GYNECOLOGY

# Predicting the risk of malignancy in adnexal masses based on the *Simple Rules* from the International Ovarian Tumor Analysis group

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**BACKGROUND:** Accurate methods to preoperatively characterize adnexal tumors are pivotal for optimal patient management. A recent metaanalysis concluded that the International Ovarian Tumor Analysis algorithms such as the *Simple Rules* are the best approaches to preoperatively classify adnexal masses as benign or malignant.

**OBJECTIVE:** We sought to develop and validate a model to predict the risk of malignancy in adnexal masses using the ultrasound features in the *Simple Rules*.

**STUDY DESIGN:** This was an international cross-sectional cohort study involving 22 oncology centers, referral centers for ultrasonography, and general hospitals. We included consecutive patients with an adnexal tumor who underwent a standardized transvaginal ultrasound examination and were selected for surgery. Data on 5020 patients were recorded in 3 phases from 2002 through 2012. The 5 *Simple Rules* features indicative of a benign tumor (B-features) and the 5 features indicative of malignancy (M-features) are based on the presence of ascites, tumor morphology, and degree of vascularity at ultrasonography. Gold standard was the histopathologic diagnosis of the adnexal mass (pathologist blinded to ultrasound findings). Logistic regression analysis was used to estimate the risk of malignancy based on the 10 ultrasound features and type of center. The diagnostic performance was evaluated by area under the receiver operating characteristic curve, sensitivity, specificity, positive likelihood ratio (LR+), negative likelihood ratio (LR−), positive predictive value (PPV), negative predictive value (NPV), and calibration curves.

**RESULTS:** Data on 4848 patients were analyzed. The malignancy rate was 43% (1402/3263) in oncology centers and 17% (263/1585) in other centers. The area under the receiver operating characteristic curve on validation data was very similar in oncology centers (0.917; 95% confidence interval, 0.901−0.931) and other centers (0.916; 95% confidence interval, 0.873−0.945). Risk estimates showed good calibration. In all, 23% of patients in the validation data set had a very low estimated risk (<1%) and 48% had a high estimated risk (≥30%). For the 1% risk cutoff, sensitivity was 99.7%, specificity 33.7%, LR+ 1.5, LR− 0.010, PPV 44.8%, and NPV 98.9%. For the 30% risk cutoff, sensitivity was 89.0%, specificity 84.7%, LR+ 5.8, LR− 0.13, PPV 75.4%, and NPV 93.9%.

**CONCLUSION:** Quantification of the risk of malignancy based on the *Simple Rules* has good diagnostic performance both in oncology centers and other centers. A simple classification based on these risk estimates may form the basis of a clinical management system. Patients with a high risk may benefit from surgery by a gynecological oncologist, while patients with a lower risk may be managed locally.

**Key words:** adnexa, color Doppler, diagnosis, diagnostic algorithm, International Ovarian Tumor Analysis, logistic regression analysis, ovarian cancer, ovarian neoplasms, preoperative evaluation, risk assessment, *Simple Rules*, ultrasonography

## Introduction

Ovarian cancer is a common and lethal disease for which early detection and treatment in high-volume centers and by specialized clinicians is known to improve survival.[1-4] Hence, accurate methods to preoperatively characterize the nature of an ovarian tumor are pivotal. In 2008 the International Ovarian Tumor Analysis (IOTA) group described the *Simple Rules*.[5] These are based on a set of 5 ultrasound features indicative of a benign tumor (B-features) and 5 ultrasound features indicative of a malignant tumor (M-features). When using the *Simple Rules*, tumors are classified as benign if only B-features are observed and as malignant if only M-features are observed. If no features are observed or if conflicting features are present, the *Simple Rules* cannot classify the tumor as benign or malignant (inconclusive results). Masses in which the *Simple Rules* yield an inconclusive result can be classified using subjective assessment by an experienced ultrasound operator or, given the high prevalence of malignancy in this group, they can all be classified as malignant to increase the sensitivity for ovarian cancer.[6] On prospective validation both by the IOTA group (2 studies including 1938 and 2403 patients, respectively)[7,8] and by other research teams (9 studies including a total of 2101 tumors),[9-17] the *Simple Rules* were applicable in 77-94% of tumors (range between studies). The malignancy rate ranged from 1-9% in cases classified as benign, from 69-94% in cases classified as malignant, and from 13-53% in inconclusive cases. In a metaanalysis comparing the ability of 19 methods to discriminate between benign and malignant adnexal masses before surgery, the *Simple Rules* had a sensitivity of 93% and a specificity of 81% when classifying inconclusive tumors as malignant.[18] In the metaanalysis the *Simple Rules* and the IOTA

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logistic regression model 2[19] were superior to all other methods. This suggests that evidence-based approaches to the preoperative characterization of adnexal masses should incorporate the use of *Simple Rules* or the logistic regression model 2. Logistic regression model 2 is a mathematical risk prediction model based on age and 5 ultrasound variables (presence of blood flow in a papillary structure, irregular cyst walls, ascites, acoustic shadows, and maximum diameter of the largest solid component).

The *Simple Rules* have been well received by clinicians, and the Royal College of Obstetricians and Gynecologists in the United Kingdom has included the *Simple Rules* in their Green Top guideline on the assessment and management of ovarian masses in premenopausal women.[20]

Despite a combination of simplicity and excellent performance, important limitations of the *Simple Rules* are the inconclusive results in a proportion of cases and the absence of an estimated risk of malignancy. The ability to provide accurate risk estimates is highly relevant for risk stratification and individualized patient management. The objective of this study was to develop and validate a model to calculate the risk of malignancy in adnexal masses based on the 10 ultrasound features in the *Simple Rules*.

## Materials and Methods

### Study design and setting

This international multicenter cross-sectional cohort study involves patients from 22 centers (oncology centers and other hospitals) (Table 1) with at least 1 adnexal (ovarian, paraovarian, or tubal) tumor selected for surgery by the managing clinician. Exclusion criteria were: (1) pregnancy at the time of examination, (2) refusal of transvaginal ultrasonography, (3) declining participation, and (4) surgical intervention >120 days after the ultrasound examination. Data collection was carried out within the framework of the IOTA collaboration. The primary aim of the IOTA studies is to develop and validate methods for making a correct diagnosis in adnexal tumors prior to surgery. This aim is pursued by prospectively examining a large number of patients with ultrasound using a standardized examination technique and standardized terms and definitions to describe ultrasound findings.[21] Through consecutive phases, data were collected from 24 centers in 10 countries. In phase 1 data were collected from 1999 through 2002, in phase 1b from 2002 through 2005, in phase 2 from 2005 through 2007, and in phase 3 from 2009 through 2012. Data from phase 1 were used to develop the *Simple Rules* and were therefore not used in the present study. The research protocols were approved by the ethics committees in each contributing center.

### Data collection

Oral and/or written informed consent was obtained in accordance with the requirements of the local ethics committee. A standardized history was taken from each patient to collect clinical information. All patients underwent a standardized transvaginal ultrasound examination by a principal investigator, who was a gynecologist or radiologist with extensive experience in gynecological ultrasound and with a special interest in adnexal masses. Transabdominal sonography was added in women with large masses that could not be visualized completely by the transvaginal approach. For women with multiple masses, the dominant mass was selected for statistical analysis.[8,19,21-24] To apply the *Simple Rules*, information on the following variables is required: the diameters of the lesion (millimeters), the diameters of the largest solid component (millimeters), type of tumor (unilocular, unilocular-solid, multilocular, multilocular-solid, solid), presence of wall irregularity, ascites, acoustic shadows, number of papillary structures, and the color score, the latter reflecting vascularization on Doppler ultrasound (1, no flow; 2, minimal flow; 3, moderate flow; 4, very strong flow). Detailed information can be found in previous reports.[8,19,21-24] The 5 B-features and the 5 M-features were not directly recorded, but were derived from the variables described above.

