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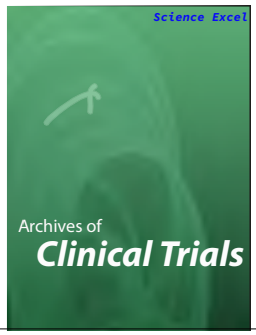

Value of 3T diffusion weighted MRI in comparison with CECT in detection of ovarian cancer and ovarian cancer recurrence

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Abstract

Purpose: To investigate the value of 3T diffusion weighted magnetic resonance imaging (DW-MRI) compared to contrast enhanced computed tomography (CECT), in the preoperative staging of patients with suspected ovarian cancer (OC) or with suspected recurrence of ovarian cancer (ROC).

Materials and methods: Thirty-two women (mean age 65 ± 14) with suspected (n = 23) or recurrent (n = 9) ovarian cancer were included prospectively in a single center study. CECT and abdominal 3T DW-MRI were performed. Both methods were used to independently score the presence of 1) ovarian tumor, 2) peritoneal or omental carcinomatosis, 3) pathological lymph nodes (LN), along with 4) liver parenchymal, 5) liver capsular, 6) diaphragmatic, and 7) extra-abdominal metastases. Findings were scored as: 0=benign, 1=suspicious for malignancy, or 2=definitely malignant. In addition, the lowest ADC values were measured in existing primary tumors. The extent of disease burden and correlation to histopathological findings were analyzed.

Results: The mean disease score was higher in DW-MRI than in CT (4.9 ± 2.6 vs. 3.5 ± 2.2, $P < 0.001$). Compared to CT, DW-MRI depicted more LN ($P = 0.001$) and diaphragmatic ($P = 0.024$) lesions. The lowest ADC values were significantly lower in malignant tumors (n = 18) than in benign tumors (n = 5) (0.640×10^{-3}mm^2/s ± 159 vs. 0.992×10^{-3}mm^2/s ± 218, $P = 0.002$).

Conclusion: The results of our prospective single center study show incremental value of abdominal 3T DW-MRI in comparison with CECT, especially in detecting diaphragmatic and peritoneal ovarian cancer metastases, excluding lymph nodal metastases and in differentiating malignant adnexal tumors from benign.

Introduction

Ovarian cancer is an infrequent tumor showing early silent metastatic growth and high recurrence rates. The treatment management depends on staging; advanced stages in particular need to be accurately assessed for optimal therapeutic management [1]. The correct staging helps surgeons to achieve complete tumor resection, as the extent of residual disease is one of the most crucial prognostic factors for patients with ovarian cancer [2,3]. The gold standard for imaging in the pre-operative staging of ovarian cancer is still body (chest, abdomen, pelvis) contrast enhanced computed tomography (CECT). The accuracy of CECT is similar to that of conventional magnetic resonance imaging (MRI) (ranging from 53% - 92% vs. 78% - 93%, respectively [4-6]. The higher field strength 3T MRI may possess accuracy comparable to surgical staging of ovarian cancer, because in simple terms, 3T MRI has twice the strength of 1.5T MRI and provides more information about structure and function of tissues, in half the time of the 1.5T machines [7]. The most important limitations of CT in the staging of ovarian cancer include the challenge of identifying small peritoneal metastases and the difficulty in differentiating between malignant and benign ovarian masses [8]. CT also lacks functional information, which could help to define lymph nodes as metastatic by using criteria other than just size.

The degree of restriction to water diffusion in biological tissues is inversely correlated to the tissue cellularity and the integrity of cell membranes. Such imaging can be performed quickly without the need for the administration of exogenous contrast medium [9]. Recent advances have enabled diffusion weighted imaging (DWI) to be widely used for tumor evaluation in the abdomen and pelvis and furthermore, whole-body DWI

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is a recent development that shows substantial promise for tumor detection, but requires further evaluation [10]. In the recent published study, the whole-body DW-MRI showed more accuracy in the characterization of primary tumors and peritoneal staging in patients with suspected ovarian cancer (OC) compared with CT and 18F-fluorodeoxyglucose positron emission tomography/ computed tomography (FDG-PET/ CT) [11]. It has been proposed that DW-MRI might become part of the standard imaging protocol for the evaluation of the female pelvis [12]. Thus, the study results so far have been controversial with existing overlap in apparent diffusion coefficient (ADC) values of adnexal masses. Some studies have shown significant differences between the mean ADC values of benign and malignant ovarian masses [13,14] while other studies do not confirm this [15,16].

Accordingly, the purpose of the current study was to evaluate the incremental value of abdominal 3T DW-MRI and assessment of ADC values as compared to CECT in the preoperative staging of patients with suspected ovarian cancer or with suspected recurrence of ovarian cancer.

Materials and methods

Study Design

Thirty-two women (mean age 65 ± 14 years) constituted the study population of our prospective single center study. The study protocol was approved by the ethical committee of our University Hospital and written informed consent was obtained from study subjects. The patients were enrolled consecutively between January 2012 and December 2012 if ovarian cancer (n = 23) or a recurrence of ovarian cancer (ROC, n = 9) was suspected by a gynaecological oncologist. The diagnostic workup included gynaecological ultrasound and CA-125 tumor marker assessment. All patients were scheduled for routine body-CT (chest, abdomen and pelvis, n = 17) or abdominal (abdomen and pelvis, n = 15) CECT and 3T abdominal MRI in close proximity, optimally on the same day. The primary tumor size, tumor´s cystic character (cystic or not cystic) and the amount of ascites (no ascites, minor or major amount of ascites, estimated by readers) were recorded. The location and the size of metastatic lesions were reported. Largest diameter of primary and metastatic masses and shortest diameter of regional lymph nodes were measured. Baseline CA-125 values and the kinetics of CA-125 changes in ROC patients at the time of the recurrence suspicion were registered. Patients with imaging artefacts (n = 2) were excluded, one due to hip prosthesis and one due to lack of cooperation with breathing instructions. Patients subsequently diagnosed with malignancies other than ovarian cancer (n = 3), or benign diseases (n = 5), were not excluded to be able to analyze differential diagnostic performance of 3T MRI between ovarian cancer, other malignancies and benign tumors, similar to the daily evaluation procedure in clinical practice.

