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Assessment and Estimation of the Risk of Malignancy in Adnexal Masses

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Abstract

Ovarian cancer remains the leading cause of death from gynecologic cancers worldwide. Case control studies have indicated that women with ovarian cancer commonly experience a pattern of symptoms that include bloating, pelvic/abdominal pain, difficulty eating/feeling full quickly, and urinary urgency or frequency. These symptoms were found to be more commonly associated with ovarian cancer, when they were newly experienced, and occurred more that 12 times per month. Recently, consensus groups have recommended that women who experience symptoms suggestive of ovarian cancer should undergo a complete physical examination, and in certain cases, transvaginal ultrasonography and CA 125 testing. Although the majority of patients with these symptoms will not have ovarian cancer, those who do will require complete surgical staging and aggressive tumor debulking to maximize their chances of survival. In this regard, it is important to establish risk profiles of patients with ultrasonographically confirmed adnexal tumors so that they can receive appropriate treatment and, when necessary, referral for specialty cancer care. The addition of ultrasonographically generated tumor morphology to patient demographics and serum biomarker profiles could improve prediction of malignancy in a clinically detectable adnexal mass.

Keywords: Adnexal Masses, Malignancy, nomogram, ADNEX.

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1. Introduction

Ovarian cancer is one of the most aggressive and lethal malignancies. According to statistics, it has the highest mortality rate among all gynecological cancers and is often discovered at an advanced stage, with a 5-year survival rate of less than 30%. Timely screening, accurate diagnosis, and proper referral are crucial for individuals with suspected ovarian cancer [1].Preoperative differentiation between benign and malignant ovarian mass can be problematic with no test or algorithm being clearly superior in terms of accuracy. Therefore, the underlying management rationale is to distinguish between benign masses and those that are potentially malignant so the morbidity and outcomes can be improved by proper triaging either for conservative management or the use of laparoscopic techniques, thus avoiding laparotomy where possible or referral to a gynecological oncologist at gynecological oncology center when appropriate [2].

Many efforts have been undertaken to develop reliable strategies for predicting malignancy in patients with ovarian masses, including tumor markers, imaging and evolving integrative models. A variety of biomarkers have developed to monitor growth of ovarian cancer amongst them CA125 which has been the most extensively studied and clinically utilized. CA125 levels of less than 35 U/mL are now accepted as normal. Elevated levels found in more than 90% of patients with advanced stage ovarian cancer but in only 50% of patients with stage I disease. In addition, elevated levels of CA125 are more strongly associated with serous, rather than mucinous tumors. Doubling of serum CA 125 levels during follow up is commonly used to define disease recurrence [3]. Owing to poor performance of single indicators to accurately predict risk of malignancy, integrative models have increasingly used to classify patients with ovarian tumors according to their risk of malignancy. Most commonly used model is the IOTA ADNEX model.

2. Assessment and Estimation of the Risk of Malignancy

When evaluating an ovarian tumor, estimating the risk of malignancy is crucial. This has been evaluated with more than eighty different models

1) Risk of Malignancy Index

The risk of malignancy index (RMI) was first described by Jacobs in 1990 and has since evolved into RMI II, RMI III, and RMI IV **[7].** But only RMI I and RMI II have been sufficiently validated, the RMI is simple to use and reproducible, but its utility is negatively affected in the premenopausal woman. This is primarily because of the incidence of endometriomas, borderline ovarian tumors, non-

epithelial ovarian tumors, and other pathologies increasing the level of CA-125 in this group **[8].** A systematic review showed pooled sensitivities and specificities of an RMI I score of 200 in detection of ovarian malignancies to be: RMI I sensitivity 78% (95% CI 71-85%), specificity 87% (95% CI 83-91%) [10].

2) IOTA Group Simple Ultrasound Rules and Logistic Regression Model LR2

Simple ultrasound rules were derived from the IOTA group data to help classify masses as benign (B-rules) or malignant (M-rules). Using these morphological rules, the reported sensitivity was 95% and the specificity was 91%, with a positive likelihood ratio of 10.37 and a negative likelihood ratio of 0.06 [11]. Women with an ovarian mass with any of the M-rules ultrasound findings should be referred to a gynecological oncology service. If the ovarian cysts are not classifiable from these rules, further investigation by a specialist in gynecological ultrasound is appropriate. Triaging women using the IOTA logistic regression model LR2 (a six-variable prediction model) has been proposed as an alternative to RMI-based protocols, with the suggestion that the IOTA protocol may avoid major surgery for more women with benign cysts, while still appropriately referring more women with a malignant cyst to a gynecological oncologist. [11].

3) The ADNEX model from the IOTA group

Given the potential advantages of accurately predicting the risk of malignancy, the International Ovarian Tumour Analysis (IOTA) group developed the Assessment of Different Neoplasias in the adnexa (ADNEX) risk prediction model, based on three clinical and six ultrasound predictor variables [4]. The clinical variables are age, serum levels of the biomarker, cancer antigen 125 (CA125), and type of center (oncology center v other). An oncology center is defined as a tertiary referral center with a specific gynecology oncology unit. The ultrasound variables are the maximum diameter of the lesion, proportion of solid tissue (defined as the largest diameter of the largest solid component divided by the largest diameter of the lesion), number of papillary projections, presence of >10 cyst locules, presence of acoustic shadows, and ascites [4]. The ADNEX multinomial logistic regression model estimates the risk of five tumour types: benign, borderline, stage I primary invasive, stage II-IV primary invasive, and secondary metastatic. The total risk of malignancy calculated by ADNEX is the sum of the risks for each malignant subtype. ADNEX has two versions: one with and one without CA125 as a predictor [4]. When we refer to ADNEX model, we refer to both versions of model. Model developed on data from 5909 patients with an adnexal mass who subsequently underwent surgery, recruited at 24 centers in 10 countries (Belgium, Italy, Czech Republic, Poland, Sweden, China, France, Spain, UK, and Canada).

