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Comparison of a Novel Multiple Marker Assay Versus the Risk of Malignancy Index for the Prediction of Epithelial Ovarian Cancer in Patients with a Pelvic Mass

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Abstract

Objectives—To compare the Risk of Malignancy Index (RMI) to the Risk of Ovarian Malignancy Algorithm (ROMA) to predict EOC in women with a pelvic mass.

Study Design—457 women with imaging results from ultrasound, CT and MRI, and serum HE4 and CA 125 determined prior to surgery for pelvic mass were evaluable. RMI values were determined using CA 125, imaging score and menopausal status. ROMA values were determined using HE4, CA 125, and menopausal status.

Results—At a set specificity of 75%, ROMA had a sensitivity of 94.3% and RMI had a sensitivity of 84.6% for distinguishing benign from EOC (p=0.0029). In patients with stage I and II disease, ROMA achieved a sensitivity of 85.3% compared with 64.7% for RMI (p<0.0001).

Conclusions—The dual marker algorithm utilizing HE4 and CA125 to calculate a ROMA value achieves a significantly higher sensitivity for identifying women with EOC than does RMI.

Keywords

ovarian cancer; pelvic mass; HE4; CA125; ROMA

INTRODUCTION

Each year between 169,000 to 289,000 women are hospitalized with an ovarian cyst or pelvic mass. This represents approximately 5% to 10% of all women in the United States who will undergo surgery for an ovarian neoplasm during their lifetime (1). The NIH Consensus Development Conference Statement estimates that anywhere from 13% to 21% of patients with a pelvic mass will be diagnosed with an invasive epithelial ovarian cancer (EOC) (2), consistent with the American Cancer Society estimate that there will be 21,550 women (13% of 169,000) in the United States diagnosed with ovarian cancer in 2009(3). Differentiating the malignant pelvic masses from the benign pelvic masses is important for optimal patient care.

It has been demonstrated that cytoreductive surgery with optimal tumor debulking increases overall survival in patients with EOC (4-6). Equally important is the concept of comprehensive surgical staging to fully evaluate the extent of disease and the detection of microscopic metastasis, as, for example, more than 30% of patients with clinical stage I ovarian cancer after their initial surgery will be upstaged upon comprehensive surgical staging (7). Recent studies indicate that women operated on by surgeons specializing in the management of EOC and at centers experienced in the surgical and medical management of patients with this disease have decreased morbidity, mortality and an increase in overall survival (8-11). Despite these findings, only half of women with ovarian cancer in the United States will have comprehensive surgery performed by high-volume surgeons, typically gynecologic oncologists, and at institutions experienced in the management of women diagnosed with this disease(12-14). Therefore, it is critical that women with a pelvic mass or ovarian cyst considered at high risk for a malignancy be referred to appropriate centers prior to their surgery in order to improve the quality of care and enhance survival for ovarian cancer patients.

The serum tumor marker CA125 is commonly used to predict the presence of a malignancy in women with a pelvic mass, but CA125 measurement has limitations. CA125 is elevated in less than half of early-stage EOC patients and in approximately 80% of women with epithelial ovarian cancer, potentially leaving 20% of ovarian cancer patients without a useful serum biomarker for the management of their disease (15;16). In addition, many premenopausal women with common benign gynecologic disorders will have an elevated serum CA125 level, and many medical conditions affecting postmenopausal women can also elevate serum CA125, resulting in the reduction of sensitivity and specificity of CA125 (16).

The combination of serum CA125 levels and pelvic sonography improves the sensitivity and specificity for predicting the presence of ovarian cancer in patients with a pelvic mass (17). Jacobs et al. developed the Risk of Malignancy Index, or RMI, an algorithm that employs ultrasound findings and architectural features of a pelvic mass, CA125 levels and menopausal status (17). Several subsequent reports have validated the predicted levels of sensitivity and specificity(18;19). The RMI is a straightforward and widely used algorithm that produces a numerical score to stratify patients into high and low-risk groups for EOC. The RMI successfully categorizes patients into high and low-risk groups, but it uses ultrasound imaging data that can have interpreter variability between users and centers. Equally important, clinical evaluation of a pelvic mass often includes CT imaging, MRI, ultrasound or a combination of imaging modalities resulting in a lack of standardization across imaging methods for risk of ovarian malignancy.

