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Research article

MRI with diffusion-weighted imaging to predict feasibility of complete cytoreduction with the peritoneal cancer index (PCI) in advanced stage ovarian cancer patients

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ABSTRACT

Objectives: To determine the diagnostic performance of MRI with diffusion-weighted imaging (DW-MRI) in assessing the peritoneal tumor load and predicting whether a complete cytoreduction can be achieved in patients with epithelial ovarian cancer (EOC).

Methods: For this observational prospective study, 25 patients with epithelial ovarian cancer scheduled for cytoreductive surgery were included. Patients underwent a 3 T DW-MRI scan prior to surgery. The MR protocol consisted of a T1 and T2 weighted, a contrast-enhanced T1 weighted, and a diffusion-weighted (b0, b1000) sequence. The Peritoneal Cancer Index (PCI) was determined on DW-MR images (MRI-PCI) by two readers, independently, and was compared to the PCI determined during surgery (S-PCI). The inter-observer agreement between the two radiologists was evaluated. In addition, receiver operating characteristics curves were calculated for predicting complete cytoreduction with the S-PCI and MRI-PCI.

Results: Staging with DW-MRI showed a correlation to surgical staging with an intraclass correlation coefficient (ICC) 0.86 and 0.85 for reader 1 and 2, respectively. Inter-observer agreement was excellent with an ICC of 0.90 (95% CI: 0.64-0.96). The MRI-PCI scores of reader 1 (AUC = 0.96), reader 2 (AUC = 0.98), and the S-PCI (AUC = 0.92) showed similar predictive values for complete cytoreduction.

Conclusion: DW-MRI is accurate in predicting the S-PCI and can be helpful to predict whether a complete resection in ovarian cancer patients is feasible.

1. Introduction

The majority of patients with epithelial ovarian cancer (60–80%) is diagnosed at an advanced stage with regional and/or distant metastases [1]. Typically, ovarian cancer patients present with peritoneal carcinomatosis, often due to direct intraperitoneal seeding from the tumor to the various regions within the peritoneal cavity via the peritoneal fluid [2]. The location and extent of the peritoneal involvement greatly influence the chance of successful cytoreductive surgery (CRS), which in turn determines long-term prognosis [3–5].

If possible, primary CRS is preferred followed by adjuvant chemotherapy. If primary CRS is not feasible due to the extent of the disease, neoadjuvant chemotherapy followed by interval CRS and adjuvant chemotherapy is performed. Recently, the use of hyperthermic intraperitoneal chemotherapy (HIPEC) was shown as a promising additional treatment option for select patients undergoing interval CRS [6]. In any case, the decision of whether a successful surgical cytoreduction is feasible can be a challenge in this patient group. Currently,

Abbreviations: ADC, apparent diffusion coefficient; AUC, area under the curve; CRS, cytoreductive surgery; CT, Computed Tomography; DW-MRI, Diffusion-weighted magnetic resonance imaging; DLS, diagnostic laparoscopy; EPI, Echo-planar imaging; FFE, Fast field echo; FIGO, International Federation of Gynecology and Obstetrics; ICC, Intraclass correlation coefficient; MRI-PCI, magnetic resonance imaging Peritoneal Cancer Index; PCI, peritoneal cancer index; ROC, receiver operator characteristics; S-PCI, Surgical Peritoneal Cancer Index; SS, single shot; TSE, Turbo spin echo

