GYNECOLOGY

Prediction of nonresectability using the updated Predictive Index value model assessed by imaging and surgery in tubo-ovarian cancer: a prospective multicenter ISAAC study

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BACKGROUND: A laparoscopy-based scoring system was developed by Fagotti et al (Fagotti or Predictive Index value (PIV)score) based on the intraoperative presence or absence of carcinomatosis on predefined sites. Later, the authors updated the PIV score calculated only in the absence of one or both absolute criteria of nonresectability (mesenteric retraction and miliary carcinomatosis of the small bowel) (updated PIV model).

OBJECTIVE: The aim was to demonstrate the noninferiority of ultrasound to other imaging methods (contrast enhanced computed tomography (CT) and whole-body diffusion-weighted magnetic resonance imaging (WB-DWI)/MRI) in predicting nonresectable tumor (defined as residual disease >1 cm) using the updated PIV model in patients with tubo-ovarian cancer. The agreement between imaging and intraoperative findings as a reference was also calculated.

STUDY DESIGN: This was a European prospective multicenter observational study. We included patients with suspected tubo-ovarian carcinoma who underwent preoperative staging and prediction of nonresectability at ultrasound, CT, WB-DWI/MRI, and surgical exploration. Ultrasound and CT were mandatory index tests, while WB-DWI/MRI was an optional test (non-available in all centers). The predictors of nonresectability were suspicious mesenteric retraction and/or miliary carcinomatosis of the small bowel or if absent, a PIV >8 (updated PIV model). The PIV score ranges from 0 to 12 according to the presence of disease in 6 predefined intra-abdominal sites (great omentum, liver surface, lesser omentum/stomach/spleen, parietal peritoneum, diaphragms, bowel serosa/mesentery). The reference standard was surgical outcome, in terms of residual disease >1 cm, assessed by laparoscopy and/or laparotomy. The area under the receiver operating characteristic curve (AUC) to assess the performance of the methods in predicting nonresectability was reported. Concordance between index tests at the detection of disease at 6 predefined sites and intraoperative exploration as reference standard was also calculated using Cohen's kappa.

RESULTS: The study was between 2018 and 2022 in 5 European gynecological oncology centers. Data from 242 patients having both mandatory index tests (ultrasound and CT) were analyzed. 145/242 (59.9%) patients had no macroscopic residual tumor after surgery (R0) (5/145 laparoscopy and 140/145 laparotomy) and 17/242 (7.0%) had residual tumor ≤1 cm (R1) (laparotomy). In 80/242 patients (33.1%), the residual tumor was>1 cm (R2), 30 of them underwent laparotomy and maximum surgery was carried out, and 50/80 underwent laparoscopy only, because cytoreduction was not feasible in all of them. After excluding 18/242 (7.4%) patients operated on but not eligible for extensive surgery, the predictive performance of 3 imaging methods was analyzed in 167 women. The AUCs of all methods in discriminating between resectable and nonresectable tumor was 0.80 for ultrasound, 0.76 for CT, 0.71 for WB-DWI/MRI, and 0.90 for surgical exploration. Ultrasound had the highest agreement (Cohen's kappa ranging from 0.59 to 0.79) than CT and WB-DWI/MRI to assess all parameters included in the updated PIV model.

CONCLUSION: Ultrasound showed noninferiority to CT and to WB-DWI/MRI in discriminating between resectable and nonresectable tumor using the updated PIV model. Ultrasound had the best agreement between imaging and intraoperative findings in the assessment of parameters included in the updated PIV model. Ultrasound is an acceptable method to assess abdominal disease and predict nonresectability in patients with tubo-ovarian cancer in the hands of specially trained ultrasound examiners.

Key words: computed tomography, laparoscopy, laparotomy, magnetic resonance, ovarian cancer, staging, ultrasonography

Introduction

More than 90% of malignant ovarian tumors are designated as tubo-ovarian carcinoma (also referred to as epithelial ovarian cancer).[1] Tubo-ovarian carcinoma is the eighth most common female cancer in the developed world,[2] with 30% to 45% 5-year survival rate. Primary debulking surgery (PDS) followed by platinum-based chemotherapy is the standard treatment for patients with advanced tubo-ovarian carcinoma.[3] In patients considered unsuitable for optimal cytoreduction (residual disease measuring less than 1 cm), neoadjuvant chemotherapy followed by interval debulking surgery (IDS) could be an appropriate, alternative choice.[3–5]

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AJOG at a Glance

Why was this study conducted?

This is the largest prospective study assessing the performance of 3 imaging methods in assessing nonresectability in patients with tubo-ovarian carcinoma.

Key findings

Ultrasound was not inferior to computed tomography (CT) and whole-body diffusion-weighted magnetic resonance imaging (WB-DWI/MRI) in predicting surgical outcome using updated Predictive Index value model.

What does this add to what is known?

Ultrasound can be used as an alternative method to CT and WB-DWI/MRI in the prediction of nonresectability when performed by experienced examiners in dedicated oncological centers.

During both PDS and IDS, the maximum surgical effort should be made to remove all visible tumor.[3,4]

Tubo-ovarian carcinoma is predominantly a peritoneal disease, and its resectability mainly depends on the evaluation of abdominal sites critical for cytoreduction. Therefore, the precise evaluation of tumor involvement at specific sites is a critical factor in the treatment decision-making process. A laparoscopic scoring model based on the intraoperative presence or the absence of tumor infiltration at predefined anatomic sites to predict nonresectability was developed by Fagotti et al in 2006[6,7] and updated in 2015 based on retrospective data.[8] In the updated Fagotti scoring model, also called updated Predictive Index value (PIV) model, the authors excluded mesenteric retraction and miliary diffuse carcinomatosis on the serosa of the small bowel from the scoring system. These findings are now regarded as absolute criteria for nonresectability and calculated PIV score only in the absence of one or both of these criteria.[8] The updated laparoscopic PIV model reached a null rate of inappropriate explorations (PPV100%) at a PIV cut-off value of >8.

