Radiology

Diffusion-weighted MRI in Advanced Epithelial Ovarian Cancer: Apparent Diffusion Coefficient as a Response Marker

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Conflicts of interest are listed at the end of this article.

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Background: Treatment of advanced epithelial ovarian cancer results in a relapse rate of 75%. Early markers of response would enable optimization of management and improved outcome in both primary and recurrent disease.

Purpose: To assess the apparent diffusion coefficient (ADC), derived from diffusion-weighted MRI, as an indicator of response, progression-free survival (PFS), and overall survival.

Materials and Methods: This prospective multicenter trial (from 2012–2016) recruited participants with stage III or IV ovarian, primary peritoneal, or fallopian tube cancer (newly diagnosed, cohort one; relapsed, cohort two) scheduled for platinum-based chemotherapy, with interval debulking surgery in cohort one. Cohort one underwent two baseline MRI examinations separated by 0–7 days to assess ADC repeatability; an additional MRI was performed after three treatment cycles. Cohort two underwent imaging at baseline and after one and three treatment cycles. ADC changes in responders and nonresponders were compared (Wilcoxon rank sum tests). PFS and overall survival were assessed by using a multivariable Cox model.

Results: A total of 125 participants (median age, 63.3 years [interquartile range, 57.0–70.7 years]; 125 women; cohort one, n = 47; cohort two, n = 78) were included. Baseline ADC (range, 77–258 $\times 10^{-5}$mm^{2}s^{-1}) was repeatable (upper and lower 95% limits of agreement of 12 $\times 10^{-5}$mm^{2}s^{-1} [95% confidence interval {CI}: 6 $\times 10^{-5}$mm^{2}s^{-1} to 18 $\times 10^{-5}$mm^{2}s^{-1}] and −15 $\times 10^{-5}$mm^{2}s^{-1} [95% CI: −21 $\times 10^{-5}$mm^{2}s^{-1} to −9 $\times 10^{-5}$mm^{2}s^{-1}]). ADC increased in 47% of cohort two after one treatment cycle, and in 58% and 53% of cohorts one and two, respectively, after three cycles. Percentage change from baseline differed between responders and nonresponders after three cycles (16.6% vs 3.9%; P = .02 [biochemical response definition]; 19.0% vs 6.2%; P = .04 [radiologic definition]). ADC increase after one cycle was associated with longer PFS in cohort two (adjusted hazard ratio, 0.86; 95% CI: 0.75, 0.98; P = .03). ADC change was not indicative of overall survival for either cohort.

Conclusion: After three cycles of platinum-based chemotherapy, apparent diffusion coefficient (ADC) changes are indicative of response. After one treatment cycle, increased ADC is indicative of improved progression-free survival in relapsed disease.

Online supplemental material is available for this article.

Advanced epithelial ovarian cancer has a response rate of approximately 85% to initial platinum-based chemotherapy, but nearly 75% of individuals experience recurrence, at which point disease is incurable (1) and 5-year survival rates are approximately 30% worldwide (2,3) (median overall survival, 29–44 months [4,5]). Age (6), performance status (6), disease stage (7,8), histologic subtype (9), grade (8), and residual disease after debulking surgery (6,7) are well-established prognostic factors for survival in newly diagnosed ovarian cancer. However, the factors associated with survival in recurrent disease are less well established, although there are recognized associations with numbers of lines of therapy and the progression-free interval from last therapy (10,11).

Abbreviations

ADC = apparent diffusion coefficient, CA-125 = cancer antigen 125, CI = confidence interval, PFS = progression-free survival, RECIST = Response Evaluation Criteria in Solid Tumors

Summary

The apparent diffusion coefficient was a repeatable marker in a multicenter trial in advanced epithelial ovarian cancer across multivendor platforms, and is an indicator of progression-free survival after one cycle of chemotherapy in relapsed disease.

Key Results

- A multicenter and multivendor trial demonstrates good repeatability of apparent diffusion coefficient (ADC) in advanced epithelial ovarian cancer; an individual exhibiting a posttreatment increase in ADC greater than 12×10^{-5}mm^{2}s^{-1} may be characterized as showing a true posttreatment increase.
- In individuals with residual measurable disease after three cycles of chemotherapy, changes in ADC discriminate between responders and nonresponders (for biochemical definition of response, 16.6% vs 3.9%; $P = .02$; for radiologic definition of response, 19.0% vs 6.2%; $P = .04$).
- In relapsed ovarian cancer, changes in ADC measured after one cycle of chemotherapy indicate longer progression-free survival (adjusted hazard ratio, 0.86; $P = .03$).

Earlier markers of response to treatment would enable greater manipulation of existing management strategies to optimize outcome in individuals at high risk of relapse after primary treatment or at subsequent recurrence.

Diffusion-weighted MRI generates contrast based on the degree to which the motion of water molecules is restricted by neighboring structures (12,13). Quantitative analysis of the diffusion-weighted MRI signal using the apparent diffusion coefficient (ADC) offers a potential imaging marker related to tumor microstructure for tumor characterization and response assessment (14). Previous studies have demonstrated that baseline ADC estimates or posttreatment changes in ADC are indicative of treatment response in many tumor types, including ovarian cancer (15), breast cancer (16), colorectal hepatic metastases (17), and lung cancer (18). However, these studies were conducted mainly in single-center or two-center studies, as exploratory end points in early-phase clinical trials. The utility of ADC in large multicenter studies using standard-of-care treatments has not been established. Attempts to collate large diffusion-weighted MRI data sets by using routine clinical imaging data have been hindered by differences in imaging protocols and analysis methods. Translation of quantitative diffusion-weighted MRI into wider clinical practice and later-phase clinical trials requires prospective, standardized, and quality-controlled multicenter trials using imaging protocols that can readily be translated into routine clinical practice to assess the relationship between ADC changes and clinical outcomes. Our aim was to conduct a quality-controlled multicenter study to assess ADC repeatability, to establish posttreatment ADC changes in responders and nonresponders with newly diagnosed and relapsed epithelial ovarian cancer defined by radiologic and biochemical response criteria, and to investigate the association of these changes with progression-free survival (PFS) and overall survival.

Materials and Methods

Study Participant Selection

Study participants (recruited from 2012–2016) gave written informed consent to participate in this multicenter study (sponsored by the Institute of Cancer Research, London, United Kingdom, with multicenter research ethics committee approval [ClinicalTrials.gov identifier NCT01505829]). Data generated or analyzed during the study are available from the corresponding author by request. Study protocol is available in Table E1 (online).

Inclusion criteria were histologically or cytologically confirmed high-grade serous, endometrioid, or clear cell ovarian, primary peritoneal, or fallopian tube cancer (stage III or IV); at least one solid lesion larger than 2 cm; or scheduled to undergo standard-of-care platinum-based chemotherapy or drug combinations including platinum. Exclusion criteria were contraindications to MRI or radiation therapy to abdomen or pelvis in preceding 6 months. Cohort one consisted of participants with newly diagnosed disease, with planned debulking surgery after three cycles of chemotherapy. Cohort two consisted of participants at first or subsequent relapse. Participants from cohort one did not enter cohort two on progression.