### Reference standard

The reference standard denotes whether the tumor is benign or malignant based on the histopathologic diagnosis of the tumor following surgical removal. Surgery was performed through laparoscopy or laparotomy, as considered appropriate by the surgeon. Excised tumor tissues were histologically examined at the local center. Histological classification was performed without knowledge of the ultrasound results. Borderline tumors were classified as malignant.

### Statistical analysis

Using the IOTA data from phases 1b and 2, we estimated the risk of malignancy by quantifying the predictive value of each of the 10 features of the *Simple Rules* and of the type of center in which the patients underwent an ultrasound examination (oncology center vs other hospital; the definition of oncology center being tertiary referral center with a specific gynecological oncology unit). The predictive values for malignancy were determined by the regression coefficients estimated by multivariable logistic regression. Interaction terms were not considered. The analysis included a random intercept to account for variability between centers.[25]

The risk estimates were externally validated on IOTA phase 3 data. The area under the receiver operating characteristic curve (AUC), sensitivity, specificity, and predictive values were calculated through a metaanalysis of center-specific results,[26] similar to a previous validation study using phase 3 data.[8] Positive likelihood ratio (LR+) and negative likelihood ratio (LR−) were derived from these results. The risk cutoffs considered to classify a mass as malignant were 1%, 3%, 5%, 10%, 15%, 20%, 25%, and 30%. Calibration plots were constructed to assess the relationship between calculated risks and observed proportions.[25,27]

After external validation, the risk calculation was updated using the same procedure but now using all available data (phases 1b, 2, and 3) to fully exploit all available information.

TABLE 1
**Sample size, prevalence of malignancy, and outcome of *Simple Rules* in 22 participating centers (n = 4848)**

| | | | | Classification using SR | | |
|---|---|---|---|---|---|---|
| Center | Data set | Patients | Malignant, N (%) | SR benign, N (%mal) | SR inconclusive, N (%mal) | SR malignant, N (%mal) |
| *All oncology centers* | | 3263 | 1402 (43) | 1436 (5) | 788 (49) | 1039 (90) |
| Leuven, Belgium | D,V | 668 | 242 (36) | 306 (4) | 153 (35) | 209 (85) |
| Rome, Italy | D,V | 661 | 365 (55) | 224 (7) | 163 (59) | 274 (92) |
| Monza, Italy | D,V | 356 | 76 (22) | 247 (4) | 69 (42) | 40 (95) |
| Prague, Czech Republic | D,V | 354 | 234 (66) | 102 (13) | 109 (77) | 143 (96) |
| Milan, Italy | D,V | 312 | 177 (57) | 112 (7) | 45 (56) | 155 (93) |
| Lublin, Poland | D,V | 285 | 102 (36) | 132 (5) | 86 (45) | 67 (85) |
| Bologna, Italy[a] | V | 213 | 65 (31) | 126 (3) | 52 (58) | 35 (89) |
| Stockholm, Sweden | V | 120 | 53 (44) | 38 (0) | 33 (27) | 49 (90) |
| Lund, Sweden | D,V | 77 | 20 (26) | 36 (0) | 20 (10) | 21 (86) |
| Beijing, China | D | 73 | 16 (22) | 36 (0) | 20 (15) | 17 (76) |
| London, United Kingdom | D | 65 | 25 (38) | 32 (6) | 18 (50) | 15 (93) |
| Udine, Italy | D,V | 64 | 19 (30) | 36 (3) | 16 (44) | 12 (92) |
| Naples 2, Italy | D,V | 15 | 8 (53) | 9 (22) | 4 (100) | 2 (100) |
| *All other centers* | | 1585 | 263 (17) | 1021 (1) | 327 (23) | 237 (76) |
| Malmö, Sweden | D,V | 462 | 100 (22) | 205 (0) | 146 (12) | 111 (74) |
| Genk, Belgium | D,V | 428 | 61 (14) | 301 (1) | 67 (21) | 60 (73) |
| Cagliari, Italy | D,V | 261 | 37 (14) | 200 (2) | 36 (33) | 25 (88) |
| Milan 2, Italy | D,V | 136 | 20 (15) | 99 (0) | 25 (40) | 12 (83) |
| Bologna, Italy[a] | D | 135 | 11 (8) | 110 (0) | 15 (27) | 10 (70) |
| Naples, Italy | D,V | 72 | 18 (25) | 42 (2) | 17 (35) | 13 (85) |
| Barcelona, Spain | V | 37 | 11 (30) | 21 (10) | 11 (55) | 5 (60) |
| Milan 3, Italy | D | 21 | 4 (19) | 13 (0) | 7 (43) | 1 (100) |
| Milan 4, Italy | V | 21 | 0 (0) | 20 (0) | 1 (0) | 0 (—) |
| Hamilton, Ontario, Canada | D | 12 | 1 (8) | 10 (0) | 2 (50) | 0 (—) |

*D*, development data; *SR*, *Simple Rules*; *V*, validation data; *%mal*, prevalence of malignancy.

[a] Bologna Center in Italy changed from other hospital to oncology center during course of International Ovarian Tumor Analysis study and is therefore listed in both categories (different patients in 2 types of centers).

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## Results

During IOTA phases 1b, 2, and 3, data on 5020 patients were recorded at 22 centers (2 centers from IOTA phase 1 did not take part in later phases). Data on 172 patients were excluded because the patients fulfilled an exclusion criterion (n = 124; 43 women were pregnant and 81 women were operated on >120 days after the ultrasound examination), data errors or uncertain/missing final histology (n = 47), or protocol violation (n = 1). This leaves data on 4848 patients (Tables 1, 2, and 3). The development set (phases 1b and 2) contains data on 2445 patients recruited at 11 oncology centers (n = 1548) and 8 other centers (n = 897). The temporal validation set (phase 3) contains data on 2403 patients recruited at 11 oncology centers (n = 1715) and 7 other centers (n = 688).

The malignancy rate was 34% (1665/4848) overall, 43% (1402/3263) in oncology centers, and 17% (263/1585) in other centers. The observed malignancy rate varied between 22-66% at oncology centers and between 0-30% at other centers. The median age was 42 years (interquartile range 32-54) for patients with a benign tumor and 57 years (interquartile range 47-66) for patients with a malignant tumor. All 80 observed combinations of the ultrasound features in the *Simple Rules* are listed in Table 4. For the same combination of features, the observed malignancy rate was usually higher in oncology centers than in other centers.

