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Preoperative staging of advanced ovarian cancer: comparison between ultrasound, CT and WB-DWI/MRI (ISAAC)

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Short title: Imaging Study on Advanced ovArian cancer (ISAAC)

Contribution:

What are the novel findings of this work? This is the first prospective study comparing the diagnostic performance of ultrasound, method of choice (CT, computed tomography) and a novel technique (WB-DWI/MRI, whole-body magnetic resonance imaging with diffusion-weighted sequence) for peritoneal and retroperitoneal lymph node staging, and prediction of non-resectability in ovarian cancer patients with surgery and histology as a reference standard. The non-resectable disease was defined as suboptimal debulking (residual tumor >1 cm) or cytoreduction not feasible on initial exploration.

What are clinical important implications of this work? High specificity of imaging is important in avoiding withholding surgery where complete cytoreduction is feasible, while high sensitivity reduces risk of unnecessary surgical explorations with suboptimal results. Based on the high specificity of expert ultrasound in ovarian cancer staging, it can be used to select ovarian cancer patients for upfront surgery or neoadjuvant chemotherapy. With the low sensitivity of all three imaging modalities to detect discrete bowel serosa and mesentery involvement, there is a potential role of diagnostic laparoscopy prior to laparotomy to spare non-feasible cases for complete cytoreduction from laparotomy incision.

Abstract

Objectives: To evaluate transvaginal and transabdominal ultrasound for assessment of sites of disease and prediction of non-resectability compared with the first-line staging method (CT, computed tomography) and a novel technique (WB-DWI/MRI, whole-body magnetic resonance imaging with diffusion-weighted sequence) in patients with suspected ovarian cancer.

Methods: New patients planned for ovarian cancer surgery at a Gynecologic oncology centre were enrolled. They underwent preoperative staging and prediction of non-resectability with ultrasound, CT, and WB-DWI/MRI, following a single predefined evaluation. Findings were compared to the reference standard (surgical and histopathological evaluation forms). The evaluation assessed peritoneal spread in 17 sites and metastatic lymph nodes in 7 sites. The prediction of non-resectability based on abdominal markers in ovarian cancer patients was based on the criteria defined by local guidelines.

Results: Sixty-seven patients with ovarian cancer were enrolled between March 2016 and October 2017. In 67 patients, 51 (76%) had advanced and 16 (24%) had early stage ovarian cancer. Out of 67 patients, diagnostic laparoscopy was performed in 16% (11/67) and laparotomy in 84% (56/67) with R0 (68%, [38/56]; R≤1cm 16% [9/56]; R>1cm 16% [9/56]). Ultrasound and WB-DWI/MRI performed significantly better than the CT in the assessment of overall peritoneal carcinomatosis (AUC 0.86-0.87 vs 0.77)(p=0.002). For assessment of retroperitoneal lymph node staging (AUC 0.72-0.76) and prediction of non-resectability in abdomen (0.74-0.80) all three methods performed not different. Ultrasound showed equal or even better specificity than WB-DWI/MRI followed by CT in assessing all sites and prediction of non-resectability. To plan bowel resection, transvaginal ultrasound compared to WB-DWI/MRI and CT showed a higher accuracy (94 %, 91% and 85% respectively) and sensitivity (94%, 91% and 89% respectively) in the detection of pelvic carcinomatosis, particularly in the evaluation of deep rectosigmoid wall infiltration when compared to the other two modalities. On the contrary, for the bowel serosal and mesenterial assessment ultrasound showed the lowest accuracy (70 %, 78% and 79% respectively) and sensitivity (42%, 65% and 65% respectively).

Conclusions:

This is the first prospective study to date documenting that in experienced hands ultrasound may be an alternative to WB-DWI/MRI and CT in the assessment of overall peritoneal assessment, retroperitoneal lymphadenopathy and prediction of tumor non-resectability based on abdominal markers in ovarian cancer patients

Introduction

High-grade serous carcinomas are the most common ovarian carcinomas, manifesting in more than 80% of cases as an advanced-stage disease with extensive peritoneal and/or distant metastatic spread, with high fatality rate (ratio of mortality/incidence 60%)[1]. A maximal effort primary debulking surgery defined as no residual disease at the end of surgery followed by platinum-based chemotherapy yields the best results. Such treatment combination has an acceptable morbidity in qualified centres, and remains the standard treatment in patients with stage III-IV epithelial ovarian cancer[2]. Neoadjuvant chemotherapy (NACT) before interval debulking surgery is an alternative treatment regimen that can be considered in selected patients, in whom complete resection at primary debulking surgery is technically not feasible due to tumour growth or localisation (*non-resectability of disease*), and/or patient cannot tolerate extensive surgery which would be necessary to resect all visible tumour (*inoperability*). Patients should not be treated with NACT because of a provider's lack of surgical expertise or due to convenience (*insufficiency*)[2]. Optimal surgical results depend highly on available surgical expertise and skills and appropriate patient selection. The selection of patients for primary debulking surgery or neoadjuvant treatment must be carried out in a specialist ovarian cancer centre, according to the European Society of Gynaecological Oncology (ESGO) Quality recommendations 2016[3] in a multidisciplinary setting. The accurate mapping of tumour burden and distribution of disease by imaging plays a central role in the treatment planning. Diagnostic work-up with the best available imaging methods depending on the local expertise, such as computed tomography (CT), positron emission tomography (PET)-CT, diffusion-weighted whole body magnetic resonance imaging (WB-DWI/MRI) or expert ultrasound with or without diagnostic laparoscopy should be used to assess the extent of disease according the ESGO-ESMO guidelines 2019 (the European Society of Gynaecological Oncology; the European Society for Medical Oncology), which were developed in a multidisciplinary setting[4]. Promising results of ultrasound[5] or WB-DWI/MRI[6] were shown in preoperative peritoneal staging over standard imaging modality (CT) but not for PET-CT over CT alone[6]. This study aimed to prospectively compare diagnostic accuracy of ultrasound, WB-DWI/MRI and CT in the assessment of abdominal sites of the disease and its resectability.

Methods

This prospective diagnostic accuracy study was initiated in the Gynecological oncology center and ran between March 2016 and October 2017. Reporting of the study follows the STARD statement for diagnostic accuracy studies published in January 2003 and updated in 2015 (www.stard-statement.org)[7-9]. Its aim was to evaluate the diagnostic performance of transvaginal and transabdominal two-dimensional ultrasound, WB-DWI/MRI and CT in the preoperative assessment of sites of disease and assessment of non-resectability of ovarian cancer patients. The reference standards were intraoperative findings supported by histological confirmation and surgical outcome of primary cytoreduction. The local ethical committee approved the study protocol (620/16 S-IV, 23.06.2016) and informed consent was obtained from all subjects.