Study Design

Five hospitals (National Health Service, United Kingdom) participated in this prospective study. Participants underwent MRI examinations, treatment, and all assessments at their recruiting institutions. Data were transferred to the lead site for analysis. Participants in cohort one underwent two baseline MRI examinations within 7 days before starting treatment for repeatability analysis (if tolerated, or a single baseline examination if not). A posttreatment MRI examination was conducted after three cycles of chemotherapy, prior to debulking surgery, or after four cycles if surgery was delayed. An additional earlier time point was considered too burdensome in this cohort and likely to limit recruitment. Participants in cohort two underwent one baseline MRI within 7 days before starting treatment, with posttreatment examinations after one and three cycles of chemotherapy. Response was defined biochemically (reduction of 50% in cancer antigen 125 [CA-125] level from baseline [19]) and radiologically (Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1) to identify complete or partial response [20]). Levels of CA-125 were measured in all participants at baseline, after three or four cycles in cohort one, and after one and three cycles in cohort two. Size measurements (RECIST version 1.1) were made by using T2-weighted MRI at the same time points. CT examinations for follow-up were performed at timings to suit clinical need and were not part of this study. Participants were followed up for PFS and overall survival data for 2 years after study entry.

MRI Protocol

MRI examinations consisted of diffusion-weighted MRI of the abdomen and pelvis, followed by T1-weighted and T2-weighted imaging in matched positions, as described in

detail in Table E1 (online). Development and standardization of the diffusion-weighted MRI protocols has been described previously (21) and consisted of a standard protocol (with minor vendor-specific variations) and regular quality assurance test-object images acquired to ensure quantitative data were consistent between centers and across time points. T1-weighted and T2-weighted sequences were also standardized (with vendor-specific variations). T2-weighted images were acquired without fat suppression to maximize lesion conspicuity.

MRI Analysis

In-house software (Adept; the Institute of Cancer Research, London, United Kingdom) was used to define regions of interest and estimate ADCs, and b = 100, 500, and 900 smm^{-2} were used to estimate ADC (b = 0 smm^{-2} was acquired but not used in ADC estimation). Up to 10 lesions, identified at diffusion-weighted MRI and verified by using T1- and T2-weighted MRI, were analyzed per participant. Regions of interest were drawn by using region growing on computed b = 1000smm^{-2} diffusion-weighted MRI (22), around the whole area of the lesion on every slice on which it appeared. In cystic ovarian lesions (cystic nature confirmed by comparison with T2-weighted images), only the solid component was included. Two observers (J.C.W. and E.P., each with 2 years of experience with pelvic MRI) performed the image analysis over the lifetime of the study. Each study participant was analyzed by the same observer, with all images available for analysis. Final regions of interest were checked by one author (N.M.d.S., with 20 years of experience). At each time point, the median ADC was estimated for all lesions in one study participant combined (hereafter, ADC_{all}) and for each lesion separately (hereafter, ADC_{lesion}) combining all fitted voxels in the regions of interest from the participant or lesion, respectively.

Statistical Analyses

Commercially available software (Stata, version 15.1; StataCorp, College Station, Tex) was used for statistical analyses (statistician, D.D.). With 5% significance and 90% power, 120 participants are required to detect a difference of 9% in the percentage change in median ADC between responders and nonresponders (assuming 3:1 ratio). P values $< .05$ were considered to indicate statistical significance.

Repeatability of ADC estimates.—Repeatability of ADC_{all} (defined as the median ADC of all fitted voxels in one study participant) was analyzed by using a Bland-Altman plot (23). Upper and lower 95% limits of agreement were estimated. A linear regression model was used to assess the relationship between the difference in ADC_{all} and the average size of the ADC_{all} measurement. Posttreatment changes were calculated as the difference in ADC_{all} between baseline and after one cycle of treatment in cohort two and after three or four cycles in cohorts one and two (mean value used in participants with two baselines); individual changes outside the 95% limits of agreement were considered true posttreatment changes outside measurement variability.

Posttreatment changes in ADC in responders and nonresponders.—The percentage change in ADC_{all} from baseline (mean value used in participants with two baselines) was calculated after three or four cycles of treatment and was compared between responders and nonresponders defined by using CA-125 and RECIST version 1.1 criteria at the same time point per cohort and with the combined cohorts by using Wilcoxon rank sum tests. For cohort two, the percentage change in ADC_{all} after one cycle was also compared between responders and nonresponders defined by using CA-125 and RECIST version 1.1 criteria after three cycles. Participants with all resolved lesions at posttreatment diffusion-weighted MRI examinations were excluded from analysis of ADC_{all} because no suitable imputation of ADC could be made.

The percentage change in ADC_{lesion} from baseline was calculated after one cycle of treatment in cohort two and after three or four cycles in cohorts one and two. The association of percentage change in ADC_{lesion} with radiologic response was assessed by using a linear mixed-effects regression model with per-participant random intercept effects. Radiologic response was treated as the dependent variable. Lesions resolved at posttreatment diffusion-weighted MRI examinations were excluded from analysis of ADC_{lesion} because no suitable imputation of ADC could be made.

Association between posttreatment changes in ADC with PFS and overall survival.—PFS and overall survival were assessed by using a multivariable Cox model including age and percentage change in ADC_{all}. For models including cohort two, the number of previous lines of therapy was included, and for models restricted to cohort two, the duration of platinum-free interval was also included. The percentage change in ADC_{all} from baseline was calculated after one cycle of treatment in cohort two and after three or four cycles in cohorts one and two. Models of both cohorts were stratified by cohort. Participants without 2-year follow-up data were censored at last MRI examination date. Participants without an event at 2-year follow-up were censored at the 2-year point.

Results

Participant Demographics and Clinical Characteristics

One hundred thirty-two participants were enrolled (Table 1). Seven participants were excluded (Fig 1), leaving 125 participants (cohort one: 47 women; median age, 60.9 years [interquartile range, 57.2–69.5 years]; cohort two: 78 women; median age, 64.9 years [interquartile range, 57.1–71.1 years]) in the final analysis.

Repeatability of ADC_{All} at Baseline

Baseline ADC_{all}, assessed across all participants, ranged from 77×10^{-5}mm^{2}s^{-1} to 258×10^{-5}mm^{2}s^{-1}. Two baseline estimates of ADC_{all} were obtained in 19 participants. Repeatability was good, with upper 95% limits of agreement of 12×10^{-5}mm^{2}s^{-1} (95% CI: 6×10^{-5}mm^{2}s^{-1} to 18×10^{-5}mm^{2}s^{-1}) and

lower 95% limits of agreement of $-15 \times 10^{-5}mm^2s^{-1}$ (95% CI: $-21 \times 10^{-5}mm^2s^{-1}$ to $-9 \times 10^{-5}mm^2s^{-1}$). There was no evidence of a relationship between the average size of ADC_{all} and the difference between two baseline estimates (coefficient, −0.15; 95% CI: −0.36, 0.06; $P = .16$ (Fig E1 [online]).