TABLE 2
**Ultrasound features of included tumors (n = 4848)**

| Ultrasound feature | Development, n = 2445 Benign, n = 1760 | Development, n = 2445 Malignant, n = 685 | Validation, n = 2403 Benign, n = 1423 | Validation, n = 2403 Malignant, n = 980 |
|---|---|---|---|---|
| Maximum lesion diameter, mm | 61 (43–85) | 89 (58–136) | 64 (47–90) | 86 (55.5–126) |
| Solid components | | | | |
| Presence of solid components | 541 (30.7%) | 638 (93.1%) | 474 (33.3%) | 916 (93.5%) |
| Maximum diameter if present, mm | 25 (13–47) | 54 (35–82) | 28 (13–54) | 59 (36.5–87) |
| No. of papillations | | | | |
| None | 1538 (87.4%) | 427 (62.3%) | 1243 (87.4%) | 777 (79.3%) |
| 1 | 137 (7.8%) | 84 (12.3%) | 96 (6.8%) | 52 (5.3%) |
| 2 | 35 (2.0%) | 23 (3.4%) | 31 (2.2%) | 31 (3.2%) |
| 3 | 22 (1.3%) | 30 (4.4%) | 26 (1.8%) | 29 (3.0%) |
| >3 | 27 (1.5%) | 121 (17.7%) | 27 (1.9%) | 91 (9.3%) |
| Color score | | | | |
| 1, No flow | 769 (43.7%) | 29 (4.2%) | 574 (40.3%) | 32 (3.3%) |
| 2, Minimal flow | 621 (35.3%) | 170 (24.8%) | 563 (40.0%) | 199 (20.3%) |
| 3, Moderate flow | 331 (18.8%) | 298 (43.5%) | 239 (16.8%) | 442 (45.1%) |
| 4, Very strong flow | 39 (2.2%) | 188 (27.5%) | 47 (3.3%) | 307 (31.3%) |
| Type of tumor | | | | |
| Unilocular | 825 (47.0%) | 10 (1.5%) | 595 (41.8%) | 5 (0.5%) |
| Unilocular-solid | 187 (10.7%) | 112 (16.5%) | 141 (9.9%) | 117 (11.9%) |
| Multilocular | 390 (22.2%) | 37 (5.4%) | 354 (24.9%) | 59 (6.0%) |
| Multilocular-solid | 196 (11.2%) | 268 (39.1%) | 179 (12.6%) | 326 (33.3%) |
| Solid | 158 (9.0%) | 257 (37.5%) | 154 (10.8%) | 473 (48.3%) |
| Irregular cyst walls | 484 (27.5%) | 457 (66.7%) | 385 (27.1%) | 572 (58.4%) |
| Ultrasound features of *Simple Rules* | | | | |
| B1, unilocular cyst | 825 (46.9%) | 10 (1.5%) | 595 (41.8%) | 5 (0.5%) |
| B2, solid components present, but <7 mm | 44 (2.5%) | 5 (0.7%) | 40 (2.8%) | 2 (0.2%) |
| B3, acoustic shadows | 307 (17.4%) | 29 (4.2%) | 265 (18.6%) | 34 (3.5%) |
| B4, smooth multilocular tumor, largest diameter <100 mm | 233 (13.2%) | 3 (0.4%) | 224 (15.7%) | 13 (1.3%) |
| B5, no blood flow; color score 1 | 769 (43.7%) | 29 (4.2%) | 574 (40.3%) | 32 (3.3%) |
| M1, irregular solid tumor | 12 (0.7%) | 97 (14.2%) | 16 (1.1%) | 189 (19.3%) |
| M2, ascites | 23 (1.3%) | 222 (32.4%) | 18 (1.3%) | 322 (32.9%) |
| M3, at least 4 papillary structures | 27 (1.5%) | 121 (17.7%) | 27 (1.9%) | 91 (9.3%) |
| M4, irregular multilocular-solid tumor, largest diameter ≥100 mm | 45 (2.6%) | 144 (21.0%) | 40 (2.8%) | 153 (15.6%) |
| M5, very strong flow; color score 4 | 39 (2.2%) | 188 (27.5%) | 47 (3.3%) | 307 (31.3%) |

Results shown are median (interquartile range) for continuous variables and N (%) for categorical variables.

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TABLE 3
**Prevalence of specific pathologies in all patients (n = 4848) and separately for patients from oncology centers and other hospitals**

| Tumor pathology | All patients, N (%) | Patients from oncology centers, N (%) | Patients from other hospitals, N (%) |
|---|---|---|---|
| *All benign pathologies* | *3183 (65.7)* | *1861 (57.0)* | *1322 (83.4)* |
| Endometrioma | 845 (17.4) | 456 (14.0) | 389 (24.5) |
| Benign teratoma (dermoid) | 512 (10.6) | 334 (10.2) | 178 (11.2) |
| Simple/parasalpingeal cyst | 285 (5.9) | 147 (4.5) | 138 (8.7) |
| Functional cyst | 128 (2.6) | 69 (2.1) | 59 (3.7) |
| Hydrosalpinx | 112 (2.3) | 53 (1.6) | 59 (3.7) |
| Peritoneal pseudocyst | 34 (0.7) | 21 (0.6) | 13 (0.8) |
| Abscess | 45 (0.9) | 34 (1.0) | 11 (0.7) |
| Fibroma | 245 (5.1) | 168 (5.1) | 77 (4.9) |
| Serous cystadenoma | 543 (11.2) | 326 (10.0) | 217 (13.7) |
| Mucinous cystadenoma | 359 (7.4) | 203 (6.2) | 156 (9.8) |
| Rare benign pathologies | 75 (1.5) | 50 (1.5) | 25 (1.6) |
| *All malignant pathologies* | *1665 (34.3)* | *1402 (43.0)* | *263 (16.6)* |
| Primary invasive stage I | 222 (4.6) | 184 (5.6) | 38 (2.4) |
| Primary invasive stage II | 82 (1.7) | 64 (2.0) | 18 (1.1) |
| Primary invasive stage III | 658 (13.6) | 579 (17.7) | 79 (5.0) |
| Primary invasive stage IV | 102 (2.1) | 88 (2.7) | 14 (0.9) |
| Rare primary invasive pathologies[a] | 113 (2.3) | 80 (2.5) | 33 (2.1) |
| Borderline stage I | 249 (5.1) | 197 (6.0) | 52 (3.3) |
| Borderline stage II | 9 (0.2) | 6 (0.2) | 3 (0.2) |
| Borderline stage III | 25 (0.5) | 23 (0.7) | 2 (0.1) |
| Borderline stage IV | 1 (0.02) | 1 (0.03) | 0 |
| Secondary metastatic cancer | 204 (4.2) | 180 (5.5) | 24 (1.5) |

[a] Including malignant sex cord-stromal tumors, germ cell tumors, mesenchymal tumors, lymphomas, and rare malignant epithelial tumors (eg, malignant Brenner tumor).

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## Results for the development set (n = 2445)

The coefficients of the regression analysis for the development data are presented in Table 5. B-features were allocated negative coefficients, and hence decrease the estimated risk of malignancy. M-features were given positive coefficients. Ultrasound examination in an oncology center was assigned a positive coefficient. The AUC of the risk estimates to predict malignancy was 0.928 (95% confidence interval [CI], 0.913–0.940). The AUC was similar in oncology centers (0.926; 95% CI, 0.910–0.940) and other centers (0.937; 95% CI, 0.896–0.963).

## Results for the validation set (n = 2403)

When externally validated, the AUC was 0.917 (95% CI, 0.902–0.930) (Figure 1, A). The AUC was very similar in oncology centers (0.917; 95% CI, 0.901–0.931) and in other centers (0.916; 95% CI, 0.873–0.945). In all but 3 centers, the AUC was at least 0.90. Two centers had an AUC of 0.89 and 1 small center had an AUC <0.80 (Figure 2). The estimated risks were well calibrated in all validation patients (Figure 1, B) and when assessed for patients from oncology centers and other hospitals separately (Figure 3).

In all, 22.8% of the patients in the validation set had a calculated risk of malignancy <1%, while 48.5% had a calculated risk ≥30%. For the 1% calculated risk cutoff, sensitivity was 99.7%, specificity 33.7%, LR+ 1.5, LR– 0.010, positive predictive value (PPV) 44.8%, and negative predictive value (NPV) 98.9%. For the 30% calculated risk cutoff, sensitivity was 89.0%, specificity 84.7%, LR+ 5.8, LR– 0.13, PPV 75.4%, and NPV 93.9% (Table 6). Sensitivity, specificity, PPV, NPV, LR+, and LR– for the same risk cutoff differed between oncology centers and other centers (Table 7).

