Risk of Ovarian Malignancy (ROMA™) - Determining the Likelihood of Malignancy in Women with Pelvic Mass

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Abstract

Ovarian cancer is a malignancy with poor prognosis and is still the leading cause of death from gynecological malignancies worldwide. A contributing factor to this has been the lack of reliable diagnostic tools for the detection of ovarian cancer. This review focuses on new bloods tests, HE4 and Risk of Malignancy Algorithm (ROMA) that have recently been introduced for risk assessment and management of ovarian cancer patients. Early detection, treatment and management of disease by specialized gynecologic oncologists and new therapeutic advances hold promise for improved outcomes in ovarian cancer patients.

Introduction

Ovarian cancer is the leading cause of death from gynecologic malignancies in the United States with annual incidence of 22,000 cases. Estimated annual mortality rate is approximately 15,460[1] cases. Ovarian cancer has a good prognosis if detected in its early stages and if treated by specialized gynecologic oncology surgeons,[2] however more than three-quarters of cases are diagnosed in the advanced stage and are associated with poor survival rates of 10-30%.[3] These poor outcomes reflect the lack of effective tools for early detection of ovarian cancer and the limitations of current treatment options for ovarian cancer, which generally include cytoreductive surgery followed by adjuvant chemotherapy.

Recent studies have shown that women with ovarian cancer develop non-specific symptoms, including pelvic or abdominal pain, increased abdominal size, bloating, urinary urgency and difficulty eating or feeling full quickly, months before diagnosis.[4] However, ovarian cancer is commonly discovered on surgery for an adnexal mass. It is estimated that 5–10% of women at some point in their lives will undergo surgical evaluation of an adnexal mass and up to one fifth of surgically removed masses will have a diagnosis of ovarian cancer . In the premenopausal women, the risk of a mass being malignant is 7-13%, while in the postmenopausal women it is 30-40%.[6] Thus, the presence of symptoms and the findings of an adnexal mass increase the risk of malignancy and should prompt thorough diagnostic evaluation.

The primary goals of diagnostic evaluation of women who present with adnexal masses are to confirm that adnexal mass is of ovarian origin and to differentiate whether it is benign or malignant. In order to determine the most appropriate management strategy that would ensure the optimal outcome for the woman with adnexal mass it is essential to effectively triage the risk for malignancy. Combination of multiple diagnostic modalities improves the physician's ability to preoperatively assess women with adnexal mass. Diagnostic techniques that are commonly used are: clinical exam and thorough medical history, imaging (e.g. transvaginal ultrasound) and serum tumor maker (e.g. CA125) measurements. According to a study by the Agency for Healthcare Research and Quality, which assessed

diagnostic strategies for distinguishing benign from malignant masses, all current diagnostic modalities showed significant trade-offs between sensitivity and specificity.[7] Although serum CA125 test does not have FDA-cleared indication as preoperative diagnostic aid in women with ovarian masses that are suspected to be malignant, CA125 is commonly used and recommended by the American Congress of Obstetricians and Gynecologists (ACOG) and the Society of Gynecologic Oncologists (SGO) for this indication.[8,9] The main clinical disadvantage of CA125 for adnexal mass assessment is its insufficient sensitivity for detecting early stage cancer and decreased specificity, due to false elevations in benign obstetric-gynecologic conditions such as endometriosis, leiomyomas, pelvic inflammatory disease and pregnancy.[10]

HE4 – ovarian cancer specific biomarker

HE4 (Human epididymis protein 4) is a member of a family of four disulphide core (WFDC) domain proteins and the function of this protein is unknown.[11] The HE4 gene is elevated in serum from women with ovarian cancer and its expression in normal tissues, including ovary, is low.[12] Several studies have indicated that using HE4 alone or in combination with CA125 may improve the accuracy for detection of ovarian cancer. In a study by Moore et al. that evaluated nine known biomarkers for ovarian cancer, HE4 showed the highest sensitivity at a set specificity for the detection of ovarian cancer, particularly in early stage disease.[13] In this study, the combination of HE4 and CA125 was a more accurate predictor of malignancy than either marker alone, with a sensitivity of 76% and a specificity of 95%. Additional studies confirmed that measuring serum HE4 concentrations along with CA125 concentrations may provide higher accuracy for detecting ovarian cancer, and may improve the accuracy for detection of ovarian cancer at an earlier stage.

