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Assessing the risk of ovarian malignancy algorithm for the conservative management of women with a pelvic mass

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HIGHLIGHTS

- ROMA with clinical assessment identifies women with a who can be managed conservatively 1/3 of women initially referred for surgery were able to undergo conservative management.
- ROMA helps triage women with a pelvic mass for non-sugical follow up.

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ABSTRACT

Objective. To evaluate the use of as an aid in the identification of women who can safely undergo conservative, non-surgical management.

Methods. All patients referred to the Program in Women's Oncology for surgery with a pelvic mass are evaluated at a prospective multidisciplinary tumor board (TB) where ROMA and imaging are used for management recommendations. This study evaluated women presented to TB with a pelvic mass between 2009 and 2013 who had either surgical or conservative management.

Results. Of the 498 patients assessed, 392 (79%) had benign disease, 22 (4%) had LMP tumors, 28 (6%) had stage I-II epithelial ovarian cancer (EOC), 36 (7%) had stage III-IV EOC and 20 (4%) had non-EOC. Using clinical assessment in conjunction with ROMA, the TB recommended observation in 188 (37.8%) women. All patients diagnosed with an invasive malignancy were recommended for surgery by the TB. In the 315 patients managed surgically, 212 were found to have benign disease and 84 women were diagnosed with an invasive malignancy. The sensitivity for the initial TB recommendations using ROMA in conjunction with clinical judgment for detecting malignancy was 100% with a specificity of 47.7% and a NPV of 100%. When including low malignant potential tumors the sensitivity was 99.1%. For stage I-IV EOC ROMA alone had a sensitivity of 95.3%.

Conclusions. ROMA in conjunction with clinical assessment can safely identify women for conservative management.

1. Introduction

In the United States, approximately 289,000 women are hospitalized each year with an ovarian cyst or pelvic mass. Although the majority of these women will be diagnosed with benign disease, 5–10% will be diagnosed with an ovarian cancer [1,2]. Obtaining a biopsy is technically challenging and discouraged in patients with presumed early stage disease, as the risk for rupture and dissemination of potentially malignant cells is a concern. The most reliable way to rule out a malignancy is with surgery and pathologic examination, which carries significant risk for morbidity, costs and potentially unnecessary major surgery. It is estimated that, in the United States, women have a 5–10% lifetime risk of undergoing surgery for a suspected ovarian neoplasm [3]. Many of the procedures performed to evaluate a pelvic mass ultimately identify a benign process. In a large ovarian cancer screening trial, 20 cases (3.5%) of malignancy were found among 570 women who underwent surgical evaluation for suspected ovarian cancer [4]. Therefore, improving methods for distinguishing benign from malignant masses would avoid unnecessary surgeries.

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Management guidelines put forth by the American College of Obstetricians and Gynecologists (ACOG) recommend that surveillance is appropriate for adnexal masses in asymptomatic premenopausal women with specific sonographic characteristics, and that in postmenopausal women, the combination of ultrasound and CA125 measurements should be used to guide decision making [5]. ACOG suggests that in postmenopausal women, most pelvic masses, with the exception of sonographically simple appearing cysts, will require surgical intervention, and that any elevation of CA125 is suspicious for malignancy [6,7]. For the detection of malignancy, the use of imaging alone, including ultrasonography, CT and MRI provides a sensitivity in the range of 82–91% and the use of CA125 measurement alone has a sensitivity ranging from 78% [8,9].

Biomarkers or panels of biomarkers are generally used in combination with each other or with imaging and clinical findings to aid in the diagnosis of epithelial ovarian cancer (EOC). The Risk of Ovarian Malignancy Algorithm (ROMA) is a logistic regression algorithm that utilizes the serum biomarkers HE4 and CA125 along with menopausal status to assess the risk that an ovarian cyst or pelvic mass is benign or malignant [10,11]. ROMA has been validated to have a high sensitivity, specificity and negative predictive value in multiple multicenter prospective trials for predicting the presence of ovarian cancer in women with a pelvic mass. The combined HE4 and CA125 algorithm was found to be highly accurate in assigning patients to risk groups, with 95% of epithelial ovarian cancers correctly classified as high risk [11–13]. These trials led to USFDA clearance for ROMA as a test to assist in triaging high risk patients to a gynecologic oncologist and is becoming a tool that is increasingly being utilized by gynecologists and other physician specialists for pelvic mass risk assessment. However, ROMA has not yet been studied or approved as a guide for the conservative management of women with a pelvic mass.

The purpose of this study was to evaluate the use of ROMA in women with an adnexal mass to assist in identifying women at low risk for malignancy who can safely undergo conservative, non-surgical, management.

2. Materials and methods

This was a retrospective cohort study designed to evaluate the use of the ROMA along with clinical evaluation through a prospective tumor board process in women diagnosed with an ovarian cyst or pelvic mass. A secondary objective was to evaluate the performance characteristics of the ROMA in this patient population. This study was approved by the Women and Infants Hospital institutional review board.