## Results for the total data set

The regression coefficients for the updated analysis on all data (n = 4848) are shown in Table 8. Feature B1 (unilocular cyst) was most predictive of a benign tumor (coefficient –3.4), while feature B3 (acoustic shadows) was least predictive (coefficient –1.7). Feature M2 (ascites) was most predictive of malignancy (coefficient 2.7) and feature M4 (irregular multilocular-solid tumor with largest diameter ≥100 mm) was least predictive (coefficient 1.0). Type of center had a coefficient of 0.9.

For example, consider a patient examined at an oncology center and in whom features B3, M2, and M5 are present. This patient has a regression score of –0.97 (intercept) – 1.66 (B3) + 2.65 (M2) + 1.55 (M5) + 0.92 (oncology center) = 2.49. The estimated risk of malignancy is 92.3%. Further details on this calculation are given in Table 8.

For patients classified as benign by the original *Simple Rules* approach (ie, only B-features present) we observed estimated risks between <0.01-15.2% (in oncology centers: <0.01-15.2%; in other hospitals: <0.01-6.7%), and for patients classified as malignant (only M-features present) between 50.2->99.9% (in oncology centers: 71.7->99.9%; in other hospitals: 50.2-99.7%). For tumors

**TABLE 4**
**All 80 observed combinations of benign and malignant ultrasound features (B- and M-features) of *Simple Rules* ranked by frequency (n = 4848), with their corresponding sample size and malignancy rate**

| Applicable B-features (B1—B2—B3—B4—B5) | Applicable M-features (M1—M2—M3—M4—M5) | All centers, N (%mal) | Oncology centers, N (%mal) | Other hospitals, N (%mal) |
|---|---|---|---|---|
| 0—0—0—0—0 | 0—0—0—0—0 | 954 (42) | 676 (50) | 278 (22) |
| 1—0—0—0—1 | 0—0—0—0—0 | 662 (1) | 377 (1) | 285 (0) |
| 1—0—0—0—0 | 0—0—0—0—0 | 513 (2) | 257 (2) | 256 (1) |
| 0—0—0—1—0 | 0—0—0—0—0 | 277 (4) | 163 (6) | 114 (1) |
| 0—0—0—0—1 | 0—0—0—0—0 | 234 (12) | 178 (16) | 56 (0) |
| 0—0—0—0—0 | 0—0—0—0—1 | 219 (78) | 173 (83) | 46 (59) |
| 0—0—0—0—0 | 0—1—0—0—0 | 192 (95) | 170 (95) | 22 (95) |
| 0—0—1—0—0 | 0—0—0—0—0 | 178 (11) | 113 (14) | 65 (6) |
| 1—0—1—0—1 | 0—0—0—0—0 | 159 (1) | 86 (1) | 73 (0) |
| 0—0—0—1—1 | 0—0—0—0—0 | 152 (3) | 95 (3) | 57 (2) |
| 0—0—0—0—0 | 0—0—0—1—0 | 146 (74) | 112 (77) | 34 (65) |
| 0—0—0—0—0 | 1—0—0—0—0 | 101 (91) | 82 (90) | 19 (95) |
| 0—0—0—0—0 | 0—1—0—0—1 | 95 (100) | 84 (100) | 11 (100) |
| 0—0—1—0—1 | 0—0—0—0—0 | 92 (3) | 63 (5) | 29 (0) |
| 0—0—0—0—0 | 0—0—1—0—0 | 91 (80) | 66 (88) | 25 (60) |
| 1—0—1—0—0 | 0—0—0—0—0 | 81 (0) | 52 (0) | 29 (0) |
| 0—0—0—0—0 | 1—1—0—0—0 | 75 (96) | 70 (96) | 5 (100) |
| 0—0—0—0—0 | 0—0—1—1—0 | 58 (78) | 44 (86) | 14 (50) |
| 0—0—0—0—0 | 1—0—0—0—1 | 56 (95) | 37 (97) | 19 (89) |
| 0—0—0—0—0 | 0—1—0—1—0 | 50 (90) | 40 (90) | 10 (90) |
| 0—0—0—0—0 | 1—1—0—0—1 | 50 (100) | 39 (100) | 11 (100) |
| 0—0—0—0—0 | 0—0—0—1—1 | 34 (82) | 27 (85) | 7 (71) |
| 0—1—0—0—0 | 0—0—0—0—0 | 33 (3) | 15 (7) | 18 (0) |
| 0—1—0—0—1 | 0—0—0—0—0 | 33 (0) | 22 (0) | 11 (0) |
| 0—0—0—0—0 | 0—0—1—0—1 | 22 (86) | 16 (94) | 6 (67) |
| 0—0—0—0—0 | 0—1—0—1—1 | 22 (95) | 19 (95) | 3 (100) |
| 0—0—1—1—0 | 0—0—0—0—0 | 22 (0) | 7 (0) | 15 (0) |
| 0—0—1—0—0 | 0—0—0—0—1 | 16 (69) | 10 (70) | 6 (67) |
| 0—0—0—0—0 | 0—0—1—1—1 | 13 (100) | 11 (100) | 2 (100) |
| 0—0—0—0—0 | 0—1—1—1—0 | 13 (100) | 13 (100) | (0) |
| 0—0—0—0—0 | 0—1—1—1—1 | 13 (100) | 11 (100) | 2 (100) |
| 0—0—0—0—1 | 0—1—0—0—0 | 13 (77) | 11 (82) | 2 (50) |
| 0—0—1—0—0 | 0—0—0—1—0 | 13 (46) | 13 (46) | (0) |
| 0—0—1—1—1 | 0—0—0—0—0 | 13 (0) | 3 (0) | 10 (0) |
| 0—0—0—0—0 | 0—1—1—0—0 | 12 (100) | 12 (100) | (0) |
| 0—0—1—0—0 | 0—1—0—0—0 | 12 (50) | 9 (56) | 3 (33) |
| 1—0—0—0—0 | 0—0—0—0—1 | 11 (0) | 3 (0) | 8 (0) |
| 0—0—0—0—1 | 0—0—1—0—0 | 10 (30) | 8 (38) | 2 (0) |

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TABLE 4

**All 80 observed combinations of benign and malignant ultrasound features (B- and M-features) of *Simple Rules* ranked by frequency (n = 4848), with their corresponding sample size and malignancy rate** *(continued)*