Different imaging modalities in predicting disease extension and nonresectability were tested to avoid unnecessary surgery in nonresectable patients and to initiate earlier systemic treatment. Computed tomography (CT) is currently the most used imaging technique for the preoperative staging of tubo-ovarian carcinoma, with a reported sensitivity of 58% to 94% and specificity of 58% to 94% to assess peritoneal carcinomatosis.[9–12] More recently, whole-body diffusion-weighted (WB-DWI)/MRI has shown higher sensitivity and specificity in the prediction of suboptimal debulking outcome compared to CT.[13] Additionally, in 2022, the results of a prospective single-unit study indicated that ultrasound may be an alternative to both CT and WB-DWI/MRI for preoperative tubo-ovarian carcinoma work-up and prediction of nonresectability.[14] Ultrasound also proved to be able to predict the laparoscopic PIV score and 2 absolute markers of nonresectability (mesenteric and visceral small bowel carcinomatosis) in patients with advanced tubo-ovarian carcinoma in a single center study.[15]

In the present prospective multicentric study, we report the performance of the updated PIV model calculated at ultrasound, CT, WB-DWI/MRI, and surgical exploration in predicting surgical nonresectability (>1 cm of residual tumor). Concordance between imaging and intraoperative findings in the assessment of all parameters included in the updated PIV model was also calculated.

Materials and methods

Study design

The present work was a part of the ISAAC single-arm, prospective, multicentric, observational, imaging study (Clinicaltrials.gov: NCT03808792). The primary objective of the ISAAC study was to test noninferiority of ultrasound to CT and WB-DWI/MRI in the prediction of surgical outcome in patients with tubo-ovarian carcinoma using ESMO-ESGO markers of nonresectability.[16] In the present study, we report data on one of the secondary endpoints of the ISAAC study: the performance of the updated PIV model assessed by ultrasound, CT, WB-DWI/MRI, and surgical exploration in predicting surgical nonresectability. The updated PIV model developed in 2015[8] includes the assessment of the presence of 2 criteria of nonresectability (ie, mesenteric retraction and miliary carcinomatosis of the small bowel) and if absent, the calculation of the PIV score. The predictor of nonresectability is mesenteric retraction and/or miliary carcinomatosis or a PIV >8.[8]

The protocol was approved by the institutional review board (29/18, 04.06.2018) at the leading institution (General University Hospital in Prague) and then by the institutional review boards of all participating centers.

All participating centers were recruited by invitation, under supervision of the ISAAC Steering Committee. Minimum requirements were 1) ultrasound experience level II or III defined by the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) certification[17] and extensive experience in ovarian cancer staging (>100 scans), 2) radiological expertise defined as minimum of 5 years of practice using CT and/or MRI in gynecologic oncology staging, 3) high surgical quality based on the Quality Indicators defined by ESGO in 2016.[16]

In particular, EFSUMB level II practitioners have performed at least 2000 gynecologic ultrasound examinations and must perform at least 500 examinations each year. EFSUMB level III practitioners are expert in gynecologic ultrasound and are regularly involved in ultrasound and/or teaching, research, and development.[17]

Participants

We included patients with abdominal or pelvic mass suspected of primary tubal,

ovarian, peritoneal carcinoma at first diagnosis or patients with upfront neoadjuvant chemotherapy planned for IDS. Other inclusion criteria were as follows: 1) patients suitable for surgery planned within 4 weeks of imaging tests; 2) age 18 to 80 years; 3) Eastern Cooperative Oncology Group performance status scale <3; 4) nonpregnant; 5) patient's agreement to undergo ultrasound, CT, and WB-DWI/MRI index tests; 6) CT not contraindicated. Ultrasound and CT were mandatory index tests, while WB-DWI/MRI was an optional test (nonavailable in all centers).

Exclusion criteria were as follows: 1) suspected benign or borderline ovarian tumors; 2) suspected metastatic (secondary) ovarian cancer; 3) biopsy-proven nonepithelial ovarian cancer; 4) no reference standard available (surgery).

Index tests

The centers were encouraged to perform all 3 imaging methods, but where WB-DWI/MRI was not available, only ultrasound and CT were performed.

Presence of mesenteric retraction and miliary carcinomatosis of the small bowel and PIV score were assessed at ultrasound, CT, WB-DWI/MRI, and surgical exploration. The PIV score included the evaluation of peritoneum on 6 sites (Supplemental Table 1): 1) greater omentum, 2) liver, 3) lesser omentum and/or stomach and/or spleen, 4) paracolic gutters and/or anterior abdominal wall, 5) diaphragm, 6) small and large bowel (except rectosigmoid). For each site, a score 2 was assigned when the parameter was positive (presence of disease according to the definition of PIV), while score 0 if no disease was observed. The PIV score ranged from 0 to 12 and a score >8 was indicative of surgical nonresectability.[8]

Both ultrasound examiners and radiologists were blinded to the results of other imaging modalities. The results of all 3 index tests were available for the multidisciplinary team meeting decision and further management. Clinical data and evaluation forms were compiled for each test (ultrasound, CT, WB-DWI/MRI) using an electronic database (REDCap software) after the procedure. Data cleaning was performed by a team of biostatisticians and study nurses of each participating center. Queries were sent to participating centers to retrieve missing information and correct inconsistencies.