Imaging protocols

MR Imaging: MRI (3 T, Philips Achieva TX, Philips Medical Systems, Best, The Netherlands) protocols used a body coil (Sense-XL-Torso) for the lower and upper abdomen with imaging from the symphysis to the phrenicocardium, and included transaxial and sagittal T2-weighted (TR 651, TE 80), transaxial diffusion-weighted ((*b*-values 0, 300, 600 (sec/mm^2)) and diffusion-weighted imaging with background body signal suppression (DWIBS, *b*-value 800) sequences. Sixteen sections were acquired in a single breath hold that lasted 20 s (see Table 1 for parameter details). ADC-maps were automatically generated for b-values of 0 and 600. Anti-peristaltic drugs and rectal or vaginal gel were not used. The patients were allowed to have a light meal before imaging, but a number of them fasted.

Table 1. *3T MR imaging parameters for evaluation of patients with suspected and recurrent ovarian cancer*

	T2	DWIBS	DW-MRI
Plane	Axial	Axial	Axial
Sequence	ssTSE	ssEPI	ssEPI
TR (ms)	4000	5580	1831
TE (ms)	80	50	48
TI (ms)	-	260	-
b-values	-	800	0,300,600
Field of view (mm)	403/253	403/249	403/249
Slice thickness (mm)	5	5	5
Number of slices	46	55	46
NSA	1	5	4
Gap (mm)	0.5	0	0.5
Phase encoding steps	251	92	124
Frequency encoding steps	312	124	124
Echo train length	51	29	39
Sense factor	2	2	2
Scan duration	0:44	2:55	2:34
Breath hold	-	Yes	Yes

Abbreviations: T2 = T2-weighted imaging, ssTSE = single shot (half-Fourier) turbo spin echo, DWIBS = diffusion weighted imaging with body background suppression, DW-MRI = diffusion weighted magnetic resonance imaging, ssEPI = ingle shot echo-planar imaging, TR = repetition time, TE = echo time, TI = time to inversion

CT Imaging: CECT scans were performed with a 16- or 64-detector row scanner (Somatom Sensation 16 or Somatom Definition AS64; Siemens Medical Systems, Erlangen, Germany) with intravenous contrast (iohexol [Omnipaque 350 mg/ml; GE Healthcare, Oslo, Norway] or iobitridol [Xenetix 350 mg I/ml], bolus 100 ml, flow rate 4 ml/s) in the portal venous phase from the thoracic apex to the symphysis pubis (body-CECT), or from the phrenicocardium to the symphysis pubis (abdominal CECT) without ingestion of oral contrast material. CECTs were reconstructed from coronal and transverse 3-5 mm thick slices.

Image Analysis and Scoring

Diffusion weighted MRIs (n = 32) were prospectively interpreted by Observer 1. Observer 2 retrospectively and independently interpreted DW-MRIs of the patients with existing primary tumors (n = 23). Both Observers were blinded to the CECT and to intra-operative and histopathological findings. Observer 1 is a radiology resident and specialist in gynecology with two years of experience in gynecological imaging, Observer 2 a radiologist with 10 years of experience

in gynecological imaging. Seven radiologists (with experience in gynecological CT ranging from 5 to 23 years) prospectively analyzed the CECT images according to established diagnostic criteria [17,18] and recorded the findings in a written clinical report as a part of their routine work. The thoracic findings on body-CTs were recorded, but the data was not used in the current study. The Observer 1, based on the prospective clinical reports, subsequently recorded the scorings of the CT images.

Seven different tumor sites were evaluated: 1) the primary tumor (when present), 2) peritoneal or omental carcinomatosis, 3) lymph nodes (LN), 4) liver parenchyma, 5) liver capsule, 6) diaphragmatic surfaces and 7) extra-abdominal tumor locations. The disease extent in each tumor site was scored as: 0 = benign, 1 = suspicious for malignancy and 2 = definitely malignant. The overall disease extent score (DS) was created by summing the scores of the individual tumor sites separately in CECT and DW-MRI.

The overall score and site specific disease scores were compared between the modalities. When available, the accuracy of assessments was compared to the histopathological findings. During the visual assessment of DW images, the criterion for malignancy was increased signal intensity in the DWIBS sequence. Observed lymph nodes were evaluated regardless of size criteria. In quantitative analyses (adnexal primary tumors), ADC values were measured on an IDS5 diagnostic workstation (version 10.2P4; Sectra Imtec, Linköping, Sweden) using magnified images on 1600×1200 displays in the region with the lowest signal on T2 weighted images, which was interpreted to represent the most solid area of the tumor. The size of the regions of interest (ROI) varied and was held as large as possible avoiding cystic and necrotic areas. The measurements were repeated in at least three ROIs on the ADC maps and the lowest ADC value was used in the statistical analysis.