| Applicable B-features (B1—B2—B3—B4—B5) | Applicable M-features (M1—M2—M3—M4—M5) | All centers, N (%mal) | Oncology centers, N (%mal) | Other hospitals, N (%mal) |
|---|---|---|---|---|
| 0—0—0—0—1 | 0—0—0—1—0 | 9 (33) | 7 (29) | 2 (50) |
| 0—0—1—0—0 | 1—0—0—0—0 | 9 (22) | 6 (17) | 3 (33) |
| 0—0—0—0—0 | 0—1—1—0—1 | 7 (100) | 7 (100) | (0) |
| 0—1—0—0—0 | 0—0—1—0—0 | 7 (43) | 4 (50) | 3 (33) |
| 0—1—1—0—0 | 0—0—0—0—0 | 5 (0) | 3 (0) | 2 (0) |
| 0—0—0—0—0 | 1—1—1—0—1 | 4 (100) | 4 (100) | (0) |
| 0—0—0—0—1 | 1—0—0—0—0 | 4 (75) | 4 (75) | (0) |
| 0—0—0—1—0 | 0—0—0—0—1 | 4 (0) | 1 (0) | 3 (0) |
| 0—0—1—0—0 | 1—0—0—0—1 | 4 (100) | 3 (100) | 1 (100) |
| 0—0—0—0—0 | 1—1—1—0—0 | 3 (100) | 2 (100) | 1 (100) |
| 0—0—1—0—0 | 0—0—1—0—0 | 3 (33) | (0) | 3 (33) |
| 0—0—1—0—0 | 0—1—0—0—1 | 3 (100) | 3 (100) | (0) |
| 0—0—1—0—1 | 1—0—0—0—0 | 3 (0) | 2 (0) | 1 (0) |
| 0—1—0—0—1 | 0—0—1—0—0 | 3 (0) | 1 (0) | 2 (0) |
| 0—1—1—0—1 | 0—0—0—0—0 | 3 (0) | 2 (0) | 1 (0) |
| 1—0—0—0—0 | 0—1—0—0—0 | 3 (0) | 1 (0) | 2 (0) |
| 0—0—0—0—1 | 0—0—1—1—0 | 2 (0) | 1 (0) | 1 (0) |
| 0—0—0—1—0 | 0—1—0—0—0 | 2 (50) | 2 (50) | (0) |
| 0—0—1—0—0 | 1—1—0—0—1 | 2 (100) | 2 (100) | (0) |
| 0—0—1—0—1 | 0—0—0—1—0 | 2 (0) | 2 (0) | (0) |
| 0—0—1—0—1 | 0—1—0—0—0 | 2 (0) | 2 (0) | (0) |
| 0—1—0—0—0 | 0—0—0—1—0 | 2 (50) | (0) | 2 (50) |
| 1—0—0—0—1 | 0—1—0—0—0 | 2 (0) | 2 (0) | (0) |
| 1—0—1—0—0 | 0—0—0—0—1 | 2 (0) | 2 (0) | (0) |
| 0—0—0—0—1 | 1—1—0—0—0 | 1 (0) | (0) | 1 (0) |
| 0—0—0—1—1 | 0—1—0—0—0 | 1 (0) | 1 (0) | (0) |
| 0—0—1—0—0 | 0—0—0—1—1 | 1 (0) | (0) | 1 (0) |
| 0—0—1—0—0 | 0—0—1—0—1 | 1 (100) | 1 (100) | (0) |
| 0—0—1—0—0 | 0—0—1—1—0 | 1 (100) | 1 (100) | (0) |
| 0—0—1—0—0 | 0—1—0—1—0 | 1 (0) | 1 (0) | (0) |
| 0—0—1—0—0 | 1—1—0—0—0 | 1 (100) | 1 (100) | (0) |
| 0—0—1—0—1 | 0—0—1—0—0 | 1 (0) | 1 (0) | (0) |
| 0—0—1—0—1 | 1—1—0—0—0 | 1 (0) | 1 (0) | (0) |
| 0—0—1—1—0 | 0—0—0—0—1 | 1 (0) | (0) | 1 (0) |
| 0—0—1—1—0 | 0—1—0—0—0 | 1 (0) | (0) | 1 (0) |
| 0—1—0—0—0 | 0—0—0—0—1 | 1 (0) | 1 (0) | (0) |
| 0—1—0—0—0 | 0—0—1—1—0 | 1 (0) | 1 (0) | (0) |
| 0—1—0—0—0 | 0—1—0—0—0 | 1 (100) | 1 (100) | (0) |

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**TABLE 4**
**All 80 observed combinations of benign and malignant ultrasound features (B- and M-features) of *Simple Rules* ranked by frequency (n = 4848), with their corresponding sample size and malignancy rate** *(continued)*

| Applicable B-features (B1—B2—B3—B4—B5) | Applicable M-features (M1—M2—M3—M4—M5) | All centers, N (%mal) | Oncology centers, N (%mal) | Other hospitals, N (%mal) |
|---|---|---|---|---|
| 0—1—0—0—0 | 0—1—1—0—0 | 1 (100) | 1 (100) | (0) |
| 0—1—0—0—1 | 0—0—0—1—0 | 1 (0) | 1 (0) | (0) |
| 1—0—1—0—0 | 0—1—0—0—0 | 1 (0) | (0) | 1 (0) |
| 1—0—1—0—1 | 0—1—0—0—0 | 1 (100) | 1 (100) | (0) |

*B-feature*, benign feature; *M-feature*, malignant feature; *%mal*, prevalence of malignancy.

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classified as inconclusive by the original *Simple Rules* approach (ie, no features or conflicting features present), we observed estimated risks between 1.3-99.1% (in oncology centers: 1.3-99.1%; in other hospitals: 2.1-88.2%), demonstrating the heterogeneity of this group.

Table 9 summarizes the range of estimated risks for individual patients depending on the number of B-features and M-features present in the tumor, based on the updated analysis (n = 4848). In general, the estimated risk of malignancy was at least 42.0% if more M-features than B-features were present (N = 1295, 27% of all tumors) and was at most 0.29% when ≥2 B-features and no M-features were present (N = 175, 3.6% of all tumors). The estimated risk when no feature was present was 48.7% for patients from oncology centers and 27.5% for patients from other centers (N = 954, 20% of all tumors). Patients with conflicting features (≥1 B-feature and ≥1 M-feature) were uncommon (N = 161, 3.3% of all tumors). The type of feature is most important in patients with only 1 B-feature and no M-features: estimated risks vary between 1.2-15.2%. Based on these results a simple classification of adnexal masses based on the number of B- and M-features present can be used (Table 10).

**TABLE 5**
**Model coefficients for 11 predictors obtained on development data (n = 2445)**

| Predictor | Coefficient | SE |
|---|---|---|
| Intercept | −1.10 | 0.26 |
| B1 (unilocular cyst) | −3.10 | 0.34 |
| B2 (solid components present, but <7 mm) | −1.55 | 0.59 |
| B3 (acoustic shadows) | −1.58 | 0.27 |
| B4 (smooth multilocular tumor with largest diameter <100 mm) | −3.59 | 0.60 |
| B5 (no blood flow; color score 1) | −1.96 | 0.24 |
| M1 (irregular solid tumor) | 2.38 | 0.39 |
| M2 (ascites) | 2.87 | 0.29 |
| M3 (at least 4 papillary structures) | 1.72 | 0.28 |
| M4 (irregular multilocular-solid tumor with largest diameter ≥100 mm) | 1.12 | 0.23 |
| M5 (very strong flow; color score 4) | 1.53 | 0.24 |
| Oncology center | 0.95 | 0.31 |

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# Comment

## Principal findings of the study

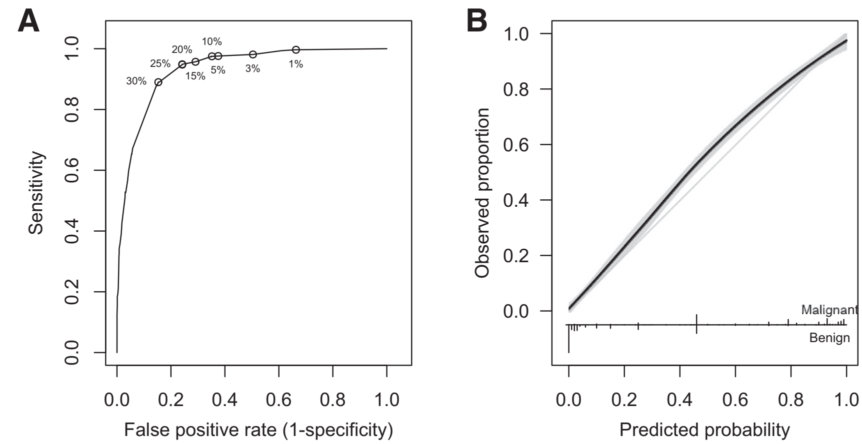
In this study we have developed a method to estimate the individual risk of malignancy in an adnexal mass using the ultrasound features in the IOTA *Simple Rules*. On prospective validation the risk estimates showed good ability to discriminate between benign and malignant tumors (AUC 0.917) and good agreement between the calculated risks of malignancy and the true prevalence of malignancy.