Percentage of Participants Exhibiting a Complete Response or a Posttreatment Change in ADC_{All}

Forty of 47 participants in cohort one underwent posttreatment MRI examinations, with complete resolution of measurable disease in four of 40 (10%) and estimates of ADC_{all} obtained in the remaining 36 of 40 (Fig 1). Twenty-one of 36 (58%) participants with residual measurable disease exhibited an increase in ADC_{all} after three or four cycles of treatment; only one of 36 participants (3%) exhibited a decrease.

Seventy of 78 participants in cohort two had estimates of ADC_{all} after one cycle, and 66 of 78 had estimates of ADC_{all} after three cycles (Fig 1). Thirty-three of 70 (47%) and 35 of 66 (53%) participants exhibited an increase in ADC_{all} after one and three cycles, respectively. Only three of 70 (4%) and five of 66 (8%) exhibited a decrease at these time points (Figs 2, 3).

Change in ADC_{All} with Response Measured by Using CA-125 and RECIST Version 1.1 Criteria

In cohort one, response as assessed by using CA-125 and RECIST version 1.1 differed, primarily because the large ovarian lesions in this treatment-naïve group responded by using CA-125 criteria without a substantial change in size. Response was recorded in 33 of 35 (94%) participants by using CA-125 criteria and in 31 of 36 (86%) participants by using RECIST version 1.1 criteria after three or four cycles of treatment. At this time point in cohort two, 47 of 65 (72%) and 44 of 66 (67%) were classed as responders by using CA-125 and RECIST version 1.1 criteria, respectively (Table 2, Fig 4).

Differences in ADC_{all} changes between CA-125 responders and nonresponders.—In participants with residual measurable disease, there was a difference in percentage change in ADC_{all} between responders and nonresponders after three or four cycles of treatment when both cohorts were considered together (16.6% vs 3.9%; $P = .02$) (Table 2). This was not evident when each cohort was considered separately at any time point ($P > .05$; only two nonresponders in cohort one).

Differences in ADC_{all} changes between RECIST version 1.1 responders and nonresponders.—There was a difference in percentage change in ADC_{all} between responders and nonresponders after three or four cycles of treatment when both cohorts were considered together (19.0% vs 6.2%; $P = .04$ (Table

Table 1: Study Participant Demographics, Clinical Characteristics, and Chemotherapy Schedule

Variable	Cohort One: Primary Ovarian Cancer	Cohort Two: Relapsed Ovarian Cancer	Overall
No. of participants	47	78	125
Age (y)*	60.9 (57.2–69.5)	64.9 (57.1–71.1)	63.3 (57.0–70.7)
Histologic subtype			
Serous	47 (100)	70 (90)	117 (94)
Serous and clear cell	…	3 (4)	3 (2)
Endometrioid	…	3 (4)	3 (2)
Carcinosarcoma	…	1 (1)	1 (1)
Clear cell	…	1 (1)	1 (1)
Previous chemotherapy			
No. of previous lines of systemic therapy*	N/A	1 (1–2)	N/A
Time since last dose of a platinum-based chemotherapy agent (wk)*	N/A	74.5 (37.0–135.0)	N/A
Previous antiangiogenic agent	0 (0)	16 (21)	16 (13)
Current chemotherapy regimen			
Carboplatin monotherapy	3 (6)	7 (9)	10 (8)
Weekly	0 (0)	0 (0)	0 (0)
3-weekly	3 (100)	7 (100)	10 (100)
Carboplatin and paclitaxel	44 (94)	6 (8)	50 (40)
Weekly carboplatin	1 (2)†	0 (0)	1 (2)
3-weekly carboplatin	43 (98)	6 (100)	49 (98)
Weekly paclitaxel	9 (20)	4 (67)	13 (26)
3-weekly paclitaxel	35 (80)	2 (33)	37 (74)
Carboplatin and gemcitabine	0 (0)	24 (31)	24 (19)
Carboplatin and liposomal doxorubicin	0 (0)	36 (46)	36 (29)
Other platinum-based treatment combination	0 (0)	5 (6)	5 (4)
Cisplatin and liposomal doxorubicin	…	2 (3)	…
Cisplatin and gemcitabine	…	1 (1)	…
Cisplatin and etoposide	…	1 (1)	…
Other	…	1 (1)	…
Also receiving bevacizumab	5 (11)	7 (9)	12 (10)

Note.—Unless otherwise specified, data are numbers with percentages in parentheses. N/A = not applicable.

* Data are medians, with interquartile range in parentheses.

† Participant in ICON8 study.