An objective risk-assessment tool that is determined through objective quantitative measures would provide reproducibility and consistency from center to center. We conducted a prospective multicenter clinical trial to validate a predictive model, called the Risk of Ovarian Malignancy Algorithm, or ROMA, to estimate the risk of EOC in women presenting with a pelvic mass(20). As part of a secondary analysis, the results of the dual marker combination of HE4 and CA125 used in the ROMA were compared with the RMI for the detection of EOC in women presenting with an ovarian cyst or pelvic mass.

METHODS

This was a prospective multicenter trial that was entered in the National Institutes of Health clinical trial registry (ClinicalTrial.gov identifier NCT00315692). All participating sites obtained institutional review board (IRB) approval from their respective institutions. To be eligible for enrollment, patients were required to be 18 years of age or older and to have a diagnosis of an ovarian cyst or a pelvic mass with a planned surgical intervention. Prior to collection of biological samples and surgery, all patients were required to give full informed consent. All patients had radiologic imaging either by pelvic ultrasound (US), computed tomography scanning (CT) and/or magnetic resonance imaging (MRI) within six weeks prior to surgery to document the presence of an ovarian cyst or pelvic mass. Immediately prior to surgery, blood and urine samples were obtained. Whole blood samples were obtained in three 10 mL serum separator tubes and one EDTA-plasma tube. Within four hours of collection, blood samples were centrifuged and the serum and plasma were collected and dispensed into multiple 5cc cryotubes and frozen to −20°C. All specimens were batch shipped on dry ice to Fujirebio Diagnostics, Inc. for distribution to one of four separate testing laboratories (University of Texas, MD Anderson Cancer Center, Houston, TX; Massachusetts General Hospital, Boston, MA; Fujirebio Diagnostics AB, Gothenburg, Sweden; and Fujirebio Diagnostics, Inc., Malvern, PA). Serum CA125 concentrations were measured by trained operators using the ARCHITECT CA125II assay (Abbott Diagnostics, Abbott Park, IL) and serum HE4 levels were determined using the HE4 EIA assay (Fujirebio Diagnostics Inc., Malvern, PA). All assays were run according to manufacturers'

instructions, and appropriate controls were within the ranges provided by the manufacturer for all runs.

Study sites were monitored for compliance with the protocol and for data accuracy. All data were captured onto case report forms and entered into a validated NetRegulus database. All patients underwent surgical removal of the ovarian masses or cysts, and if a patient was diagnosed with an epithelial ovarian cancer, surgical staging was required by protocol. Tissue specimens were obtained from all patients and centrally reviewed by three gynecologic pathologists to verify the diagnoses made by the site pathologists. Two gynecologic oncologists reviewed the histopathology results from the site pathologist and the central review pathologists to determine concordance and the final consensus for histopathological diagnosis. All histological evaluations were conducted blinded to laboratory values for the biomarker assays and laboratory testing was conducted blinded to histological outcome. Serum levels for HE4 and CA125II, as well as the ROMA value determined for the protocol, were withheld from the physicians and patients participating in the study.

For the purpose of analysis, women were considered to be postmenopausal if they had not had a menstrual period for >1 year prior to their study blood draw, or if they were >55 years old and the date of the last menstrual period was unknown. Women were considered to be premenopausal if they had a period within one year of the study blood draw or if they were <48 years old and the date of their last menstrual period was unknown. Follicle stimulating hormone testing was utilized to determine menopausal status for women between the ages of 48 and 55 who had an unknown last menstrual period or who had a hysterectomy with ovarian preservation.

Predictive Probability Calculations

The primary endpoint of the clinical study was to classify patients with a pelvic mass into high or low-risk groups for having EOC using the serum biomarkers CA125 and HE4 in the following predictive probability algorithm (ROMA):

$$\text{Premenopausal:Predictive Index (PI)} = -12.0 + 2.38 * \text{LN (HE4)} + 0.0626 * \text{LN (CA 125)}$$

$$\text{Postmenopausal:Predictive Index (PI)} = -8.09 + 1.04 * \text{LN (HE4)} + 0.732 * \text{LN (CA 125)}$$

$$\text{Predicted Probablity (PP)} = \exp(\text{PI}) / [1/\exp(\text{PI})]$$

The predictive probability algorithm (ROMA) was developed from two separate pilot studies as described in previous publication publications(20;21) and validated in this national trial.

Imaging Analysis

All patients were required to have either a pelvic ultrasound, CT scan, MRI or any combination of imaging modalities for documentation of an ovarian cyst or pelvic mass. Imaging reports were captured for all patients and results entered into the trial database. An RMI imaging score was calculated using the architectural features of the ovarian cyst or pelvic mass and assigned an imaging score as described by Jacobs et al (17). Briefly, one

point each was allocated to the following imaging findings, if present, as follows: multilocular cyst, solid nodule, bilateral cyst, ascites and distant metastasis.

