# ASSESSING CHEMOTHERAPY RESPONSE IN METASTATIC OVARIAN CANCER: THE VALUE OF HISTOGRAM ANALYSIS OF APPARENT DIFFUSION COEFFICIENTS

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**Introduction:** Peritoneal carcinomatosis is the hallmark of advanced ovarian cancer and its sensitivity to chemotherapy determines patient prognosis. Conventional monitoring of chemotherapeutic outcome relies on morphological (Response Evaluation Criteria in Solid Tumours-RECIST)[1] and biochemical (serum CA125) criteria[2], which have limited predictive value and suboptimal accuracy in the early course of treatment. Qualitative Diffusion-Weighted Imaging (DWI) has been shown to improve staging accuracy by enhancing the detectability of peritoneal implants[3], and the feasibility of quantitative DWI at multiple disease sites (primary ovarian and metastatic peritoneal or omental) has been documented[4]. Histogram analysis of Apparent Diffusion Coefficients (ADC), which captures within-tumour heterogeneity, has been explored in neurooncology for lesion characterisation[5] and prediction of clinical outcome[6] but has not been investigated for assessment of peritoneal disease. The purpose of this study was to evaluate metrics derived from ADC histograms in assessing chemotherapy response in patients with metastatic ovarian cancer.

**Materials and Methods:** Forty-five females (median age, 65 years) with advanced ovarian ($n$=32) or primary peritoneal cancer ($n$=13) underwent imaging on a Siemens Avanto 1.5T system before and after the 1st, 3rd and 6th cycle of platinum- or taxane-based chemotherapy. Following administration of an antispasmodic agent (hyoscine butylbromide 20 mg im) and standard T1W and T2W imaging, free-breathing axial double spin-echo echo-planar DWI was performed in the abdomen (40 sections) and pelvis (50 sections) 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 ten patients DWI was repeated in the same session for assessment of reproducibility. In-house software DiffusionView was used to segment regions of interest on consecutive sections encompassing the entire volume of primary and metastatic lesions (up to five largest per-subject), and to extract pixel-by-pixel ADCs (computed from mono-exponential fitting of all $b$-values). Per-lesion ADC histograms were produced (bin width, 1 x 10$^{-6}$ mm$^2$/s) and the following parameters were analysed with a linear mixed-effects model to account for within-patient correlation of multiple lesions: mean, centile points [C10, C25, C50, C75, C90] and histogram skew. Per-patient total ADC histograms (weighted for lesion volume) and their change were compared between responders and non-responders with parametric tests. Linear discriminant analysis (LDA) was applied to identify the combination of parameters with the highest predictive accuracy. Response status was determined after the 6th cycle on imaging (>30% reduction in maximum diameter) per-lesion and on biochemistry (>50% reduction in serum CA125 concentration) per-patient. Two-sided $P$<.05 determined statistical significance.

**Results:** The coefficient of mean ADC reproducibility was 5.4%. 126 lesions (90 peritoneal, 21 omental, 13 ovarian, 2 visceral) were evaluated, among which 96 were classified as responding and 30 as non-responding. There were 34 biochemical responders and 11 non-responders. Pretreatment ADCs were not significantly different between the two groups (per-lesion, $P \geq .524$; per-patient, $P \geq .347$). Per-lesion histogram parameters are summarised in the table. Responding lesions demonstrated a significant, early and persistent increase in all ADCs ($P < .001$) and decrease in skew ($P \leq .043$), whereas in non-responding lesions no early change was noted ($P \geq .089$) and only C50 and C75 increased significantly ($P = .034$ and $P = .036$ respectively) after the 3rd cycle. The differential histogram changes are displayed graphically in Figure 1. In per-patient analysis, responders showed significant increase in total ADCs both after the 1st and 3rd cycle ($P < .001$) and decrease of total skewness after the 3rd ($P < .001$), whereas in non-responders only total C75 increased transiently after the 1st cycle ($P = .042$). After the 6th cycle parameters in both groups were comparable to baseline. Highest accuracy in separating responders from non-responders was found in percentage C25 change (post-1st cycle, %ΔC25 = 14.14% ± 14.91, area under curve [AUC] = .791; post-3rd cycle, %ΔC25 = 26.67% ± 24.34, AUC = .818). On LDA the best combination of parameters was not superior (post-1st cycle, $AUC_{\%\Delta C25+\%\Delta C50}$ = .774; post-3rd cycle, $AUC_{\%\Delta C10+\%\Delta C25}$ = .779) to %ΔC25.