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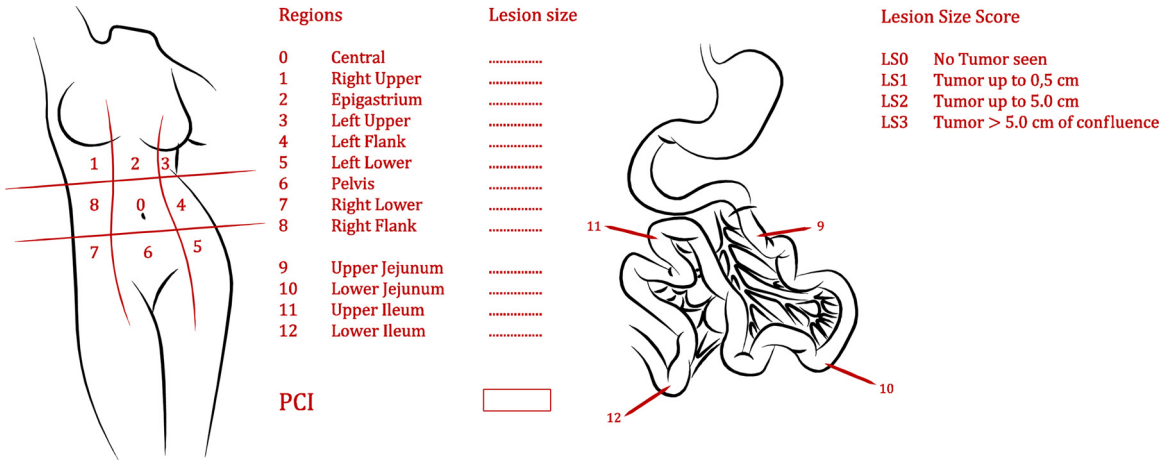

Fig. 1. Schematic drawing of the Peritoneal Cancer Index as described by Jacquet and Sugarbaker [7]. (Courtesy of E.M.L.E. Jansen).

this decision is made based on physical examination, performance status, tumor biomarkers, and findings on computed tomography (CT). Complete CRS is often infeasible in the presence of extensive peritoneal carcinomatosis, which would necessitate the need for multiple organ resections and extensive peritoneal stripping thereby exposing the patient to morbidities that outweigh the potential benefit of cytoreduction. In gastrointestinal cancers, the extent of the peritoneal involvement is described using the Peritoneal Cancer Index (PCI), an internationally validated surgical score which combines both the volume and location of peritoneal lesions (Fig. 1) [7]. The prognostic value of the PCI has been well established for predicting complete cytoreduction as well as disease-free and overall survival in colorectal cancer [8–11]. This scoring system has also been successfully implemented in patients with ovarian cancer and has shown prognostic and predictive value on the outcome of cytoreductive surgery [12–15]. However, unlike colon cancer, a consensus has yet to be determined over a scoring system for ovarian cancer to determine to proceed with surgery.

Diagnostic laparoscopy has shown to be an effective tool to determine the peritoneal tumor load and identify patients at risk of residual disease after surgery [16]. However, this is an invasive procedure that comes with patient burden a risk of intraoperative complications [17,18]. Naturally, a non-invasive tool for peritoneal load assessment would be of great value to both treatment and surgical planning. Unfortunately, CT is unable to accurately predict the extent of peritoneal involvement [19–23] and thus has limited ability to predict suboptimal cytoreduction in ovarian cancer patients [24–27]. Studies describing an external validation of CT-based prediction models showed accuracies of 0.34-0.67 [26]. Magnetic resonance imaging including diffusion-weighted sequences(DW-MRI) has a better soft tissue contrast resolution and potentially allows for the detection of small peritoneal lesions (< 5 mm) that are often missed on CT [28]. Recently, DW-MRI has shown promising results for diagnosing and staging ovarian cancer [24,29]. In colorectal cancer, DW-MRI has recently shown to be able to predict resectability with a high accuracy of 0.90-0.96 using solely the PCI as a cut-off criterion [30]. However, its potential for predicting the PCI in advanced stage ovarian cancer patients has not been investigated yet.

Therefore, the purpose of this study is to assess the potential of DW-MRI in predicting the peritoneal cancer index (PCI) in advanced stage ovarian cancer patients and predict whether a complete cytoreduction can be achieved. To the best of our knowledge, the present study is the first to describe the PCI using DW-MRI in an exclusively ovarian cancer cohort.

