New Tools for The Management of Adnexal Masses

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"Progress in science depends on new techniques, new discoveries and new ideas, probably in that order".

Sydney Brenner. 2002 Nobel Prize in Medicine.

The management of the adnexal mass has always been a controversial issue. The probability that an adnexal mass is a malignant neoplasm of the ovary generates a decision making sequence that can lead to several scenarios. The first scenario, the most frequent, is overtreatment. In this case the patient undergoes surgery, which is ultimately unnecessary, because it possibly was a functional structure of the ovary. This scenario is especially problematic in young women, due to possible sequelae on the ovarian reserve.

The second scenario is sub-treatment. The patient presents a malignant lesion but this possibility has been underestimated and a surgical intervention is performed by a team without training in the management of this type of tumors. The most immediate consequence is that the patient in many cases must be reoperated due to an incomplete ovarian surgical protocol, in order to establish the precise stage and/or perform the indicated surgical procedure, which negatively affects the prognosis.

The third scenario is the adequate management of the adnexal mass, performing a sufficient surgical intervention, with an adequate staging in the case of a malignant the lesion, or avoiding an intervention if it is a functional structure. The correct evaluation of an adnexal mass should aim diagnostic accuracy in the highest proportion of cases. As demonstrated by Bristow et al[1], the survival of the patient with ovarian cancer (OC) depends on an accurate assessment of the adnexal mass, early diagnosis and the initial surgical approach with a team trained in a specialized oncology center.

Efforts have been made to develop diagnostic tools for timely and effective management of the adnexal masses and for their precise characterization. Transvaginal ultrasound, in combination with other parameters, such as tumor markers, highlighting CA125 and HE4, is used efficiently for decision making in the case of pelvic tumors, as evaluated in a previous article in this blog.[2].

Recently, Veronika Seebacher et al[3] published a study in August 2017, which evaluates a tool for estimating the risk of OC in patients with an adnexal mass, incorporating plasma fibrinogen as a marker. Fibrinogen, a key protein in the coagulation pathway, is also an acute phase

reactant, which is linked to events such as inflammation and stress. This group of researchers reported an independent association between high fibrinogen levels and OC. To prove that this protein could be useful to define the risk of malignancy of an adnexal mass, 906 patients undergoing surgery due to the presence of adnexal masses, that had plasma CA 125 and fibrinogen determination, were retrospectively evaluated. The prevalence of OC and borderline tumors in patients evaluated was 26.6%, i.e. 241 patients (21% invasive epithelial carcinomas and 5.6% borderline tumors). In this analysis, 13.35% of pre-menopausal patients included in the evaluation and 43.1% the menopausal patients had OC. A sensitivity of 55.2% and a specificity of 78.5% was found for OC detection using 400 mg/dl as upper limit of plasma Fibrinogen.

The ROC analysis (*Receiver Operating Characteristic*) is a graphic representation of the sensitivity upon the specificity for a binary classifier system, resulting in more accurate when is closer to 1. The area under the curve (AUC) of Fibrinogen to detect OC was 0.74 (95% CI 0.7-0.78). ROC analysis for other parameters, shows an AUC of 0.88 (95% CI 0.85-0.9) for CA125 measurement, 0.73 (95% CI 0.69-0.77) for the identification of an ecosonographic M criterion, criteria of malignancy according to International Ovarian Tumour Analysis (IOTA), and 0.69 (CI 95% 0.65-0.73) for the menopausal status. Fibrinogen upper limit value was adjusted to 342 mg/dl to reduce the number of false negatives, improving sensitivity to 78% at the expense of specificity. The combination of higher values of Fibrinogen and CA125, for the prediction of OC, leads to an increase of the positive and negative predictive value, and a decrease of 50% in the number of patients undergoing a surgical procedure to detect one case of OC.

To improve the sensitivity and specificity, the different parameters used in the prediction of malignancy in adnexal mass can be combined, which was done in this study. The combination of Fibrinogen > 342 mg/dl, CA125 > 35 u/l, post-menopausal status or age > 50 years and the presence of a criterion M (IOTA) on the ultrasound was used, obtaining a precision for the detection of OC of 0.91 measured by the area under the curve (95% CI 0.87-0.94), closest to 1. The authors designed a nomogram that gives different values to the four diagnostic elements: the elevated CA125 added 10 points, Fibrinogen 5 points, menopause 5 points and a pathological ultrasound 7 points. The probability of malignancy is calculated according to the total amount yielded with the scale:
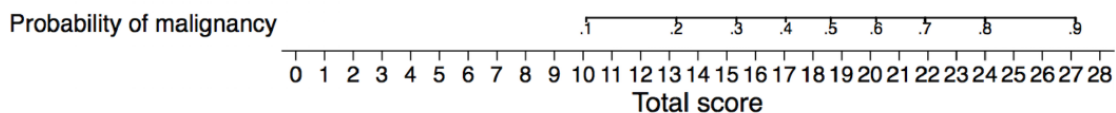
Using this scale and proceeding to surgical resolution of patients with a score between 13 and 14 points (probability of malignancy equal to or greater than 20%), the net reduction in unnecessary surgeries would be 42.5%, a proportion that would prevent nearly half of surgeries that are performed without a scale of estimation, with high precision and the ability to use it as a method of triage, in order to refer patients to a Gynecology Oncology service.

Although ultrasound is the most useful tool for preoperative diagnosis of an adnexal mass, and scales for the estimation of risk of IOTA and GI-RADS reaches a high diagnostic certainty, it is, in both cases, a diagnostic presumption that without an integral vision could generate false positive cases that would mean an unnecessary surgical intervention. The use of a nomogram,

as proposed by the authors, incorporates several risk factors for OC, estimating the probability with an individualized, and certainly, a more objective way, using a scale for the estimation of continuous risk.

It is necessary to validate this tool in a larger group of patients, however, it looks like an interesting option to identify those patients who have a higher probability that an adnexal mass could require more extensive surgery and a cancer management expert team. A timely and technically correct surgery allows the optimal surgical treatment and a proper staging of the disease, which will guarantee increased survival in patients with ovarian cancer. In this way, we would be closer to the early diagnosis of OC, with the unquestionable benefit of offering better survival.

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