A standardized ultrasound examination was performed using Samsung HERA I10 or Voluson E10 machine, equipped with a 5 to 9 MHz endocavity transducer and a 3.5 to 7 MHz abdominal matrix curved transducer were used.

Contrast-enhanced CT scan was performed using a 128-slice scanner (Somatom Definition EdgeSiemens Healthineers, Erlangen, Germany). At the start of the examination, iodinated contrast agent (Iomeron 350, Bracco) was administered intravenously via an indwelling canula. The images were reconstructed in 0.75 mm slices with 5 mm multiplanar reconstruction.

WB-DWI/MRI was performed with parallel radiofrequency transmission using phased-array surface and posterior coils on a 3-Tesla MRI scanner (MAGNETOM Skyra, Siemens Healthineers, Erlangen, Germany, later Ingenia Elition 3T, Philips, Best, The Netherlands) with a wide bore MRI system (open bore diameter 70 cm). WB-DWI/MRI was performed as a multistation acquisition to cover the neck, chest, upper abdomen, and pelvis with the following sequences: T2 (with and without fat saturation), DWI with background suppression, and postcontrast T1 weighted images. We used contrast agent gadobutrol (Gadovist, Bayer) or gadopteridol (ProHance, Bracco).

Reference standard

Surgery was chosen as reference standard because no imaging modality is able to detect the miliary tumor spread with sufficient accuracy. Regarding the surgical approach (diagnostic laparoscopy and/or laparotomy), the decision was made during the multidisciplinary team meeting and based on the internal policy of each department.

The surgical outcome, in terms of residual disease>1 cm, was the reference standard for the preoperative and intraoperative assessment of nonresectability using the updated PIV model. Intraoperative (visual) findings, in combination with pathological findings (if available), were used as reference standard for the assessment of the imaging methods in the detection of disease at all sites included in the PIV model.

At the end of surgery, surgeons described the surgical outcome as a complete (R0, no macroscopic residual tumor left in situ), optimal (R1, residual tumor ≤1 cm), or suboptimal (R2, residual tumor >1 cm). The nonresectable disease (R2) included the following: 1) cases with residual tumor>1 cm after maximal surgical effort was made after laparotomy (suboptimal cytoreduction), 2) cases in which cytoreduction was judged not technically feasible during diagnostic laparoscopy and/or explorative laparotomy due to tumor growth or localization. Patients who were operated on but noneligible for extensive surgery (not tolerating the kind of surgery necessary to resect all tumor sites) were also reported by surgeons in the evaluation form.

Statistical analysis

Surgical outcome (residual disease >1 cm) was the reference standard to predict nonresectability disease on imaging or intraoperative surgery. The predictors of nonresectability were suspicious mesenteric retraction and/or miliary carcinomatosis of the small bowel or, if absent, a PIV >8.[8] For the calculation of the performance of the different methods to predict nonresectability, inoperable patients (those who could not tolerate extensive surgery) were excluded. The area under the receiver operating characteristic curve (AUC) to assess the performance of the methods in predicting nonresectability was reported. Sensitivity, specificity, accuracy, positive, and negative predictive values (PPV and NPV) and accuracy were also calculated. The AUCs were compared using a test for noninferiority, following the formula of Liu et al[18] for paired areas under ROC curves with 5% noninferiority margin and 0.05 significance level. CT and WB-DWI/MRI were used as the reference, with noninferiority of ultrasound compared to CT and WB-DWI/MRI being the focus of the tests.

The sample size required to reach statistical significance at 90% power was

calculated using a method developed by Zhou, McClish and Obuchowski[19] with 5% noninferiority margin. The estimate for AUC 0.78 resulted in 166 patients for the analysis.

Sensitivity, specificity, PPV, NPV as well as the agreement between index tests and surgical exploration in assessing parameters included in the updated PIV model were evaluated. Agreement was calculated using Cohen's kappa and interpreted as poor for κ=0 to 0.2, fair for κ=0.21 to 0.40, moderate for κ=0.41 to 0.60, good for κ=0.61 to 0.80, and very good for κ=0.81 to 1.0. For this calculation, all of the study population was included in the analysis.[20]

Results

Five gynecologic oncology centers from 3 countries were involved: Czech Republic (General University Hospital in Prague), Italy (Fondazione IRCCS Istituto Nazionale dei Tumori, Milan; European Institute of Oncology, Milan; and Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome), and Spain (Clinica Universidad de Navarra).

A total of 287 patients were included and 242 of them were considered in the analysis between 2018 and 2022 (Figure 1 and Supplemental Table 2). All 242 patients underwent both CT and ultrasound examination, whereas MRI was performed in 182 (75.2%) of them.

Clinical, surgical, and histological characteristics of the study population are shown in Table 1. The mean (±SD) age at diagnosis was 60.5 (±11.1) years. 22/242 (9.1%) underwent neoadjuvant chemotherapy. 145/242 (59.9%) patients had no macroscopic residual tumor after surgery (R0) (5/145 laparoscopy and 140/145 laparotomy) and 17/242 (7.0%) had residual tumor ≤1 cm (R1) (laparotomy). In 80/242 patients (33.1%), the residual tumor was>1 cm (R2), 30 of them underwent laparotomy (maximum surgery was carried out in 23/30 and 7/30 were noneligible for extensive surgery), and 50/80 underwent laparoscopy only because cytoreduction was not feasible in all of them (due to tumor growth and/or patient's condition). After excluding 18 patients operated on but not eligible for extensive surgery (7 managed by laparotomy with residual tumor>1 cm and 11 managed by laparoscopy where surgery was not feasible), the performance of methods in predicting nonresectability was calculated in a cohort of 224 patients who underwent ultrasound and CT (Table 2) and in a cohort of patients with all 3 methods available (167/224, 75%) (Table 3). For the latter cohort, the AUC was 0.80 for ultrasound, 0.76 for CT, 0.71 for WB-DWI/MRI, and 0.90 for surgical exploration. All 4 methods had good (>80%) to high specificity but sensitivity was low for ultrasound, CT, WB-DWI/MRI and good (>80%) for surgical exploration. Ultrasound was noninferior to CT (P=.005) but also to MRI (P<.001) to predict nonresectablity using updated PIV model. The performance of imaging methods in each single center is reported in Supplementary Figure.

