Diagnostic accuracy performance of the international ovarian tumour analysis (IOTA) simple rules and assessment of different neoplasias in the adnexa (ADNEX) model for identifying benign or malignant adnexal masses against histopathological diagnosis in patients seen and admitted at Dr. Jose Fabella Memorial Hospital*

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ABSTRACT

Objective: To know the diagnostic accuracy performance of the International Ovarian Tumour Analysis (IOTA) Simple Rules and Assessment of Different NEoplasias in the AdneXa (IOTA-ADNEX) Model for identifying benign or malignant adnexal masses against histopathological diagnosis.

Methods: This was a prospective single-center, cross-sectional diagnostic accuracy study including 53 women with an adnexal mass between May 2017 and March 2018. Pelvic ultrasound examination was done and serum levels of tumor marker CA 125 were obtained in all subjects prior to surgery. Adnexal masses were categorized according to the IOTA Simple rules and IOTA ADNEX model. The gold standard was histopathological diagnosis. The sensitivity, specificity, positive and negative predictive values of each scoring system utilized was determined and compared with the histopathologic result.

Results: Using the IOTA Simple rules, 35 adnexal masses classified as benign are 94.28 % truly benign by histopathologic diagnosis and 5.72% came out to be malignant; All 12 malignant tumors were truly malignant; there were 6 inconclusive tumors and came out to be malignant. In this study, IOTA Simple rules obtained a sensitivity of 90%, specificity of 100%, positive predictive value of 100%, Negative predictive value of 94% and Accuracy of 96%. Using the baseline risks assessment proposed by IOTA ADNEX Model, overall computation are as follows: (1) Sensitivity of 96.88 %, (2) Specificity of 90.48, (3) Positive Predictive Value of 93.94%, and a (4) Negative Predicitve Value of 95%

Conclusion: The majority of adnexal masses in our study were classified correctly using the IOTA Simple rules and IOTA ADNEX model. Due to high statistical significant values obtained by IOTA Simple rules, its use is validated and is encouraged to be the standard of use in scoring adnexal masses. In this study, we are able to prove that by subjective expert opinion from an expert sonographer in reclassifying those that are unclassified by IOTA simple rules approximates 100% accuracy.

Keywords: IOTA simple rules, IOTA ADNEX model, adnexal masses, ovarian neoplasm, ovarian cancer

INTRODUCTION

Adnexal masses are considered as one of the leading disorders in gynecology. The World Health Organization noted that Philippines had a 5-year prevalence rate of 18.9% (2012) for ovarian cancer,[1] being the 6th highest cause of mortality (4.3%) among the different cancer types in females, and with increasing incidence and trend over 20 years (1990-2013)[2].

A careful evaluation of ovarian masses necessitates meticulous physical examination, most importantly doing a thorough abdominal and bimanual pelvic examination. The size and physical characteristics of the cyst is as important as the other laboratory findings. For benign masses, conservative management with laparoscopic and fertility-sparing surgery are preferred. Laparoscopy is associated with reduced morbidity and lower cost when compared with laparotomy[3]. If malignancy is being considered, extensive surgery is a necessity and should be performed in an oncology center. This in mind is essential to optimize care and thereby higher survival among patient [4-5].

Patients with ovarian cancer may be symptom free

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for a long time and initial symptoms are non-specific. Malignant ovarian tumors are made to be discovered at a late stage in 75% of cases and are associated with the highest mortality figures among all other gynecological cancers[6]. The most important factor for patient's survival is the stage at time of diagnosis[7].

No single diagnostic tool is good enough in the preoperative determination of ovarian malignancy but ultrasound assessment by an experienced sonographer can properly estimate the risk of malignancy[8]. Ultrasound examination, more specifically the subjective assessment by an expert sonographer, is considered the best way to differentiate malignant from benign adnexal masses prior to surgery[9]. Although histopathology remains the only definitive diagnosis of an ovarian pathology, there are typical sonographic characteristics of an ovarian mass which can help determine whether the mass is likely to become benign or malignant in nature.

In order to support the diagnosis of adnexal masses, different ultrasound-based prediction models and scoring systems have been developed. As OB-GYN sonologists, we are currently adopting the International Ovarian Tumour Analysis Simple Rules (IOTA SIMPLE RULES) and the recently developed Assessment of Different NEoplasias in the AdneXa Model (IOTA-ADNEX), which predicts if a mass is malignant, but also, to a certain range, the probable stage of malignant condition. Insight into this type and staging makes it possible to optimize treatment, which may reduce morbidity and enhance the chances of patients' survival[5]. The distinction of a true malignant tumor versus a borderline malignancy is important for the management of premenopausal women in the setting of preserving fertility.