Intra- and Inter-observer Analyses

To assess intra-observer repeatability, the ADC measurements of primary tumors and visual analyses of the disease scores were performed twice by Observer 1 (at least 6 months between the two assessments). To assess inter-observer reproducibility, the analyses were independently performed by Observer 2.

Surgical Protocol

Newly diagnosed patients underwent a primary debulking procedure (n = 16) or interval debulking surgery after neoadjuvant chemotherapy (n = 4) with surgical histopathological staging (n = 20/23). One 80 year-old patient with advanced ovarian cancer received a primary tumor biopsy and was treated with chemotherapy (1/23). One patient underwent explorative laparoscopy confirming ovarian cancer with peritoneal carcinomatosis and metastatic diaphragmatic lesions (1/23). One patient with prominent ovaries and pleural fluid with benign cytology received a consensus diagnosis of benign disease during clinical follow-up (1/23).

Histopathological Protocol

Gynecological pathologist (experience more than 10 years) from our institution interpreted the findings in a routine manner using the revised World Health Organization histologic classification for ovarian neoplasms [19].

Statistical Analysis

The paired samples T-test was used to compare the disease score sums between CECT and DW-MRI (results of Observer 1). Wilcoxon signed ranks test was used to compare the disease scores in different tumor sites. One-way ANOVA was used to test the differences in ADC values in primary tumors. We examined the intra- and inter-rater repeatability of the ADC values by calculating intra-class correlation coefficients and the intra- and inter-rater repeatability of tumor site disease scores by calculating Kappa coefficients (κ). Statistical analysis was performed by using the SPSS 19.0 software package. A P-value < 0.05 was considered statistically significant.

Results

Thirty-two females (mean age 65 years, range 26 - 87 years) were studied. Twenty-three patients (72%) were suspected to have ovarian cancer and nine patients (28%) were suspected to have recurrent ovarian cancer. The primary tumor size varied from 2 cm to 24 cm, with the tumor type being cystic in 80% of cases. The tumor marker CA 125 ranged from 5 to 5234 IU/L, (mean 614 IU/L). In patients with histopathological analysis of the primary tumor (n = 23), 15/23 (65%) patients had newly diagnosed ovarian cancer, three had other malignancies (13%) and five (22%) had a benign histological finding (Table 2).

The mean interval between the CECT and DW-MRI examinations was 8 days and 16 patients (50%) had both examinations within 5 days. During MRI-examination 11 patients (34%) had minor and 9 (28%) had severe ascites. MR-imaging was feasible in all patients.

The overall disease extent score was higher in DW-MRI (4.9 ± 2.6) than in CT (3.5 ± 2.2, P < 0 .001). Of the seven different tumor sites DW-MRI disease scores were significantly higher than CT disease scores in lymph nodes (P = 0.001) and diaphragm (P = 0.024). Disease scores were not significantly different for CT and DW-MRI in the other sites with following results: primary tumor (P = 0.102), peritoneal / omental carcinomatosis (P = .083), liver parenchymal (P = 0.414), liver capsular (P = 0.317), and extra-abdominal (P = 0.114) locations.

When analysing benign (DS = 0) and definitely malignant (DS = 2) disease scores of primary tumors, the positive predictive value (PPV) of DW-MRI was 100% (TP = 16, FP = 0) and the negative predictive value (NPV) was 67% (TN = 2, FN = 1). For CT, the PPV was 94% (TP = 17, FP = 1), while the NPV was not applicable. In further analysis, when suspicious for malignancy (DS = 1) and definitely malignant (DS = 2) disease scores were combined, the PPV and NPV for DW-MRI were 89% and 75%, respectively; while the PPV for CECT was 78% (Table 3). The diagnostic accuracy of the disease scores in the other tumor sites is also shown in Table 3.

Lymph Node Metastases

Lymph nodes, located as para-aortic, para-caval, para-iliac and mesenteric or peri-portal, varied in size from 4 to 20 mm. By DW-MRI, the LNs were scored as definitely malignant in 14 patients and as suspicious for malignancy in 8 cases. The LN-scores were equal by both modalities 18/32 times. Of the six discrepant cases (by DW-MRI definitely malignant / by CT benign) four patients underwent surgery, and three of them were proven to have lymph node metastases. One patient underwent interval debulking surgery after neoadjuvant chemotherapy, and metastases were found on the surface of the sigmoid colon and omentum, but not in the removed lymph nodes.

Table 2. *Clinicopathological Features of Patients with Suspected and Recurrent Ovarian Cancer*