2. Methods and materials

2.1. Patients

This prospective observational cohort study was approved by the institutional ethics review board. Advanced stage ovarian cancer (FIGO stage IIb and above) patients were included, whom all provided written informed consent. All patients were considered for cytoreductive surgery and scheduled for either diagnostic laparoscopy or exploratory laparotomy from June 2016 to May 2018. Patients are considered for cytoreductive surgery if the initial diagnostic workup (including physical examinations, hematological-biochemical examinations, tumor biomarkers, and CT scans) considers a successful CRS feasible. If initial diagnostic workup is inconclusive, diagnostic laparoscopy served as a complementary resectability assessment. If there are indications of an unresectable disease load, patients were treated with neoadjuvant chemotherapy and interval cytoreductive surgery after positive response assessment with CT. Patients with contra-indications for MR-imaging (e.g. claustrophobia, pacemakers, metallic foreign bodies) were excluded from participation.

2.2. Imaging

Patients underwent a DW-MRI scan prior to surgery. The scans were performed on a 3 T MR scanner (Achieva or Ingenia, Philips Healthcare, Best, NL) using an external phased array coil. The dedicated MR protocol consisted of a T2 (SS TSE) weighted sequence, a diffusion-weighted (SS EPI with fat suppression) sequence, and T1 weighted (mDixon 3D FFE) sequences pre- and post-gadolinium administration (gadoterate meglumine, 0.5 mmol/ml, Dotarem®; Guerbet), as previously described by Van 't Sant et al. [30]. T1 and T2 imaging were acquired in the axial and coronal plane and diffusion-weighted imaging was acquired in the axial plane with coronal reconstruction. The diffusion-weighted sequence parameters include a b-value of 0 s/mm and 1000s/mm. Apparent diffusion coefficient (ADC) maps were calculated from the diffusion-weighted images. All pulse sequences were performed using free-breathing acquisition techniques except for the T1 weighted imaging which is respiration-triggered, imaging is acquired at expiration. One hour before the scan, patients were requested to drink 1 L of unaltered pineapple juice. The pineapple juice acts as an intraluminal negative oral contrast agent due to the high manganese content. An antispasmodic agent was also administered (butylscopolamine bromide, Buscopan®, 20 mg/ml, Boehringer Ingelheim). The total scan time was 35 min.

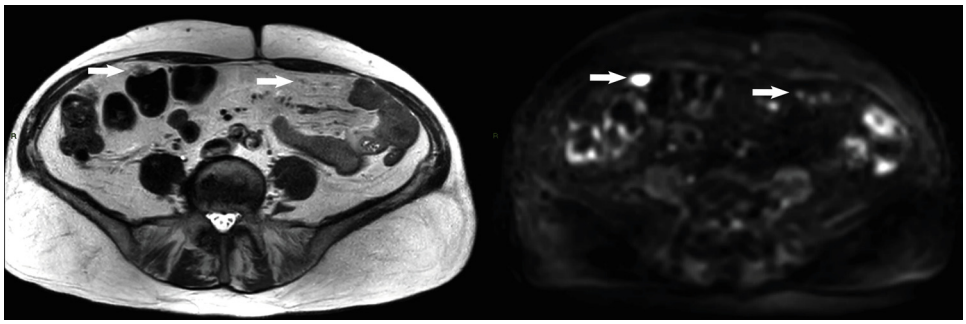

Fig. 2. T2 weighted (right) and diffusion-weighted (left) MR image of omental lesions (arrows) (region 0 of the PCI) in a 72-year-old patient with FIGO IIIC ovarian cancer. The lesion on the right can clearly be seen on both T2 and DWI. The small (< 5 mm) omental lesions on the would have been easily missed on T2 alone and likely not seen on CT. Lesions were resected at cytoreductive surgery and confirmed malignant at pathology.