The following equation was used to calculate a risk of malignancy index:

$$\text{RMI} = \text{U} \times \text{M} \times \text{serum CA 125}$$

Where:

U= 0 for imaging score of 0

U= 1 for imaging score of 1

U= 3 for imaging score of 2-5

M= 1 if premenopausal

M= 3 if postmenopausal

Three independent gynecologic oncologists reviewed the imaging reports for each patient using pelvic ultrasound, CT scan, MRI or any combination of imaging that was reported for each patient. In order to be considered evaluable and included in the analysis, at least two out of the three reviewers had to agree on the imaging findings and scores. For patients with two of the reviewers in agreement, an RMI was calculated using the above equation developed by Jacobs et al (17). The imaging reviewers were blinded to tumor marker and pathology results.

Statistical Analysis

For both statistical and medical reasons, cut-points for the ROMA predictive probabilities and RMI values that provided a specificity of 75% were determined. We chose 75% specificity because it would be clinically acceptable if 75% of all patients with benign disease were to remain with their obstetrician-gynecologist for their treatment. If the sensitivity then exceeded 80% at 75% specificity, so that at least 80% of patients with malignant pelvic masses would be referred to gynecologic oncologists, then the ROMA test would provide significant medical benefit. The 75% specificity-thresholds for the ROMA predictive probability were determined separately in the pre- and post-menopausal groups as described previously and were 12.9% and 27.8%, respectively. A single threshold for the RMI values was determined for the entire group, as the menopausal status is one of the inputs for the RMI calculation, and was 137.8. Using these thresholds, separate 2×2 tables for the pre- and post-menopausal groups for ROMA and RMI were constructed to determine the number of true positives, true negatives, false positives, and false negatives results. These results were combined to determine the sensitivity and specificity which are intrinsic properties of the two tests (ROMA, RMI), and the positive predictive value (PPV) and negative predictive value (NPV) which are dependent on the incidence of cancer in the screened population, and overall agreement between the RMI and ROMA results to differentiate benign disease and EOC in the overall patient population. The sensitivities for ROMA and RMI were compared using a test of equality of proportions using large sample statistics (*prtest* command in Stata v10 [Stata Corp, College Station, TX]). Although the primary focus is on 75% specificity due to clinical considerations, a broader coverage of specificities above and below 75% was additionally examined by comparing the area under the curve (AUC) for ROMA and RMI. The AUC is the average sensitivity when averaged over the full range of specificities. For all statistical comparisons a level of $p < 0.05$ was accepted as statistically significant.

RESULTS

Twelve geographically dispersed sites enrolled 566 patients into the trial between December 2005 and February 2007. Of the 531 patients evaluable for primary endpoint of the protocol, 457 patients had sufficient imaging results from a pelvic ultrasound, CT scan, or MRI to determine an RMI score and were evaluable for the secondary analysis. Among these 457 patients, there were 123 EOCs (17 stage I, 17 stage II, 80 stage III, 6 stage IV and 3 unstaged), 22 low malignant potential (LMP) tumors and 312 patients with benign disease. There were 212 premenopausal and 245 postmenopausal patients (Table 1).

Consensus between the three imaging reviewers was 78.4% when comparing the imaging scores. As part of the imaging work-up there were 390 (85%) patients that had a pelvic ultrasound, 283 patients that had a CT scan (62%) and 34 (7%) patients that had a MRI. There were 210 (46%) patients that had both a US and CT scan, 22 (5%) patients with a US and MRI and 2 patients with a CT scan and MRI. Only 8 (2%) patients had an US, CT scan and MRI (Table 2).

Examination of benign cases (n=312) and all stages of EOC (n=123) at a set specificity of 75% revealed that the ROMA obtained a sensitivity of 94.3% (95% CI: 88.6 - 97.7%) and the RMI had a sensitivity of 84.6% (95% CI: 76.9 – 90.4%) for disease from EOC (Table 3, p=0.0029). In patien distinguishing benign ts with stage I and II disease (n=34), the ROMA achieved a sensitivity of 85.3% (95% CI: 68.9 – 95.0%), compared with 64.7% (95% CI: 46.5 – 80.3%) for the RMI (p<0.0001). For patients with stage I, II, IIIA, IIIB and node positive only IIIC disease (n=44), the ROMA had a sensitivity of 88.6% (95% CI: 75.4 – 96.2%) and the RMI had a sensitivity of 68.2% (95% CI: 52.4 – 81.4%) [p=0.0037]. The sensitivity for EOC stage III and IV patients (n = 86) was 98.8% (95% CI: 93.7 – 100%) for the ROMA and 93.0% (95% CI: 85.4 – 97.4%) for the RMI (p=0.0350). Examination of benign cases vs. all stages of LMP tumors plus all stages of EOC patients (n=145) at a set specificity of 75% revealed that the ROMA had a sensitivity of 89.0% (95% CI: 82.7 – 93.6%) and the RMI had a sensitivity of 80.7% (95% CI: 73.3 – 86.8%) [p=0.0113].