	Patient	Histology	Age (years)	FIGO stage	Grading
Ovarian cancer	1	Mucinous ovarian cystadenocarcinoma	58	IC	2
	2	Serous tubal intraepithelial carcinoma	65	IV	2
	5	Peritoneal adenocarcinoma	74	IV	
	6	Ovarian carcinosarcoma	70	IIIC	3
	10	Serous ovarian cystadenocarcinoma	86	IIIB	2
	11	Suspected ovarian carcinoma	87	III	
	12	Serous ovarian carcinoma	73	IV	2
	13	Mucinous ovarian carcinoma	48	IV	2
	14	Serous ovarian cystadenocarcinoma	61	IV	3
	15	Serous ovarian cystadenocarcinoma	71	IIIC	3
	16	Mucinous ovarian cystadenocarcinoma	55	IIIC	2
	17	Ovarian clear cell carcinoma	66	IV	3
	20	Ovarian carcinosarcoma	58	IIIC	3
	21	Serous ovarian cystadenocarcinoma	75	IV	2
	30	Serous tubal carcinoma	80	IIIC	3
Recurrent ovarian cancer	4	Ovarian psammocarcinoma	29	IV	1
	7	Tubal adenocarcinoma	69	IV	3
	9	Ovarian adenocarcinoma	56	IIIC	3
	23	Peritoneal carcinomatosis (PC)	71	IIIC	3
	25	Ovarian cancer and PC	69	IV	
	27	Ovarian cancer	78	IV	
	28	Serous ovarian cystadenocarcinoma	68	IIIC	3
	29	Ovarian cystadenocarcinoma	66	IV	
	31	Serous ovarian cancer	73	IIIC	3
	24	B-cell lymphoma (bowel biopsy)	73		
Other malignancy	32	Mucinous appendix carcinoma (pseudomyxoma)	57		
	18	Retroperitoneal leiomyosarcoma	50	IV	3
	3	Uterine leiomyoma	26	benign	
Benign disease	8	Endometriosis	47	benign	
	19	Pleural cells benign (Papa class 2), prominent ovaries	83	benign	
	22	Benign ovarian cystadenoma	72	benign	
	26	Benign mucinous cystadenoma	51	benign	

Diaphragmatic Metastases

In four cases, the diaphragmatic metastatic lesions were only depicted in DW-MRI and were missed in CT (Figure 1). Lesion sizes varied from 1.2 to 1.7 cm. Two of the cases were histopathologically confirmed to be metastatic. Two patients with recurrent ovarian cancer did not undergo surgery.

Liver and Liver Capsular Metastases

One liver metastasis in a ROC patient was prospectively missed by CECT (Figure 2). Another liver metastasis in a newly diagnosed ovarian cancer patient was evaluated as suspicious in CECT, but definitely malignant in DW-MRI and was further confirmed by the surgical histopathological findings. One suspicious (DS = 1) liver capsular lesion was depicted by DW-MRI and was not confirmed by palpation in the following surgery. No suspicious liver capsular lesions were observed by CECT.

Extra-abdominal Metastases

By DW-MRI, definitely malignant extra-abdominal lesions were found in 10/32 patients (31%) and one suspicious lesion was depicted. Nine definitely malignant supradiaphragmatic lesions were detected in the cardiophrenic space with sizes ranging between 5 and 15 mm. One 14 mm lesion was located parasternal. Four of these ten (40%) lesions were not depicted in CECT (Figure 3), three in newly diagnosed patients and

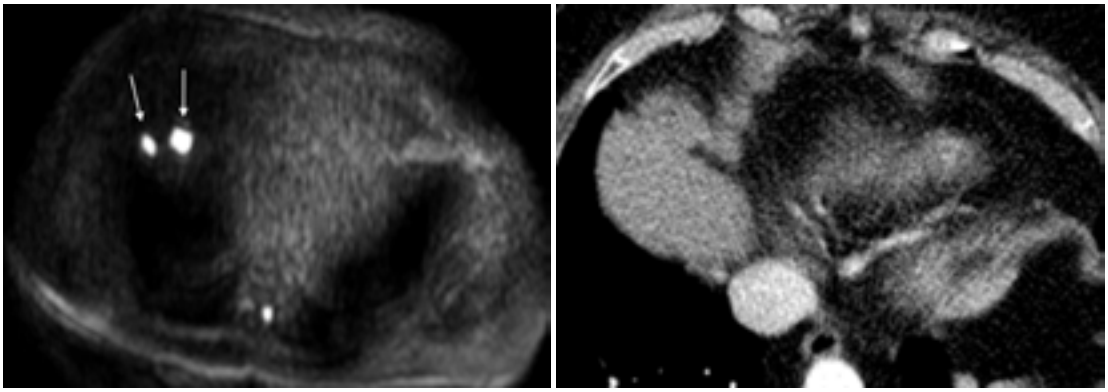

Figure 1. *A 69-year-old woman with recurrent non-operable ovarian cancer (Stage IV). Progressive disease was suspected due to a rise of the tumor marker CA 125. Diaphragmatic metastases were depicted in DW MRI (5608/52, b = 800 sec/mm²) (a), but missed in CECT (b).*

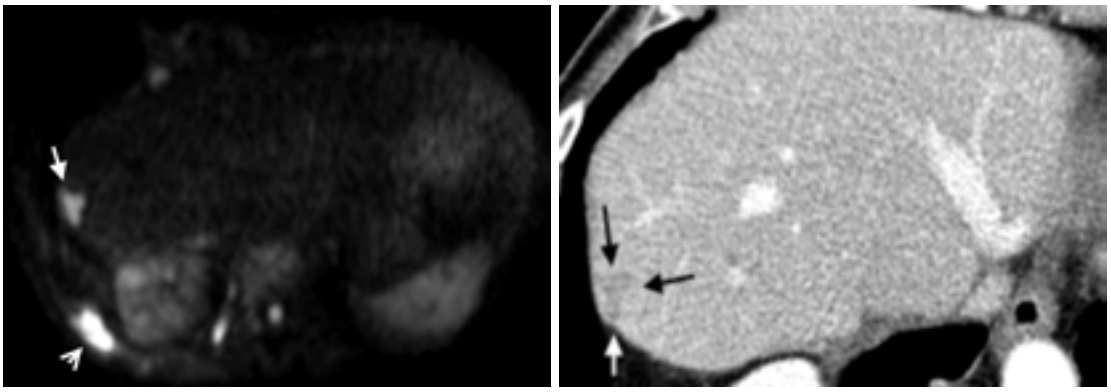

Figure 2. *A 68-year-old woman with recurrent serous ovarian cystadenocarcinoma (Stage IIIC). No liver lesions were depicted in a scheduled control whole-body CECT. After suspected liver metastasis was detected in transverse plane DW-MRI (5608, 52, b = 800 sec/mm²) (a) (arrow) the correlating flat lesion was found in the CECT retrospectively (b). Also seen on DW-MRI (a) the recurrence of the diaphragmatic metastasis (arrowhead). The patient underwent a liver-resection and diaphragmatic resection.*