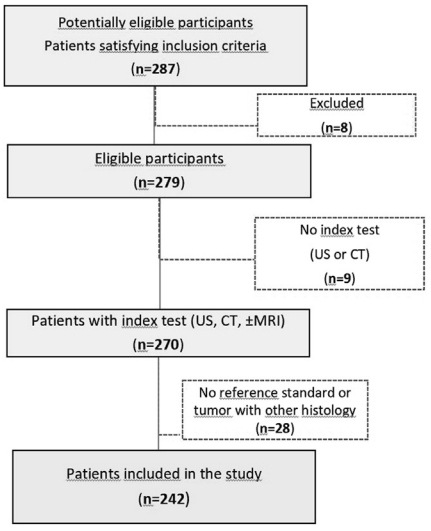
All 3 imaging methods had high to good specificity (>80%) for the assessment of all parameters included in the updated PIV model, except for CT in the assessment of parietal peritoneum (76.9%), whereas the sensitivity was good (>80%) only for ultrasound and MRI in the assessment of great omentum. Greater omentum was the most frequent site involved by disease described by all methods followed by parietal peritoneum and diaphragms (Supplemental Table 3). Ultrasound had the highest Cohen's κ for all parameters included in the updated PIV model (ranging from 0.5 to 0.78) than CT and WB-DWI/MRI (Table 4 and Figure 2).

Comment

Principal findings

In this study, we demonstrated that ultrasound was not inferior to CT and to WB-DWI/MRI in predicting nonresectable tumor, using the updated PIV model as a predictor. Among imaging methods, ultrasound examination performed by an experienced examiner showed the highest agreement with explorative surgical findings in assessing all parameters included in updated PIV model.

FIGURE 1
Flow diagram



Results in the context of what is known

Previous authors used the laparoscopic PIV score proposed by Fagotti et al[21,22] for triaging patients with advanced ovarian cancer. In particular, Fleming et al[21] calculated the PIV score in a prospective study including 215 patients who underwent laparoscopy: patients with PIV<8 were offered upfront surgery and those with PIV≥8 received neoadjuvant chemotherapy. They found that 88% of patients who underwent upfront surgery had no gross residual disease (R0). Later, Di Donna et al,[23] assessed the concordance between 6 radiological (CT) and surgical (laparotomy) parameters included in PIV score in 100 patients with ovarian cancer. The agreement, in terms of Cohen's k, between CT and laparotomy for the 6 parameters ranged between 0.13 and 0.33 and the performance of radiologic PIV in predicting residual disease (R>0 cm) was AUC=0.64. The low performance of CT could be related to the retrospective design.

In a previous prospective single-center study,[15] Moruzzi et al analyzed the agreement between preoperative ultrasound examination and laparoscopic findings in assessing the extension of intra-abdominal disease using all parameters included in the updated PIV model in 264 women with suspected

TABLE 1
Clinical, surgical, and histological characteristics of study population

Parameter	N=242
Age	60.5±11.1
BMI	25.5±5.0
Family history of gynecological cancer including breast cancer	62 (25.6)
Personal history of gynecological cancer including breast cancer	17 (7.0%)
Previous NACT	22 (9.1%)
CA125 (U/mL)	419 (19–4105)
CEA	1.8 (0.4–8.0)
Symptoms	168 (69.4%)
Tense ascites	18/162 (11.1%)
Intraperitoneal fluid	162 (66.9%)
If yes: Intraperitoneal fluid volume (ml)	300 (20–5000)
Surgery	
Approach	
Laparoscopy[a]	55 (22.7)
Laparotomy	162 (67.0)
Combined	25 (10.3)
Type of surgery[b] (multiple choice)	
Salpingoophorectomy unilateral or bilateral	175/187 (93.6)
Hysterectomy	152/187 (81.3)
Peritonectomy	111/187 (59.4)
Rectosigmoid resection	48/187 (25.7)
Omentectomy (supracolic/infracolic)	156/187 (83.4)
Appendectomy	83/187 (44.4)
Splenectomy	17/187 (9.1)
Liver resection	4/187 (2.1)
Colon resection for except rectosigmoid	6/187 (3.2)
Small bowel resection/excision	14/187 (7.5)
Diaphragmatic stripping or resection	47/187 (25.1)
Resection of stomach	3/187 (1.6)
Resection of pancreas	2/187 (1.1)
Resection of lesser omental nodules inluding nodules in hepatic hilum	11/187 (5.9)
Cholecystectomy	4/187 (2.1)
Para-aortic lymphadenectomy/sampling	63/187 (33.7)
Pelvic lymphadenectomy/sampling	60/187 (32.1)
Inguino-femoral lymphadenectomy/sampling	5/187 (2.7)
Others	16/187 (8.6)

(continued)

advanced tubo-ovarian carcinoma. In the ISAAC study, we have slightly better results than the Moruzzi study in the assessment of liver surface, lesser omentum/lesser curvature of stomach/spleen, parietal peritoneum, and 2 absolute criteria of nonresectability. These differences could be explained by the fact that the present study is multicenter including different ultrasound examiners from several centers and different reference standards (only laparoscopic findings for the previous study, laparoscopic or laparotomic findings for the present study). Additionally, in the previous study, no other imaging methods were analyzed.