Participants

Patients were selected from all referrals to the center. Patients referred with suspected gynaecological cancers had their history taken, examined and the expert ultrasound was performed to characterize the mass. Patients with suspected adnexal or peritoneal cancer fit for surgery (i.e. having no major medical conditions contraindicating surgery) were enrolled in the study, if inclusion criteria were fulfilled (Figure 1). The informed consent was requested, all three index tests (ultrasound, CT and WB-DWI/MRI) were scheduled and basic demographic data were collected including age, weight and height (BMI), and menopausal status. The results of all three index tests were available for the multidisciplinary team discussion. The decision to treat by primary debulking surgery or only diagnostic laparoscopy was based on the departmental guidelines considering medical comorbidities and disease-related factors[2]. Patients with atypical tumour morphology and/or tumour spread suspicious of secondary ovarian cancer were first subjected to a tru-cut biopsy and additional diagnostic tests where applicable[10, 11]. The pathognomic ultrasound parameters suggestive of metastatic tumours were published by authors[12, 13].

Inclusion criteria encompassed (1) primary invasive ovarian, tubal or peritoneal cancer using subjective assessment (pattern recognition) by an experienced sonographer, (2) surgery (laparoscopy and/or laparotomy) planned within 4 weeks, (3) age between 18 and 80 years, (4) ECOG grade < 3 (ECOG, Criteria of the Eastern Cooperative Oncology Group)[14], (5) non-pregnant patient, (6) CT and/or WB-DWI/MRI not contraindicated, (7) patient's agreement to undergo three index tests, (8) informed consent signed.

Exclusion criteria were following: (1) benign and borderline ovarian tumours, (2) non-epithelial tumours, (3) secondary tumours, (4) previous neoadjuvant chemotherapy, (5) refusal or withdrawal of written informed consent, (6) current pregnancy, (7) any of index test missing (ultrasound, CT or WB-DWI/MRI), or (8) no reference standard available (no surgery performed), (9) time lapse between ultrasound and surgery more than 4 weeks. For the purposes of the study longer timeframe could allow tumors to develop or spread further, making early imaging evaluation incorrect.

Test methods (index tests)

Three index tests (ultrasound, CT, and WB-DWI/MRI) following a single predefined evaluation form were performed (appendix 1). The standardized evaluation assessed peritoneal spread in 17 sites and metastatic lymph nodes in 7 sites (inguinal, retroperitoneal infra- and suprarenal, visceral celiac and mesenteric, supraclavicular, mediastinal, axillary). Moreover, the evaluation form also included the description of fluidothorax and pleural carcinomatosis, table with criteria of non-resectability and the clinical FIGO (the International Federation of Gynecology and Obstetrics) staging system[15]. The classification of carcinomatosis and lymph nodes are included in supplementary figure 1 and 2.

Imaging readers were also well instructed and educated about standardized approach and criteria of non-resectability in abdomen (Figure 2)[16]. Cases were labelled as non-resectable when one or more markers of non-resectability were identified. Extra-abdominal markers of non-resectability were not considered, since surgical reference would be missing for some of them (small apical lung metastases or metastases in deep brain structures) or some metastatic lesions are resectable under certain circumstances (lungs, brain).

Both, sonographers and radiologists were blinded to the results of other imaging modalities. The results of all three index tests were available for the clinical decision and further management. Clinical data and evaluation forms were filled in for each test (Ultrasound, CT, WB-DWI/MRI) using electronic database immediately after the procedure.

Ultrasound

All patients underwent ultrasound examination under the study protocol, disregarding if they had any recent scans, including the one based on which they were included in the study. Ultrasound examinations were performed by one of three most senior examiners (DF, MZ and FF) experienced in transvaginal and transabdominal ultrasound (>15, >10, and >5 years respectively) without any patient preparation. The ultrasound scan was performed with Voluson E8 and E10 (GE Medical Systems, Zipf, Austria) with a RIC5-9 transducer probe with a frequency 5 to 9 MHz, matrix convex probe 3.5 to 7 MHz transducer, and a linear array ultrasound transducer probe 4 to 13 MHz. During systematic approach pelvis, abdomen including groins were routinely assessed. The assessment of supraclavicular and axillary lymph nodes was also included in the protocol. The systematic approach how to scan pelvis and abdomen (prepared by authors) is available on the web site of the International Society of Ultrasound in Obstetrics and Gynecology [Pelvic imaging (isuog.org), Abdominal scan (isuog.org)] and takes approximately 20 minutes. The used methodology for staging including assessment of local tumor extent, lymph nodes and distant metastases was published previously by the authors[17]. The appearance of peritoneal carcinomatosis was also described in a narrative review in 2011[18] as hypoechogenic perfused lesions (Figure 3, video 1). Hyperechogenic appearance of peritoneal carcinomatosis with multiple hyperechogenic spots corresponding to the presence of psammoma bodies were described in the less frequent low-grade serous cancer[19]. The liver parenchymal metastases are rarely present as isolated intraparenchymal leasion/-s but the liver is usually involved due to the

subcapsular hypoechogenic carcinomatosis infiltrating liver parenchyma (Supplementary figure 3, video 2). The terms for carcinomatosis description are schematically presented in appendix 1 including schematic drawing. The classification for carcinomatosis is schematically summarized in supplementary figure 1.

To assess the lymph nodes, high frequency linear array probe (7.5-14 MHz) was used for peripheral lymph nodes. Endocavitary probes (≥5MHz) enabled the high resolution for pelvic iliac and visceral lymph nodes, while curved array probe (up to 9 MHz) was used for abdominal parietal and visceral lymph nodes (Supplementary figure 2). The lymph node status was defined by using pattern recognition, i.e. subjective assessment of the ultrasound appearance of the lymph node. The ultrasound evaluation of lymph nodes on the basis of their gray scale ultrasound morphology and the vascular pattern on color or power Doppler ultrasound is schematically demonstrated in the supplementary figure 4, the ultrasound findings of partially and completely infiltrated inguinal lymph nodes is presented in the supplementary figure 5 and video 3. The classification of lymph nodes is schematically summarized in supplementary figure 2. The international consensus how to scan inguinal lymph nodes and how to differentiate infiltrated and non-infiltrated lymph nodes has been recently accepted by the journal of Ultrasound in Obstetrics and Gynecology (Terms, definitions and measurements to describe the sonographic features of inguinal lymph nodes in patients with vulvar cancer: a consensus opinion from the Vulvar International Tumor Analysis (VITA) group)[20]. Due to the limitation of ultrasound to assess chest, the evaluation of mediastinal lymph nodes was marked on ultrasound as non-accessible. If we look specifically on cardiophrenic lymph nodes, the most frequently infiltrated are anterior group of these lymph nodes which are visualised in some cases using convex array probe.

CT of thorax, abdomen and pelvis

The radiologist (MM) had more than 15 years of experience with a special interest in gynecological oncology. CT was performed on Somatom Emotion CT (Siemens Medical System, Erlangen, Germany). Before CT examination oral and intravenous contrasts were administrated. The acquisition of data from thorax, abdomen and pelvis took 2-3 minutes, then multiplanar reconstruction was performed (Supplementary figure 6). When a referred patient already had a CT done elsewhere, the study radiologists decided about the quality of imaging and necessity to repeat the scan. Tests with sufficient quality, if performed within 4 weeks prior to surgery, were used for the evaluation to avoid unnecessary radiation. Criteria for intraperitoneal metastases (peritoneal carcinomatosis) included fibronodular stranding, enhanced soft tissue nodules, plaques or mass-like lesions (Figure 3). The criteria for infiltrated lymph nodes were increased size (>10 mm short axis diameter and >5 mm short axis diameter in cardiophrenic nodes), or suspicious clusters of smaller lymph nodes, derangement of internal architecture (e.g. heterogenity, presence of central necrosis) and irregular margins. Additionally, the infiltrated lymph nodes, except for necrotic areas, showed enhancement after intravenous contrast administration.