The IOTA Simple Rules and IOTA-ADNEX Model have been validated in a number of foreign studies. However, it has a few local data and reproducibility has not been tested in the local setting particularly in this institution. The use of IOTA Simple Rules was adopted in 2016 and the IOTA-ADNEX Model in the mid-2017 in this Institution.

RESEARCH QUESTION

"What is the diagnostic accuracy performance of IOTA Simple Rules and IOTA-ADNEX Model in identifying benign or malignant adnexal masses against histopathological diagnosis in patients seen and admitted at Dr. Jose Fabella Memorial Hospital?"

RESEARCH OBJECTIVES

General Objective:

To know the diagnostic accuracy performance of the International Ovarian Tumour Analysis (IOTA) Simple Rules and Assessment of Different Neoplasias in the Adnexa (IOTA-ADNEX) Model for identifying benign or malignant adnexal masses against histopathological diagnosis.

Specific Objectives:

- To determine the proportion of subjects with ovarian tumor read as malignant by IOTA Simple Rules among those determined malignant by histopathological biopsy (Sensitivity).
- To determine the proportion of subjects with ovarian tumor read as malignant by the Assessment of Different Neoplasias in the Adnexa (IOTA-ADNEX) Model among those determined malignant by histopathological biopsy (Sensitivity).
- To know the proportion of subjects who were determined malignant by histopathological biopsy among those screened by the IOTA Simple Rules as malignant (Positive Predictive Value).
- To know the proportion of subjects who were determined malignant by histopathological biopsy among those screened by Assessment of Different Neoplasias in the Adnexa (IOTA-ADNEX) Model as malignant (Positive Predictive Value).
- To determine the proportion of subjects with ovarian tumor read as benign by IOTA Simple Rules among those determined benign by histopathological biopsy (Specificity).
- To determine the proportion of subjects with ovarian tumor read as benign by the Assessment of Different Neoplasias in the Adnexa (IOTA-ADNEX) Model among those confirmed to be benign by histopathological biopsy (Specificity).
- To know the proportion of subjects who were determined benign by histopathological biopsy among those screened by the IOTA Simple Rules as benign (Negative Predictive Value).
- To know the proportion of subjects who were determined benign by histopathological biopsy among those screened by Assessment of Different Neoplasias in the Adnexa (IOTA-ADNEX) Model as benign (Negative Predictive Value).
- To determine the proportion of benign, borderline and malignant ovarian mass confirmed by histopathological biopsy among those tumors considered to be Unclassified by IOTA Simple Rules.
- To determine the distribution of the final pathological diagnosis of the adnexal masses.

REVIEW OF RELATED LITERATURE

When deciding on the type of surgery for an adnexal mass in a patient, estimating the potential for malignancy is an essential part. Ultrasonography is an excellent diagnostic tool for discriminating among benign and malignant adnexal masses[9]. An important goal among OB-GYN sonologists is to resolve the differences between normal physiologic findings, inflammatory changes, benign neoplastic processes and an ovarian malignancy. There are different prediction models developed over time but with no consensus yet on which is universally acceptable.

IOTA SIMPLE RULES

One of the limiting factors for an early diagnosis is the need of standardized terms used in gynaecological sonography. In 2008, Timmerman et al., with the International Ovarian Tumor Analysis (IOTA) group, proposed simple ultrasound-based rules in predicting ovarian malignancy in 200810. It aims to help sonologists discriminate benign and malignant adnexal mass in a context of describing morphological features of ovarian masses through a standardized examination technique.

The model included 5 ultrasonographic features suggestive of being benign (B-features) and 5 features suggestive of being malignant (M-features)[10] as described below:

Table 1. The IOTA simple rules for identifying a benign or malignant tumor

Rules for predicting a malignant tumor (M-rules)	
M1	Irregular solid tumor
M2	Presence of ascites
M3	At least four papillary structures
M4	Irregular multilocular solid tumor with largest diameter ≥100 mm
M5	Very strong blood flow (color score 4)
Rules for predicting a benign tumor (B-rules)	
B1	Unilocular
B2	Presence of solid components with the largest diameter <7 mm
B3	Presence of acoustic shadows
B4	Smooth multilocular tumor with largest diameter <100 mm
B5	No blood flow (color score 1)