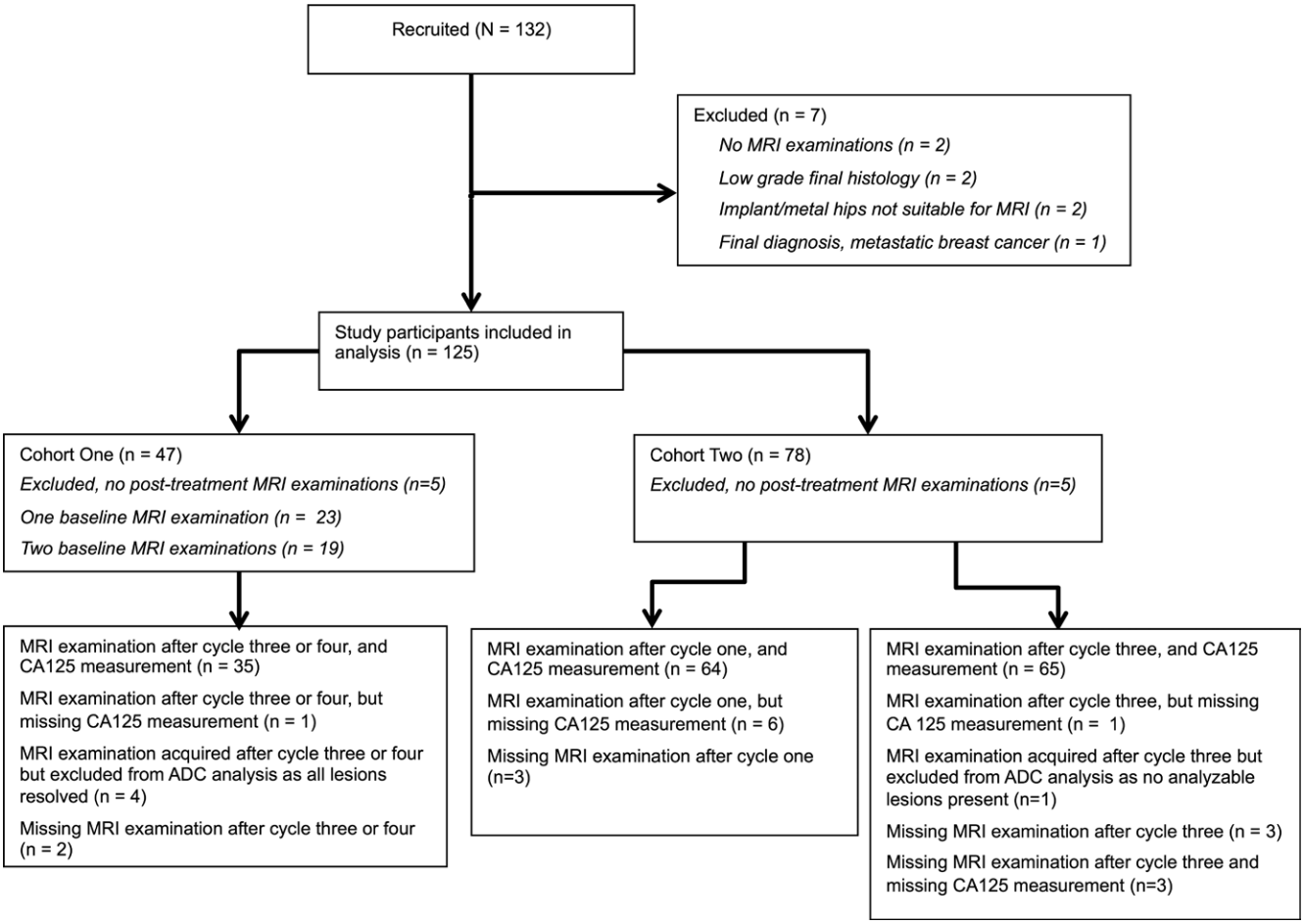

Figure 1: Flowchart shows study participant inclusion and exclusion. Seven participants were excluded after registration, as they either did not undergo any MRI examinations (no examinations, ***n*** = 2) or they were found not to have met inclusion criteria for study (low-grade disease, ***n*** = 2; implant or metal hips, ***n*** = 2; final diagnosis of metastatic breast cancer, ***n*** = 1). In cohort one, median interval between start of cycle three or four and posttreatment MRI examination was 19 days (range, 15–27 days). In cohort two, median interval between start of cycle one and MRI examination after cycle one was 21 days (range, 16–28 days); median interval between start of cycle three and MRI examination after cycle three was 22 days (range, 16–29 days). ADC = apparent diffusion coefficient, CA125 = cancer antigen 125.

2). There was also a difference for cohort one considered separately after three or four cycles (21.8% vs 3.9%; $P = .01$ (Table 2) but not for cohort two after one or three cycles ($P = .06$ and $P = .5$, respectively) (Table 2).

Association of Change in ADC_{Lesion} with Response Measured by Radiologic Criteria

In participants with residual measurable disease, percentage change in ADC_{lesion} from baseline measured after one or three or four cycles of treatment did not show any difference between responding and nonresponding lesions defined as per RECIST version 1.1 in cohorts one and two assessed together ($P = .3$) (Table 3) or in the two cohorts assessed separately (cohort one, $P = .5$; cohort two, $P = .3$) (Table 3).

Association of ADC_{All} Change with PFS and Overall Survival

In 70 participants in cohort two with residual measurable disease, the percentage change in ADC_{all} measured after one cycle of treatment was associated with longer PFS (adjusted hazard ratio, 0.86; 95% CI: 0.75, 0.98; $P = .03$) (Table 4). However, after three or four cycles of treatment, the percentage change in ADC_{all} was not associated with PFS in either cohort (cohort one, $P = .7$; cohort two, $P = .2$) or in the two cohorts assessed together ($P = .2$). The change in ADC_{all} was not associated with overall survival for either cohort at any time point ($P > .05$). The number of previous lines of therapy and duration of platinum-free interval were associated with PFS in cohort two (adjusted hazard ratio, 1.38; 95% CI: 1.13, 1.69; $P = .002$ and adjusted hazard ratio, 0.77; 95% CI: 0.63, 0.95; $P = .02$, respectively, after one cycle; adjusted hazard ratio, 1.38; 95% CI: 1.12, 1.72; $P = .003$ and adjusted hazard ratio, 0.78; 95% CI: 0.63, 0.97; $P = .03$ after three cycles) but not with overall survival ($P > .05$) (Table 4).

Discussion

This prospective study shows that the apparent diffusion coefficient (ADC) increase in patients with epithelial ovarian cancer after three or four cycles of platinum-based chemotherapy is greater in responders (by using cancer antigen 125 [CA-125] or Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1 criteria) than in nonresponders. Importantly, in relapsed disease, where a third of individuals do not respond to rechallenge with platinum-based chemotherapy, an early (after one cy-