WB-DWI/MRI

The radiologist (AB) had more than 15 years of experience with a special interest in gynecological oncology. WB-DWI/MRI was performed with parallel radiofrequency transmission and phased-array surface coils using 3 Tesla MRI scanner (MAGNETOM Skyra, Siemens Medical System, Erlangen, Germany). WB-DWI/MRI imaging protocol is presented in supplementary figure 7. Sequences were acquired at four imaging stations, covering the head and neck, chest, upper abdomen and pelvis including postcontrast scans aquisition. The examination took approximately 1 hour. Criteria for intraperitoneal metastases and infiltrated lymph nodes were identical to CT. Moreover, peritoneal lesions and infiltrated lymph nodes showed restriction of diffusion using DWI (Figure 3) and were hyperintense with low signal intensity on apparent diffusion coefficient (ADC) maps.

Laboratory tests

CA 125 was requested (if not available) for all patients. Other tumor markers such as CEA, CA 19-9, CA 15-3 etc were optional and reserved for cases suspicious of secondary ovarian cancer[21].

Outcome

Reference standards differed based on the two aims – (1) diagnostic accuracy of imaging in the preoperative assessment of sites of disease with intraoperative and histological findings as reference standard, and (2) assessment of non-resectability with surgical outcome as a reference standard. If surgery did not assess specific sites (for example retroperitoneal lymph nodes during diagnostic laparoscopy), this was stated in the report and analysis was made accordingly (the individual site of a subject with missing surgical reference were not included in the analysis). Only final staging TNM and FIGO staging was established on the surgical exploration in combination with pathology integrating also imaging findings after discussion at a multidisciplinary team meeting and served as a reference standard to be compared with clinical staging made up by each of index tests.

The standard surgical staging was performed, if cytoreduction was deemed feasible on initial exploration using laparoscopy and/or laparotomy[22]. Surgical staging routinely included systematic lymph node dissection of the pelvis and the paraaortic regions up to the left renal vessel origin and/or sampling of enlarged lymph nodes when indicated by imaging in combination with palpation of the remaining lymph nodes. In cases of diagnostic laparoscopy, the retroperitoneal lymph nodes were not accessible and these cases were excluded from analysis of retroperitoneal lymph nodes.

The tumor extent was described using the same predefined protocol as for preoperative imaging (Appendix 2). Additionally, surgeons staged the disease using the FIGO (the International Federation of Gynecology and Obstetrics)[15] staging system. The intraoperative (visual) findings were used as a reference standard for peritoneal assessment of the abdomen and pelvis. Final histology reports were used to complete data on the primary tumour, involvement of the resected tissues such as the depth of bowel infiltration, type of hepatic or splenic infiltration, lymph node infiltration, malignant pleural effusion, confirmation of distant metastasis and final FIGO staging[23](Appendix 3). Final TNM and FIGO staging integrating surgical findings, pathology and imaging was based on a correlation of various modalities after discussion in a multidisciplinary team and the method used to determine tumor status (T), lymph node status (N), and systemic status (M) was recorded as pathological (p) or imaging (i). Distant metastasis (M1) was considered for biopsy to confirm or rule out metastatic diseases. The reference assessment for pleural effusion / pleural involvement (M1a) was cytology on effusion aspiration. Patients with abdominal parenchymal metastasis or metastasis to extra-abdominal organs (M1b) underwent biopsy (tru-cut biopsy or fine-needle aspiration biopsy) or sampling of enlarged lymph nodes such as axillary or supraclavicular or inguinal, if technically available. In case of missing biopsy, the distant metastatic lesion was followed-up with imaging during adjuvant treatment to confirm reaction of the metastatic disease to

treatment. Partial or complete regression in platinum sensitive disease and/or progression in platinum refractory/resistent disease was taken as an indirect confirmation of positive reference standard.

Surgical outcome at the end of surgery was used as a reference standard to the assessment of disease resectability (Appendix 2). Surgeons described the surgical outcome as a complete cytoreduction (no macroscopic residual tumour left in situ), optimal cytoreduction (≤1cm residual tumour), suboptimal (>1 cm residual tumour), not feasible (as determined by initial exploration). The term non-resectable disease includes cases with suboptimal cytoreduction (>1 cm residual tumour) and non-feasible outcomes.

Data analysis

Absolute and relative frequencies were used to describe true and false positive and negative combinations of each respective preoperative imaging (index) test and reference standard: (1) intraoperative findings complemented with the pathological report for diagnostic accuracy study assessing sites of disease, and (2) surgical outcome for prediction of non-resectability. The diagnostic power of examined methods as potential predictors was assessed on the basis of the Receiver Operating Characteristics (ROC) curves[24]. The ROC analysis was performed using ROC web calculator (Eng, 2006, http://www.jrocfit.org) for curve fitting, SPSS 17.02 (SPSS Inc., 2009) for the AUC computation and testing and MedCalc 11.1.0.0 (MedCalc Software 1993-2009) for computation of sensitivity and specificity, positive predictive value (PPV), negative predictive value (NPV) and overall accuracy with 95% confidence interval. The computation was based on binormal assumption. Significance of the ROC curve analysis was based on calculated area under the curve (AUC) with corresponding 95% confidence interval; AUC values were tested using algorithm published in Hanley and McNeil (1982). The level of significance was set for all tests as p-value ≤0.05. A matched-pair design was employed to evaluate ultrasound and cross-sectional imaging in the same subjects in the assessment of overall peritoneal carcinomatosis. The ROC curve served as the endpoint to assess diagnostic accuracy. The hypothesis of ultrasound being non-inferior to cross-sectional imaging was tested, using a 5 % non-inferiority margin[25]. Sensitivity, specificity, and proportion of correct diagnosis depend upon some specified decision thresholds and doesn't provide an overall characterization of the accuracy for the diagnostic procedure itself. On the other hand, the ROC curve is a summary measure for the accuracy of diagnostic procedures as it incorporates both sensitivity and specificity.

Results

A study ran from March 2016 to October 2017 with the objectives of comparing ultrasound, CT and WB-DWI/MRI in assessing sites of disease in abdomen and non-resectability in patients with advanced ovarian cancer. An interim-analysis of initial pilot study on 21 patients, which ran from March to August 2016 was presented during 27th World Congress on Ultrasound in Obstetrics and Gynecology[26]. The final results confirmed the preliminary data from the interim analysis after the first 21 patients [26].

