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ORIGINAL ARTICLE

Institutional results of OncoOVARIAN Dx - a novel algorithm for the preoperative evaluation of adnexal masses

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Summary

Purpose: *The purpose of this study was to evaluate the predictive performance of OncoOVARIAN Dx algorithm, which takes into account tumor markers (beta HCG, CA 19.9, CEA, AFP, CA 125, HE4), general biochemistry and clinical data (age, menopause, comorbidities) in patients scheduled for surgical removal of a suspicious adnexal tumor in comparison with the Risk of Malignancy Algorithm (ROMA) model.*

Methods: *Consecutive women diagnosed with an adnexal tumor mass and scheduled for surgical intervention at a single tertiary cancer between October 2018 - June 2019 were enrolled. Preoperative values of tumor markers and general biochemistry (ASAT, ALAT, GGT, total bilirubin, creatinine) were determined. Following surgery with adequate surgical staging, a definite pathological diagnosis was made and used as reference.*

Results: *A total of 50 patients were selected, including 20 benign, 5 borderline and 25 malignant epithelial ovarian cancer (EOC) cases on final pathology. Borderline tumors comprised 3 serous and 2 mucinous FIGO stage I cases. Malignant tumors included 17 high grade serous, 4 endometrioid and 4 mucinous types, FIGO stage IA-IIIC. The two models demonstrated very good correlation (Phi 0.78, p<0.001). The sensibility (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV) of OncoOVARIAN Dx versus ROMA model were 76.66% vs. 60%, 95% vs. 100%, 95.83% vs. 100%, 73.07% vs. 62.5%, respectively. In postmenopausal patients higher Se (85.71%), Sp (100%) and PPV (100%) were observed for OncoOVARIAN Dx.*

Conclusions: *OncoOVARIAN Dx model demonstrated higher Se and NPV compared to ROMA and could be a useful marker in the preoperative management of adnexal masses; however larger studies are warranted to validate and further refine this algorithm.*

Key words: *OncoOvarian Dx, ovarian cancer, preoperative diagnosis, ROMA*

Introduction

Adnexal masses are frequently encountered during imaging and have a prevalence in the general population between 4-18% [1-5]. Preoperative characterization is of utmost importance, trying to avoid unnecessary surgery in benign lesion and redirecting adnexal masses suspicious for malignancy towards a specialized gynaecooncology department. In the United States there are 9 kinds of operation for each confirmed adnexal cancer in comparison with 2.3 operations for any other malignancy in oncology centres [6]. Ovarian cancer is the leading cause of gynaecologic cancer death with an estimated 67.771 new cases and 44.576 deaths in Europe in 2018 [7]. Besides initial FIGO staging, surgical

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outcome is one of the main prognostic factors [8], hence the initial management by a gynaecologic oncologist can impact the long-term prognosis of these patients [9,10]. However, only a subset are referred for initial management to a gynecologic oncologist [11]. Malignant masses should be managed without interruption of the ovarian capsule and adequate surgical staging [12], otherwise a negative impact in long-term outcome or a change in the need for adjuvant treatment might be inflicted [13]. Benign lesions should be approached conservatively taking into account the potential loss of ovarian function, fertility issues and aesthetic outcome [12]. Evidence-based guidelines on imaging evaluation have been recently published [6], however the role of serum biomarkers has not been clearly defined [14], with several algorithms currently deployed such as the Risk of Malignancy Index score [15], OVA1 [16] and the Risk of Malignancy Algorithm (ROMA) [17]. In the present study we aimed to prospectively evaluate the clinical performance of a novel algorithm OncoOVARIAN Dx which combines biochemical (ASAT, ALAT, GGT, total bilirubin, creatinine) and tumor markers values (AFP, β-hCG, CA 19.9, CA 125, CEA, HE 4) with patient clinical data in comparison with ROMA in a real-world tertiary cancer centre in women presenting with a pelvic mass.

Methods

Patients from the Oncological Institute Cluj-Napoca, Romania, planned for surgical evaluation and/or treatment of an adnexal mass were prospectively selected between October 2018 and June 2019 after they signed the informed consent form. The subjects had preoperative imaging, and, besides the standard preoperative evaluation, a separate blood sample was taken by venipuncture. After the surgical intervention the tumor was examined by an experienced pathologist for final pathological diagnosis. Serum was separated after centrifugation at 3500 rpm for 10 min and stored at -80°C. Determination of biochemical markers (ALAT, ASAT, GGT, total bilirubin,creatinine) were performed with commercial kits (PZ Cormay SA, Poland) and analyzed on the automatic analyser Prestige 24i (Tokyo Boeki, Japan). Tumor markers CA 125, CA 19-9, HCG, AFP, CEA were determined with commercial kits on a closed automated CLIA system (Immulite 1000, Siemens, Germany). HE4 (epididymal protein 4) was determined by ELISA method, with a commercial kit from Elabscience (Elabscience Biotechnology, USA). For all determinations the intra- and inter-assay coefficients of variation were <10%. ROMA score (Ovarian Malignancy Risk Algorithm) was calculated according to the formula [18] and evaluation of the risk for ovarian cancer with MBDA OncoOVARIAN Dx (Multiple Biomarkers Disease Activity for OncoOvarian) was generated by the Bioprognos platform (www.bioprognos.com/en). The platform requires to include, beside laboratory values, clinical information such as presence of ascites, pericardial/pleural effusions, cholestasis, jaundice, chronic liver disease, pancreatitis, renal failure, and metrorrhagia. Clinical data was retrieved from patient files and from the Institutional electronic database.