Significant increases in AUC for ROMA compared to RMI occurred in distinguishing benign disease from all EOC (ROMA-AUC vs RMI-AUC, p = 0.0001), from EOC stage I & II (ROMA-AUC vs RMI-AUC, p = 0.0007), from EOC stage I, II, IIIA, IIIB, and node positive only IIIC disease (ROMA-AUC vs RMI-AUC, p = 0.0002, from EOC stage III and IV (ROMA-AUC vs RMI-AUC, p = 0.0198), and from LMP tumors and all EOC tumors (ROMA-AUC vs RMI-AUC, p = 0.0015) as illustrated in Table 4.

COMMENT

Accurate triage and referral of women with a pelvic mass to appropriate surgeons and institutions will result in improved care for all women ultimately diagnosed with an EOC. As well, an effective triage tool will allow women at low-risk of malignancy to stay in their community and receive treatment from their primary gynecologist or surgeon.

HE4 is complementary to CA125 as it is not falsely elevated in many of the benign gynecologic conditions that can cause an elevated CA125 level in premenopausal women. For such women, a dual marker algorithm that places increased weight upon HE4, can increase the specificity of the dual marker combination by decreasing the contribution of an erroneously elevated serum CA125. Also, for the 20% of ovarian cancer patients whose tumors do not express CA125 as a marker for their disease, serum HE4 is elevated in greater than 50% of these patients (21). Additionally, in patients with early-stage disease, HE4 has been shown to have greater sensitivity than CA125 alone (21). Each of these factors

contributes to the complementary nature of HE4 to CA125, which increases the sensitivity and specificity of the dual marker algorithm over that of either biomarker alone.

Currently, a well-established algorithm for predicting the risk of malignancy in women with a pelvic mass utilizes a combination of CA125 serum levels, pelvic sonography, as well as menopausal status (17). Jacobs et al. examined the predictive value of combining various ultrasound findings and ovarian mass characteristics along with serum CA125 levels and menopausal status to calculate a Risk of Malignancy Index (RMI). With a RMI score of 200, the authors reported a sensitivity of 85.4% and a specificity of 96.9% for predicting benign from malignant pelvic masses. As well, in the same data set an RMI score of 50 the algorithm achieved a sensitivity of 95% with a specificity of 76%. Recognizing the subjective nature of sonography, Bailey et al. examined the RMI algorithm in a diverse population of patients, allowing for variation in sonography and differences in CA125 assays, in order to validate the RMI in a typical clinical setting. When the RMI cutoff was greater than 200 for the detection of EOC and LMP tumors in patients with a pelvic mass, the RMI algorithm achieved a sensitivity of 87.4%, a specificity of 56.8%, a positive predictive value of 86.8% and a negative predictive value of 58.1% (18). In a separate study of the RMI, Manjunath et al. found a sensitivity of 73%, a specificity of 91%, a positive predictive value of 93% and a negative predictive value of 67%(19). The differences in these data are likely due to differences in interpretation of ultrasound findings as well as variation between the two patient populations.

In the current study, the RMI score was calculated using pelvic sonography, CT scans, MRI or any combination of the three imaging modalities. The sensitivities reported in the current study for the RMI were similar to those reported by Bailey et al. for RMI. In order to compare the calculated RMI for patients in this study to the ROMA, we set the specificity at 75% for analysis of both algorithms. Examining benign and invasive EOC, the RMI algorithm achieved a sensitivity of 84.6%, whereas the ROMA achieved a sensitivity of 94.3%, which was significantly higher. The predictive probability algorithm, or ROMA, without the utilization of imaging, achieved a higher sensitivity at a set specificity when considering EOC and LMP tumors as well (Table 3). The ROMA also achieved a significantly higher sensitivity for patients with stage I and II invasive EOC and for patients with tumors grossly confined to the pelvis or with less than 2cm disease in the upper abdomen, as seen in the patients with stage I, II, IIIA, IIIB, and IIIC based on positive lymph nodes alone (Table 3). In addition, when averaged over all specificities, the average sensitivity (or AUC) was higher in ROMA than RMI for comparisons of many tumor subgroups with benign disease (Table 4).