Table 3. *Comparison of the accuracy of DW-MRI and CECT disease scores with histopathological correlation, according to tumor site in patients with newly diagnosed adnexal tumors.*

Tumor site	Imaging	TP	FP	FN	TN	PPV	NPV
Primary tumor	DW-MRI	17	2	1	3	89	75
n = 23	CECT	18	5	0	0	78	-
PC	DW-MRI	12	1	2	6	92	75
n = 21	CECT	11	2	3	5	86	63
Lymph nodes	DW-MRI	6	7	0	8	46	100
n = 21	CECT	5	1	2	13	83	87
Diaphragmatic	DW-MRI	6	0	1	14	100	93
n = 21	CECT	1	0	6	14	-	70
Liver parenchymal	DW-MRI	1	0	-	-	-	-
n = 21	CECT	1	0	0	0	-	-
Liver capsular	DW-MRI	One observed lesion					
n = 21 (no histology)	CECT	No observed lesions					
Extra-abdominal n=21 (no histology)	DW-MRI CECT	Suspected metastatic lesions in 8 patients Suspected metastatic lesions in 5 patients					

Note. ─ By two patients other histopathological correlations than primary tumor are missing: One 80 years old patient with advanced ovarian cancer underwent only primary tumor biopsy. One patient with prominent ovaries and pleural fluid with benign cytology received a consensus diagnosis of benign disease during clinical follow-up.

one in a patient with recurrent disease. Patients with the extra-abdominal lesions did not undergo surgery or biopsy according to current surgical guidelines; thus, there was no histopathological confirmation.

Peritoneal Metastases

In two cases, DW-MRI revealed small mesenteric, hyperintense nodules, which were interpreted as mesenteric carcinomatosis and confirmed in the debulking operation (Figure 4). CT missed these diagnoses.

Primary Tumor

The false positive primary tumor with false positive peritoneal carcinomatosis diagnosed on CT was correctly excluded by high ADC value (1.310 x 10^{-3} mm^2/s) and low SI on DWI and was further confirmed as advanced endometriosis. DW-MRI missed one primary tumor (Figure 5). The baseline tumour marker CA 125 (IU/L) values did not differ significantly between malignant and benign tumors (P = 0.654) (Table 4).

Recurrent Ovarian Cancer

Seven of nine patients (78%) with recurrent ovarian cancer had an elevated tumor marker as the indication for imaging. The mean rise in tumor marker was 62.5% (range from 23% to 170%). Two patients were suspected to have recurrence by routine CECT. Four patients (44%) showed no or uncertain disease progression by CECT imaging; whereas DW-MRI showed a clear progression. In two cases, also recurrent by CT, DW-MRI depicted additional metastatic lesions in diaphragmatic, liver parenchymal, or parasternal locations. In three patients, the CECT and DW-MRI findings were identical.

ADC Values

The lowest ADC values measured in the primary tumors of patients with existing histopathology (n = 23) were significantly lower in the malignant tumors (n = 18) compared with the benign tumors (n = 5) (0.640 ± 159 vs. 0.992 ± 218, P = 0.001). There was no significant difference of the ADC values between ovarian cancer and the other malignancies detected (P = 0.765).

Table 4. *The study populations' ADC lowest values and tumor marker CA 125 levels according to histological tumor types.*

Tumor type	ADC lowest value x 10^{-3} mm^2/s	CA 125 IU/L
Ovarian cancer n=15	0.621 (0.398 - 0.814) in primary tumor	865 (11 - 5234)
Other malignancy n=3	0.736 (0.558 - 1.010) in primary tumor	61 (5 - 133)
Benign tumor n=5	0.992 (0.750 - 1.310) in primary tumor	196 (9 - 807)
Recurrent disease n=9	0.573 (0.451 - 0.787) in metastatic lesion	613 (32 - 3968)

Note.— Data represent the mean (range).

Table 5. *The intra- and inter-observer variability of DW-MRI disease scores between two observers when analyzing different tumor sites visually on the DWIBS sequence (b=800 mm^2/sec).*

Tumor site	Intra-observer Cohen's kappa (n = 23)	Inter-observer Cohen's kappa (n = 23)
Primary tumor	0.6	0.8
Peritoneal carcinomatosis	0.7	0.9
Lymph nodes	0.4	0.7
Diaphragm	0.5	0.3
Extra-abdominal	0.7	0.6
Liver parenchyma	-	-
Liver capsule	-	-

Note. — DS 0=benign, DS 1=suspicion of malignancy, DS 2=definitely malignant. Liver parenchymal and liver capsular tumor sites were not evaluable because of too few observations.