Although developed on data from patients that underwent surgery, the performance of ADNEX has also been evaluated in cohorts that included patients managed without surgery [12]. ADNEX is included in national guidelines (e.g., in Belgium, the Netherlands, and Sweden), and recommended by scientific societies, such as the International Society of Ultrasound in Obstetrics and Gynecology, European Society of Gynecological Oncology, European Society for Gynecological Endoscopy, and American College of Radiology. Also, manufacturers of ultrasound machines have begun to incorporate ADNEX directly into their machines [13]. Several external validation studies of ADNEX have carried out. So far, five published systematic reviews and meta-analyses of ADNEX have summarized 22 external validation studies. All of systematic reviews evaluated ADNEX only as a diagnostic test, reporting a summary sensitivity and specificity at a threshold for estimated risk of malignancy of 10% or 15% [14].

4) ROMA

Risk of ovarian malignancy algorithm (ROMA) is a quantitative test using CA125, HE4 concentration, and menopausal status to generate a predictive index for epithelial ovarian cancer. Before surgery, serum levels of CA 125 and HE4 are measured, and ROMA score is calculated. In 2011, Moore et al. [15] found that ROMA identified 94% of all epithelial ovarian cancers as high risk and 75% of all benign diseases as low risk. They found ROMA to be 100% sensitive in premenopausal patients. After successful completion of this community-based trial, ROMA was approved by the FDA for distinguishing malignant from benign pelvic masses in 2011 [15]. Among the premenopausal group, ROMA and HE4 had similar sensitivity to diagnose epithelial ovarian cancer but the sensitivity of ROMA was less than CA 125. In terms of specificity, ROMA was found to be more specific than CA 125 but less specific than HE4 [16]. In the postmenopausal group. Bandiera et al. [16] found ROMA to be less sensitive than CA 125 but more sensitive than HE4, while ROMA was more specific than CA 125 [16].

3. Evolution of the Nomogram

Regarding laboratory markers, several factors involved in inflammation and coagulation, such as C-reactive protein (CRP), albumin (Alb), D-dimer, fibrinogen, and thrombopoietin, are frequently associated with tumor development, progression, and poor prognosis in malignancies [17]. Fibrinogen represents one of major acute phase proteins, and its biosynthesis increases with inflammation and stress [18]. Therefore, elevated plasma fibrinogen levels can be detected during acute phase of inflammatory response and serve as additional markers for various inflammatory processes [19]. Regarding malignant diseases, elevated plasma fibrinogen levels have identified to serve as independent prognostic parameters in these malignancies [20]. In ovarian cancer, elevated plasma fibrinogen levels have also found to be predictive of a higher rate of non-optimal cytoreduction and a poorer response to chemotherapy [21]. Moreover, quantification of white blood cells (WBCs), lymphocytes, monocytes, neutrophils, and platelets from full blood counts found to be closely correlated with disease status and outcome. In addition, several combinatorial parameters, such as lymphocyte-to-monocyte ratio (LMR), fibrinogen-to-albumin ratio (FAR), platelet-to-lymphocyte ratio (PLR), and neutrophil-to-lymphocyte ratio (NLR) have been identified as prognostic biomarkers in several malignancies, including ovarian cancer [22].

These parameters were integrated into a novel nomogram created by Guo et al., [5] to formulate a tool to predict malignancy in ovarian masses and improve the therapeutic plans and surgical options for patients with ovarian cancer [5]. The nomogram issued by Guo et al. [5] is an integrative model using ultrasound findings, tumor

markers and inflammatory markers. It is based on age, CA125, Fibrinogen/Albumin ratio, Monocyte/lymphocyte ratio and ultrasound examination (M features) to categorize individuals with ovarian masses based on their likelihood of malignancy, including those with early-stage ovarian cancer. It has been found that various cancers have been linked to increased monocytes and decreased lymphocytes, reflecting host's immunological state. High MLR enhances tumor angiogenesis, proliferation, migration, and invasion. Plasma fibrinogen levels indicate inflammation and linked to tumor development, angiogenesis, metastasis, and prognosis in patients with ovarian cancer. Low serum Alb levels indicate malnutrition in patients, may weaken anti-tumor response and result in a bad prognosis [6]. Thus, it was reasonable to use indicators representing patients' systemic status for purpose of predicting risk of malignancy and prognosis in patients with ovarian cancer [5]. Guo et al. [5] conducted their study on two independent groups: 894 patients in training cohort and 383 patients in validation cohort.

Additionally, to explore performance of nomogram model in the early diagnosis of ovarian cancer, 246 patients with early-stage ovarian cancer (FIGO stage I and stage II) and 781 patients with benign tumors were included in another validation cohort. After internal validation they found that the nomogram model yielded a perfect AUC of 0.897, compared to an AUC of 0.792 for CA125, indicating its promising application for malignancy prediction. Compared to currently available models, including ROMA, CPH-I, and RMI, their nomogram demonstrated superior efficacy in predicting malignancy, and exhibited potential value in identifying early-stage ovarian cancer. Furthermore, Guo et al., [5] concluded that the nomogram model had better performance than CA125 alone and believed that clinical use of their nomogram not only helps guide clinicians and patients in deciding whether to perform surgery or not but also avoid unnecessary surgery in patients with benign ovarian masses. Although the internal validation of nomogram model performed and had excellent calibration, the generalizability of this model still requires external validation with use of additional databases from other regions and countries, to consider differences in epidemiology and clinical behavior that exist between ethnic groups [25].

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