Patients

Patients scheduled for ovarian cancer surgery at the Gynecologic oncology centre were enrolled (Figure 4). Data from sixty-seven patients with ovarian cancer were analysed. Out of 67 patients, 51 (76%) had advanced and 16 (24%) had early stage ovarian cancer. After discussion at the multidisciplinary team meeting, 11 patients not suitable for primary debulking surgery underwent only diagnostic laparoscopy in view of assumed non-resectability prior to neoadjuvant chemotherapy. The combined approach (diagnostic laparoscopy followed by primary laparotomy during one setting) was indicated in 12% (8/67) of patients with equivocal findings of resectability status on imaging. In the remaining cases 72% of cases (48/67) primary laparotomy was planned and performed. Altogether, attempt for primary cytoreduction was made in 84% (56/67). Out of those, the complete resection was achieved in 68% (38/56), optimal debulking (residual disease < 1 cm) in 16% (9/56) and suboptimal debulking (residual disease > 1 cm) in 16% (9/56). Study group characteristics are provided in table 1. We assessed peritoneal spread in 17 sites and metastatic lymph nodes in 7 sites for each of imaging method compared to reference standard, the results which are presented in full on-line (Supplementary table 1 and 2). The comparative diagnostic accuracies of imaging methods with reference standard in the correct assessment of final FIGO staging and the prediction of non-resectability are shown in supplementary table 3 and 4.

Ultrasound and WB-DWI/MRI performed significantly better than CT (AUC: 0.86-0.87 vs 0.77) in the assessment of overall peritoneal carcinomatosis. For assessment of retroperitoneal lymph node staging (AUC: 0.72-0.76) and prediction of non-resectability in abdomen (AUC: 0.74-0.80), all three methods performed comparably (Figure 5).

Non-inferiority was tested for overall carcinomatosis, and it was demonstrated that comparing the AUCs of ultrasound (0.87) and CT (0.77)(p = 0.002), ultrasound was not inferior to CT. The difference of ultrasound performance (AUC 0.87) and WB-DWI/MRI (AUC 0.86) did not prove statistically significant, but only by a very small margin (p-value = 0.057). Given the smaller number of subjects in the dataset, it may be cautious to interpret it as ultrasound being inferior to MRI.

Peritoneal carcinomatosis

Supplementary table 1 presented sensitivities, specificities, positive and predictive value, accuracy and calculated area under the curve (AUC) of all imaging modalities with intraoperative visualisation complemented with the pathological report as reference standard in 17 different pelvic and abdominal sites. The results showed that the ultrasound had higher or identical specificity to WB-DWI/MRI followed by CT on all parameters evaluated, but lower sensitivity in the abdomen in comparison to both cross-sectional imaging. Choosing ROC area as the endpoints for assessing diagnostic findings of all three methods, ROC curve based on calculated area under the curve corresponded significantly to the intraoperative and histologic findings (p<0.001) with the exception of ultrasound assessment of mesenterial carcinomatosis. Ultrasound achieved marginally better results over WB-DWI/MRI and CT in the assessment of pelvic carcinomatosis, specifically deep rectosigmoid wall infiltration defined as an infiltration of muscularis propria and deeper when compared to pathology.

Lymph node metastases

Altogether, 56 out of 67 patients underwent lymph node biopsy of regional (retroperitoneal) lymph nodes, either as a sampling of enlarged lymph nodes (21) or systematic dissection of pelvic (35) and paraortic lymph nodes (34), respectively. In the remaining 11 cases diagnostic laparoscopy was performed, hence retroperitonal lymph nodes were not accessible. Sampling of non-regional lymph nodes including axillary (1), celiac (2), mesenteric (2), inguinal (1) was also performed. The histology of excised lymph node/-s served as reference standard. The supplementary table 2 presents the results of the evaluated visceral and retroperitoneal lymph node sites. Suspicious mediastinal lymph nodes (2) on imaging were not surgically biopsied or surgically removed, based on the MDT decision the cases were staged as FIGO IV and were followed-up during adjuvant chemotherapy. The observed regression of lymph nodes during adjuvant treatment was regarded as an indirect confirmation of cancerous infiltration (i.e. positive reference standard).

In the overall assessment of retroperitoneal lymph nodes (infra- and suprarenal) when imaging was compared to histology, ultrasound and WB-DWI/MRI showed similar results (AUC 0.76, p=0.001), followed by CT (AUC 0.72, p=0.005) (Figure 5). Infrarenal area was assessed more accurately by all three methods in comparison to the suprarenal region.

FIGO stage

Supplementary table 3 demonstrates final FIGO staging integrating surgical, pathologic and imaging findings after discussion in the MDT. Best modality to assign correct FIGO stage was WB-DWI/MRI (65.7%, 44/67), followed by ultrasound (61.2%, 41/67) and CT (59.7% (10/67). Altogether, FIGO stage IV was detected in 10.4% (7/67) and represented by involvement of pleura (3), and infiltrated celiac (2), inguinal (1), axillary (1) and mediastinal lymph nodes (2). In all except 2 cases of mediastinal lymph nodes the stage IV was confirmed by sampling of suspicious lymph nodes. As it is mentioned in the previous paragraph, the last 2 patients with mediastinal lymph nodes on CT and/or WB-DWI/MRI were lacking biopsy, hence they were followed-up using imaging during adjuvant treatment to confirm evidence on metastatic disease.

Prediction of non-resectability in abdomen

Image readers identified the following amount of cases with markers of non-resectability (Figure 2): diffuse small bowel infiltration only (1), diffuse infiltration of its root only (2), their combination (13), and infiltration of celiac trunc (1). Supplementary table 4 shows diagnostic accuracy of each imaging modality for prediction of non-resectability with surgical outcome as reference standard. In regards to AUC, all three imaging results corresponded well to the surgical outcome (ultrasound AUC 0.80, p<0.001, CT AUC 0.75, p=0.003, WB-DWI/MRI AUC 0.74, p=0.004). Lower false negative cases on ultrasound in the detection of bowel serosal carcinomatosis in non-resectable cases may be due to the dynamic aspects of ultrasound examination, which is particularly marked in the higher tumor volume making the diagnosis easier. The high tumor volume in non-resectable cases causes diffuse (plaque-like) carcinomatosis and reduces peristalsis with bowel dilation. Moreover, adhesions among affected loops can be seen on ultrasound as a lack of sliding sign (i.e. organs sliding against each other). High resolution transvaginal probe further increases the detection rate as it allows detailed observation of the bowel loops including ileal loops in the pelvis as presenting in Figure 6 and video 4.

Discussion

This is the first prospective study documenting the diagnostic performance of ultrasound, method of choice (CT) and a novel technique (WB-DWI/MRI) in peritoneal and lymph node staging, and prediction of non-resectability in ovarian cancer patients with surgery and histology as a reference standard. Based on the higher or identical specificity of ultrasound than WB-DWI/MRI and CT on all sites evaluated, ultrasound can be used as an alternative to cross-imaging for the initial selection of patients for primary debulking or neoadjuvant chemotherapy. The lower sensitivity of all three imaging modalities in identification of small volume carcinomatosis on small bowel serosa and its mesentery was the major factor related to suboptimal surgical outcome.