Other studies have compared the performance of imaging methods, in particular of ultrasound to CT (standard staging modality) and/or to WB-DWI/MRI (novel staging imaging modality) in assessing the spread of disease.[11,13,14] However, no study has compared these 3 imaging modalities in a large population and with multicentric design.

Clinical implications

Our data suggest that ultrasound examination could be used as an imaging method of choice in the assessment of abdominal disease and prediction of nonresectability when performed by experienced examiners in dedicated oncological centers. This is in line with the 2024 ESMO–ESGO-ESP guidelines that recommended contrast-enhanced CT, MRI, or whole-body positron emission tomography-CT with a structured radiology report as options for the initial evaluation of patients with advanced tubo-ovarian carcinoma; ultrasound by an expert sonographer may be used to assess tumor extent and resectability in the pelvic and abdominal cavity.[1]

Access to a preoperative imaging method able to examine tumor nonresectability in patients with tubo-ovarian carcinoma is clinically important. It allows personalization of treatment, operating room programing, and risk planning related to

TABLE 1
Clinical, surgical, and histological characteristics of study population
(continued)

Parameter	N=242
FIGO stage	
I	33 (13.6)
II	13 (5.4)
IIIA	12 (5.0)
IIIB	20 (8.3)
IIIC	120 (49.6)
IV	44 (18.2)
Outcome	
R0	145 (59.9)
R1	17 (7.0)
R2	80 (33.1)
Reason for outcome R2	
Suboptimal cytoreduction (after maximum surgical effort during laparotomy)	23 (28.75)
Cytoreduction not feasible for tumor growth and localization	39 (48.75)
Explorative laparotomy	0 (0.0)
Diagnostic laparoscopy	39
Noneligible for extensive surgery (inoperability)[c]	18 (22.5)
Laparotomy with suboptimal surgical outcome	7
Diagnostic laparoscopy only	11
Histology	
Type of primary tubo-ovarian carcinoma	
Low grade serous carcinoma	17 (7.0)
High grade serous carcinoma	199 (82.2)
Endometrioid carcinoma	8 (3.3)
Clear cells carcinoma	6 (2.5)
Undifferentiated carcinoma	6 (2.5)
Mucinous carcinoma	5 (2.1)
Serous mucinous carcinoma	1 (0.4)
Tumor origin	
Tube	111 (45.9)
Ovary	129 (53.3)
Peritoneum	2 (0.8)

Results are given as n (%) or mean±SD or median (range 5—95 percentile). Age was not available for 7 patients. CA125 was not available for 7 patients. CEA was not available for 84 patients.

BMI, body mass index; *CT*, contrast-enhanced computed tomography; *WB-DWI/MRI*, whole-body diffusion-weighted magnetic resonance imaging; *NACT*, neoadjuvant chemotherapy; *FIGO*, International Federation of Gynecology and Obstetrics; *R0*, complete removal of all visible tumor; *R1*, optimal debulking with residual tumor≤10 mm; *R2*, residual tumor>10 mm.

[a] Laparoscopic approach (R0, 5/55, R2 due to cytoreduction not feasible for tumor growth and localization, 50/55); [b] Type of surgery was calculated in patients who underwent laparotomy and laparoscopy plus laparotomy; [c] Inoperability group included frail patients who could not tolerate extensive surgery.

surgery. Additionally, it can allow selection of patients who may benefit from imaging-guided core-needle biopsy for rapid histological diagnosis and molecular profiling. Finally, preoperative imaging should not be omitted in order to avoid extensive debulking surgery in the peritoneal cavity when there is a risk of residual tumor remaining in situ due to retroperitoneal involvement.

Research implications

Other future studies should explore the role of AI applied to imaging to predict nonresectability. For example, studies with developing models (ie, machine learning models) that incorporate imaging findings, radiomics features, and molecular profiles may permit more precise selection of patients eligible for cytoreduction.

Strengths and limitations

To the best of our knowledge, this is the largest prospective study evaluating the performance of 3 imaging methods in assessing nonresectability in consecutive patients with tubo-ovarian carcinoma. The sample size for assessment of ultrasound noninferiority was estimated in the protocol and reached accordingly and all 5 third-level gynecologic oncology centers met the minimum requirements for imaging and surgical quality. ESGO quality indicators were followed at all participating centers being accredited by ESGO in advanced ovarian cancer surgery, achieving a complete cytoreduction rate of at least 50%. The use of standardized methodology and predefined evaluation forms for the assessment of all variables using Redcap platform is another strength. A possible limitation of the study could be the use of both laparoscopic and laparotomic findings as reference standard. Indeed, laparotomy is more precise in evaluating surgical parameters. Another possible limitation is including only suboptimally cytoreduced cases (residual tumor>1 cm) in the nonresectability group rather than including all incompletely resected cases (R>0 cm);

TABLE 2
Performance of diagnostic procedures to predict nonresectability using updated PIV model

Method	N	AUC (95% CI)	*P*-value	TN (%)	FN (%)	FP (%)	TP (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	OA (%)
US	224	0.779 (0.700–0.857)	<.001	153 (68.3)	24 (10.7)	9 (4.0)	38 (17.0)	61.3	94.4	80.9	86.4	85.3
CT	224	0.731 (0.649–0.813)	<.001	148 (66.1)	28 (12.5)	14 (6.3)	34 (15.2)	54.8	91.4	70.8	84.1	81.3
SUR	224	0.892 (0.838–0.947)	<.001	148 (66.1)	8 (3.6)	14 (6.3)	54 (24.1)	87.1	91.4	79.4	94.9	90.2

In this analysis, inoperability group (patients who could not tolerate surgery) was excluded. Predictors of nonresectability were diffuse miliary carcinomatosis on the small intestine loops and/or diffuse deep infiltration of the root of the small bowel mesentery or PIV >8.[7] The reference standard was surgical outcome (more than 1 cm residual tumor).