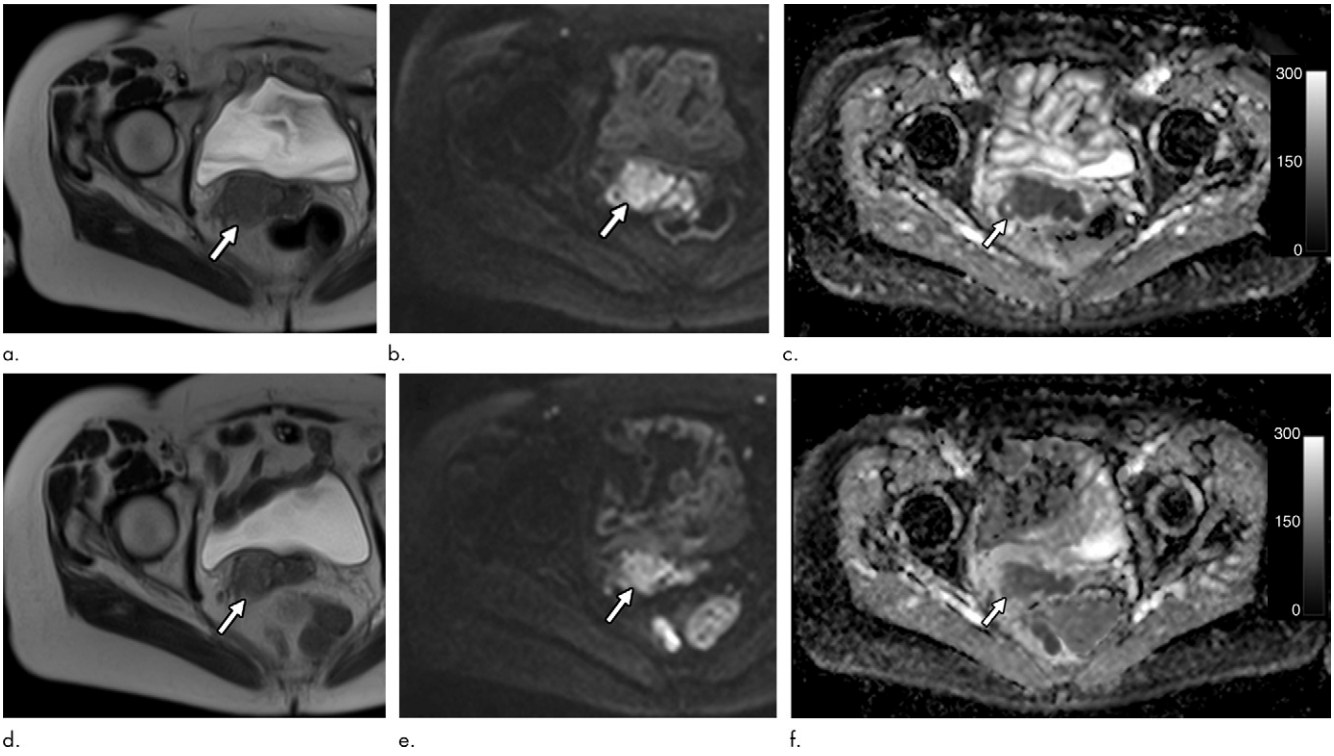

Figure 2: Images in a 75-year-old woman with relapsed epithelial ovarian cancer show treatment response: **(a)** axial T2-weighted MRI with **(b)** corresponding axial high-*b*-value diffusion-weighted MRI ($b = 900 s mm^{-2}$), **(c)** apparent diffusion coefficient (ADC) map at baseline, and **(d–f)** matched sections of same imaging sequences after one cycle of treatment. (Scalebar on ADC map is in units of $10^{-5} mm^2 s^{-1}$. Response was defined by using cancer antigen 125 and Response Evaluation Criteria in Solid Tumors version 1.1 criteria.) There is a central recurrent tumor mass (arrows). Although there was no substantial change in volume, ADC of mass increased after treatment. ADC_{lesion} (defined as median ADC of all fitted voxels in one lesion) was $93 \times 10^{-5} mm^2 s^{-1}$ at baseline, $104 \times 10^{-5} mm^2 s^{-1}$ after one cycle of treatment, and $117 \times 10^{-5} mm^2 s^{-1}$ after three cycles of treatment. ADC_{all} (defined as median ADC of all fitted voxels in one study participant) was $92 \times 10^{-5} mm^2 s^{-1}$ at baseline, $110 \times 10^{-5} mm^2 s^{-1}$ after one cycle of treatment, and $114 \times 10^{-5} mm^2 s^{-1}$ after three cycles of treatment. Changes in ADC_{all} between baseline and posttreatment measurements were larger than upper 95% limits of agreement. MRI protocols are described in Table E1 (online).

cle) increase in ADC in those with residual disease may be used independently of other clinical factors (duration of platinum-free interval, number of previous lines of therapy) to identify response and to indicate longer progression-free survival (PFS). We also saw an association of platinum-free interval and number of lines of prior therapy with PFS but not with overall survival, although larger series have indicated an association with both outcome measures (10,11). Moreover, our data confirm that high-quality, robust, quantitative diffusion-weighted MRI data can be obtained in multicenter quality-controlled studies by using standardized diffusion-weighted MRI protocols.

The baseline repeatability of our ADC estimates (upper and lower 95% limits of agreement of $12 \times 10^{-5} mm^2 s^{-1}$ and $-15 \times 10^{-5} mm^2 s^{-1}$, respectively) compares favorably with previous reports of upper and lower 95% limits of agreement of 12.1% and −10.8%, respectively, in a combined analysis of multiple single-center clinical trials (24). Good repeatability of a quantitative imaging marker confers high sensitivity to posttreatment changes. Our data provide evidence that ADC is suitable for use in clinical trials and clinical practice as set out by international standards groups (25,26). Inter- and intraobserver agreement of ADC estimates has been reported previously in advanced epithelial ovarian cancer (intraclass correlation coefficients of 0.86 (95% confidence interval [CI]: 0.52, 0.94) and 0.93 (95% CI: 0.87, 0.96), respectively) (15).

Low ADC has been shown to reflect higher cellularity in preclinical (27) and clinical studies (28), with increased ADC posttreatment reflecting increased extracellular space (29). In our study, larger ADC increases in responders compared with nonresponders indicates that ADC measurements detect microstructural changes in response to treatment and that these are detected early. This should allow early treatment alterations in nonresponders. Appropriate selection of time points for ADC measurements is, therefore, critical. In addition, the longer PFS observed with ADC changes in the relapsed cohort illustrates the value of ADC measurements in partial responders. In future, derivation of radiomic (statistical) features that describe textural heterogeneity, performed at the optimal time point, may provide a more in-depth evaluation of alterations in cellular architecture as tumors respond to treatment. As this requires larger participant numbers, data sharing through accessible managed image repositories is being investigated.

A small number of previous studies have evaluated posttreatment ADC changes in multicenter body oncology studies. A 10-center study of 272 patients with breast cancer demonstrated that ADC changes after 12 weeks of neoadjuvant chemotherapy was predictive of a complete pathologic response (30). However, a three-center study, with differences in protocols between centers, did not find additional diagnostic value in ADC changes in cervical tumors following radiation therapy (31). The importance