The strength of this study lies in its prospective design, the use of standardized terminology and methodology for ovarian cancer staging as defined in the previous papers[17, 18], and the use of a predefined protocol for all three imaging modalities and surgery. The final results confirmed the preliminary data from the interim analysis after the first 21 patients [26].

The limitation of the study might be a preselection of patients since those not considered fit for primary surgery were referred to neoadjuvant chemotherapy instead of surgery and not enrolled in the study. There may be also an element of limited observer experience in WB-DWI/MRI contributing to our data results. Although we followed the original protocol by Michielsen[6], the whole body DWI MRI doesn't have many areas of use in our hospital and as such is not used frequently. It was only since 2015 the equipment was available and the technical protocol was gradually developed and perfected, study started in March 2016. The reader was a very experienced radiologist who has more than 15 years of experience in gynaecological oncology imaging, including whole body CT staging of ovarian cancer and a conventional MRI as well as DWI MRI in gynaecological oncology. The experience in image reading was therefore regarded transferable. The potential limitation therefore was the improving protocol potentially leading to increasing image quality during the study. Furthermore, the interobserver analysis was missing because only one independent reader for WB-DWI/MRI and for CT were available in the study and the patients would not accept ultrasound examination provided separately by each of 3 sonographers. Lastly, in contrast to the work of Michielsen et al. [6] we did not compare ultrasound with PET-CT due to the lower sensitivity of PET-CT in comparison to WB-DWI/MRI for detecting bowel mesenterial and visceral metastases. The addition of PET-CT would also increase the number of procedures per patient and unnecessary radiation load.

In 2014 Michielsen et al. included 23 ovarian cancer cases in a study group of 32 patients with benign and malignant disease and showed an excellent per-lesion performance for peritoneal and lymph node staging for WB-DWI/MRI in comparison with CT. In their second study from 2017 on 94 subjects with primary ovarian cancer, the authors confirmed significantly better prediction of incomplete resection and correct FIGO staging for WB-DWI/MRI in comparison with CT[6, 27]. We have used the same technical protocol for WB-DWI/MRI and CT (supplementary table 7 and 8) to be able to compare our data with these previous studies[6, 27] (Table 2, Figure 7 and 8, video 5). We have shown that in pelvis endovaginal ultrasound in comparison to WB-DWI/MRI and CT showed higher accuracy (94 %, 91% and 85% respectively). Ultrasound was more accurate particularly in the evaluation of deep rectosigmoid wall infiltration when compared to the other two modalities. We have confirmed the results of the previous ultrasound studies[17, 28], which justifies its potential use for the preoperative planning of rectosigmoid resection. In the abdomen, the accuracy of ultrasound was equal or even better than WB-DWI/MRI and CT in the assessment of liver parenchyma and its surface (88% vs 74% vs 77%), lesser omentum (92% vs 89% vs 89%) and greater omentum (87% vs 87% vs 84%), and in the anterior abdominal wall (91% vs 87% and

85%). On the other hand, ultrasound showed the worst results followed by WB-DWI/MRI and CT in the bowel serosa and mesentery assessment with accuracy (70%, 78% and 79% respectively)(Supplementary table 1). The intraoperative findings of infiltrated root of bowel mesentery or small bowel serosa undetected on preoperative imaging mainly led to a residual disease at the end of the surgery. Based on these findings, there is a potential role for diagnostic laparoscopy to detect small-sized serosal and mesenteric metastases prior to laparotomy to avoid unnecessary laparotomy. Ultrasound showed also lower accuracy than WB-DWI/MRI and CT when depicting diaphragm (left and right 74% and 72% vs 86% and 84% vs 86 and 81%) and paracolic gutters (75% vs 88% vs 76%), but an infiltrated diaphragm or paracolic gutters could be routinely cytoreduced and do not belong to the clinically relevant markers of inoperability[22]. In the assessment of retroperitoneal lymph nodes (79-83%) and in the prediction of non-resectability (85-90%), all three methods achieved similar accuracy.

There are only few studies comparing ultrasound with other modern imaging techniques in ovarian cancer staging. Historically first study produced by Tempany et al. comparing ultrasound, conventional MRI and CT was published by the Radiological Diagnostic Oncology Group in 2000[29], on 118 cases (73/118, 62% advanced stage) showing promising role of ultrasound in the hepatic assessment in comparison to MRI and CT (ultrasound sensitivity 57%, versus MRI and CT 40%)[29]. In our study, sensitivity of ultrasound (54%) remains similar, but performance of WB-DWI MRI (77%) and CT (69%) improved. Tempany et al showed that sensitivity of ultrasound (32%) was not significantly different from MRI (38%) and CT (43%) for lymph node metastasis detection, in line with our results (sensitivity of ultrasound, WB-DWI/MRI and CT, 52%, 52% and 48%). Tempany reported ultrasound sensitivity (69%) inferior to MRI (95%) and CT (92%) in the peritoneal assessment, which can be related to lower resolution of ultrasound 20 years ago. In our study, the sensitivity of ultrasound was still lower than cross-sectional imaging but higher than 85% (sensitivity of ultrasound, WB-DWI/MRI and CT, 86%, 95% and 93%). In 2019, Alcázar et al. published data of 93 patients with ovarian cancer (56/93, 60% advanced ovarian cancers) and showed good agreement between clinical stage and surgical stage for ultrasound (kappa index: 0.69) and CT scan (kappa index: 0.70)[5]. Overall accuracy to determine tumour stage was 71% for ultrasound and 75% for CT scan[5].

This study offers promising data on novel use of ultrasound and is currently being validated in a multicentric prospective ISAAC study (NCT03808792), which also focuses on interobserver agreement in the preoperative ultrasound staging of ovarian cancer.

Conclusion

This study showed slightly better diagnostic performance of ultrasound and WB-DWI/MRI to CT in the assessment of peritoneal carcinomatosis and comparable results of all three methods for lymph node staging and the prediction of non-resectability based on abdominal markers in ovarian cancer patients. In gynecologic oncology centres with expert sonographers and high-end equipment, ultrasound can be used not only for ovarian mass characterization but also as a useful alternative to cross-section methods for ovarian cancer staging and prediction of non-resectability.

Acknowledgement

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Figure Legends

Figure 1 Study protocol

ECOG (the Eastern Cooperative Oncology Group) performance status[14], US, ultrasound, CT, computed tomography, WB-DWI/MRI, whole body diffusion weighted magnetic resonance imaging, ISAAC, Imaging Study on Advanced ovArian cancer (ISAAC), MDT, multidisciplinary team, BOT, borderline ovarian tumour.

*Patient agreed to undergo three imaging methods and no contraindication for CT and WB-DWI/MRI are known.

Figure 2 Markers of non-resectability

Non-resectable disease is defined as at least one of the following markers published by ESGO[3, 4].