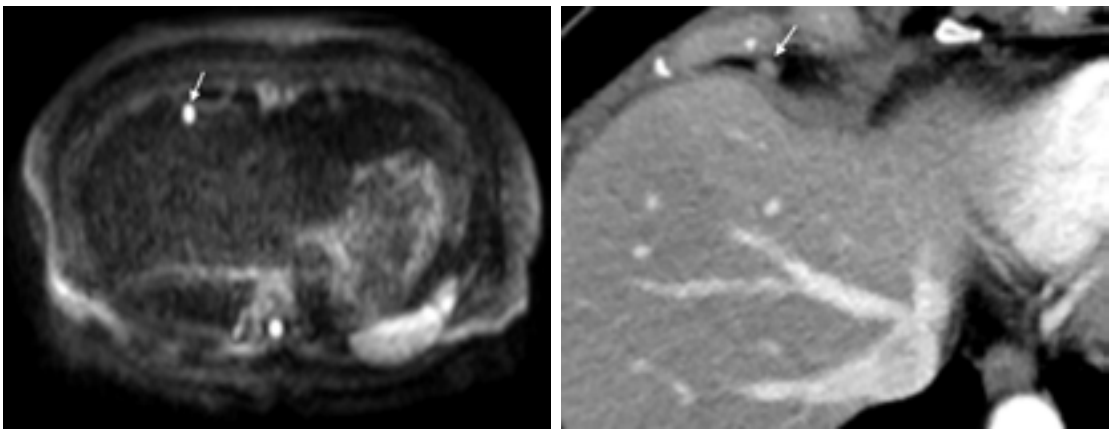

Figure 3. *A 71 year-old woman with newly diagnosed Stage IIIC ovarian cancer with a suspected malignant cardiophrenic lymph node in DWIBS (a) (5608, 52, b=800 sec/mm^2), without histopathological correlation. The same lymph node did not fulfill the size criteria for malignancy in CECT (b).*

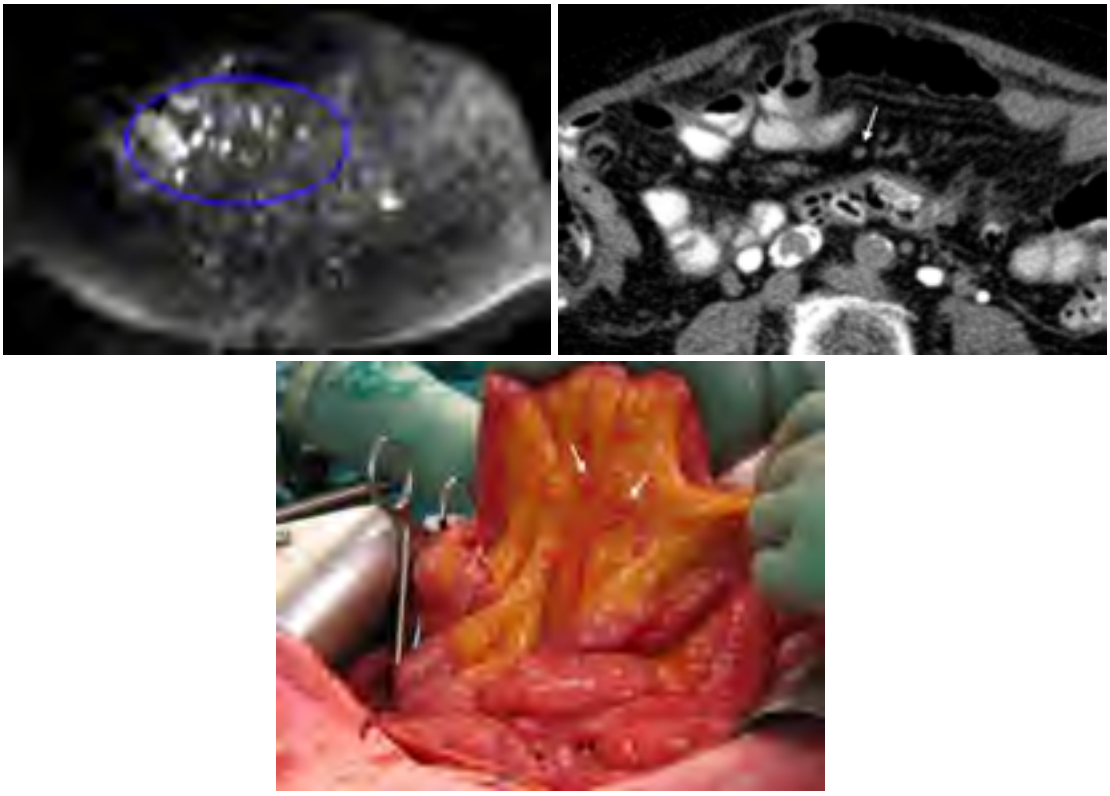

Figure 4. *Mesenterial metastases of an 80 year-old patient with a newly diagnosed serous tubal carcinoma (Stage IIIC) as shown by DWIBS (5608, 52, b=800 sec/mm²) (a), CECT (b) and intraoperatively (c).*

Figure 5. *DW-MRI missed one primary tumor in a 71 year-old woman with newly diagnosed serous ovarian cystadenocarcinoma (Stage IIIC). Intraoperatively the normal appearing ovary was buried in adhesive sigmoid colon (arrow) and a microscopic carcinoma was found on the surface of it by histopathology.*

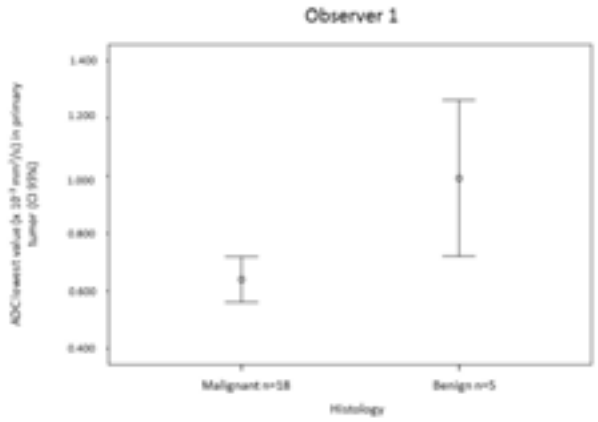

Figure 6. *ADC values of malignant primary tumors were significantly lower than those of benign tumors in the current study population (P = 0.001).*

Intra- and inter-observer intra-class correlation coefficients in primary tumor ADC values were 0.82 and 0.94, respectively. The per tumor site intra- and inter-observer agreements by visual analyses are shown in Table 5.

