (semi-automated)	12.20	26.89	-21.19	8.51	18.11	-15.33	2.22	4.45	-4.26	1.34	2.65	-2.59
Inter-observer Reproducibility (semi-automated)	17.38	40.23	-28.69	11.24	24.56	-19.72	4.21	8.59	-7.91	4.00	8.16	-7.54
Intra-observer Reproducibility (manual)	12.32	27.19	-21.38	8.67	18.49	-15.60	4.34	8.88	-8.15	3.98	8.12	-7.51
Intra-observer Reproducibility (CT longest diameter)	9.20	19.73	-16.48	6.86	14.37	-12.56						

Volume decrease post treatment per lesion at 80% sensitivity was -47.61% (SA Obs 1), -55.94% (M Obs 1), and -47.03% (SA Obs 2).This was a larger reduction than the 95% lower Confidence Interval (C.I.) for baseline variability. Per lesion change in volume with treatment is approximately four times the intra-observer and two and a half times the inter-observer CV values.

Median ADC increase post treatment per lesion at 80% sensitivity was 27.83% (SA Obs 1), 26.71% (M Obs 1), and 27.39% (SA Obs 2). This was greater than the 95% upper C.I. for baseline variability. Per lesion change in median ADC with treatment is greater than six times the intra-observer and inter-observer CV values.

DISCUSSION AND CONCLUSIONS: The intra- and inter-observer variabilities for baseline volume and median ADC assessments do not affect sensitivity for the assessment of response as the variability is less than the volume and median ADC response thresholds post-three cycles of treatment at 80% sensitivity. A limitation of the sensitivity analysis is that only two non-responding patients (seven lesions) were included. The CV of the median ADCs are low (1.3 to 4.3%) as would be expected for median values. The variability of baseline volume measurements is greater than twice the variability of median ADC measurements, which is likely due to the subjective nature of outlining the tumor contour even using a SA method. Per patient tumor burden assessment demonstrates less variability than per lesion tumor burden assessment.

REFERENCES: [1] Kyriazi S et al. Radiol. 2011;261(1):182-92. [2] Beer AJ et al. Radiol. 2006;239(2):472-80. [3] Lee SM et al. Abdom Imaging. 2009;34(4):430-40. [4] Eisenhauer EA et al. Eur J Cancer. 2009;45(2):228-47.

ACKNOWLEDGEMENTS: CRUK and EPSRC Cancer Imaging Centre in association with MRC and Department of Health (England; grant C1060/A103334), NIHR funding to the Clinical Research Facility in Imaging and the Biomedical Research Centre. We acknowledge the support of the National Institute for Health Research, through the Cancer Research Network (NCRN).