 Figure 3 Pelvic peritoneal carcinomatosis (a) visceral carcinomatosis infiltrating bladder, vesicouterine plica in front of the uterus, dorsally from the uterus there is a rectosigmoid and pouch of Douglas in sagittal plane on the ultrasound, (b-c) in transverse plane on T1 weighted MRI and CECT, (d) visceral carcinomatosis infiltrates hypoechogenic muscle layer of rectosigmoid on ultrasound in sagittal plane, (e) in DWI peritoneal lesions show restriction of diffusion and are hyperintense with low signal intensity, (f) specimen demonstrating deep invasion in rectosigmoid. C., carcinomatosis; MRI T1 FS Gd VIBE, T1-weighted magnetic resonance imaging after intravenous gadolinium; VIBE, volumetric interpolated breath-hold examination; CECT, contrast enhanced computed tomography; DWI, diffusion weighted imaging.

Figure 4 Flow-chart of enrolled patients

Figure 5 Diagnostic performance of ultrasound, WB-DWI/MRI and CECT

AUC, area under curve. WB-DWI/MRI (whole-body diffusion weighted MRI);CECT, contrast enhanced computed tomography. US, ultrasound.

Figure 6 Small bowel serosal carcinomatosis

(a-c) Diffuse visceral carcinomatosis on small bowel (ileum) on ultrasound and contrast enhanced computed tomography in transverse and coronal plane. CECT, contrast enhanced computed tomography. Video 4.

Figure 7 Peritoneal carcinomatosis

Ultrasound, contrast-enhanced computed tomography and magnetic resonance with diffusion-weighted images are demonstrating peritoneal metastases in transverse plane (unless stated otherwise): (a-d) peritoneal visceral implant on the right not-infiltrated ovary, (e-f) parietal isolated nodule on the right pelvic side wall and diffuse visceral carcinomatosis on rectosigmoid, (i-l) visceral focal nodule on the splenic surface, (m-p) omental infiltration, (q-x) visceral nodules in omental bursa and on stomach (in sagittal plane on ultrasound). C., carcinomatosis; MRI T1 FS Gd VIBE, T1-weighted magnetic resonance imaging after intravenous gadolinium; VIBE, volumetric interpolated breath-hold examination; CECT, contrast enhanced computed tomography; DWI, diffusion weighted imaging. Video 5.

Figure 8 Peritoneal carcinomatosis

Magnetic resonance with diffusion-weighted images is demonstrating peritoneal metastases in coronal plane (a continuation of figure 7): (a-b) peritoneal visceral carcinomatosis on rectosigmoid and infracolic omental infiltration, (c-d) visceral nodules on stomach, nodular infiltration of supra- and infracolic omentum and diffuse infiltration of infracolic omentum (omental cake). C., carcinomatosis; MRI T1 FS Gd VIBE, T1-weighted magnetic resonance imaging after intravenous gadolinium; VIBE, volumetric interpolated breath-hold examination; DWI, diffusion weighted imaging. Coronal reconstructions on the WB-DWI/MRI images are essential in reading the examination to assess the diaphragms, small bowel mesentery and serosa etc).

Supplementary Files

Supplementary figure 1 Peritoneal involvement (carcinomatosis) classification

Supplementary figure 2 Lymph node classification. Schematic images of peripheral (top) and non-peripheral (bottom) lymph nodes. These could be the site of lymphatic spread from gynecological malignancies. Non-peripheral abdominal and pelvic lymph nodes are divided into parietal nodes(which are found along major abdominal vessels) and visceral nodes(which are found along vessels supplying visceral organs).

Supplementary figure 3 Liver involvement

(a-c) Subcapsular visceral carcinomatosis deeply infiltrating liver parenchyma and isolated intraparenchymal metastases on ultrasound and contrast enhanced computed tomography in transverse plane. CECT, contrast-enhanced computed tomography. Video 3.

Supplementary figure 4 Ultrasound evaluation of lymph node status

1, capsule; 2, cortex; 3, medulla; 4, hilum; 5, longitudinal hilar vessels; 6, transcapsular vessels. Using ultrasound assessment, the lymph nodes are classified as non-infiltrated, suspicious of infiltration, infiltrated (highly suggestive of metastatic infiltration). Suspicious lymph nodes are those with overlapping *non-infiltrated* and *infiltrated* features.

Supplementary figure 5 Schematic drawings, grey-scale ultrasound images, and color Doppler images of metastatic inguinal lymph nodes

1, capsule; 2, cortex; 3, residual medulla; 4, hilum; 5, longitudinal hilar vessels with characteristic hilar flow; 6, transcapsular flow with penetrating vessels.

(a-c) lymph node with partial metastatic infiltration characterized by a large intranodal metastasis and a small residuum of the normal lymph node with visible medulla and hilar vascular flow combined with transcapsular flow penetrating the intranodal metastasis. The intranodal metastasis shows capsular interruption and cystic (anechoic) areas. (d-f) lymph node with complete metastatic infiltration. It has a round shape and inhomogenous diffuse cortical echogenicity with sand pattern. The nodal core-sign is absent. Only vessels penetrating the node from outside with a transcapsular flow pattern are visible (moderate color score). A hyperechogenic perinodal ring is also present. Video 4.

Supplementary figure 6 Contrast enhanced computed tomography imaging protocol
CECT, contrast-enhanced computed tomography; MPR, multiplanar reconstructions.

Supplementary figure 7 Whole-body diffusion weighted magnetic resonance imaging protocol

WB-DWI/MRI, whole body diffusion weighted magnetic resonance imaging; TRA, transversal plane; COR, coronal plane; HASTE, (half -Fourier acquisition *s*ingle-shot turbo spin echo); VIBE (volumetric interpolated breath-hold examination); FS, fat saturation; DWI, diffusion weighted images; ADC, apparent diffusion coefficient; Gd, gadolinium.

Supplementary Tables

Supplementary table 1 Pelvic and abdominal peritoneal involvement

Supplementary table 2 Lymph node involvement

Supplementary table 3 Comparison of ultrasound, WB-DWI/MRI and CT for FIGO staging

Supplementary table 4 Markers of non-resectability

Video Legends

Video 1 Pelvic carcinomatosis

Images accompanying video 1 are presenting in Figure 3.

Video 2 Liver involvement

Images accompanying video 3 are presenting in Supplementary figure 3.

Video 3 Metastatic inguinal lymp nodes

Images accompanying video 3 are presenting in Supplementary figure 5.

Video 4 Small bowel serosal carcinomatosis

Images accompanying video 4 are presenting in Figure 6.

Video 5 Peritonal carcinomatosis

Images accompanying video 5 are presenting in Figure 7.