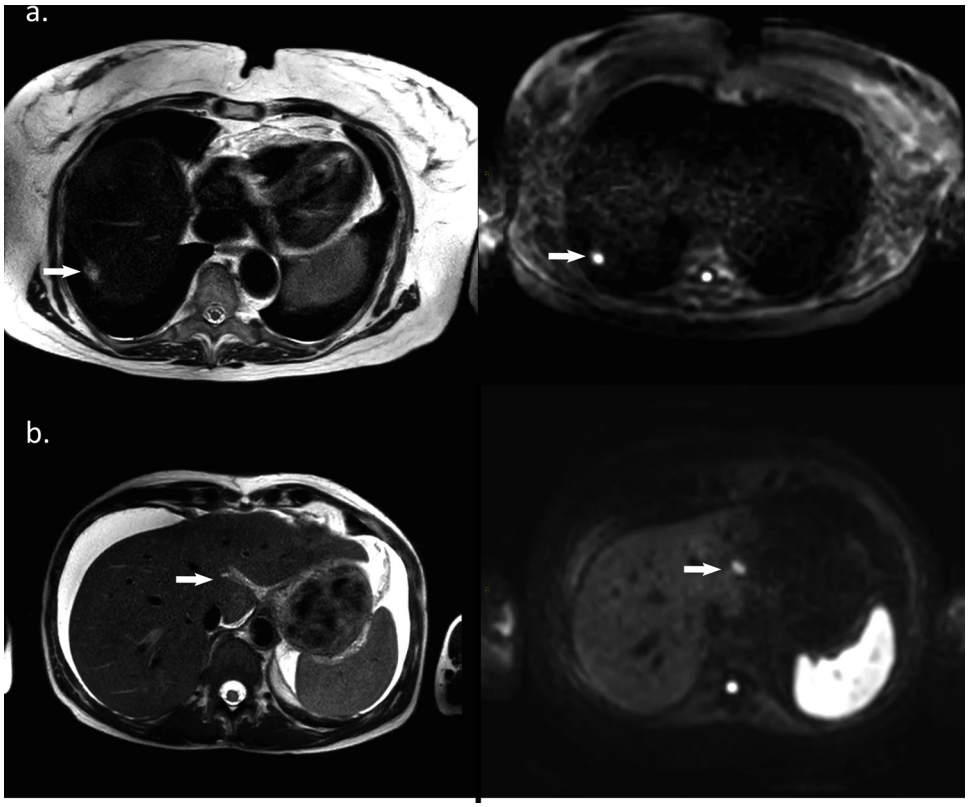

Fig. 3. T2 weighted (right) and diffusion-weighted (left) MR images of other disease localizations: a. A retro-hepatic peritoneal lesion (arrow) (region 1 of the PCI) in a patient with FIGO IIIC ovarian cancer. The lesion is delineated on the T2 weighted images and is not to be missed on the DW image. The lesion was resected at cytoreductive surgery and confirmed malignant at pathology. b. A lesion (arrow) in the falciform ligament (region 2 of the PCI) in a 50-year-old patient with FIGO IV ovarian cancer. Also, a large amount of ascites can be seen. The lesion was found at open exploration but no cytoreduction took place because the tumor load was deemed too extensive to be feasible.

2.3. Radiological evaluation

Two abdominal radiologists with respectively 10 and 5 years of experience in reading DW-MRI, evaluated the images independently. Figs. 2 and 3 show examples of peritoneal lesions as seen on T2 and DW images. Upon visual assessment, lesions were considered suspicious of being malignant if they showed peritoneal tumor nodules/masses involving the peritoneum, omentum or mesentery with post contrast enhancement or restricted diffusion indicated by high signal on the DWI images. Peritoneal thickening with post contrast enhancement or restricted diffusion indicated by high signal on the DWI images was also considered malignant disease. Both radiologists used a surgically validated scoring system, the Peritoneal Cancer Index (PCI) as described by Sugarbaker et al. [31], to assess the extent of peritoneal metastases on MRI (MRI-PCI). The PCI identifies 13 regions of the abdomen of which four are reserved for the small bowel. For each region a lesion size score of 0–3 is assigned based on the tumor size (0 = no tumor visible; 1 = tumor < 0.5 cm; 2 = tumor < 0.5-5 cm; and 3 = tumor > 5 cm or confluent respectively).