A weakness in our analysis of the RMI is that there was no central radiology review or standardization of the imaging reports. If this were done as part of the clinical trial with standardization of imaging techniques and reporting, the RMI might have performed better. However, using a combination of imaging with US, CT scans and MRI, the detection of metastatic disease and ascites would be improved over that of US alone and therefore would improve the accuracy of the RMI. Equally important, the use of radiologic studies without central review simulates current clinical practice patterns and may more accurately reflect actual clinical practice. Compared with ultrasonography, a serum biomarker algorithm for prediction of the risk of ovarian malignancy provides objective results that may be more consistent and reproducible between centers and between regions.

The Risk of Ovarian Malignancy Algorithm, utilizing the dual marker combination of HE4 and CA125 can be used to classify both postmenopausal and premenopausal women into high and low-risk groups, allowing for the effective triage of women to appropriate centers for their care.

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CONDENSATION

The Risk of Ovarian Malignancy Algorithm showed greater sensitivity for epithelial ovarian cancer than the Risk of Malignancy Index in 457 women with pelvic mass.

Table 1

Pathology distribution for all cases with imaging scores

Pathology	Premenopausal (N)	Postmenopausal (N)	All Patients (N)
Benign	180	132	312
EOC	16	107	123
LMP	16	6	22
Total	212	245	457

Table 2

Imaging combinations for US, CT scan and MRI

	N	US only	CT only	MRI only	US + CT	US + MRI	CT & MRI	US, CT & MRI
Benign	312	124	24	1	137	19	2	5
LMP	22	8	2	0	10	1	0	1
EOC Stage I & II	34	9	6	0	19	0	0	0
EOC Stage III & IV	86	9	30	1	42	2	0	2
Unstaged	3	0	1	0	2	0	0	0
Total	457	150	63	2	210	22	2	8
% of Total	100%	33%	14%	<1%	46%	5%	<1%	2%

Table 3

Risk stratification of pre- and post-menopausal women with pelvic masses based upon ROMA and RMI at a set specificity of 75%.

	N		Sensitivity			Positive Predictive Value		Negative Predictive Value		Overall Agreement	
	Benign	Cancer	ROMA	RMI	*pretest* p-value	ROMA	RMI	ROMA	RMI	ROMA	RMI
Benign vs. EOC & LMP	312 (68%)	145 (32%)	89.0%	80.7%	0.0113	62.3%	59.7%	93.6%	89.3%	79.4%	76.6%
Benign vs. Stage I-IV EOC	312 (72%)	123 (28%)	94.3%	84.6%	0.0029	59.8%	56.8%	97.1%	92.5%	80.5%	77.5%
Benign vs. Stage I-II EOC	312 (90%)	34 (10%)	85.3%	64.7%	0.0000	27.1%	21.8%	97.9%	95.1%	76.0%	73.7%
Benign vs. Stage III-IV EOC	312 (78%)	86 (22%)	98.8%	93.0%	0.0350	52.1%	50.3%	99.6%	97.5%	80.2%	78.6%
Benign vs. Stage I-IIIb & Stage IIIc (Omentum- & LN+)	312 (88%)	44 (12%)	88.6%	68.2%	0.0037	33.3%	27.5%	97.9%	94.3%	76.7%	73.9%

Table 4

Comparison of the ROC AUC for ROMA and RMI

Group	N (%)		ROC-AUC (95% CI)		
	Benign	Cancer	ROMA	RMI	p-value
Benign vs. EOC & LMP	312 (68%)	145 (32%)	91.3% (88.2 - 94.4%)	84.4% (79.8 - 88.9%)	0.0015
Benign vs. Stage I-IV EOC	312 (72%)	123 (28%)	95.3% (93.0 - 97.5%)	87.0% (82.5 - 91.6%)	0.0001
Benign vs. Stage I-II EOC	312 (90%)	34 (10%)	90.9% (85.7 - 96.0%)	76.2% (67.0 - 85.5%)	0.0007
Benign vs. Stage III-IV EOC	312 (78%)	86 (22%)	97.6% (95.9 - 99.4%)	91.9% (87.0 - 96.8%)	0.0198
Benign vs. Stage I-IIIb & Stage IIIc (Omentum- & LN+)	312 (88%)	44 (12%)	92.1% (87.9 - 96.2%)	75.8% (66.9 - 84.6%)	0.0002