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# DIFFERENTIAL DIAGNOSIS OF A PELVIC MASS: IMPROVED ALGORITHMS AND NOVEL BIOMARKERS

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Ovarian cancer remains a formidable challenge. In the United States, some 21,880 women developed ovarian cancer and 13,850 died from the disease in 2010,[1] consistent with a cure rate across all stages of less than 40% with significantly lower rates of long term survival in women diagnosed with high grade serous cancers in advanced stage. Despite a modest rate of cure, five year survival has increased significantly ($P < 0.05$) from 37% to 46% over the last three decades[2] due to the more consistent use of cytoreductive surgery and combination chemotherapy with platinum compounds and taxanes.

In addition to total abdominal hysterectomy, bilateral salpingo-oophorectomy and omentectomy, gynecologic oncologists attempt to remove as many implants as possible from the surface of the bowel, liver, stomach and parietal peritoneum. Cytoreduction has been considered optimal when no residual nodule exceeds 1.5 cm in greatest dimension.[3] While this is associated with improved prognosis, even better outcomes are observed when residual nodules are no greater than 5 mm in diameter.[4] Such cytoreductive surgery has several theoretical advantages. Removal of bulky tumor reduces the number of hypoxic, poorly perfused cells. Residual cells can be recruited into cell cycle, potentiating the effects of cytotoxic chemotherapy. A fraction of chemoresistant clones can be resected. Host immunocompetence may also be improved when the tumor burden is reduced.

In a meta-analysis of 53 studies involving 6,885 patients, optimal cytoreduction was associated with improved overall survival of approximately 11 months.[5] While these are retrospective studies, it appeared that each 10% improvement in optimal cytoreduction resulted in a 5.5% increase in survival.

Gynecologic oncologists are specially trained to conduct cytoreductive surgery. Both individual reports and meta-analysis indicate that referral to a gynecologic oncologist improves outcomes for ovarian cancer patients with higher adherence to guidelines, a higher fraction of optimal cytoreduction, optimal chemotherapy and improved overall survival.[6,78,9] Despite these advantages, only 30–50% of women with ovarian cancer are referred to gynecologic oncologists in the United States.[10,11] Failure to refer patients with ovarian cancer to specialized surgeons is more frequent for poor, rural and elderly patients. Often, the decision whether to refer a patient is in the hands of the general gynecologist, but one recent report suggests that family practitioners and internists refer less than half of appropriate patients to specialized surgeons.[12]

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Referral to a gynecologic oncologist assures that the patient will be optimally staged and maximal cytoreduction can be performed if metastatic ovarian cancer is found. Should disease appear to be in early stage, careful abdominal exploration with retroperitoneal lymph node dissection can be undertaken. If the pelvic mass is benign, the outcome of surgery should be at least equivalent to that obtained in the community. From the perspective of the community gynecologist, referral assures the best outcome for the patient. Disadvantages from the patient's perceptive include leaving a gynecologist whom she may have known and trusted for years, meeting and accepting a new surgeon and commuting to a new facility or even to a new city for surgery. From the community gynecologist's perspective, referral of a patient means loss of revenue.

More than 200,000 women undergo exploratory surgery for a pelvic mass each year in the United States and 13–21% of these operations will diagnose cancer.[13,14] In pre-menopausal women, approximately 10% of masses are malignant, whereas in postmenopausal women 20% are malignant. Results of imaging as well as the patient's age can aid in distinguishing benign neoplasms that can be removed by the general gynecologist or surgeon from malignant masses that should be resected by specially trained gynecologic oncologists. Biomarkers can also distinguish benign from malignant pelvic masses. Algorithms have been developed that combine age, imaging and biomarkers into a single value to assess the risk of a mass being malignant.

More than two decades ago, Ian Jacobs calculated a risk of malignancy index (RMI) utilizing ultrasound, menopausal status and serum CA125.[15] In multiple reports, sensitivity for predicting malignant disease has ranged from 71–88% and specificity from 97–74%.[16,17,18,19,20] The RMI is used throughout the United Kingdom and multiple studies have confirmed its value.[21]

The Society of Gynecologic Oncology and the American College of Obstetrics and Gynecology have developed criteria for referring a patient with an adnexal mass to a gynecologic oncologist in the United States. These criteria include elevated CA125, ascites, evidence of local or distant metastases and a positive family history of breast or ovarian cancer. Prospective evaluation of these criteria in multiple institutions suggest that their sensitivity is low, e.g., 47% sensitivity at 77% specificity in one study,[22] particularly in premenopausal women with early stage disease.[23]

High sensitivity is critical to assure that women with cancer undergo surgery in the best qualified hands. High specificity is desirable for patient convenience and to assure the best use of the gynecologic oncologists' efforts. As gynecologic oncologists can remove benign or malignant lesions with equal facility, poor specificity should not affect patient outcomes.

