Tumour markers, ultrasonography, and ovarian cancer diagnosis

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Early diagnosis and/or prevention of ovarian cancer are still a problem. In a recent paper published in *Eur. J. Gynaecol. Oncol.*, *34* (6), 2013, we read Bozkurt *et al.*'s study [1]. They reported finding a significantly higher serum level of CA-125 and CA 15-3 ($p = 0.000$) in order to distinguish benign and malign ovarian neoplasms. The sensitivity and specificity were, respectively, 90.5% and 96.1% for CA 15-3; positive and negative predictive value (PPV, NPV) were, respectively, 80.6% and 90.5% for CA-125. The different test combinations between those tumour markers and CA 19-9, carcinoembryonic antigen, and alpha-fetoprotein did not have a contribution in the differential diagnostic between benign and malignant ovarian tumours.

Pelvic examination, ultrasonography (US), color-Doppler, and tumor-markers (TM) are indicated for diagnosis of ovarian cancer. Gene expression microarrays, proteomics, tumor microenvironment, and mathematical models are being tested. Nonetheless, the differentiation between benign and malignant ovarian neoplasm is a clinical challenge [2]. A study using association of US (with Doppler) and TM, analysing tumours stage and histological types (non-neoplastic findings, benign, and malignant neoplasia) showed that sensitivity, specificity, PPV, and NPV in malignant tumours are, respectively, 90.9, 84.3, 40, and 98.7%. Using those methods, 73% of malignant cases were diagnosed in Stages I or II [3].

The tumour stage and histological types of the cases analysed by Bozkurt *et al.* [1] were not cited. Their findings confirm other results in literature but the absence of these analyses is very important for interpretation of the data. We hope that the authors will address these points in the future.

References

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Reply from M. Bozkurt, A.E. Yumru1, İ. Aral

We have read with interest the comments made by the Author of the Letter to the Editor. The concerns raised regarding the stages of our ovarian cancer patients gives us the opportunity to highlight some important points. Sadly, ovarian cancer continues to be one of the leading health concerns worldwide.

In our discussed study, the sensitivity, specificity, PPV, and NPV of CA-125 with a cut-off 35 U/ml, were 78.9%, 86.9%, 63.8%, and 93.3%, respectively. The diagnostic odds ratio of CA-125 with a cut-off of 35 U/ml, was 25. With a cut-off 65 U/ml, the sensitivity, specificity, PPV, and NPV values were 65.7%, 95.3%, 80.6%, and 90.5%, respectively. For CA 15-3, the sensitivity, specificity, PPV, and NPV were 26.3% 96.1%, 66.6%, and 81.6%, respectively.

We have included 38 ovarian carcinomas in our research: 25 (65.78%) of serous type, four (10.52%) of mucinous type, eight (21.5%) of endometrioid type, and one (2.63%) of clear cell type epithelial ovarian carcinoma. Twenty-four of these 38 malign ovarian carcinomas were in advanced stage. CA-125 was above the normal range in ten (71%) of 14 early stage patients. It is interesting that all the early stage patients were in Stage 2.

Thus, the sensitivity, specificity, PPV, NPV, and diagnostic accuracy values of CA-125 cannot be studied in Stage 1 patients. Although it is rare to encounter ovarian cancer patient at admission to the obstetric and gynecology clinic in

the early stage, we have considered the lack of Stage 1 patients as a limitation in our research. CA-125 levels are reported above the normal range in 20 (83.3%) of 24 (18 patients in Stage 3, six patients in Stage 4) advanced stage ovarian cancer patients. With CA-125 and CA15-3 combined, four more patients were diagnosed with malign adnexal masses (34 of 38 patients: 89.4%).

Due to the fact that CA-125 level remains constant in blood flow at the early stages of the disease and it is also affected by various pathologies, many tumor markers have been studied extensively and the most promising one is found to be the human epididymis protein 4 (HE4).

Risk of Ovarian Malignancy Algorithm (ROMA) algorithm is formed by the combination of CA-125 and HE4. ROMA uses the results of HE4 and CA125 to generate a predictive index (PI) for ovarian carcinoma.

Evaluating all tumor markers, none of them seem to be ideal for diagnosis of ovarian cancer yet although HE4 research is promising. As a result, the combination of patient age, family history, vaginal examination findings, imaging tools like Doppler sonography and magnetic resonance imaging, tumor markers, risk of malignancy index (RMI), and the use of the ROMA algorithm are the most appropriate approaches in the distinction between benign and malign adnexal masses. Perhaps the most important point worth mentioning here is that the most ideal approach for an accurate diagnosis is the combination of diagnostic and imaging modalities.

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