Discussion

In the current prospective single center study, we showed abdominal 3T DW-MRI to provide incremental diagnostic value in the staging of ovarian cancer and detecting recurrence as an adjunct to CECT. Clear difference was observed especially in detecting diaphragmatic and peritoneal metastases, excluding LN metastases and in differentiating malignant adnexal tumors from benign tumors.

The advantages of the non-contrast DW-MRI are that it is feasible in patients in whom contrast agent administration should be avoided and it can easily be added to any routine MR protocol. Using overlap techniques, we did not have difficulty covering the entire abdomen, which has previously been considered a problem [20]. Further, we consider the advantages of MRI such as superior soft tissue contrast to overweight disadvantages as longer examination time compared to CECT. Including MRI protocols only necessary sequences can shorten the acquisition time not to mention MRI technical developments of the last years.

Diagnostic performance of DW-MRI and CECT in primary tumors and metastatic sites:

The diagnostic performance between DW-MRI and CECT was investigated by comparing the radiological site-specific disease scores with intra-operative and histopathological findings. Both scores, “definitely malignant” and “suspicious for malignancy”, counted as malignant, as counterpart to findings scored as clearly “benign”. In line with the results of the study group Michielsen et al. [21] we observed better PPVs of DW-MRI than CECT in the primary tumor and metastatic sites. In our study, the PPV of DW-MRI for primary tumor was 89% versus 78% for CECT and respectively 92% versus 86% for the peritoneal carcinomatosis site. The PPV of DW-MRI for diaphragmatic metastatic site was 100% with six true positive findings as CECT missed the diaphragmatic metastatic lesions in six patients being false negative. On lymph nodal metastatic site the PPV of DW-MRI remained low (46%) reflecting the non-specificity of visual LN diagnostics depending on increased signal intensity on DW sequences leading obviously to overestimation. On the other hand, in LNs the NPV of DW-MRI was 100 % indicating that DW-MRI can reliably exclude LN disease extent. Altogether, we observed slightly better negative predictive values in all metastatic tumor sites. The highest NPV was found on the lymph nodal site, 100% as mentioned above, and the lowest on peritoneal carcinomatosis site 75%. Albeit, only one liver capsule metastasis occurred in the study population, it showed that multiple small liver capsule metastases were not visible in the same patient on the CECT scanned on the same day.

Correct staging of ovarian cancer is crucial as it guides the patient management and treatment. Incremental findings observed by DW-MRI may play an important role in correct classification of patients between stages IIIC or IV and in the treatment decision between primary debulking surgery (PDS) or neoadjuvant chemotherapy (NACT) followed by interval debulking surgery [22]. Gynaecologist colleagues usually consider periportal, hepatic, mesenteric root or multiple bowel serosal metastasis indicating a low success rate for R0 resection in PDS in ovarian cancer patients. If diffusion weighted MRI can reliably detect these decisive lesions a diagnostic laparoscopy would be redundant for ovarian cancer patients avoiding also scarred adhesions in the following interval debulking operation. Further studies will show, if there will be a benefit for ovarian cancer patients in overall survival (OS) or in the recurrence rate if the therapy choice would depend on more sensitive DW-MRI in the future. Interestingly, perioperative moderate or severe morbidity as well as quality of life (QoL) scores were initially stated to be more favourable in NACT/ interval debulking surgery arm than PDS in advanced epithelial ovarian cancer (AEOC) patients with very high tumor load [23]. After completion of patient enrolment in this ”Scorpion” study neoadjuvant chemotherapy and primary debulking surgery have the same efficacy when used at their maximal possibilities, but the toxicity profile is different. Further, the Rates of complete resection (R0) were superior in the arm B (= neoadjuvant chemotherapy followed by interval debulking surgery and adjuvant chemotherapy) as major postoperative complications were registered, mainly distributed in arm A (primary debulking surgery followed by adjuvant chemotherapy). The differences were statistically significant [24].

Michielsen et al. [11] reported that confirmed peritoneal carcinomatosis (208 regions in 32 patients) was smaller than one centimetre in 36% of all peritoneal regions. The results of our study parallel their findings. In the current study DW-MRI depicted hyperintense metastatic proven mesenteric lymph nodes with shortest diameter of six millimetres, not diagnosed on CT (Figre 4a). These LNs were intra-operatively and histopathological verified to be malignant. A pre-operative diagnosis of pathologic mesenteric lymph nodal site in ovarian cancer is relevant, because it can predict a mesenteric root bulky disease, which counts to one of the important advocate to choose NACT instead of primary debulking surgery. The detection of malignancy in normal size lymph nodes is known to be challenging and inaccurate [5,25]. Both metastatic and non-metastatic LNs can present with high signal intensity in DW-MRI; however, the mean and minimum ADC region values reported for metastatic nodal sites are significantly lower than those found at normal sites [26]. Developing quantitative evaluation by measuring ADC values may increase specificity of the LN diagnostics in the future.