Statistics

Descriptive analysis used counts and frequencies for categorical variables, and means, medians, interquartile ranges and standard deviations for continuous variables. Chi square (x^2) test was used to detect significant associations between selected clinical variables. Independent samples t-test for equality of means was used where appropriate.

The present study received favorable approval from the Institutional Ethics Committee. All patients signed the informed consent and their data were processed anonymously.

Results

Fifty patients were included in the present study. The mean age of the study population was 54 years (SD 11.4). Patients with benign tumors were significantly younger (mean age 49.3 years,

Table 1. Clinical characteristics of the study group

Characteristics	*Result n (%)*
Mean age, years	54 (SD 11.4)
Menopausal status	
Premenopausal	19 (38)
Postmenopausal <1 year	5 (10)
Postmenopausal >1 year	26 (52)
Histological types	
Benign tumors	20 (40)
Borderline tumors	5 (10)
Mucinous	2 (4)
Serous	3 (6)
Malignant tumors	25 (50)
Endometrioid	4 (8)
Mucinous	4 (8)
High grade serous	17 (34)
2014 FIGO stage for malignant tumors	
I	7 (14)
IA	4 (8)
IB	2 (4)
IC	1 (2)
II	4 (8)
IIA	3 (6)
IIB	1 (2)
III	14 (28)
IIIA	1 (2)
IIIB	1 (2)
IIIC	12 (24)

mean age difference 7.9 years, p=0.014) in comparison with patients that had borderline/malignant tumors (mean age 57.2 years). According to the menopausal status, 26 (52%) patients were menopausal for more than one year. Among menopausal patients >1 year there was a significantly higher likelihood of a definite diagnosis of borderline/malignant tumor (OR 7, 95% CI 1.95-25.13, p=0.002) in comparison with premenopausal / postmenopausal patients <1 year. Definite pathology revealed there were 20 (40%) patients with benign tumors, 5 (10%) with borderline tumors and 25 (25%) with malignant ovarian tumors. Benign tumors comprised ovarian cystadenomas (n=5), endometriotic cysts (n=4), ovarian cystadenofibromas (n=3), serous cysts (n=2), ovarian fibromas (n=2), inflammatory processes (n=2), rete ovarii cyst (n=1) and mature teratoma (n=1). Among borderline tumors, there were 3 serous borderline tumors and 2 mucinous borderline tumors. Malignant tumors were represented by 4 mucinous, 4 endometrioid and 17 high grade serous ovarian tumors. Borderline tumors were limited to 2014 FIGO stage I, while malignant tumors had the following FIGO stage distribution: 7 (28%) stage I, 4 (16%) stage II and 14 (56%) stage III. Full patient details are presented in Table 1. Analysis of serum tumor marker levels was performed for all patients. Values of all 6 tumor markers stratified according to histological type are presented in Figure 1 and Table 2.