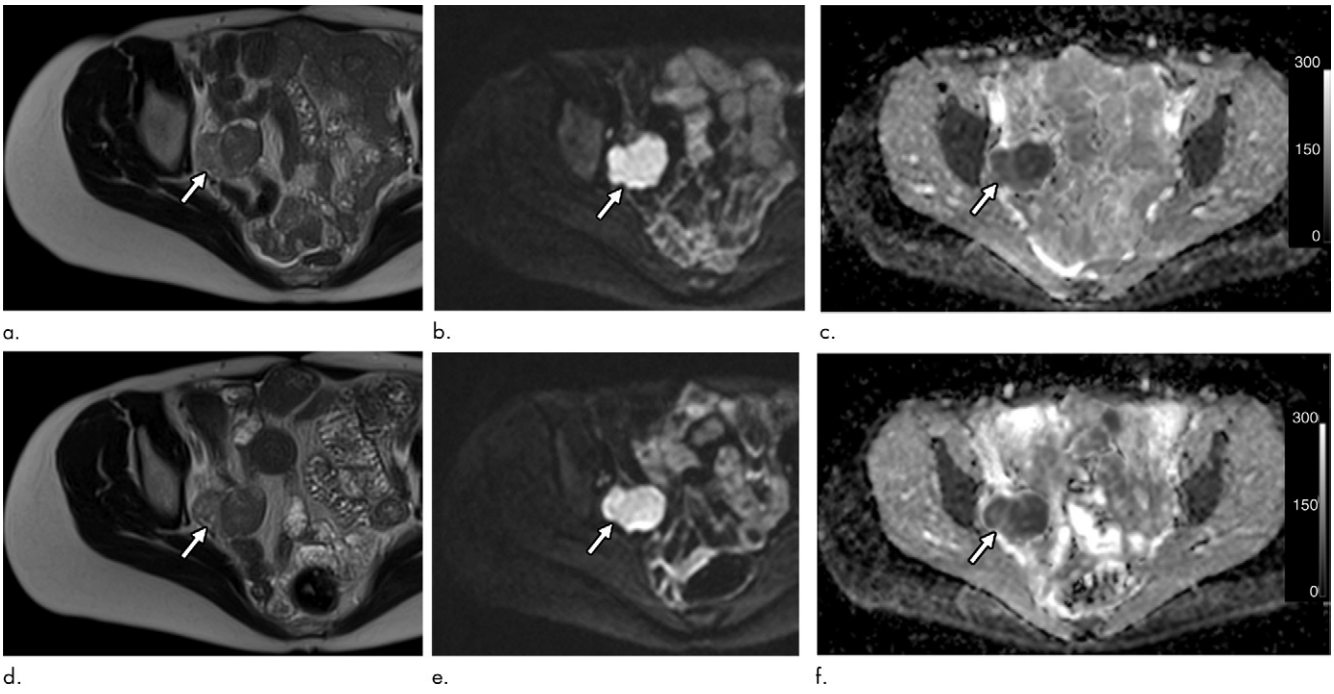

Figure 3: Images in a 52-year-old woman with relapsed epithelial ovarian cancer show no treatment response: **(a)** axial T2-weighted MRI with **(b)** corresponding axial high-*b*-value diffusion-weighted MRI ($b = 900 s mm^{-2}$), **(c)** apparent diffusion coefficient (ADC) maps at baseline, and **(d–f)** matched sections of same imaging sequences after one cycle of treatment. (Scalebar on ADC map is in units of $10^{-5} mm^2 s^{-1}$. Nonresponder was defined by using cancer antigen 125 and Response Evaluation Criteria in Solid Tumors version 1.1 criteria.) There is a solid right-sided mass (arrows) attached to bowel, which showed virtually no change after one cycle of treatment. ADC_{lesion} (defined as median ADC of all fitted voxels in one lesion) was $102 \times 10^{-5} mm^2 s^{-1}$ at baseline, $107 \times 10^{-5} mm^2 s^{-1}$ after one cycle of treatment, and $115 \times 10^{-5} mm^2 s^{-1}$ after three cycles of treatment. ADC_{all} (defined as median ADC of all fitted voxels in one study participant) was $105 \times 10^{-5} mm^2 s^{-1}$ at baseline, $107 \times 10^{-5} mm^2 s^{-1}$ after one cycle of treatment, and $115 \times 10^{-5} mm^2 s^{-1}$ after three cycles of treatment. Changes in ADC_{all} between baseline and posttreatment measurements were smaller than upper 95% limits of agreement. MRI protocols are described in Table E1 (online).

of standardized high-quality diffusion-weighted MRI protocols has also been highlighted by a multicenter study of diffusion-weighted MRI in endometrial cancer, which found that staging results by using MRIs acquired in standard clinical practice did not achieve the accuracy reported in single-center studies (32). More multicenter studies using high-quality standardized diffusion-weighted MRI protocols are required to establish the conditions required for repeatable and reproducible ADC estimates (33). The diffusion-weighted MRI protocols used in our study include 1.5-T MRI scanners from the three main manufacturers, using manufacturers' product sequences, and are suitable to be replicated at other centers.

Our study had limitations. First, our per-participant analysis (ADC_{all}, defined as the median ADC of all fitted voxels in one study participant) excluded participants whose lesions all resolved after treatment. The per-lesion analysis (ADC_{lesion}, defined as the median ADC of all fitted voxels in one lesion) excluded lesions that resolved after treatment because it was not possible to assign a posttreatment ADC value, meaning the largest ADC changes were potentially excluded from the analysis. Second, all analysis was carried out at the lead site by using in-house software; appropriate software and standardized analysis methods will be required for routine evaluation of ADC, measured over the whole tumor volume, in clinical imaging departments. Also, heterogeneity of response within and between lesions was outside the scope of our analysis; inter- and intraobserver agreement were also not assessed. Finally, we only included participants who were willing to undergo the MRI examinations in addition to their routine assessments and were able to lie still for the examination; the applicability of the results in more challenging cohorts remains to be tested.

In conclusion, apparent diffusion coefficient (ADC) measurements are robust in a multicenter setting and provide a noninvasive method to detect early microstructural changes that occur in response to treatment of advanced epithelial ovarian cancer, which is particularly relevant for relapsed disease. Where there was residual measurable disease, ADC changes were greater in responders than in nonresponders after three cycles of treatment. Finally, and most importantly, in relapsed disease, early increases in ADC (measured after one cycle of chemotherapy) were indicative of longer progression-free survival. Future investigation of the value of ADC at an early time point in relation to other clinical and biochemical factors and of pretreatment ADC alone in predicting response in relapsed disease is needed.

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Table 2: Percentage Change in ADC_{All} in Responders and Nonresponders with Residual Measurable Disease, Defined by Using CA-125 and RECIST Version 1.1 Criteria

Cohort	Time Point for ADC_{All} Measurement	Time Point for CA-125 or RECIST Response Assessment	Response	No.	Median Change in ADC_{All} (%)	Interquartile Range	*P* Value
Response by Using CA-125							
1 and 2	After cycle 3 or 4	After cycle 3 or 4	No	20	3.9	−1.9 to 20.4	.02*
			Yes	80	16.6	3.3 to 32.4	
1	After cycle 3 or 4	After cycle 3 or 4	No	2	3.6	−1.1 to 8.3	.2
			Yes	33	17.1	3.4 to 33.4	
2	After cycle 1	After cycle 1	No	45	6.8	−2.9 to 15.2	.3
			Yes	19	12.9	1.6 to 28.4	
2	After cycle 1	After cycle 3	No	19	6.9	0.9 to 13.6	.5
			Yes	48	11.5	−1.9 to 26.7	
2	After cycle 3	After cycle 3	No	18	3.9	−2.2 to 23.8	.1
			Yes	47	13.8	1.7 to 32.6	
Response by Using RECIST Version 1.1							
1 and 2	After cycle 3 or 4	After cycle 3 or 4	No	27	6.2	−1.8 to 23.4	.04*
			Yes	75	19.0	2.4 to 32.6	
1	After cycle 3 or 4	After cycle 3 or 4	No	5	3.9	−11.3 to 6.6	.01*
			Yes	31	21.8	10.3 to 37.0	
2	After cycle 1	After cycle 3	No	22	6.4	−4.3 to 13.2	.06
			Yes	42	12.3	0.2 to 19.5	
2	After cycle 3	After cycle 3	No	22	10.0	−0.8 to 27.6	.5
			Yes	44	13.3	0.4 to 28.8	

Note.—Cohort one consisted of participants with newly diagnosed disease. Cohort two consisted of participants at first or subsequent relapse. There was no evidence of a difference between cohorts in the percentage change in ADC_{all}, defined as median ADC of all fitted voxels in one study participant, after three or four cycles of treatment (*t* test, $P = .8$). *P* values show results from Wilcoxon rank sum tests between responders and nonresponders. ADC = apparent diffusion coefficient, CA-125 = cancer antigen 125, RECIST = Response Evaluation Criteria in Solid Tumors.

* Denotes $P < .05$.