Table 1 Characteristics of the study population

Characteristic	Descriptive statistic
Age (years), mean (SD)	61.4 (10.5)
BMI	26.5 (5.5)
Postmenopausal status	
Yes	51 (76.1%)
No	16 (23.9%)
CA 125 (U/mL), mean (SD)	602.0 (886.5)
0-200	20 (29.9%)
201-500	22 (32.8%)
501-1000	8 (11.9%)
1001-2000	9 (13.4%)
>2000	3 (4.5%)
NA	5 (7.5%)
Origin	
Ovary	14 (20.9%)
Tube	51 (76.1%)
Peritoneum	2 (3.0%)
Histology of cancer	
High-grade serous	54 (80.6%)
Endometrioid	3 (4.5%)
Clear cell	0 (0%)
Mucinous	0 (0%)
Other	10 (13.4%)
FIGO stage	
IA	6 (9.0%)
IB	2 (3.0%)
IC	6 (9.0%)
IIB	2 (3.0%)
IIIA	7 (10.4%)
IIIB	5 (7.5%)
IIIC	32 (47.8%)
IV	7 (10.4%)
Surgical approach	
Diagnostic laparoscopy*	11 (16.4%)
Primary cytoreduction	56 (83.6%)
Primary laparotomy	48 (71.6%)
Combined approach	8 (11.9)
Type of procedure	
Only biopsy	21 (31.3%)
Paraaortic lymphadenectomy	34 (50.7%)
Pelvic lymphadenectomy	35 (52.2%)
Splenectomy	10 (14.9%)

Colon resection	14 (20.9%)
Small bowel resection	4 (6.0%)
Liver resection	3 (4.5%)
Peritonectomy	14 (20.9%)
Modified posterior exenteration	13 (19.4%)
Appendicectomy	23 (34.3%)
Omentectomy	52 (77.6%)
Postoperative residual tumor (R) after primary cytoreduction	
R0 (no residuum, complete debulking)	38 (68.0%)
R≤1 cm (optimal debulking)	9 (16.0%)
R>1 cm (suboptimal debulking)	9 (16.0%)
Fluidothorax	9 (13.4%)
Intraoperative ascites (mL)	1353.7 (1849.9)
No	19 (28.4)
Pelvis	17 (25.4)
Subdiaphragmatic	3 (4.5)
Intraabdominal	28 (41.8)

Data given as absolute and relative frequencies for categorical variables, and mean and SD for continuous variables. FIGO (The International Federation of Gynecology and Obstetrics) classification rules published in 2014 were used[15]. ECOG grade developed by the Eastern Cooperative Oncology Group[14]. BMI, body mass index.

*Disease determined as non-resectable (non-feasible for cytoreduction) by initial laparoscopic exploration.

Type of infiltration	Study group	Imaging	TN	FN	FP	TP	Specificity	Sensitivity	PPV	NPV	Accuracy	AUC	Difference of AUC
Pelvic involvement	Our study	US	19	3	1	44	0.95 (0.75-1.0)	0.94 (0.82-0.99)	0.98 (0.88-0.10)	0.86 (0.65-0.97)	0.94 (0.85-0.98)	0.94 (0.87; 1.00)	**<0.001**
		WB-DWI/MRI	18	4	2	43	0.90 (0.68-0.99)	0.91 (0.80-0.98)	0.96 (0.85-0.99)	0.82 (0.60-0.95)	0.91 (0.82-0.97)	0.91 (0.82; 1.00)	**<0.001**
		CT	14	5	5	42	0.74 (0.49; 0.91)	0.89 (0.77; 0.96)	0.89 (0.77; 0.96)	0.74 (0.49; 0.91)	0.85 (0.74; 0.92)	0.82 (0.69; 0.94)	**<0.001**
	Michielsen study[6]	WB-DWI/MRI	20	3	1	33	0.95 (0.76; 1.00)	0.92 (0.78; 0.98)	0.97 (0.85; 1.00)	0.87 (0.66; 0.97)	0.93 (0.83; 0.98)	0.94 (0.87; 1.00)	**<0.001**
		CT	20	16	1	20	0.95 (0.76; 1.00)	0.56 (0.38; 0.72)	0.95 (0.76; 1.00)	0.56 (0.38; 0.72)	0.70 (0.57; 0.82)	0.75 (0.61; 0.89)	**0.001**
Bowel visceral and mesenterial involvement	Our study	US	34	18	2	13	0.94 (0.25; 0.61)	0.42 (0.81; 0.993)	0.87 (0.60; 0.98)	0.65 (0.51; 0.78)	0.70 (0.58; 0.81)	0.68 (0.55; 0.81)	**0.011**
		WB-DWI/MRI	32	11	4	20	0.89 (0.45; 0.81)	0.65 (0.74; 0.969)	0.83 (0.63; 0.95)	0.74 (0.59; 0.86)	0.78 (0.66; 0.87)	0.77 (0.65; 0.89)	**<0.001**
		CT	33	11	3	20	0.92 (0.45; 0.81)	0.65 (0.78; 0.982)	0.87 (0.66; 0.97)	0.75 (0.60; 0.87)	0.79 (0.67; 0.88)	0.78 (0.66; 0.90)	**<0.001**
	Michielsen study[6]	WB-DWI/MRI	59	7	15	34	0.80 (0.69; 0.88)	0.83 (0.68; 0.93)	0.69 (0.55; 0.82)	0.89 (0.79; 0.96)	0.81 (0.72; 0.88)	0.82 (0.74; 0.90)	**<0.001**
		CT	67	21	7	20	0.91 (0.81; 0.96)	0.49 (0.33; 0.65)	0.74 (0.54; 0.89)	0.76 (0.66; 0.85)	0.76 (0.67; 0.83)	0.70 (0.60; 0.80)	**<0.001**
Overall peritoneal staging	Our study	US	21	6	3	37	0.88 (0.74; 1.00)	0.86 (0.76; 0.96)	0.93 (0.84; 1.00)	0.78 (0.62; 0.94)	0.87 (0.78; 0.95)	0.87 (0.77; 0.97)	**<0.001**
		WB-DWI/MRI	19	3	5	40	0.79 (0.63; 0.95)	0.93 (0.80; 1.00)	0.89 (0.80; 0.98)	0.86 (0.72; 1.00)	0.88 (0.80; 0.96)	0.86 (0.76; 0.97)	**<0.001**
		CT	14	2	10	41	0.58 (0.39; 0.79)	0.95 (0.89; 1.00)	0.80 (0.70; 0.91)	0.88 (0.71; 1.00)	0.82 (0.73; 0.91)	0.77 (0.64; 0.90)	**<0.001**
	Michielsen study[6]	WB-DWI/MRI	243	19	24	189	0.91 (0.87; 0.94)	0.91 (0.86; 0.94)	0.89 (0.84; 0.93)	0.93 (0.89; 0.96)	0.91 (0.88; 0.93)	0.91 (0.88; 0.94)	**<0.001**
		CT	220	72	47	136	0.82 (0.77; 0.87)	0.65 (0.58; 0.72)	0.74 (0.67; 0.80)	0.75 (0.70; 0.80)	0.75 (0.71; 0.79)	0.74 (0.70; 0.78)	**<0.001**
Lymph nodes (retroperitoneal infra-/suprarenal)	Our study	US	37	10	0	11	1.00 (-)	0.52 (0.30; 0.74)	1.00 (-)	0.79 (0.64; 0.89)	0.83 (0.71; 0.91)	0.76 (0.62; 0.91)	**0.001**
		WB-DWI/MRI	37	10	0	11	1.00 (-)	0.52 (0.30; 0.74)	1.00 (-)	0.79 (0.64; 0.89)	0.83 (0.71; 0.91)	0.76 (0.62; 0.91)	**0.001**
		CT	36	11	1	10	0.97 (0.86; 1.00)	0.48 (0.26; 0.70)	0.91 (0.59; 1.00)	0.77 (0.62; 0.88)	0.79 (0.67; 0.89)	0.72 (0.58; 0.87)	**0.005**
	Michielsen study[6]	WB-DWI/MRI	29	3	3	10	0.91 (0.75; 0.98)	0.77 (0.46; 0.95)	0.77 (0.46; 0.95)	0.91 (0.75; 0.98)	0.87 (0.73; 0.95)	0.84 (0.72; 0.96)	**<0.001**