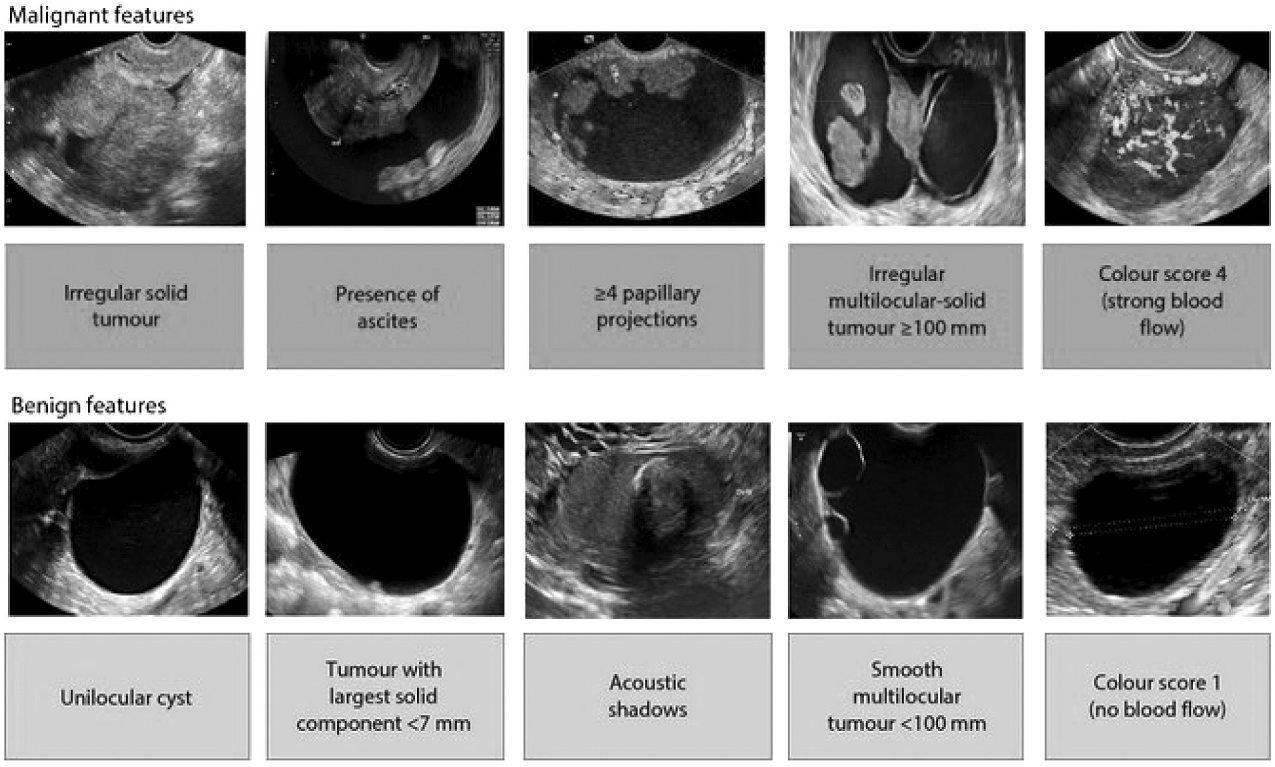


Figure 1. Sonographic features for identifying a benign or malignant tumor using IOTA simple rules

To interpret, if one or more B-features are present in the absence of M-features, the mass will be classified as benign, and vice versa. If both B- and M-features are present or if none of the 10 features is present, the simple rules will yield inconclusive result[11]. In cases of inconclusive result, it was proposed that patient must be referred for a thorough examination of the mass by an experienced sonologist because this may provide a more accurate diagnosis[9].

Timmerman et. Al, validated the ability of the IOTA Simple Rules in his studies in 2008 and 2010 to differentiate between benign and malignant masses. Several studies done by different investigators sought to validate the IOTA Simple Rules by calculating the specificity, sensitivity, negative and positive predictive values. Results yielded good diagnostic performance in different institutions including oncology centers, with high sensitivity of 92%, specificity of 96% as presented by Timmerman et al[11]. Shown in Table 2 are the different published studies on IOTA simple rules:

Table 2: Comparison of results from previous published IOTA simple rules studies

AUTHOR AND YEAR OF STUDY	NO. OF PATIENTS	SENSITIVITY (%)	SPECIFICITY (%)
TIMMERMAN D ET AL (2008)	507	95	91
TIMMERMAN D ET AL (2010)	1938	92	96
FATHALLLAH K ET AL (2011)	122	73	97
HARTMAN CA ET AL (2012)	103	91	87
SAYASNEH A ET AL (2013)	255	87	98
ALCAZAR JL ET AL (2013)	340	88	97
NUNES N ET AL (2012)	303	96	89
SUGANDHA ET AL (2017)	50	92	85

IOTA ADNEX MODEL

In 2014, the IOTA group proposed a multiclass, polytomous model the Assessment of Different Neoplasias in the AdneXa (IOTA-ADNEX) Model, the first risk model to differentiate between benign, borderline tumors, stage I invasive, stage II-IV invasive ovarian cancer and secondary metastatic cancer (Van Calster et al., 2014). This model predicts whether a mass is malignant, but also, to a certain range, the type of malignancy.