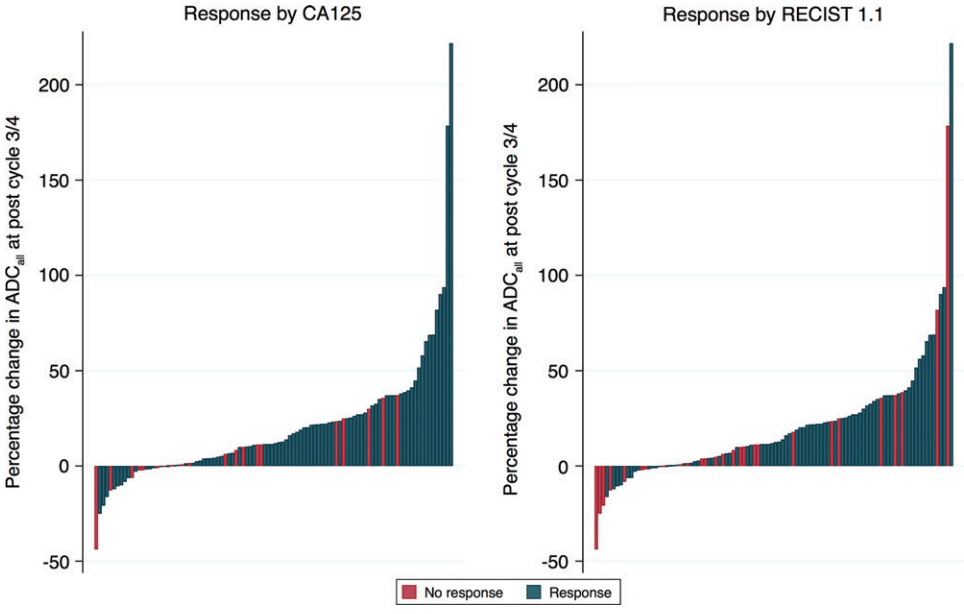

Figure 4: Waterfall plot shows ADC_{all} (defined as median apparent diffusion coefficient [ADC] of all fitted voxels in one study participant) percentage change in responders and nonresponders, defined by using cancer antigen 125 (CA125) and Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria.

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Table 3: Association of Percentage Change in ADC_{Lesion} with Radiologic Response after Three or Four Cycles of Treatment by Using a Linear Mixed Effects Regression Model

Cohort	Time Point for ADC_{Lesion} Measurement	No. of Unresolved Lesions Included in Analysis	Coefficient	95% Confidence Interval	*P* Value
1 and 2	After cycle 3 or 4	223*	−5.0	−14.2, 4.2	.3
1	After cycle 3 or 4	81†	−3.9	−15.7, 7.9	.5
2	After cycle 1	145‡	4.8	−4.3, 13.8	.3
2	After cycle 3	142§	−6.9	−19.6, 5.8	.3

Note.—The smallest lesion included at baseline had a volume of 175 mm^3. Radiologic response (treated as the dependent variable) was defined as a 30% reduction in lesion diameter. ADC = apparent diffusion coefficient, ADC_{lesion} = median ADC of all fitted voxels in one lesion.

* 59 lesions resolved after three or four cycles in cohorts one and two combined.

† 38 lesions resolved after three or four cycles in cohort one.

‡ 10 lesions resolved after one cycle in cohort two.

§ 21 lesions resolved after three cycles in cohort two.

Table 4: Association of Percentage Change in ADC_{All} with PFS and OS

Cohort	Time Point for ADC_{All} Measurement	Variable	Adjusted Hazard Ratio*	95% Confidence Interval	*P* Value
		PFS			
1 and 2	After cycle 3 or 4	Age (per 10 y)	0.97	0.76, 1.24	.8
		No. of previous lines of therapy	1.40	1.14, 1.72	.001†
		Percentage change in ADC_{all} after cycle 3 or 4 (per 10%)	0.95	0.87, 1.03	.2
1	After cycle 3 or 4	Age (per 10 y)	1.27	0.83, 1.95	.3
		Percentage change in ADC_{all} after cycle 1 (per 10%)	0.96	0.80, 1.16	.7
2	After cycle 1	Age (per 10 y)	0.78	0.58, 1.05	.1
		No. of previous lines of therapy	1.38	1.13, 1.69	.002†
		Duration of platinum-free interval (y)	0.77	0.63, 0.95	.02†
		Percentage change in ADC_{all} after cycle 1 (per 10%)	0.86	0.75, 0.98	.03†
2	After cycle 3	Age (per 10 y)	0.79	0.58, 1.08	.1
		No. of previous lines of therapy	1.38	1.12, 1.72	.003†
		Duration of platinum-free interval (y)	0.78	0.63, 0.97	.03†
		Percentage change in ADC_{all} after cycle three (per 10%)	0.93	0.85, 1.03	.2
		OS			
1 and 2	After cycle 3 or 4	Age (per 10 y)	1.06	0.77, 1.45	.7
		No. of previous lines of therapy	0.96	0.73, 1.25	.7
		Percentage change in ADC_{all} after cycle 3 or 4 (per 10%)	1.00	0.91, 1.09	>.9
1	After cycle 3 or 4	Age (per 10 y)	1.37	0.70, 2.67	0.4
		Percentage change in ADC_{all} after cycle 1 (per 10%)	0.78	0.54, 1.12	0.2
2	After cycle 1	Age (per 10 y)	0.95	0.65, 1.39	0.8
		No. of previous lines of therapy	0.99	0.78, 1.25	0.9
		Duration of platinum-free interval (y)	0.95	0.76, 1.18	0.6
		Percentage change in ADC_{all} after cycle 1 (per 10%)	1.01	0.88, 1.14	0.9
2	After cycle 3	Age (per 10 y)	0.84	0.55, 1.27	0.4
		No. of previous lines of therapy	0.96	0.73, 1.25	0.8
		Duration of platinum-free interval (y)	0.98	0.80, 1.21	0.9
		Percentage change in ADC_{all} after cycle 3 (per 10%)	1.01	0.94, 1.10	0.7

Note.—Censored data in survival analysis as follows. For progression-free survival (PFS) (cohort 1): No patients were missing data on disease progression. One patient was excluded from analyses due to quality control concerns with the date of death. Twenty-seven patients were reported with disease progression, four patients died without prior reported progression, and 15 patients were alive without an event and were censored. For PFS (cohort 2): two patients were missing data on disease progression so were censored at last MRI examination date. Fifty-one patients were reported with disease progression, seven patients died without prior reported progression, and 18 patients were alive without an event and were censored. For overall survival (OS) (cohort 1): No patients were missing data at 2-year follow-up. Seventeen patients had died after 2 years of follow-up, and 30 were alive and censored. For OS (cohort 2): two patients were missing data at 2-year follow-up so were censored at last MRI examination date. Thirty-four patients had died after 2 years of follow-up, and 42 were alive and censored. The association of cancer antigen 125 response, Response Evaluation Criteria in Solid Tumors version 1.1 response, and cohort with PFS and OS was not part of the present study, but is included in Table E2 (online). ADC = apparent diffusion coefficient, ADC_{all} = median ADC of all fitted voxels in one study participant.

* The "hazard" in the survival analysis was disease progression for PFS analysis, and death for OS analysis. A hazard ratio less than 1 therefore indicates a lower incidence of progression (PFS) or death (OS), while a hazard ratio greater than 1 indicates a greater incidence of progression (PFS) or death (OS).

† Denotes $P < .05$.