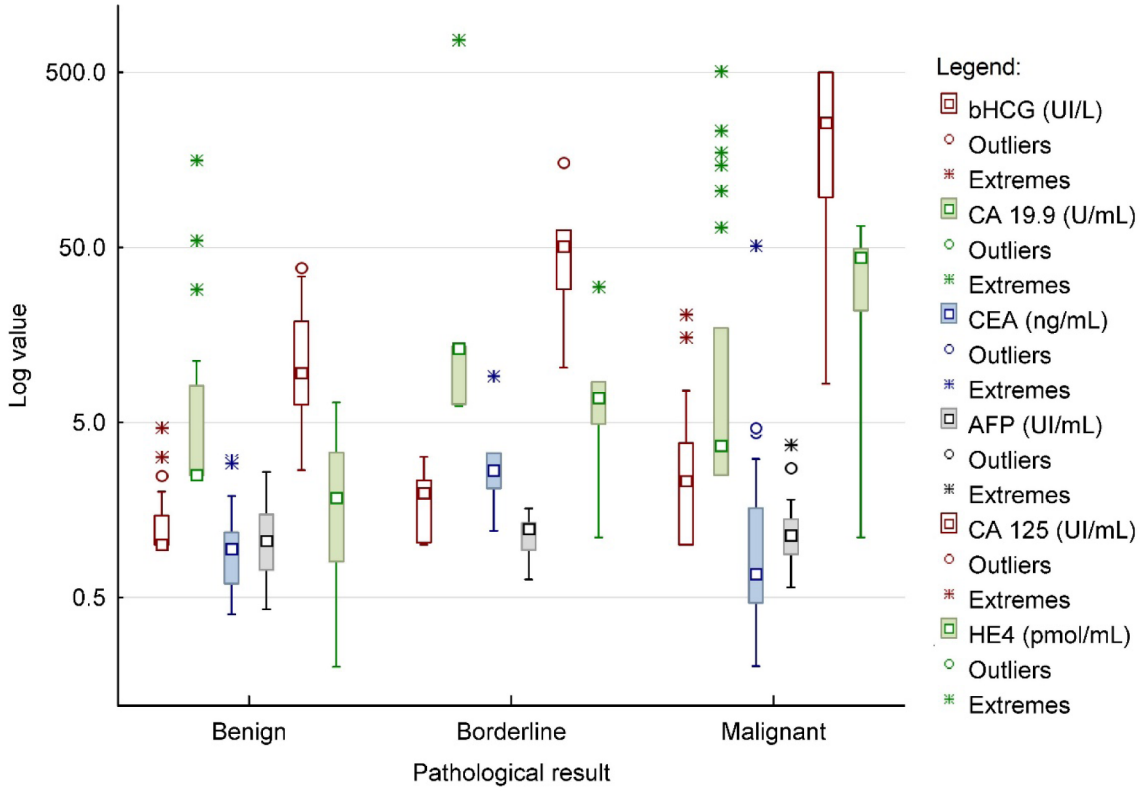

Figure 1. Box Plot of tumor markers.

Table 2. Median and interquartile values of tumor markers according to histology

Histology	*Percentile*	*bHCG (UI/L)*	*CA 19.9 (U/mL)*	*CEA (ng/mL)*	*AFP (UI/mL)*	*CA 125 (UI/mL)*	*HE4 (pmol/mL)*
Benign	25	1.00	2.50	0.60	0.70	6.13	0.80
n=20	50	1.00	2.50	0.95	1.05	9.59	1.85
	75	1.48	9.10	1.18	1.52	19.35	3.43
Borderline	25	1.02	6.28	1.65	0.78	19.55	3.00
n=5	50	1.97	13.20	2.65	1.23	50.60	6.90
	75	2.75	389.80	6.27	1.47	107.25	19.15
Malignant	25	1.00	2.50	0.46	0.85	85.75	18.40
n=25	50	2.31	3.67	0.68	1.13	257.00	43.80
	75	4.13	41.10	1.72	1.41	500.00	49.30

Table 3. Clinical performance of ROMA and OncoOVARIAN Dx algorithms

ROMA (all patients)	*Pathological result*		*Se (%)*	*60*
	Malignant	*Borderline/Benign*	*Sp*	*100*
Low risk	18	0	PPV	100
High risk	12	20	NPV	62.5
OncoOvarian Dx (all patients)	*Pathological result*		*Se (%)*	*76.66*
	Malignant	*Borderline/Benign*	*Sp*	*95*
Low risk	23	1	PPV	95.83
Intermediate/high risk	7	19	NPV	73.07
ROMA (postmenopause>1 year)	*Pathological result*		*Se (%)*	*71.42*
	Malignant	*Borderline/Benign*	*Sp*	*100*
Low risk	15	0	PPV	100
High risk	6	5	NPV	45.45
OncoOvarian Dx (postmenopause>1 year)	*Pathological result*	*Se*	*85.71*	
	Malignant	*Borderline/Benign*	*Sp*	*100*
Low risk	18	0	PPV	100
Intermediate/high risk	3	5	NPV	62.5

Se: sensitivity, Sp: specificity, PPV: positive predictive value, NPV: negative predictive value

The OncoOVARIAN Dx algorithm stratified patients into low, intermediate and high risk of malignancy according to manufacturer's prespecified thresholds while the ROMA algorithm stratified patients into low and high risk of malignancy. In the overall study population, the two models demonstrated very good correlation (Phi 0.78, p<0.001), however OncoOvarian Dx demonstrated higher Se (76.66%) and NPV (73.07%) compared to ROMA algorithm (Se 60%, NPV 62.5%) that demonstrated a 5% higher Sp and PPV compared to OncoOVARIAN Dx (Table 3). In the borderline/malignant subgroup of 30 patients, there were 12 patients deemed ROMA low risk and 5 of these patients had OncoOVARIAN Dx moderate/high risk. In the whole study population there was no instance of a case labelled OncoOvarian low risk with ROMA corresponding high risk. There was only one benign case on final pathology correctly labelled ROMA low risk and deemed OncoOVARIAN Dx high risk. Among the 7 borderline/malignant cases on final pathology that were interpreted as OncoOVARIAN Dx low risk 5 were FIGO stage IA, 1 was FIGO stage IB, and one was FIGO stage IIA through microscopic fallopian tube involvement. Investigating mucinous histology in borderline/malignant cases, ROMA algorithm identified as high risk only 1/6 (16.6%) cases while OncoOvarian Dx identified as high risk 4/6 (66.6%) cases. In endometrioid histology the two algorithms had identical performance, correctly identifying as intermediate or high risk 3/4 (75%) of the cases.