			TN	FN	FP	TP	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC	p-value
		CT	25	6	7	7	0.78 (0.60; 0.91)	0.54 (0.25; 0.81)	0.50 (0.23; 0.77)	0.81 (0.63; 0.93)	0.71 (0.56; 0.84)	0.66 (0.49; 0.83)	0.096
Prediction of non-resectability	Our study	US	50	6	1	10	0.98 (0.35; 0.85)	0.63 (0.90; 1.000)	0.91 (0.59; 1.00)	0.89 (0.78; 0.96)	0.90 (0.80; 0.96)	0.80 (0.65; 0.95)	**<0.001**
		WB-DWI/MRI	50	8	1	8	0.98 (0.25; 0.75)	0.50 (0.90; 1.000)	0.89 (0.52; 1.00)	0.86 (0.75; 0.94)	0.87 (0.76; 0.94)	0.74 (0.57; 0.90)	**0.004**
		CT	48	7	3	9	0.94 (0.30; 0.80)	0.56 (0.84; 0.988)	0.75 (0.43; 0.95)	0.87 (0.76; 0.95)	0.85 (0.74; 0.93)	0.75 (0.59; 0.91)	**0.003**
	Michielsen study[27]	WB-DWI/MRI	43	3	1	47	0.98 (0.88; 1.00)	0.94 (0.83; 0.99)	0.98 (0.89; 1.00)	0.93 (0.82; 0.99)	0.96 (0.89; 0.99)	0.96 (0.92; 1.00)	**<0.001**
		CT	34	17	10	33	0.77 (0.62; 0.89)	0.66 (0.51; 0.79)	0.77 (0.61; 0.88)	0.67 (0.52; 0.79)	0.71 (0.61; 0.80)	0.72 (0.62; 0.82)	**<0.001**

Table 2 Comparison of the study results with the results of Michielsen et al.[6, 27]

Table presents sensitivities, specificities, positive and negative predictive value, accuracy and calculated area under the curve of all three imaging modalities (US, ultrasound, CT, computed tomography, WB-DWI/MRI, whole body diffusion weighted imaging) with intraoperative visualisation complemented with the pathological report as reference standard. The level of significance was set for AUC as p-value ≤0.05. US, ultrasound; CT, computed tomography; WB-DWI/MRI, whole body diffusion weighted imaging; TN, true negative; FN, false negative; FP, false positive; TP, true positive; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; AUC, area under the curve.

Patient referral to gynecological oncologist: clinical examination

Inclusion criteria assessment

- Patients highly suspicious of primary ovarian, tubal or peritoneal cancer
- Surgery (laparoscopy or laparotomy) planned within 4 weeks
- 18> age < 80
- ECOG grade <3
- Non-pregnant
- US, CECT, WB-DWI/MRI *

Informed consent signature

Included
Informed consent signed

Patient's registration into ISAAC database

Included
Form 1: Clinical data form

Index tests

Included	Excluded: US, CECT, WB-DWI/MRI form not available

Form 2: US form	Form 3: CT form	Form 4: WB-DWI/MRI

MDT meeting: decision on the treatment

Excluded: Patients not scheduled for surgery

Tru-cut biopsy proven secondary tumor

Surgery laparotomy/ laparoscopy

Included	Excluded: Surgery ≥4 weeks after index tests
Form 5: Surgical form	Surgical form not available

Pathological report

Excluded: Secondary tumors

Non-epithelial tumors

Included	Benign or BOT
Form 6: Pathological form	

Final analysis

a   Markers of non-resectability

b   Markers of non-resectability

Retroperitoneal Suprarenal LN

Mesenteric LN

Celiac LN

1. Diffuse carcinomatosis on the small intestine loops when the resection will cause short bowel syndrome.
2. Diffuse deep infiltration of the root of the small bowel mesentery.
3. Diffuse carcinomatosis and/or deep infiltration of the stomach/duodenum (only limited excision is possible).
4. Diffuse carcinomatosis and/or deep infiltration of the head or middle part of pancreas (tail of the pancreas can be resected).
5. Non-resectable liver metastasis (central or multisegmental).
6. Diffuse carcinomatosis and/or infiltration of the hepatic hilum and coeliac trunc, including hepatic arteries, and left gastric artery.
7. Non resectable lymph node metastasis (i.e. multiple visceral [mesenterial +/- coeliac] lymph nodes involvement).

Peritoneal Carcinomatosis

Ultrasound	MRI T1 FS Gd VIBE	CECT
a — Visceral c., Uterus, Visceral c.	b — Visceral c., Uterus, Visceral c., Rectum	c — Visceral c., Uterus, Visceral c., Rectum
Ultrasound	MRI DWI	Specimen
d — Visceral c., Rectum	e — Visceral c., Visceral c.	f — Visceral c.

Suitable participants (n=81)
Malignant adnexal mass **or**
peritoneal cancer on ultrasound
Fit for surgery
18 > Age < 80
ECOG PS < 3
No pregnant
No contraindication to CT or WB-
D...
In...

Index test (n=79)
US + CT + WB-DWI/MRI
ISAAC protocol

Reference standard (n=70):
Surgery (DOL or laparotomy)
ISAAC protocol

Final diagnosis (n=67)

Excluded (n=2)
No index test (WB-
DWI/MRI)
Excluded (n=9)
Tru-cut biopsy proven secondary
ovarian cancer (6)
No reference standard
– patients no scheduled for
surgery (3)

Excluded (n=3)
No reference standard
– no surgical form (1)
– surgery >4 weeks after the
index tests (1)
Secondary cancer (1)

Peritoneal Carcinomatosis

Ultrasound	CECT	CECT

a — Visceral c., Ileum

b — Ileum, Visceral c.

c — Ileum, Visceral c.

Peritoneal Carcinomatosis

| Ultrasound | CECT | MRI T1 FS Gd VIBE | MRI DWI |

Peritoneal Carcinomatosis (continued)

a. MRI T1 FS Gd VIBE — Infracolic omental infiltration; Visceral carcinomatosis on rectosigmoid

b. MRI DWI — Infracolic omental infiltration; Visceral carcinomatosis on rectosigmoid

c. MRI T1 FS Gd VIBE

d. MRI DWI — Visceral carcinomatosis on stomach; Nodule in infracolic omentum; Nodule in supracolic omentum; Infracolic omental cake; Infracolic omental cake