Insight into the specific tumor type makes it possible to optimize treatment, which may reduce morbidity and enhance the chances of survival[5]. The distinction of a true malignant tumor versus a borderline malignancy is important for the management of premenopausal women in the setting of preserving fertility.

The ADNEX model was introduced and validated using information from the IOTA phase 1-3 datasets. It originally consisted of prospectively collected patients who were referred for a sonogram to institutions or centers for a suspected adnexal mass. Involving twenty-four centers in 10 countries, the model was conducted on 3506 patients recruited between 1999 and 2007, temporally validated on 2403 patients recruited between 2009 and 2012, and then updated on all 5909 patients in the final study analysis.

The model comprises of three (3) clinical predictors and six (6) ultrasonographic predictors. The clinical predictors are age (years), level of serum CA-125 (U/mL) and type of hospital to which the patient has been referred for ultrasound examination (oncology centers vs other hospitals). The ultrasound predictors are the largest diameter of the mass (mm), proportion of solid tissue (%), number of papillary projections present (0,1,2,3, >3), presence of more than 10 cyst locules (yes/no), acoustic shadows (yes/no), presence of ascites (yes/no) as shown by Figure 2 and Table 3 below[13].

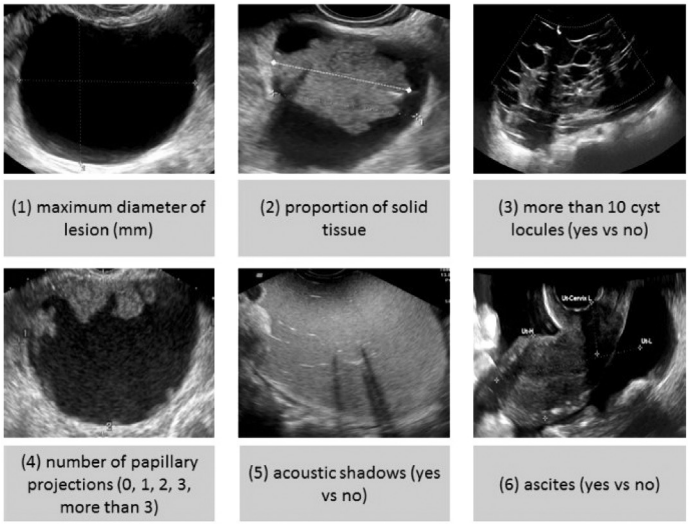


Figure 2. Ultrasound characteristics selected as predictors in the ADNEX model

The absolute risk will be calculated with an outcome of a risk estimate expressed as percentage for 5 different types of adnexal pathology. A risk estimate for the overall risk of malignancy will be given as well (sum of

Table 3. Nine predictors in the IOTA ADNEX model

1. Age of the patient at examination	(years)
2. Oncology center (referral center for gyn-oncol)?	(yes/no)
3. Maximal diameter of the lesion	(mm)
4. Maximal diameter of the largest solid part	(mm)
5. More than 10 locules?	(yes/no)
6. Number of papillations (papillary projections)	(0,1,2,3, >3)
7. Acoustic shadows present?	(yes/no)
8. Ascites (fluid outside pelvis) present?	(yes/no)
9. (U/ml) Serum CA-125	(U/ml)

the estimates for all 4 subtypes of malignancy) as shown below:

Figure 3. IOTA ADNEX MODEL Result page as displayed in Samsung WS80A

Figure 4. IOTA ADNEX MODEL Ultrasound page results as displayed in Samsung WS80A

With the increasing trend in mortality rate for ovarian cancer in the Philippines, it is but appropriate to validate within our own local setting, specially conducting the first in our institution, the diagnostic accuracy performance of the both IOTA Simple Rules and IOTA-ADNEX Model in discriminating benign and malignant adnexal masses.

STUDY DESIGN AND SETTING

This was a prospective, single-center, cross-sectional diagnostic accuracy study done at a tertiary care hospital using data collected prospectively between May 2017 to March 2018. A single OB-GYN ultrasound fellow (Principal Investigator) and an experienced consultant ultrasonographer (Senior Investigator) with more than 10 years' experience in gynecological ultrasound (Level-3 examiner) were involved in assessing all consecutively recruited patients with adnexal pathology.