2.4. Surgical evaluation

At exploratory laparotomy or diagnostic laparoscopy, the abdominal cavity of each patient was systematically evaluated to determine the extent of disease and to decide whether complete or optimal cytoreductive surgery is feasible by at least one gynecological oncologist and in case of an incomplete CRS a 2nd gynecological oncologist was consulted to confirm that successful surgery was infeasible. Reasons for not being able to resect all visible disease were extensive agglutinated intra-abdominal disease requiring (multiple) bowel resection and/or resection of the stomach or spleen or liver; extensive serosa involvement of the bowel requiring multiple resections (> 1.5 m bowel resection needed); extensive disease at diaphragmatic level (1 > cm in diameter). Based on this exploration the S-PCI was determined as described above and served as reference standard. The final surgical outcome was recorded and labeled as complete (no visible residual tumor), optimal (up to 1 cm of residual tumor), incomplete (more than 1 cm residual tumor), or not feasible (as determined by diagnostic laparoscopy).

2.5. Data analysis

Statistical tests were performed using R statistical software (version 3.5.1, R Foundation for statistical computing, Vienna, Austria). Inter-observer agreement between the two radiologists and between the MRI-PCI and S-PCI was determined using the Intraclass Correlation Coefficient (ICC). The PCI scores of the gynecologists were also compared to the MRI-PCI scores of the two respective radiologists using Bland-Altman analysis. Receiver Operating Characteristics (ROC) curves were calculated to compare the diagnostic value of S-PCI and MRI-PCI to predict whether complete cytoreduction could be achieved.

3. Results

3.1. Patients

Twenty-eight were included patients of which three were not evaluable and therefore excluded; one patient had contra-indications for MRI, one patient was found to have colorectal rather than ovarian cancer in the definitive histology and one patient since no reliable S-PCI could be determined due to extensive fibrosis. Baseline characteristics of 25 patients that constituted the final study cohort are presented in Table 1. The majority of patients showed serous histopathology and had FIGO stage III. The mean age of the patients was 62 years (SD: ± 9). Seventeen patients received neoadjuvant chemotherapy. The abdominal assessment was done during exploratory laparotomy in 20 patients and during diagnostic laparoscopy in 5 patients. In 17 patients, surgery was feasible and complete, in 4 patients optimal cytoreductive surgery was achieved. In four patients the tumor load was deemed too extensive for a successful cytoreductive surgery.

3.2. S-PCI vs. MRI-PCI

The mean S-PCI was 10.62 (SD: ± 7.9). The mean MRI-PCI was 12.44 (SD: ± 10.3) for reader 1 and 9.76 (SD: ± 8.8) for reader 2. The MRI-PCI scores of both reader 1 and 2 showed a good correlation with the S-PCI, showing an intraclass correlation coefficient (ICC) of 0.86 (95% confidence interval (CI): 0.70-0.94) and of 0.85 (95% CI: 0.70-0.93), respectively. Fig. 4 shows the Bland-Altman plots comparing the MRI-PCI of both readers with the S-PCI. The average difference between the MRI-PCI and S-PCI was 1.88 (± 4.50) for reader 1 and -0.80 (± 4.53) for reader 2. Staging the PCI with DW-MRI, readers were able to achieve an intraobserver agreement with an intra-class correlation coefficient of 0.90 (95% CI: 0.64-0.96).

Table 1
Patient characteristics (n = 25).