| Para-meter | Responding | | | | | | Non-Responding | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Pre | Post-1st | $P$ | Post-3rd | $P$ | Post-6th | $P$ | Pre | Post-1st | $P$ | Post-3rd | $P$ | Post-6th | $P$ |
| ADC mean | 1063 ±213 | 1209 ±234 | **<.001** | 1297 ±239 | **<.001** | 1071 ±247 | .129 | 1083 ±193 | 1101 ±199 | .162 | 1134 ±280 | .077 | 1037 ±218 | .521 |
| C10 | 812 ±193 | 934 ±189 | **<.001** | 1031 ±211 | **<.001** | 825 ±219 | .123 | 844 ±156 | 834 ±163 | .451 | 879 ±231 | .088 | 811 ±188 | .344 |
| C25 | 898 ±199 | 1037 ±211 | **<.001** | 1135 ±226 | **<.001** | 945 ±284 | .156 | 927 ±169 | 919 ±178 | .488 | 979 ±260 | .062 | 890 ±197 | .373 |
| C50 | 1185 ±337 | 1172 ±246 | **<.001** | 1268 ±249 | **<.001** | 1040 ±251 | .200 | 1196 ±229 | 1049 ±163 | .255 | 1114 ±305 | **.034** | 999 ±216 | .542 |
| C75 | 1185 ±337 | 1345 ±285 | **<.001** | 1434 ±274 | **<.001** | 1176 ±270 | .230 | 1196 ±229 | 1231 ±238 | .110 | 1281 ±345 | **.036** | 1150 ±247 | .614 |
| C90 | 1387 ±272 | 1545 ±320 | **<.001** | 1601 ±302 | **<.001** | 1346 ±330 | .388 | 1368 ±262 | 1444 ±285 | .089 | 1472 ±372 | .085 | 1318 ±282 | .784 |
| Skew | 1.054 ± .53 | .816 ± .74 | **.043** | .576 ± .55 | **<.001** | .716 ± .34 | .466 | .959 ±.76 | .998 ± .55 | .606 | 1.028 ± .66 | .924 | .912 ± 56 | .606 |

ADC histogram parameters (mean ± SD) per-lesion at different timepoints. $P$ values refer to comparisons between intra-treatment and baseline values. ADC units are 10$^{-6}$ mm$^2$/s and skew has no units.

**Discussion & Conclusion:** Quantitative DWI in advanced ovarian cancer is highly reproducible. An early and sustained increase of ADC mean and centiles, as well as decrease of histogram skewness, indicates subsequent chemotherapeutic response. The ability of ADC histograms to capture tumour heterogeneity may provide useful information for refining treatment monitoring.

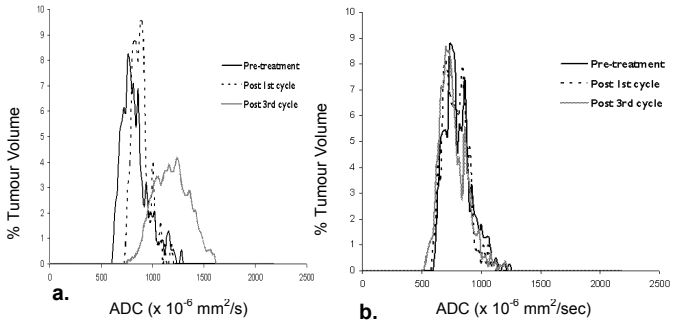


Figure 1. Evolution of ADC histograms (normalised for tumour volume) in a responding (a) and non-responding (b) peritoneal lesion. A sustained shift of the histograms to the right with reduction of skewness is noted in the responding lesion, whereas the shape and location of the histogram curves in the non-responding lesion are essentially stable across treatment timepoints.

**References:** [1] Eisenhauer EA et al. *Eur J Cancer* 2009;45:228-247, [2] Rustin GJ et al. *J Clin Oncol*. 1996;14:1545-1551, [3] Low RN et al. *Am. J Roentgenol*. 2009;193:461-470, [4] Sala E et al. *Eur Radiol*. 2010;20:491-496, [5] Tozer DJ et al. *NMR Biomed* 2007;20:49-57, [6] Pope WB et al. *Radiology* 2009;252:182-189.

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