AUC, area under curve; *CI*, confidence interval; *CT*, contrast-enhanced computed tomography; *FN*, false negative rate; *N*, number; *NPV*, negative predictive value; *OA*, overall accuracy; *PPV*, positive predictive value; *SUR*, surgery; *TN*, true negative rate; *US*, ultrasound; *WB-DWI/MRI*, whole-body diffusion-weighted magnetic resonance imaging.

however, the number of cases with optimal cytoreduction (residual disease≤1 cm) was very low (only 17, 7.0%). The inclusion of cases after neoadjuvant chemotherapy may also lead to additional misunderstandings, as it is more difficult to differentiate residual fibrosis from cancer tissue, especially in the absence of ascites. However, the number of cases after neoadjuvant chemotherapy was very low (only 22 patients). This low number reflects the study protocol, which allows patients to be enrolled in the study only once, either during first diagnosis or after neoadjuvant chemotherapy.

Furthermore, the mean body mass index (BMI) of our population was 25.5±5.0 and a subanalysis according to BMI was not performed. Previously, Moruzzi et al[15] demonstrated that the agreement between ultrasound and surgical findings was lower in obese women (BMI>30 kg/m^2) than in the general population for the assessment of the great omentum, liver surface, and parietal peritoneum. This may limit the generalizability of our results to patients with high BMI. However, we are analyzing the factors which may influence the accuracy of each imaging method including the impact of BMI, as it is one of the secondary objectives of the ISAAC study. The results will be published in the near future.

In the present study, 3 imaging methods were assessed. However, it should be noted that MRI was not available in all participating centers and was performed in only 75% of the patients, which might skew the results.

One can also argue that the results of our study are applicable only in centers with trained sonographers available where ultrasound is anticipated as routine imaging method in gynecologic cancer staging. However, mirroring these positive results, many scientific societies including ESGO have already recognized the role of ultrasound and are introducing an adequate ultrasound training in their curricula.[24] Lastly, we arbitrarily used cut-off PIV>8 and, therefore, before individual cancer centers introduce updated PIV model in daily practice, individual PIV cut offs

TABLE 3
Performance of diagnostic procedures to predict nonresectability in patients with magnetic resonance imaging available using updated PIV model

Method	N	AUC (95% CI)	*P*-value	TN (%)	FN (%)	FP (%)	TP (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	OA (%)
US	167	0.800 (0.714–0.885)	<.001	111 (66.5)	16 (9.6)	8 (4.8)	32 (19.2)	66.7	93.3	80.0	87.4	85.6
CT	167	0.758 (0.668–0.847)	<.001	106 (63.5)	18 (10.8)	13 (7.8)	30 (18.0)	62.5	89.1	69.8	85.5	81.4
MRI	167	0.708 (0.611–0.805)	<.001	114 (68.3)	26 (15.6)	5 (3.0)	22 (13.2)	45.8	95.8	81.5	81.4	81.4
SUR	167	0.902 (0.843–0.960)	<.001	108 (64.7)	5 (3.0)	11 (6.6)	43 (25.7)	89.6	90.8	79.6	95.6	90.4

In this analysis, inoperability group (patients who could not tolerate surgery) was excluded. Predictors of nonresectability were diffuse miliary carcinomatosis on the small intestine loops and/or diffuse deep infiltration of the root of the small bowel mesentery or PIV >8. The reference standard was surgical outcome (more than 1 cm residual tumor). Ultrasound is noninferior to CT (*P*=.005). Ultrasound is noninferior to MRI (*P*<.001).

AUC, area under curve; *CI*, confidence interval; *CT*, contrast-enhanced computed tomography; *FN*, false negative rate; *MRI*, whole-body diffusion-weighted magnetic resonance imaging; *N*, number; *NPV*, negative predictive value; *OA*, overall accuracy; *PPV*, positive predictive value; *SUR*, surgery; *TN*, true negative rate; *US*, ultrasound.

TABLE 4
Concordance between imaging methods (ultrasound, CT, and MRI) and surgical exploration in the assessment of parameters included in updated PIV model in 242 patients with primary tubo-ovarian carcinoma

Variables	AUC (95%CI)	*P*-value	Sensitivity (%)	Specificity(%)	PPV (%)	NPV (%)	OA (%)	Cohen's k
Greater omentum								
US vs SUR	0.884 (0.838—0.931)	<.001	86.8	90.1	89.7	87.2	88.4	0.769
CT vs SUR	0.814 (0.757—0.871)	<.001	76.0	86.8	85.2	78.4	81.4	0.628
MRI vs SUR	0.822 (0.757—0.887)	<.001	84.2	80.2	84.2	80.2	82.4	0.644
Liver surface								
US vs SUR	0.868 (0.771—0.965)	<.001	75.0	98.6	87.5	96.8	95.9	0.785
CT vs SUR	0.868 (0.771—0.965)	<.001	75.0	98.6	87.5	96.8	95.9	0.325
MRI vs SUR	0.680 (0.545—0.814)	.005	43.5	92.5	45.5	91.9	86.3	0.366
Lesser omentum and/or stomach and/or spleen								
US vs SUR	0.773 (0.695—0.852)	<.001	59.7	95.0	80.4	87.2	86.0	0.597
CT vs SUR	0.707 (0.626—0.788)	<.001	58.1	83.3	54.5	85.2	76.9	0.405
MRI vs SUR	0.675 (0.582—0.768)	<.001	48.1	86.9	59.5	80.7	75.8	0.371
Parietal peritoneum								
US vs SUR	0.828 (0.771—0.886)	<.001	74.7	90.9	85.1	83.9	84.3	0.669
CT vs SUR	0.738 (0.673—0.804)	<.001	70.7	76.9	68.0	79.1	74.4	0.473
MRI vs SUR	0.750 (0.676—0.824)	<.001	65.1	84.8	78.3	74.3	75.8	0.506
Diaphragm								
US vs SUR	0.780 (0.718—0.842)	<.001	62.2	93.9	89.6	74.5	79.3	0.574
CT vs SUR	0.752 (0.688—0.816)	<.001	60.4	90.1	83.8	72.8	76.4	0.515
MRI vs SUR	0.709 (0.632—0.785)	<.001	53.8	87.9	81.7	65.6	70.9	0.418