Mean age in years (SD)	62 (± 9)
Histological type	
● Serous	21
● Mucinous	0
● Endometrioid	2
● Borderline	1
● Undifferentiated	1
FIGO Tumor Stage	
● IIb	3
● III	11
● IV	6
● Recurrent	5
Mean serum tumor markers (SD)	
● CA125	185 kU/l (± 296)
● HE4	210 pmol/l (± 253)
Neoadjuvant chemotherapy	17
Surgical exploration	
● Exploratory laparotomy	20
● Diagnostic laparoscopy	5
Surgical Outcome	
● Complete	17
● Optimal	4
● Not feasible	4

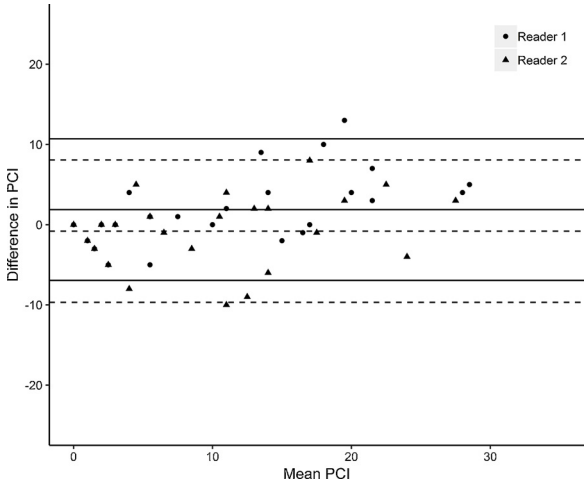

Fig. 4. Bland Altman plot of the MRI-PCIs of reader 1 (circles and solid lines) and 2 (triangles and dashed lines) compared to the S-PCI. In a Bland-Altman plot, the difference between the MRI-PCI and the S-PCI is plotted against the mean of the two measurements per patient. Reference lines are added representing the mean difference (middle lines) and the mean difference ± 1.96 times the standard deviation of the differences (top and bottom lines), also called the Limits of Agreement. All but two points lay between the Limits of Agreement, one for each reader.

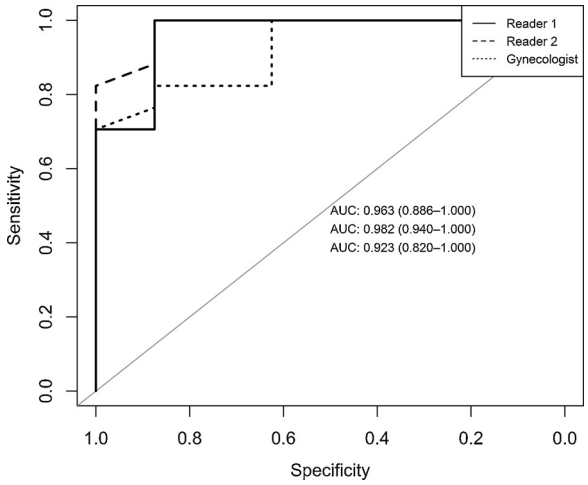

Fig. 5. Receiver operating characteristics (ROC) curve of the MRI-PCI of reader 1 (solid line) and 2 (short dashed line) and the S-PCI (long dashed line) of the gynecological oncologists to predict whether complete cytoreduction was feasible.

3.3. PCI vs. Surgical outcome

Fig. 5 shows the Receiver operating characteristics (ROC) curves indicating both readers' performance as well as the performance of the S-PCI to select patients for whom a complete resection was feasible. The MRI-PCIs of reader 1 and 2 showed AUCs of respectively 0.96 (95% confidence interval: 0.89–1.00) and 0.98 (95% confidence interval: 0.94–1.00). In this small patient cohort, the most optimal PCI cut-off would be 20 for reader 1 and 15 for reader 2, in both cases with sensitivities of 1.00 and specificities of 0.88. The performance of the MRI-PCI is similar to that of the S-PCI, which showed an AUC of 0.93 (0.82–1.00).

4. Discussion

In the patient cohort, the MRI-PCI seems equally accurate to surgical inspection (S-PCI) to select patients in which a complete resection could be achieved.