A subgroup analysis of the clinical performance of OncoOVARIAN Dx and ROMA algorithms in postmenopausal patients >1 year demonstrates a higher Se (85.71%) and NPV (62.5%) for OncoOvarian Dx compared to ROMA (Se 71.42%, NPV 45.45%) with equal Sp (100%) and PPV (100%). Additionally, the Se, Sp, PPV, NPV of OncoOVARIAN Dx in the postmenopausal >1year group vs whole study population were 85.71% vs 76.66%, 100% vs 95 %, 100% vs 95.83%, 62.5 vs 73.07%.

Discussion

For women diagnosed with ovarian cancer the institution where they receive their first surgery will likely impact their survival, with maximum results obtained in the care of a specialised gynecologic oncologists [19]. Unfortunately, in a large retrospective series from the United States more than half of ovarian cancer patients received non-guideline care, with low facility case volume as one of the independent predictors. Additionally, non-guideline care and lower facility case volume were both independently associated with a worse overall survival [20]. In this context, accurate preoperative knowledge of the malignant potential of an adnexal mass is important to triage high risk patients to high volume expert oncological centers. Currently there are several algorithms available, however a definitive verdict has not been established. The Risk of Malignancy Index is the simple

product of serum CA125 value, the ultrasound scan result (0, 1 or 3) and the menopausal status (1 if premenopausal, 3 if postmenopausal), first published by Jacobs et al in 1990 [21] and its value has been repeatedly tested in several studies [15]. For a cut-off value of 200, the associated sensitivity and specificity were 85% and 97%, respectively. Two tests are FDA-approved in the United States. First, The Risk of Ovarian Malignancy Algorithm (ROMA), is a qualitative serum test in the form of a mathematical function combining the results of HE4, CA 125 and menopausal status into a numerical score that should be used as an adjunctive complementary test. The performance for ovarian cancer detection in premenopausal women ranged between 53.3-72.7% (Se) and 74.2-87.9% (Sp) and in postmenopausal women between 82.5-90.8% (Se) and 66.3%-84.6% (Sp) [22-24]. The OVA1 Test is the second FDA-approved algorithm that combines the results of five serum immunoassays (CA125, transthyretin, apolipoprotein A-1, β2-microglobulin, transferrin) into a single numerical score and patient risk of malignancy is stratified using a cut-off specific to menopausal status. The pivotal study [25] and a subsequent study [16] that also incorporated the clinical impression demonstrated a sensitivity of 92.4-92.5% and a specificity of 42.8-53.5%. In the present study we compared the performance of OncoOVARIAN Dx with ROMA given that is was readily accessible. In the overall study population OncoOvarian Dx demonstrated higher Se (76.66%) and NPV (73.07%) compared to ROMA algorithm (Se 60%, NPV 62.5%) with a 5% inferior Sp (95% vs 100%) and PPV (100% vs 95.83%). Investigating the clinical performance in the subgroup of postmenopausal patients (>1 year since menopause) we found an improvement of OncoOVARIAN Dx Se (85.71% vs 76.66%), Sp (100% vs 95%) and PPV (100% vs 95.83%) compared to values from the overall population although there was a decrease in NPV performance (62.5% vs 73.07%). OncoOvarian Dx was more reliable in detecting malignant mucinous ovarian tumors (detection rate 4 out of 6 cases, 66.6%) in comparison with ROMA (detection rate 1 out of 6 cases, 16.6%).

A potential limitation of the current study is the relative limited number of included subjects, making it hard to draw definitive conclusions and the limited number of samples with less frequent histological types where a separate analysis of the model performance would be interesting to perform. The relatively high frequency of borderline/malignant cases is another drawback, given that the study was performed on patients that were referred to a dedicated high-volume center, hence, in a community-based setting where the frequency of malignancy would be lower we would expect a decrease in PPV and an increase in the model`s NPV.

In conclusion, OncoOVARIAN Dx algorithm for the preoperative assessment of adnexal masses demonstrated higher Se and NPV relative to the ROMA algorithm, however larger prospective studies are warranted to validate and further refine this algorithm.

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Conflict of interests

The authors declare no conflict of interests.

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