(continued)

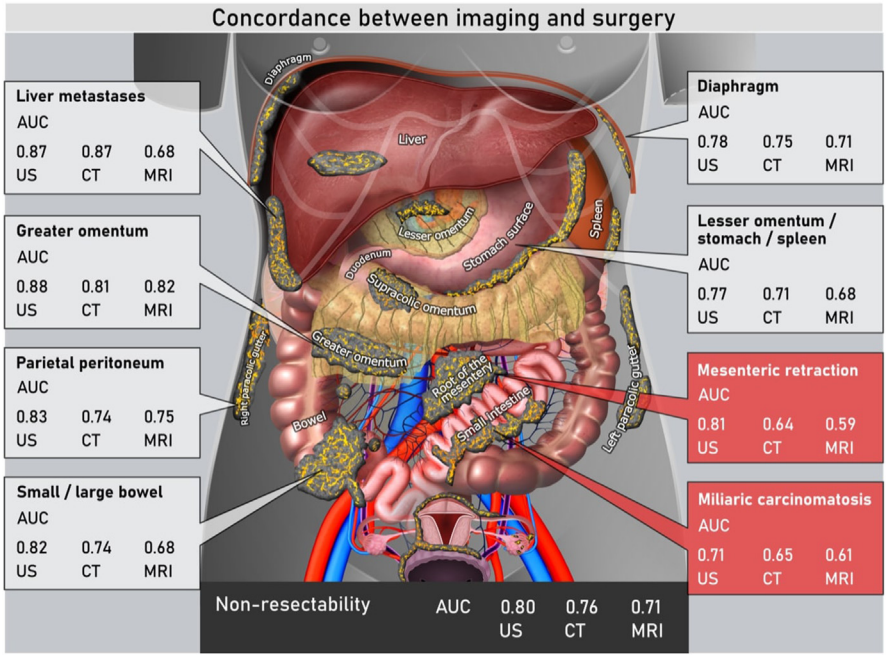
TABLE 4
Concordance between imaging methods (ultrasound, CT, and MRI) and surgical exploration in the assessment of parameters included in updated PIV model in 242 patients with primary tubo-ovarian carcinoma *(continued)*

Variables	AUC (95%CI)	*P*-value	Sensitivity (%)	Specificity(%)	PPV (%)	NPV (%)	OA (%)	Cohen's k
Small/large bowel (except rectosigmoid) necessitating resection								
US vs SUR	0.820 (0.757–0.882)	<.001	65.9	98.0	95.2	82.7	86.0	0.681
CT vs SUR	0.735 (0.665–0.805)	<.001	54.9	92.1	80.6	77.2	78.1	0.502
[a]MRI vs SUR	0.684 (0.601–0.767)	<.001	40.5	96.3	88.2	70.3	73.6	0.403
Absolute criteria of nonresectability								
Miliaric bowel carcinomatosis								
US vs SUR	0.712 (0.624–0.800)	<.001	45.6	96.8	81.3	85.2	84.7	0.499
CT vs SUR	0.648 (0.558–0.738)	<.001	35.1	94.6	66.7	82.5	80.6	0.355
[a]MRI vs SUR	0.605 (0.503–0.707)	.034	23.9	97.1	73.3	79.0	78.6	0.270
Mesenteric retraction								
US vs SUR	0.806 (0.716–0.895)	<.001	63.6	97.5	84.8	92.3	91.3	0.677
CT vs SUR	0.638 (0.536–0.740)	.004	29.5	98.0	76.5	86.2	85.5	0.362
[a]MRI vs SUR	0.591 (0.480–0.702)	.088	21.6	96.6	61.5	82.8	81.3	0.240

US, ultrasound; *CT*, contrast-enhanced computed tomography; *WB-DWI/MRI*, whole-body diffusion weighted magnetic resonance imaging; *SUR*, surgery; *OA*, overall accuracy.

[a] MRI form was available only for 75% of the patients. Agreement is interpreted as being poor for κ=0 to 0.2, fair for κ=0.21 to 0.40, moderate for κ=0.41 to 0.60, good for κ=0.61 to 0.80, and very good for κ=0.81 to 1.0.

FIGURE 2
Performance of imaging methods in assessing the parameters included in the updated PIV model



of respective index tests predicting nonresectability should be set up in order to increase their predictive performance.

The performance of imaging methods in assessing the parameters included in the updated PIV model used as reference standard intraoperative (visual) findings in combination with pathological findings (if available) (Table 4), while surgical outcome (residual disease>1 cm) was the reference standard to predict nonresectability disease on imaging in this figure (Table 3).