Additionally, a number of studies demonstrated improved specificity of HE4 for discriminating ovarian cancers from benign gynecologic disease. Huhtinen et al. was first to report that serum concentration of HE4 was significantly higher in patients with endometrial and ovarian cancer than in patients with ovarian endometriomas or other types of endometriosis.[14] These results were later confirmed in studies reported by Montagnana et al [15] and Holcomb et al.[16] Recently, in a large study of

1042 pre- and postmenopausal women with benign gynecological disorders HE4 was found to be less frequently elevated than CA125 in several benign diseases.[17] For example, HE4 was elevated in only 3% of premenopausal women with endometriosis, while in the same group CA125 was elevated in 72% of women. Unlike CA125 which can be elevated in one fourth of pregnant women and a third of patients with pelvic inflammatory diseases (PID), HE4 is not elevated in pregnancy and PID. [16,18] In addition, in healthy premenopausal women HE4 does not appear to oscillate during menstrual cycle.[19]

ROMA™ test is an aid in determining the likelihood of malignancy in women who present with an adnexal mass

In September 2011, the ROMA test received clearance from the FDA as an aid in assessing whether a premenopausal or postmenopausal woman who presents with an adnexal mass is at high or low likelihood of having a malignancy. ROMA is a qualitative serum test that combines the results of 2 biomarkers - HE4, CA125 and menopausal status into a single score and is indicated for women who meet the following criteria: over age 18 and adnexal mass present for which surgery is planned.

The effectiveness of ROMA to aid in estimating the risk of malignancy was determined in a prospective, multi centre, blinded clinical trial of 461 women over 18 years (240 pre- and 221 post-menopausal) presenting with an adnexal mass that requires surgical intervention.[20] For each patient, an initial cancer risk assessment (ICRA) was completed by a non-gynecological oncologist, providing the generalist's assessment of the patient's mass as benign (negative) or malignant (positive) based upon the information available to the generalist during their work-up of the patient. The corresponding histopathology reports were collected and the stratification into low and a high risk groups for finding malignancy on surgery was determined using ROMA. The incidence of ovarian cancers was 10%. ROMA achieved 100% sensitivity at 74.5% specificity, a positive predictive value (PPV) of 13.8% and a negative predictive value (NPV) of 100% for stratification of premenopausal women with epithelial ovarian cancer into low likelihood and high likelihood groups of having malignancy. In postmenopausal women, ROMA had 92.3% sensitivity at 76.8% specificity, a PPV of 50.0% and NPV of 97.5% for stratification into low

and high likelihood groups of having malignancy. When considering all women together ROMA had a sensitivity of 93.8%, a specificity of 74.9% and a NPV of 99.0%.

In a separate prospective, multi centre trial conducted at 12 US tertiary care institutions, 566 women undergoing surgery for adnexal mass were classified using ROMA into high and low likelihood groups for having epithelial ovarian cancer.[21] The incidence of ovarian cancers in this cohort was 23%. In the postmenopausal group at specificity of 75.0%, ROMA had sensitivity of 92.3%. In the premenopausal group at the specificity of 74.8% ROMA provided a sensitivity of 76.5% for classifying into high likelihood and low likelihood groups for having malignancy.

Additionally, seven distinct, single centre, multinational studies were published that validated the use of ROMA for adnexal mass risk stratification. [22-28] Combined, these studies assessed over 4,000 women with adnexal mass that were scheduled to undergo surgery in the United States, Europe and Asia. The range of sensitivity for ROMA test was from 75% – 94%, at specificity from 75% - 95%. ROMA demonstrated consistent and reliable performance for classifying women with adnexal mass into high risk and low likelihood groups for epithelial ovarian cancer.

Conclusions

In the US, women with adnexal masses present primarily to gynecologists, primary care physicians or general surgeons for initial diagnostic evaluation. According to a Practice Bulletin from the American Congress of Obstetrics and Gynecology (ACOG) an important dilemma is faced by these physicians as to which patients are appropriate for referral to a gynecologic oncologist, and/or to an institution experienced in gynecologic cancer surgery. Several recent studies have demonstrated that ovarian cancer patients managed by gynecologic oncologists and at high volume institutions are more likely to undergo complete surgical staging, and optimal cytoreductive surgery with fewer complications and better survival rates than patients treated by surgeons less familiar with the management of ovarian cancer. Based on the available clinical evidence, ROMA test represents an important tool for improved triage of women diagnosed with an adnexal mass which can ultimately lead to improved patient outcomes.

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