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References

1. Horowitz NS, Miller A, Rungruang B, et al. Does aggressive surgery improve outcomes? Interaction between preoperative disease burden and complex surgery in patients with advanced-stage ovarian cancer: an analysis of GOG 182. J Clin Oncol 2015;33(8):937–943.
2. Gockley A, Melamed A, Bregar AJ, et al. Outcomes of women with high-grade and low-grade advanced-stage serous epithelial ovarian cancer. Obstet Gynecol 2017;129(3):439–447.
3. Matz M, Coleman MP, Carreira H, et al. Worldwide comparison of ovarian cancer survival: Histological group and stage at diagnosis (CONCORD-2). Gynecol Oncol 2017;144(2):396–404 [Published correction appears in Gynecol Oncol 2017;147(3):725.] https://doi.org/10.1016/j.ygyno.2016.11.019.
4. du Bois A, Lück HJ, Meier W, et al. A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer. J Natl Cancer Inst 2003;95(17):1320–1329.
5. Vergote I, Tropé CG, Amant F, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N Engl J Med 2010;363(10):943–953.
6. Winter WE 3rd, Maxwell GL, Tian C, et al. Prognostic factors for stage III epithelial ovarian cancer: a Gynecologic Oncology Group Study. J Clin Oncol 2007;25(24):3621–3627.
7. Chan JK, Loizzi V, Lin YG, Osann K, Brewster WR, DiSaia PJ. Stages III and IV invasive epithelial ovarian carcinoma in younger versus older women: what prognostic factors are important? Obstet Gynecol 2003;102(1):156–161.
8. Asher V, Lee J, Bali A. Preoperative serum albumin is an independent prognostic predictor of survival in ovarian cancer. Med Oncol 2012;29(3):2005–2009.
9. Clamp AR, McNeish I, Dean A, et al. 929O_PRICON8: A GCIG phase III randomised trial evaluating weekly dose-dense chemotherapy integration in first-line epithelial ovarian/fallopian tube/primary peritoneal carcinoma (EOC) treatment: Results of primary progression-free survival (PFS) analysis. Ann Oncol 2017;28(suppl_5):mdx440.039.
10. Classe JM, Jaffre I, Frenel JS, et al. Prognostic factors for patients treated for a recurrent FIGO stage III ovarian cancer: a retrospective study of 108 cases. Eur J Surg Oncol 2011;37(11):971–977.
11. Petrillo M, Fagotti A, Ferrandina G, et al. Ovarian cancer patients with localized relapse: clinical outcome and prognostic factors. Gynecol Oncol 2013;131(1):36–41.
12. Wesbey GE, Moseley ME, Ehman RL. Translational molecular self-diffusion in magnetic resonance imaging. II. Measurement of the self-diffusion coefficient. Invest Radiol 1984;19(6):491–498.
13. Le Bihan D, Turner R, Moonen CT, Pekar J. Imaging of diffusion and microcirculation with gradient sensitization: design, strategy, and significance. J Magn Reson Imaging 1991;1(1):7–28.
14. Taouli B, Beer AJ, Chenevert T, et al. Diffusion-weighted imaging outside the brain: Consensus statement from an ISMRM-sponsored workshop. J Magn Reson Imaging 2016;44(3):521–540.
15. Kyriazi S, Collins DJ, Messiou C, et al. Metastatic ovarian and primary peritoneal cancer: assessing chemotherapy response with diffusion-weighted MR imaging: value of histogram analysis of apparent diffusion coefficients. Radiology 2011; 261(1):182–192.
16. Sharma U, Danishad KKA, Seenu V, Jagannathan NR. Longitudinal study of the assessment by MRI and diffusion-weighted imaging of tumor response in patients with locally advanced breast cancer undergoing neoadjuvant chemotherapy. NMR Biomed 2009;22(1):104–113.
17. Koh DM, Scurr E, Collins D, et al. Predicting response of colorectal hepatic metastasis: value of pretreatment apparent diffusion coefficients. AJR Am J Roentgenol 2007;188(4):1001–1008.
18. Yabuuchi H, Hatakenaka M, Takayama K, et al. Non-small cell lung cancer: detection of early response to chemotherapy by using contrast-enhanced dynamic and diffusion-weighted MR imaging. Radiology 2011;261(2):598–604.
19. Rustin GJS, Vergote I, Eisenhauer E, et al. Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA 125 agreed by the Gynecological Cancer Intergroup (GCIG). Int J Gynecol Cancer 2011;21(2):419–423.
20. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228–247.
21. Winfield JM, Collins DJ, Priest AN, et al. A framework for optimization of diffusion-weighted MRI protocols for large field-of-view abdominal-pelvic imaging in multicenter studies. Med Phys 2016;43(1):95–110.
22. Blackledge MD, Leach MO, Collins DJ, Koh DM. Computed diffusion-weighted MR imaging may improve tumor detection. Radiology 2011;261(2):573–581.
23. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1(8476):307–310.
24. Winfield JM, Tunariu N, Rata M, et al. Extracranial soft-tissue tumors: repeatability of apparent diffusion coefficient estimates from diffusion-weighted MR imaging. Radiology 2017;284(1):88–99.
25. Raunig DL, McShane LM, Pennello G, et al. Quantitative imaging biomarkers: a review of statistical methods for technical performance assessment. Stat Methods Med Res 2015;24(1):27–67.
26. Sullivan DC, Obuchowski NA, Kessler LG, et al. Metrology standards for quantitative imaging biomarkers. Radiology 2015;277(3):813–825.
27. Hill DK, Heindl A, Zormpas-Petridis K, et al. Non-Invasive Prostate Cancer Characterization with Diffusion-Weighted MRI: Insight from *In silico* Studies of a Transgenic Mouse Model. Front Oncol 2017;7:290.
28. Guo AC, Cummings TJ, Dash RC, Provenzale JM. Lymphomas and high-grade astrocytomas: comparison of water diffusibility and histologic characteristics. Radiology 2002;224(1):177–183.
29. Chenevert TL, McKeever PE, Ross BD. Monitoring early response of experimental brain tumors to therapy using diffusion magnetic resonance imaging. Clin Cancer Res 1997;3(9):1457–1466.
30. Partridge SC, Zhang Z, Newitt DC, et al. Diffusion-weighted MRI findings predict pathologic response in neoadjuvant treatment of breast cancer: the ACRIN 6698 Multicenter Trial. Radiology 2018;289(3):618–627.
31. Thomeer MG, Vandecaveye V, Braun L, et al. Evaluation of T2-W MR imaging and diffusion-weighted imaging for the early post-treatment local response assessment of patients treated conservatively for cervical cancer: a multicentre study. Eur Radiol 2019;29(1):309–318.
32. Soneji ND, Bharwani N, Ferri A, Stewart V, Rockall A. Pre-operative MRI staging of endometrial cancer in a multicentre cancer network: can we match single centre study results? Eur Radiol 2018;28(11):4725–4734.
33. Shukla-Dave A, Obuchowski NA, Chenevert TL, et al. Quantitative imaging biomarkers alliance (QIBA) recommendations for improved precision of DWI and DCE-MRI derived biomarkers in multicenter oncology trials. J Magn Reson Imaging 2019;49(7):e101–e121.