Conclusions

Ultrasound showed noninferiority to CT and to WB-DWI/MRI in predicting nonresectable tumor using the updated PIV score. Ultrasound is an acceptable method to assess abdominal disease and predict nonresectability in patients with tubo-ovarian cancer in the hands of specially trained ultrasound examiners. ■

GLOSSARY

AUC Area under the receiver operating characteristic curveBMI Body mass indexCT Computed tomographyIDS Interval debulking surgeryNPV Negative predictive valuePDS Primary debulking surgeryPIV Predictive Index valuePPV Positive predictive valueWB-DWI/MRI Whole-body diffusion-weighted magnetic resonance imaging

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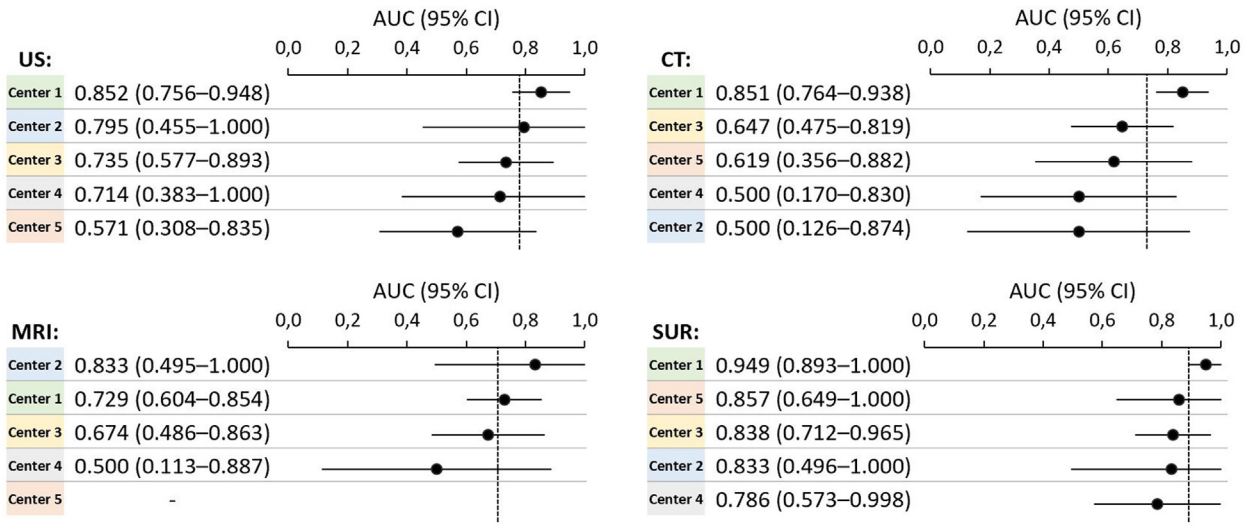
SUPPLEMENTAL FIGURE
Performance of imaging methods in each single center



SUPPLEMENTAL TABLE 1
Parameters included the Predictive Index value score evaluated at ultrasound, computed tomography, and magnetic resonance imaging

Sites	Disease definition
Greater omentum	Omental cake with tumor diffusion along the transverse colon up to the large stomach curvature
Liver surface	Any surface lesion larger than 2 cm[a]
Lesser omentum and/or stomach and/or splenic surface	Presence of obvious neoplastic involvement of the surface of stomach (small curvature), and/or lesser omentum, and/or surface of the spleen
Parietal peritoneum (except diaphragm)	Widespread infiltrating carcinomatosis and/or confluent nodules to the most part of the anterior abdominal wall and/or paracolic gutters
Diaphragm	Widespread infiltrating carcinomatosis and/or confluent nodules to the most part of the diaphragmatic surface
Bowel infiltration (except rectosigmoid[b])	Carcinomatosis on small/large bowel (except rectosigmoid) necessitating resection.

[a] If it was thin layer of carcinomatosis, the largest diameter and not the thickness was measured; [b] Recto-sigmoid involvement was excluded due to its pelvic localization since posterior exenteration is considered a standard surgical procedure in advanced tubo-ovarian carcinoma.

SUPPLEMENTAL TABLE 2
Overview of excluded patients by center

Type of center	No. of patients	Excluded (%)	Included (%)
PCR	136	16 (11.8)	120 (88.2)
PSP	32	3 (9.4)	29 (90.6)
RIT	28	10 (35.7)	18 (64.3)
NIT	60	3 (5.0)	57 (95.0)
CIT	23	5 (21.7)	18 (78.3)
Total	279	37 (13.3)	242 (86.7)

CIT, Milan, Italy; *NIT*, Milan, Italy; *PCR*, Prague Czech Republic; *PSP*, Pamplona, Spain; *RIT*, Rome, Italy.

SUPPLEMENTAL TABLE 3

Distribution of disease at sites involved in the updated Predictive Index value model at imaging and surgery in 242 patients with primary tubo-ovarian carcinoma

Six sites of carcinomatosis (PIV score)	US(%)	CT (%)	MRI (%)[a]	SUR (%)
Greater omentum	48.3	44.6	55.5	50.0
Liver surface	9.9	12.8	12.1	11.6
Lesser omentum and/or serosa of stomach and/or splenic surface	19.0	27.3	23.1	25.6
Parietal peritoneum	36.0	42.6	37.9	40.9
Diaphragm	31.8	33.1	33.0	45.9
Small/large bowel (except rectosigmoid) or necessitating resection.	26.0	25.6	18.7	37.6
None of the above present	42.1	39.7	37.4	38.0
Absolute criteria of non-resectability				
Miliaric bowel carcinomatosis	13.2	12.4	8.2	23.6
Mesenteric retraction	13.6	7.0	7.1	18.2

CT, contrast-enhanced computed tomography; *SUR*, surgery; *US*, ultrasound; *WB-DWI/MRI*, whole-body diffusion-weighted magnetic resonance imaging.

[a] MRI form was available only for 75% of patients.