At our institution, all patients with a pelvic mass referred to the Program in Women's Oncology for surgery are presented prospectively to our multidisciplinary gynecologic oncology tumor board for determination of management recommendations. Women referred to the program between 2009 and 2013 were included in this evaluation. All imaging was prospectively reviewed at each TB by a radiologist specializing in women's reproductive imaging. To be included in the study, each patient must have had the diagnosis of a pelvic mass and had their data reviewed prospectively at the TB including imaging (ultrasound and/or computerized tomography and/or magnetic resonance imaging), biomarkers (HE4 and CA125), have a known menopausal status and have either at least 3 months of follow-up and a minimum of two evaluations or have undergone surgery. For patients who underwent follow-up, the time interval for re-imaging was determined by the examining radiologist and in accordance with the society of radiologists' consensus guidelines. A ROMA score was calculated for each patient. In premenopausal women, a ROMA score of <6% was considered low risk for ovarian malignancy. In post-menopausal women, a ROMA score of <10% was considered low risk for ovarian malignancy.

Patients who underwent conservative management as well as patients who underwent surgical management were evaluated. Patients who underwent conservative management with longitudinal follow-up of at least 3 months were evaluated for stability of their pelvic mass or for the subsequent diagnosis of malignancy. All patients who underwent conservative management as part of their initial TB recommendation were reviewed at TB on multiple occasions during the follow-up period. All patients who underwent surgical management were presented to TB prior to surgery and subsequently had a pathologic evaluation. Women with incomplete data and women who were pregnant at the time of diagnosis of their pelvic mass were excluded from analysis.

A list of women who met the inclusion criteria was obtained from the tumor board records. A chart review was performed using the patient's medical records, the tumor board records and the pathology database to obtain demographic data (age, race, ethnicity, menopausal status) and initial HE4 and CA125 levels, imaging results including ultrasound, MRI and/or CT as well as the initial tumor board recommendation (surgery or conservative follow-up). For patients who underwent conservative management, follow-up data was collected, including subsequent tumor markers and imaging results as well as subsequent tumor board recommendations. For patients who underwent surgical management, pathologic data was collected, including histology and, if malignant, FIGO and TNM stage.

Serum CA125 levels were measured on the Immulite 2000 platform (Siemens, Los Angeles, CA, USA). Serum HE4 levels were measured using the Fujirebio HE4 EIA kit (Fujirebio Diagnostics Inc., Malvern, PA, USA). ROMA calculations were performed using the previously published algorithm with cut points determined in our laboratory for the Immulite CA125 and HE4 EIA combinations. The performance characteristics of ROMA were evaluated by determining the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy in both the conservative management and surgical management groups.

3. Results

A total of 507 patients diagnosed with a pelvic mass and presented to the tumor board were identified. Nine patients did not meet the inclusion criteria for the study and were excluded from the analyses, leaving 498 evaluable patients. In the evaluable patient set, there were 173 pre-menopausal (35%) and 325 post-menopausal (65%) women with a median age of 56 years (range = 15–90). There were 392 women with benign disease (78.7%) and 106 cancers, including 22 (4.4%) low malignant potential (LMP) tumors, 28 (5.6%) stage I–II EOC, 36 (7.2%) stage III–IV EOC, 9 (1.8%) non-epithelial ovarian cancers and 11 (2.3%) metastatic cancers to the ovaries. In this cohort, the incidence of all invasive cancer was 16.9%, with an incidence of EOC of 12.8% (Table 1).

The initial tumor board recommendations took into account both ROMA and clinical assessment with imaging. There were a total of 392 women diagnosed with benign masses. Of the women presenting with a benign pelvic mass, 205 (52.3%) were recommended to undergo surgery and 187 (47.7%) were initially recommended to undergo observation. Of the 106 women diagnosed with a malignancy or LMP tumor, only 1 patient with an LMP tumor was recommended for observation while the remainder were recommended for surgery (Table 2). Overall, the sensitivity for the initial TB recommendations using ROMA in conjunction with clinical judgment for detecting malignancy including low malignant potential (LMP) tumors was 99.1% (95% CI: 94.9–100%), specificity was 47.7% (95% CI: 42.7–52.8%) and the NPV was 99.5% (95% CI: 97.1–100%) (Table 3). When LMP tumors were excluded as malignancies, the overall sensitivity was 100% (95% CI: 95.7–100%), specificity was 47.7% (95% CI: 42.7–52.8%) and the NPV was 100% (95% CI: 98.0–100%). Of the patients who underwent conservative management with follow-up imaging, 69.4% had >1 year of follow-up with 39.9% having >2 years of follow-up, 18.0% had 6–12 months of follow-up and 12.0% had <6 months of follow-up with only 4 patients having their only follow-up at 3 months.