## Implications of the work

The *Simple Rules* are intuitively attractive because of their ease of use.[9-17,20] However, when used as originally suggested they allow only a categorization of tumors into 3 groups: benign, malignant, or inconclusive. In this study we show that the *Simple Rules* can also be used to estimate the risk of malignancy in every adnexal mass and so can be used for individualized patient management. The type of center also needed to be included in our risk estimation, because the risk of a malignant tumor is higher in oncology centers than in others. The B-feature B1 (unilocular cyst) was most predictive of a benign tumor, while the B-feature B3 (acoustic shadows) was least predictive. The M-feature M2 (ascites) was most predictive of malignancy while the

**FIGURE 1**

**Validation data performance for the calculated risk of malignancy**




Validation **A**, receiver operating characteristic (ROC) and **B**, calibration curves for calculated risk of malignancy (n = 2403). In ROC curve, results for cutoffs 20% and 25% nearly coincide. Gray line, ideal calibration; black line, calibration curve; gray area, 95% confidence band. In calibration plot, distribution of estimated risks of malignancy is depicted in histogram at bottom, positive bins showing number of patients with malignant tumors, and negative bins showing number of patients with benign tumors.

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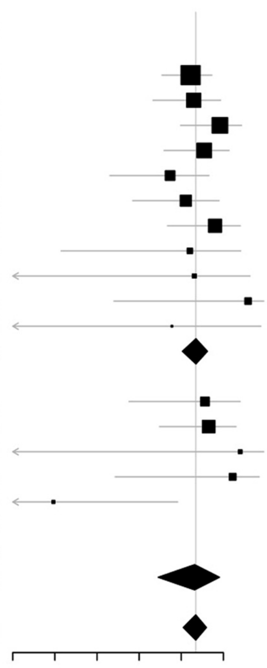
**FIGURE 2**

**Metaanalysis of center-specific AUCs on the validation data**

| Center | N | Malignant | AUC (95% CI) |
|---|---|---|---|
| Rome, IT (RIT) | 443 | 265 (60%) | 0.91 (0.88–0.94) |
| Prague, CZ (PCR) | 264 | 183 (69%) | 0.91 (0.87–0.95) |
| Milan, IT (CIT) | 218 | 124 (57%) | 0.95 (0.90–0.97) |
| Bologna, IT (BIT) | 213 | 65 (31%) | 0.93 (0.88–0.96) |
| Lublin, PL (LPO) | 131 | 49 (37%) | 0.89 (0.82–0.93) |
| Leuven, BE (LBE) | 129 | 60 (47%) | 0.91 (0.84–0.94) |
| Stockholm, SE (SSW) | 120 | 53 (44%) | 0.94 (0.88–0.97) |
| Monza, IT (OIT) | 105 | 24 (23%) | 0.91 (0.76–0.97) |
| Udine, IT (UDI) | 47 | 12 (26%) | 0.92 (0.69–0.98) |
| Lund, SE (LSW) | 39 | 13 (33%) | 0.98 (0.82–1.00) |
| Naples, IT (GIT) | 6 | 3 (50%) | 0.89 (0.26–0.99) |
| **All oncology centers** | | | **0.92 (0.90–0.93)** |
| Genk, BE (GBE) | 228 | 34 (15%) | 0.93 (0.84–0.97) |
| Malmo, SE (MSW) | 201 | 47 (23%) | 0.93 (0.87–0.97) |
| Cagliari, IT (SIT) | 107 | 17 (16%) | 0.97 (0.69–1.00) |
| Milan, IT (MIT) | 86 | 15 (17%) | 0.96 (0.82–0.99) |
| Barcelona, ES (BSP) | 37 | 11 (30%) | 0.75 (0.51–0.90) |
| Naples, IT (NIT) | 8 | 5 (63%) | 1 (NC) |
| Milan, IT (FIT) | 21 | 0 (0%) | NC |
| **All other centers** | | | **0.92 (0.87–0.95)** |
| **All centers** | | | **0.92 (0.90–0.93)** |




Forest plot with center-specific validation areas under receiver operating characteristic curve (AUC) (total n = 2403).

*BE*, Belgium; *CI*, confidence interval; *CZ*, Czech Republic; *ES*, Spain; *IT*, Italy; *NC*, not computed; *PL*, Poland; *SE*, Sweden.

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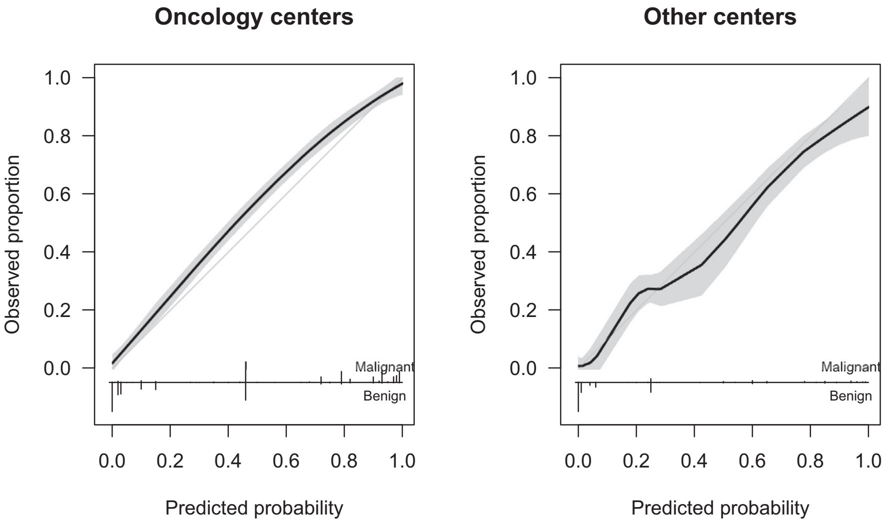
M-feature M4 (irregular multilocular-solid tumor with largest diameter ≥100 mm) was least predictive. Many clinicians would probably agree that conservative management could be an option for tumors with a very low risk of malignancy (eg, <1%), provided that this is appropriate when taking clinical circumstances into account. In the current study 23% of the validation patients fell into this group (16% of patients in oncology centers and 31% of patients in other centers). Some clinicians might consider conservative management also for patients with a risk of malignancy <3% (32% of the validation patients in the study), at least if the patient is asymptomatic and if she is seen in a nononcology center. On the other hand, most clinicians would probably agree that patients with a risk of malignancy ≥30% would benefit from being referred to a gynecologic oncology center for further investigation and treatment. In the current study, 48% of the validation patients belonged to this high-risk group (61% of patients in oncology centers and 18% of patients in other centers). Patients with intermediate risks could be managed differently depending on local circumstances, eg, depending on whether there is liberal or restricted access to ultrasound experts or gynecologic oncologic surgery. Some might want to operate on patients with intermediate risks in regional centers or refer such patients for second opinion ultrasonography by an expert.

The coefficients can be used to calculate a reliable and well-calibrated individual risk estimate. Using Table 9, this risk of malignancy can be directly read off for 97% of all patients without the need for a computer. The other 3% of patients have tumors with both M-features and B-features, for these patients the precise individual risk estimate needs to be calculated using a computer or mobile app. However, they all belong to the elevated risk and very high-risk groups. Table 10 shows an even simpler classification of patients into different risk groups. Our results may lay the basis for a clinically useful imaging and management system such as the Gynecologic Imaging Reporting and Data System,[28]

**FIGURE 3**
**Validation data calibration curves with stratification for type of cancer**




Validation calibration curves by type of center (total n = 2403). Gray line, ideal calibration; black line, calibration curve; gray area, 95% confidence band. In calibration plots, distribution of estimated risks of malignancy is depicted in histogram at bottom, positive bins showing number of patients with malignant tumors, and negative bins showing number of patients with benign tumors.