Proteomic techniques have identified seven biomarkers that distinguish benign from malignant pelvic masses.[24] FDA approval has been obtained for the OVA1 panel that includes CA125 and conventional immunoassays for four of the seven proteomic biomarkers: apolipoprotein A1, transthyretin, transferrin, and B2-microglobulin. Use of OVA1 provides 96% sensitivity at 28% specificity in post-menopausal women and 85% sensitivity at 40% specificity for pre-menopausal women. The negative predictive value for women judged at low risk is 94%–96%.

The OVA1 multivariate index incorporates data from imaging and menopausal status in addition to levels of the five biomarkers. Two factors are known to interfere with the biomarker tests: triglycerides >4.5 g/L or rheumatoid factor >250 IU/mL. A study was designed to measure how much the OVA1 panel improved the clinical judgment of community practitioners and gynecologic oncologists.[25,26] Overall, this OVA1 registration study enrolled 516 women. As 53% of participants were enrolled by non-gynecologic

oncologists, the study included a majority of women directly from the community. At surgery there were 363 benign tumors and 161 malignancies of which 151 were ovarian cancers. The multi-marker assay detected 76% of the malignancies that had been missed by CA125. The OVA1 algorithm exhibited greater sensitivity, but lower specificity than physician assessment. In the hands of gynecologic oncologists, addition of the OVA1 panel improved the sensitivity from 78% to 98%, but decreased specificity from 75% to 26%. A high negative predictive value of 98% was, however, obtained with OVA1.

A second approach to distinguish benign from malignant pelvic masses has involved a combination of the human epididymal protein 4 (HE4) and CA125. HE4, a whey acidic protein encoded by *WFDC2*, was discovered be upregulated on arrays that compared gene expression in ovarian cancers to that in normal tissues.[27] Serum HE4 is less sensitive than serum CA125 for detecting early stage ovarian cancers among healthy women, but has better sensitivity and specificity for distinguishing malignant from benign pelvic masses, particularly in premenopausal patients. Values of HE4 can be increased by renal failure and advancing age.

Moore et al, had evaluated a number of different biomarkers for their ability to distinguish malignant from benign pelvic masses and found that a combination of CA125 and HE4 provided the highest area under a Receiver Operator Characteristic curve (91.4%).[28] Using data from this pilot trial augmented with premenopausal stored samples from patients with benign and malignant masses, a risk of malignancy algorithm (ROMA) was developed by Skates and Moore, incorporating CA125, HE4, and menopausal status, but not imaging data.[29] Separate logistical formulas were developed for premenopausal and for postmenopausal women with pelvic masses, assigning them to high and low risk groups. A prospective double blinded 12 center trial was initially conducted largely in patients who had been referred to tertiary centers for care. A total of 531 evaluable patients were enrolled with 117 invasive and borderline ovarian cancers. Overall, the ROMA algorithm yielded 93% sensitivity at 75% specificity with a negative predictive value of 93–94%. In premenopausal patients the sensitivity was lower, where 76% sensitivity was obtained at 75% specificity. Using these data, ROMA was compared to the RMI and found superior.[30] ROMA achieved 94% sensitivity and the RMI 85% at 75% specificity (P= 0.0029). This was particularly evident in stage I and II cancers, where ROMA detected 85% and RMI 65% (P<.0001).

The ROMA algorithm was evaluated in a second low risk trial with 472 community patients who had a total of 89 cancers.[31] The algorithm provided 94% sensitivity and 75% specificity overall. In premenopausal patients, sensitivity was 100% in this particular study. The negative predictive value was 98%. Based on this second clinical trial, ROMA recently achieved approval by the FDA in the United States. Subsequent reports have provided mixed results with some confirming the predictive value of the ROMA[32,33,34,35,36] and others finding that it does not improve upon algorithms which use CA125 or HE4 alone.[37,38,39]

OVA1 has not been compared directly to ROMA, but is likely to be as sensitive, but substantially less specific (75% vs. 40% or less). Both have high negative predictive values (96%–99%). While the difference in specificity should not affect patient outcomes, it could affect distribution of medical resources. Neither OVA1 nor ROMA is a screening test and should be used only for women who are definitely going to exploratory surgery. The real challenge is to encourage use of either test.

Others markers have been evaluated to improve pre-operative identification of women with malignant pelvic masses. Using multiplex assays, 65 biomarkers were evaluated for the

ability to distinguish malignant and benign pelvic masses.[40] CA125 and HE4 provided the greatest level of discrimination. Multivariate analysis identified several panels that improved upon CA125 and HE4, but they did not outperform the 2 biomarker panel in an independent validation set.

At present we have the RMI, OVA1 and ROMA. If a sensitivity is >90% at 75% specificity can be confirmed, how much room do we have for improvement? The challenge will be to implement these algorithms and assays in the United States.

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