ONCOLOGY

Comparison of a novel multiple marker assay vs the Risk of Malignancy Index for the prediction of epithelial ovarian cancer in patients with a pelvic mass

Richard G. Moore, MD; Moune Jabre-Raughley, MD; Amy K. Brown, MD; Katina M. Robison, MD; M. Craig Miller, BS; W. Jeffery Allard, PhD; Robert J. Kurman, MD; Robert C. Bast, MD; Steven J. Skates, PhD

OBJECTIVE: We sought to compare the Risk of Malignancy Index (RMI) to the Risk of Ovarian Malignancy Algorithm (ROMA) to predict epithelial ovarian cancer (EOC) in women with a pelvic mass.

STUDY DESIGN: In all, 457 women with imaging results from ultrasound, computed tomography, magnetic resonance imaging, and serum HE4 and CA125 determined prior to surgery for pelvic mass were evaluable. RMI values were determined using CA125, imaging score, and menopausal status. ROMA values were determined using HE4, CA125, 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 status from EOC ($P = .0029$). In patients with stage I and II disease, ROMA achieved a sensitivity of 85.3% compared with 64.7% for RMI ($P < .0001$).

CONCLUSION: 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.

Key words: CA125, HE4, ovarian cancer, pelvic mass, ROMA

Cite this article as: Moore RG, Jabre-Raughley M, Brown AK, et al. Comparison of a novel multiple marker assay vs the Risk of Malignancy Index for the prediction of epithelial ovarian cancer in patients with a pelvic mass. Am J Obstet Gynecol 2010;203:228.e1-6.

Each year between 169,000 and 289,000 women are hospitalized with an ovarian cyst or pelvic mass. This represents approximately 5-10% of all women in the United States who will undergo surgery for an ovarian neoplasm during their lifetime.[1] The National Institutes of Health (NIH) Consensus Development Conference Statement estimates that anywhere from 13-21% 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 would 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

From the Program in Women's Oncology, Department of Obstetrics and Gynecology, Women & Infants Hospital of Rhode Island, Warren Alpert Medical School, Brown University, Providence, RI (Drs Moore, Jabre-Raughley, and Robison); the Department of Obstetrics and Gynecology, Hartford Hospital, Hartford, CT (Dr Brown); Medivice consulting, New Durham, NH (Mr Miller and Dr Allard); the Department of Pathology, Johns Hopkins Medical School, Baltimore, MD (Dr Kurman); the Department of Experimental Therapeutics, University of Texas M.D. Anderson Cancer Center, Houston, TX (Dr Bast); and the Department of Obstetrics and Gynecology, Massachusetts General Hospital, Harvard Medical School, Boston, MA (Dr Skates).

Presented at the 40th Annual Meeting on Women's Cancer, Society of Gynecologic Oncologists, San Antonio, TX, Feb. 5-8, 2009.

Received Dec. 1, 2009; revised Feb. 22, 2010; accepted March 17, 2010.

Reprints: Richard G. Moore, MD, 101 Dudley St., Program in Women's Oncology, Department of Obstetrics and Gynecology, Women and Infants' Hospital of Rhode Island, Alpert Medical School, Brown University, Providence, RI 02905. rmoore@wihri.org.

Financial support was provided by National Cancer Institute Grants CA086381 and CA105009, the M.D. Anderson Cancer Center Ovarian Specialized Programs of Research Excellence 1 P50 Grant, and Fujirebio Diagnostics Inc.

Participating institutions: Richard Moore, MD, Women and Infants' Hospital of Rhode Island, Providence, RI; Dan Schlitzer, MD, Healthcare for Women Inc, New Bedford, MA; Steven DePasquale, MD, Chattanooga Gyn-Oncology, Chattanooga, TN; Walter Gajewski, MD, New Hanover Regional Medical Center, Wilmington, NC; Laura Havrilesky, MD, Duke University Medical Center, Durham, NC; Donald Chamberlain, MD, Chattanooga Gyn-Oncology, Chattanooga, TN; Amy Kirkpatrick Brown, MD, MPH, Hartford Hospital, Hartford, and New Britain General Hospital of Central Connecticut, New Britain, CT; Alan Gordon, MD, Arizona Gyn-Oncology, Phoenix, AZ; Scott McMeekin, MD, Oklahoma University Health Science Center, Oklahoma City, OK; Howard Homesley, MD, Brody School of Medicine, Leo Jenkins Cancer Center, Greenville, NC; Elizabeth Swisher, MD, University of Washington Medical Center, Seattle, WA; Audrey Garrett, MD, Northwest Gynecologic Oncology, Eugene, OR; Alexander Burnett, MD, University of Arkansas for Medical Sciences, Little Rock, AR.

0002-9378/$36.00 • • doi: 10.1016/j.ajog.2010.03.043

metastasis, as, for example, >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 and 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 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 EOC, 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[17] developed the Risk of Malignancy Index (RMI) an algorithm that employs ultrasound (US) findings and architectural features of a pelvic mass, CA125 levels, and menopausal status. 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 numeric 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 US imaging data that can have interpreter variability between users and centers. Equally important, clinical evaluation of a pelvic mass often includes computed tomography (CT) imaging, magnetic resonance imaging (MRI), US, 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 (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.

Materials and Methods

This was a prospective multicenter trial that was entered in the NIH clinical trial registry (ClinicalTrial.gov identifier NCT00315692). All participating sites obtained institutional review board approval from their respective institutions. To be eligible for enrollment, patients were required to be aged ≥18 years and 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 by pelvic US, CT scanning, and/or MRI within 6 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 3 10-mL serum separator tubes and 1 EDTA plasma tube. Within 4 hours of collection, blood samples were centrifuged and the serum and plasma were collected and dispensed into multiple 5-mL cryotubes and frozen to –20°C. All specimens were batch shipped on dry ice to Fujirebio Diagnostics Inc (Malvern, PA) for distribution to 1 of 4 separate testing laboratories (University of Texas M.D. 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). 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 (NetRegulus, Inc., Centennial, CO). All patients underwent surgical removal of the ovarian masses or cysts, and if a patient was diagnosed with EOC, surgical staging was required by protocol. Tissue specimens were obtained from all patients and centrally reviewed by 3 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 histologic evaluations were conducted blinded to laboratory values for the biomarker assays and laboratory testing was conducted blinded to histologic 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