Our results are in concordance with the study of Michielsen et al. which demonstrated that DW-MRI was 95.7% accurate (whereas CT was only 71.3% accurate) in predicting incomplete resection by identifying certain high-risk disease localizations such as peritoneal disease by the duodenum, stomach or celiac trunk and diffuse serosal carcinomatosis in patients with ovarian cancer [24]. Similarly, by comparing the detection of specific presentations of intra-abdominal disease with DW-MRI to exploratory laparotomy, Espada et al. created their own predictive score for suboptimal cytoreductive surgery which showed similar AUC values as in this study, namely 0.94 for DW-MRI and 0.95 for exploratory laparoscopy [32]. For this predictive model, 1 point was given to each of 9 different disease presentations such as milliary visceral peritoneum implants, massive ascites, and involvement of diaphragm. Currently, surgical staging is the most accurate manner available for the assessment of the extent of peritoneal metastases in advanced stage ovarian cancer patients. Diagnostic laparoscopy has shown to be able to reduce the number of unsuccessful laparotomies from 39% to 10%, in a randomized controlled setting for ovarian cancer patients considered for primary cytoreductive surgery [16]. Additionally, in the laparoscopy group, 38% of patients were diverted from primary cytoreductive surgery and were given neoadjuvant chemotherapy for interval cytoreductive surgery. However, diagnostic laparoscopy remains a surgical procedure with a risk of either intra- and postoperative complications (6.2–22%) [17,18] or port site metastases [33]. This means there is a need for other diagnostic strategies such as DW-MRI.

Diffusion-weighted imaging is well known to be able to support oncological imaging by aiding the identification of tumor tissue and assessing tumor response to treatment. In this case, the b1000 diffusion-weighted imaging is exploited to identify suspicious lesions which can be correlated anatomically with T2 imaging. However common pitfalls in the assessment of b1000 images can be “T2 shine-through” and normal lymph nodes, which are high on b1000 images, that can lead to false positives if misinterpreted. Knowledge of clinical and histological information is vital to the interpretation of the diffusion-weighted imaging as well as the use of conventional T2 weighted and/or T1 weighted imaging for adequate anatomical correlation. Ascites does not hamper with the interpretation of DWI images, because ascites will be hypointense on b1000 images while tumor will be hyperintense. However, mucinous tumors can also mimic ascites and show high ADC values which can in turn lead to false-negatives [34].

The S-PCI scores in this study (AUC: 0.93) seemed to perform somewhat better in predicting complete cytoreduction than those previously reported. In a study of Lampe et al. the PCI was retrospectively determined from the surgical reports of 98 patients with FIGO III-IV stage ovarian cancer and the obtained PCI showed an AUC of 0.84 for identifying patients with a complete cytoreduction [14]. Similarly, a large retrospective Danish study of 507 ovarian cancer patients (FIGO III-IV) showed that S-PCI could be used to detect patients with a complete cytoreduction with an AUC of 0.75-0.79 [15]. PCI cut-off points can be helpful for patient selection. In this patient cohort, the most optimal cut-off point differed between radiologists by five points (15 and 20). Using these cut-offs, both readers were able to identify all true complete resections (no residual disease) and under-staged one patient who received an optimal resection (residual tumor present under 10 mm), instead. In literature S-PCI cut-off points were suggested of 16 and 20 to predict complete and optimal (residual tumor present under 10 mm), respectively are suggested [35,36].

The difference between the cut-offs of both readers can be explained by the small patient numbers in this pilot study. In order to conclusively determine the ability of DW-MRI to accurately describe the distribution and extent of disease, a larger study population will be needed. Currently, a multicenter prospective study (NCT03399344) is running to follow-up on these results. In the current study, a CT-PCI was disregarded in the analysis because, for patients receiving neoadjuvant chemotherapy, the CT evaluation is performed after two cycles whereas the DW-MRI was performed just before surgery. The possible confounding effect of the last third chemotherapy cycle was deemed too large for a fair assessment of the disease load found during surgery. In this pilot cohort, the majority (17/25%) of patients received neoadjuvant chemotherapy.

If the promising results of our study are validated in larger cohorts and DW-MRI were to show a similar diagnostic value as diagnostic laparoscopy, than DW-MRI should be regarded as a robust non-invasive selection tool to determine whether a complete resection is feasible in advanced ovarian cancer patients.

Disclosure statement

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