The inter-observer agreement of the disease scores by visual analysis on DWI was perfect for peritoneal carcinomatosis tumor site and substantial for primary tumor and lymph nodal tumor site. Only fair intra-observer agreement for the lymph nodal site probably reflects the learning curve of the Observer 1 and the general awareness of the tendency of DWI to rather poor sensitivity in LN diagnostics. The interval between the ratings were proceeded after at least six months.

ADC Assessment in differentiation between benign and malignant adnexal lesions:

Studies about the utility of quantitative ADC values in ovarian cancer diagnostics exist, considered feasible and so being in line with the current study. In 2018, Pi et al. [27] estimated in their meta-analysis the diagnostic performance

of quantitative ADC values for predicting malignancy of ovarian lesions, with pooled sensitivity and specificity values of 0.91 and 0.91, respectively, and an AUC of 0.96. These findings demonstrated that quantitative ADC values are useful diagnostic markers for distinguishing between malignant and benign ovarian lesions. However, the cut-off ADC values for malignancy reported in their study (1.15 – 1.36 $x10^{-3}$ mm^2/s) were clearly higher than in our study where the lowest ADC values were significantly lower in malignant tumors than in benign tumors (0.640 $x10^{-3}mm^2/s \pm 159$ vs. 0.992 $x\ 10^{-3}mm^2/s \pm 218$, $P = 0.002$). To notice, even despite of the same procedure, assessing the solid components as region of interest in measuring the ADC. Standardized measurement protocols or cut-off values are not available for ADC measurements in OC. The scanner type and size and positioning of regions of interest, and b-values vary in published studies, leading to differences in reported ADC values.

Different maximal b values have been reported to calculate the apparent diffusion coefficient, mostly around 500 - 1000 sec/mm^2 [28]. For calculation of ADC values a monoexponential fit has been recommended with one b value greater than 100 sec/mm^2 and another *b* value greater than 500 sec/mm^2 (most often b = 1000 sec/mm^2) [29]. However, most examinations also include a b value of 0 sec/mm^2 for easy detection of blood vessel anomalies. We selected b values from zero and 600 sec/mm^2 and 800 sec/mm^2 for the DWIBS sequence and did not have problems with reduced signal to noise ratios for primary tumor lesion diagnoses or with the capability to differentiate benign from malignant lesions.

Deeper going studies on ADCs show a negative correlation between the mean ADC values and histologic grade and surgical stage [30]. Further, reduced ADCs, measured in whole lesion single plane-ROI, are associated with histological severity and worse outcome in ovarian cancer patients [31]. The known biological tumor heterogeneity of adnexal lesions creates a challenge in standardizing the ADC asssesment. In a previous study, a significant inverse correlation between ADC values and tumor cellularity in epithelial ovarian cancer was observed. The mean ADC value of clear cell carcinoma (CCC) was higher than those of HGSC and EC, seemingly due to the low cellularity of CCC [32].

Diagnostic performance of DW-MRI and CECT in patients with recurrence suspicion:

In the current study, CECT and DW-MRI agreed in the findings only in three patients with the recurrent disease. 44% of the patients with histopathological proven recurrent disease showed none or uncertain disease progression by CECT imaging whereas DW-MRI showed a clear progression. An uncertainty in the diagnosis of recurrent ovarian cancer can delate the treatment decision, which could be crucial for patients as in ovarian cancer the tumor marker dynamic is often not usable and warning clinical symptoms can be very unspecific. Another study showed also a better detection of ovarian cancer recurrence on DWI/MRI than on CT, as well a better prediction of complete resection of recurrent lesions [33].

The strength of our study is its prospective nature and its use in daily clinical routine in pre-operative setting and in ovarian cancer recurrence suspicion. Further, we strongly tested the power of diffusion weighted imaging technique, as our protocol included solely non-contrast sequences. Still, our study has several limitations. The number of patients is small and not quite all underwent surgical resection and histopathological confirmation. In particular, extra-abdominal and supra-diaphragmatic lesions were not biopsied according to current clinical and surgical guidelines. In the future, histopathological confirmation of suspected cardiophrenic metastatic lesions should be obtained. If the DW-hyperintense cardiophrenic LNs can be authenticated to be metastatic, it would lead to upstaging of ovarian cancer. The time interval between CT and MRI in the current study was relatively long especially in a few patients with recurrent disease. Although, this counts to the normal management in recurrence suspicions, where the incremental imaging diagnostics often follow only after a certain clinical observation time.

Our study protocol combined both CECT and DW-MRI prospectively and pre-operative. This study, as well the referred studies published by now, speak for supporting the DW-MRI to become the first-line radiological imaging modality, in both, the preoperative staging of ovarian cancer and in detection of ovarian cancer recurrence. The role of radiologist is important to drive this change. DWI and assessment of ADC values may increase radiologists' confidence in the staging of ovarian cancer and differentiating malignant tumors from benign, supporting the patient management by gynecologists. Not to forget, transvaginal and Doppler ultrasound performed by gynecological oncologist colleagues is not likely to be omitted.

In conclusion, the results of our prospective single center study show incremental value of abdominal 3T DW-MRI in comparison with CECT, especially in detecting diaphragmatic and peritoneal ovarian cancer metastases, excluding lymph nodal metastases and in differentiating malignant adnexal tumors from benign. Larger-scale studies including different types of adnexal tumors and standardization of DW-MRI techniques are needed.

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