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as shown in Tables 9 and 10. While the Gynecologic Imaging Reporting and Data System is based on subjective assessment of ultrasound images, this new system would be based on more objective ultrasound criteria and type of center.

The *Simple Rules* risk classification is an alternative to other algorithms such as the Risk of Malignancy Index (RMI),[29] the Risk of Ovarian Malignancy Algorithm (ROMA),[30] OVA-1,[31,32] and the IOTA logistic regression models (logistics regression model 1, logistic regression model 2,[19] Assessment of Different Neoplasias in the Adnexa[24]). Three studies have compared the IOTA methods with RMI and ROMA on the same study population.[8,12,33,34] logistic regression model 2 and the *Simple Rules* (classifying inconclusive cases as malignant) reached higher diagnostic accuracies than RMI[8,12,33] and logistic regression model 2 outperformed ROMA.[34] These findings were confirmed in a systematic review and metaanalysis comparing the diagnostic performance of 19 prediction models.[18] The multivariate index assay OVA-1 has been validated by 2 large multicenter studies in the United States.[31,32] OVA-1 has never been compared with IOTA algorithms on the same set of patients, but it seems to have lower specificity at similar sensitivity, resulting in much higher rates of false-positive results.[35,36]

When prospectively validated on IOTA phase 3 data (ie, on the validation set in the present study), the *Simple Rules* risk estimates, logistic regression model 2, and subjective assessment (using 6 levels of diagnostic confidence) had similar diagnostic performance in terms of discrimination between benign and malignant tumors: the AUC for logistic regression model 2 was 0.918 (95% CI, 0.905–0.930),[8] for subjective assessment 0.914 (95% CI, 0.886–0.936),[8] and for the *Simple Rules* risk estimate 0.917 (95% CI, 0.902–0.930). The discriminative ability of the ADNEX model was slightly better: AUC 0.943 (95% CI, 0.934–0.952).[24] The ADNEX model has

**TABLE 6**
**Sensitivity, specificity, likelihood ratios, and predictive values for *Simple Rules* risk estimates (different cutoffs) on validation data (n = 2403)**

| Cutoff for risk of malignancy | Size of high-risk group, n (%) | Sensitivity (95% CI) | Specificity (95% CI) | PPV (95% CI) | NPV (95% CI) | LR+ | LR− |
|---|---|---|---|---|---|---|---|
| 1% | 1856 (77.2) | 99.7 (97.8–99.9) | 33.7 (25.5–43.0) | 44.8 (35.4–54.7) | 98.9 (97.3–99.5) | 1.502 | 0.010 |
| 3% | 1637 (68.1) | 98.2 (96.9–98.9) | 49.6 (41.0–58.2) | 52.0 (43.6–60.2) | 98.1 (96.4–99.1) | 1.947 | 0.038 |
| 5% | 1500 (62.4) | 97.6 (96.0–98.6) | 62.5 (52.2–71.1) | 59.2 (50.9–67.1) | 98.1 (96.2–99.1) | 2.601 | 0.039 |
| 10% | 1454 (60.5) | 97.5 (95.8–98.5) | 64.8 (53.4–74.7) | 61.5 (53.9–68.6) | 98.0 (96.2–99.0) | 2.771 | 0.039 |
| 15% | 1376 (57.3) | 95.7 (93.2–97.3) | 70.9 (61.7–78.6) | 64.7 (56.0–72.5) | 97.3 (94.8–98.7) | 3.289 | 0.061 |
| 20% | 1299 (54.1) | 94.9 (92.2–96.7) | 75.8 (69.0–81.5) | 68.8 (59.4–76.8) | 97.0 (94.0–98.5) | 3.924 | 0.068 |
| 25% | 1294 (53.8) | 94.8 (92.3–96.5) | 75.8 (69.1–81.5) | 68.6 (59.2–76.8) | 96.8 (93.9–98.3) | 3.919 | 0.069 |
| 30% | 1165 (48.5) | 89.0 (78.2–94.8) | 84.7 (75.2–91.0) | 75.4 (68.3–81.3) | 93.9 (90.8–96.0) | 5.811 | 0.130 |

Sensitivities, specificities, PPV, and NPV computed using metaanalysis of center-specific results.

*CI*, confidence interval; *LR+*, positive likelihood ratio; *LR−*, negative likelihood ratio; *NPV*, negative predictive value; *PPV*, positive predictive value.

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TABLE 7

**Sensitivity, specificity, likelihood ratios, and predictive values for *Simple Rules* risk estimates (different cutoffs) on validation data in oncology centers (n = 1715) and other centers (n = 688)**

| Cutoff for risk of malignancy | Center type | Size of high-risk group, n (%) | Sensitivity (95% CI) | Specificity (95% CI) | PPV (95% CI) | NPV (95% CI) | LR+ | LR− |
|---|---|---|---|---|---|---|---|---|
| 1% | Oncology | 1439 (83.9) | 99.7 (99.0–99.9) | 27.3 (20.3–35.5) | 51.5 (41.0–61.8) | 98.9 (96.5–99.7) | 1.370 | 0.012 |
| | Other | 417 (60.6) | 98.3 (84.5–99.8) | 48.0 (37.4–58.8) | 29.7 (25.4–34.4) | 99.3 (91.4–100.0) | 1.890 | 0.035 |
| 3% | Oncology | 1312 (76.5) | 98.4 (97.3–99.1) | 41.3 (34.8–48.1) | 56.3 (46.0–66.1) | 97.1 (94.1–98.6) | 1.678 | 0.038 |
| | Other | 325 (47.2) | 98.5 (85.0–99.9) | 66.4 (52.6–77.9) | 38.4 (33.0–44.2) | 99.5 (93.6–100.0) | 2.934 | 0.023 |
| 5% | Oncology | 1201 (70.0) | 97.8 (96.3–98.7) | 57.0 (46.9–66.5) | 64.7 (57.0–71.7) | 97.0 (94.6–98.4) | 2.272 | 0.039 |
| | Other | 299 (43.5) | 98.4 (84.9–99.9) | 72.5 (57.5–83.7) | 44.2 (34.6–54.1) | 99.5 (94.0–100.0) | 3.583 | 0.022 |
| 10% | Oncology | 1199 (69.9) | 97.8 (96.4–98.7) | 57.2 (47.3–66.4) | 64.8 (57.0–71.8) | 97.0 (94.6–98.4) | 2.283 | 0.038 |
| | Other | 255 (37.1) | 96.7 (90.1–98.9) | 80.1 (67.7–88.6) | 51.4 (42.0–60.8) | 99.2 (96.0–99.8) | 4.868 | 0.041 |
| 15% | Oncology | 1121 (65.4) | 96.1 (93.3–97.7) | 65.6 (56.6–73.7) | 69.1 (60.7–76.7) | 95.7 (92.3–97.6) | 2.796 | 0.060 |
| | Other | 255 (37.1) | 96.7 (90.1–98.9) | 80.1 (67.7–88.6) | 51.4 (42.0–60.8) | 99.2 (96.0–99.8) | 4.868 | 0.041 |
| 20% | Oncology | 1045 (60.9) | 94.9 (92.0–96.8) | 73.4 (66.9–79.1) | 74.2 (65.8–81.1) | 95.0 (91.4–97.2) | 3.573 | 0.069 |
| | Other | 254 (36.9) | 96.7 (90.1–98.9) | 80.2 (67.9–88.6) | 51.6 (42.2–60.9) | 99.2 (96.0–99.8) | 4.895 | 0.041 |
| 25% | Oncology | 1045 (60.9) | 94.9 (92.0–96.8) | 73.4 (66.9–79.1) | 74.2 (65.8–81.1) | 94.0 (91.4–97.2) | 3.573 | 0.069 |
| | Other | 249 (36.2) | 95.8 (90.1–98.3) | 80.2 (67.9–88.6) | 51.3 (41.3–61.2) | 98.8 (96.9–99.5) | 4.845 | 0.053 |
| 30% | Oncology | 1042 (60.8) | 94.9 (91.8–96.9) | 73.7 (67.2–79.3) | 74.4 (65.7–81.5) | 95.0 (91.2–97.2) | 3.607 | 0.069 |
| | Other | 123 (17.9) | 63.3 (44.5–78.8) | 94.8 (91.0–97.1) | 71.4 (62.7–78.8) | 92.1 (87.1–95.3) | 12.280 | 0.387 |

Sensitivities, specificities, PPV, and NPV computed using metaanalysis of center-specific results.

*CI*, confidence interval; *LR+*, positive likelihood ratio; *LR−*, negative likelihood ratio; *NPV*, negative predictive value; *PPV*, positive predictive value.

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TABLE 8

**Model coefficients for 11 predictors updated using all data (n = 4848)**

| Predictor | Coefficient | SE |
|---|---|---|
| Intercept | −0.97 | 0.24 |
| B1 (unilocular cyst) | −3.41 | 0.27 |
| B2 (solid components present, but <7 mm) | −2.25 | 0.46 |
| B3 (acoustic shadows) | −1.66 | 0.18 |
| B4 (smooth multilocular tumor with largest diameter <100 mm) | −2.75 | 0.27 |
| B5 (no blood flow; color score 1) | −1.86 | 0.17 |
| M1 (irregular solid tumor) | 2.19 | 0.24 |
| M2 (ascites) | 2.65 | 0.21 |
| M3 (at least 4 papillary structures) | 1.53 | 0.20 |
| M4 (irregular multilocular-solid tumor with largest diameter ≥100 mm) | 0.98 | 0.16 |
| M5 (very strong flow; color score 4) | 1.55 | 0.16 |
| Ultrasound examination at oncology center | 0.92 | 0.27 |

To use this model to estimate risk of malignancy, add −0.97 (intercept) to applicable coefficients to obtain regression score (RS). Conversion of RS into risk estimate is done using formula: exp(RS)/[1+exp(RS)], where exp is the natural exponential function.

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the advantage over the other methods of not only differentiating benign from malignant disease but also giving risk estimates for 4 subgroups of malignant disease (borderline tumors, stage I invasive ovarian cancer, stage II-IV invasive ovarian cancer, and metastases in the ovaries from other primary tumors).[24,37]

Because cancer antigen-125 is not used as a variable in the *Simple Rules*, it is not included in the *Simple Rules* risk classification. However, adding information on serum cancer antigen-125 levels to ultrasound information does not seem to improve mathematical models to discriminate between benign and malignant adnexal masses.[38]

Instead of using an algorithm, experienced examiners might still prefer to give an instant diagnosis using the IOTA *Easy Descriptors*. This is feasible in 42-46% of patients.[8,39,40] The *Easy Descriptors* apply to endometriomas,

**TABLE 9**
**Summary figure of *Simple Rules* features combinations and associated risk of malignancy (in %) when updated using all data (n = 4848)**

| Oncology centers | | No. of M-features: 0 | 1 (M4) | 1 (M3) | 1 (M5) | 1 (M1) | 1 (M2) | 2 | >2 |
|---|---|---|---|---|---|---|---|---|---|
| No. of B-features | 0 | 48.7 | 71.7 | 81.4 | 81.7 | 89.5 | 93.1 | 92.1–99.2 | 98.2– ≥99.9 |
| | 1 (B3) | 15.2 | Specific combinations are rare, consider suspicious (risks estimated to be between 12.9–71.9% depending on which B- and M-feature) | | | | | Rare finding, consider highly suspicious | |
| | 1 (B5) | 12.8 | | | | | | | |
| | 1 (B2) | 9.1 | | | | | | | |
| | 1 (B4) | 5.7 | | | | | | | |
| | 1 (B1) | 3.1 | | | | | | | |
| | 2 | 0.49–2.7 | Rare finding, consider suspicious | | | | | | |
| | >2 | 0.09–0.29 | | | | | | | |

| Other centers | | No. of M-features: 0 | 1 (M4) | 1 (M3) | 1 (M5) | 1 (M1) | 1 (M2) | 2 | >2 |
|---|---|---|---|---|---|---|---|---|---|
| No. of B-features | 0 | 27.5 | 50.2 | 63.6 | 64 | 77.2 | 84.3 | 82.3–98.0 | 95.6–99.7 |
| | 1 (B3) | 6.7 | Specific combinations are rare, consider suspicious (risks estimated to be between 5.6–50.5% depending on which B- and M-feature) | | | | | Rare finding, consider highly suspicious | |
| | 1 (B5) | 5.6 | | | | | | | |
| | 1 (B2) | 3.8 | | | | | | | |
| | 1 (B4) | 2.4 | | | | | | | |
| | 1 (B1) | 1.2 | | | | | | | |
| | 2 | 0.19–1.1 | Rare finding, consider suspicious | | | | | | |
| | >2 | ≤0.01–0.12 | | | | | | | |

Dark green = very low risk; green = low risk; yellow = moderate risk; orange = elevated risk; red = very high risk. These Tables are intended to be used together with original *Simple Rules* form.[5]

*B-feature*, benign feature; *M-feature*, malignant feature.

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**TABLE 10**
**Summary classification of Simple Rules risk calculation based on all data (n = 4848)**

| Features | Observed malignancy rate | Estimated individual risk of malignancy | Classification |
|---|---|---|---|
| No M-features AND >2 B-features | 1/175 (0.6%) | <0.01–0.29% | Very low risk |
| - No M-features AND 2 B-features<br>- No M-features AND feature B1 present | 20/1560 (1.3%) | 0.19–2.7%<br>1.2–3.1% | Low risk |
| No M-features AND 1 B-feature present (except B1) | 60/722 (8.3%) | 2.4–15.2% | Intermediate risk |
| - No features<br>- Equal no. of M- and B-features<br>- >0 M-features, but more B- than M-features | 451/1096 (41.1%) | 27.5–48.7%<br>5.6–78.1%<br>1.3–28.4% | Elevated risk |
| More M- than B-features present | 1133/1295 (87.5%) | 42.0–>99.9% | Very high risk |

This simplified system only provides risk ranges for no. of B- and M-features present, but facilitates clinical triaging in absence of electronic devices. Personalized risk estimates can be obtained in second step.

*B-feature*, benign feature; *M-feature*, malignant feature.

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dermoid cysts, simple cysts, and obvious malignancies.[39]

In future studies, the *Simple Rules* risk estimates need to be prospectively and externally validated, and their use in a classification system for clinical management has to be investigated.

## Strengths and weaknesses

The strength of this study is the use of a large multinational database in which patients were prospectively collected using well-defined terms, definitions, and measurements. After development and temporal validation, the risk calculation was updated using all 4848 patients. The large sample size is likely to yield generalizable results.

The study also has limitations. First, our risk calculation model was developed and validated exclusively on patients who underwent surgery. This is because we found it necessary to use the histological diagnosis as the gold standard. Second, all ultrasound examiners in the study were experienced, and so our results may not be applicable with less experienced operators. However, published studies have shown that the *Simple Rules* retain their performance in the hands of less-experienced examiners.[10-12,14-17] This is likely to be also true of our *Simple Rules* risk calculation system, because the same ultrasound variables were used to calculate the risks.

## Conclusions

We conclude that individual risk estimates can be derived from the 10 ultrasound features in the *Simple Rules* with performance similar to the best previously published algorithms. A simple classification based on these risk estimates may form the basis of a clinical management system. This will hopefully facilitate choosing optimal treatment for all patients presenting with adnexal masses. ■

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