METHODS

Study Subjects

Inclusion Criteria:

- Female patients with one or bilateral adnexal mass/ masses judged not to be a physiologic cyst
- Examined with transvaginal or transrectal with or without transabdominal ultrasound by the principal investigator
- Candidate for surgical intervention within 120 days from the time of ultrasound scan
- Availability of histopathology result
- Availability of the CA-125 levels

Inclusion Criteria:

- Refusal to participate in the study
- Patient with a previous bilateral oophorectomy
- Adnexal mass co-existing with pregnancy

Sample Size

Sample size calculation was at least 52, given 95% confidence interval, using the Slovin's formula:

Sample size (n) = N / (1 + Ne2)
where: N = average population size
e = margin of error
n = 59 patients / [1 + (59 x 0.052) = 52 subjects
Year 2015 Ovarian Cysts Surgery: 54 Patients
Year 2016 Ovarian Cysts Surgery: 64 Patients
Total: 118 Patients
Average: 59 Patients
Sample (N): 52 Patients

Study Procedure

The study was submitted to the Medical Research Ethics Committee of Dr. Jose Fabella Memorial Hospital for approval. All female patients with adnexal mass/es seen and underwent surgery in this institution were recruited

in the study from May 2017 to March 2018. Written and nformed consent were asked from the patients prior to their ultrasound scan and followed up until surgery.

Recruited patients underwent standardized transvaginal or transrectal grayscale and color Doppler ultrasound examination, using Samsung WS80A Ultrasound Machine (Samsung Healthcare Ultrasound, Korea). Only the principal investigator will be the one to do ultrasound examination and counterchecked by the senior investigator. The decision to operate was made by the attending physician based on the full clinical picture, including the ultrasound report, the latter being based on the principal investigators objective assessment of the ultrasound disease. If more than one mass was seen, the mass with the most complex morphology on the ultrasound scan was used. If similar morphology was seen from both masses, the biggest or the one most accessible by ultrasound was used. Transabdominal sonography was added for patients with large mass/es that could not be visualized in full by a transvaginal or transrectal probe. Patients with a previous hysterectomy who were 50 years of age or older and patients with amenorrhea of more than 1 year were defined as postmenopausal.

The principal investigator, counterchecked by the senior consultant in charge, was the sole person in charge in the assessment of the sonographic tumor morphology based on the nomenclature of the IOTA group, recording the ultrasound findings in a safe and secure electronic data-collection system together with demographic data, tumor markers and tumor diagnosis based on subjective assessment. All ultrasound assessments were done prior to surgical intervention and obtaining the final histolopathological diagnosis. Patients were required to have a measurement of their CA-125.

Histopathologic diagnosis was used as the clinical reference standard for all patients in this study. Results were obtained by either surgery or biopsy of a metastasis and added to the database. The pathologists were blinded from the results of the ultrasound examination. Tumors were classified based on the World Health Organization International Classification of Ovarian Tumors. Tumor stage was defined according to the International Federation of Gynecologists and Obstetricians (FIGO) 2012 classification.

Adnexal masses were classified as either (1) benign, (2) malignant or (3) unclassified using the IOTA Simple Rules. Afterwhich, it is subjected for computation of risk of malignancy using the ADNEX Model. Obtained results were compared with the final histopathological report.

The IOTA simple rules model included 5 ultrasonographic features suggestive of being benign (B-features) and 5 features suggestive of being malignant (M-features). For inconclusive results, the senior investigator has the experienced judgement to call whether to assign the mass to be having benign or malignant features.

The ADNEX Model uses nine predictors. There are three (3) clinical variables: age, serum CA-125 level, and type of center (oncology referral center vs other); and six (6) ultrasound variables: maximal diameter of lesion, proportion of solid tissue, more than 10 cyst locules, number of papillary projections, acoustic shadows, and ascites. The data were entered in the application available *(http://www.iotagroup.org/adnexmodel)* in the Samsung WS80A. Risk was calculated with an outcome of a risk estimate expressed as percentage for 5 different types of adnexal pathology: (1) benign, (2) borderline, (3) stage I – invasive, (4) stage II-IV invasive and (5) secondary metastatic cancer. A risk estimate for the overall potential for malignancy were likewise given (sum of the estimates for all four (4) subtypes of malignancy). A cut-off of $\geq$ 10% for the overall risk of malignancy were used to predict malignancy.

Outcome Description

The outcome of the study is to know the diagnostic accuracy performance of the IOTA simple rules and IOTA-ADNEX Model for identifying benign or malignant adnexal masses against histopathological diagnosis.

Statistical Data Analysis

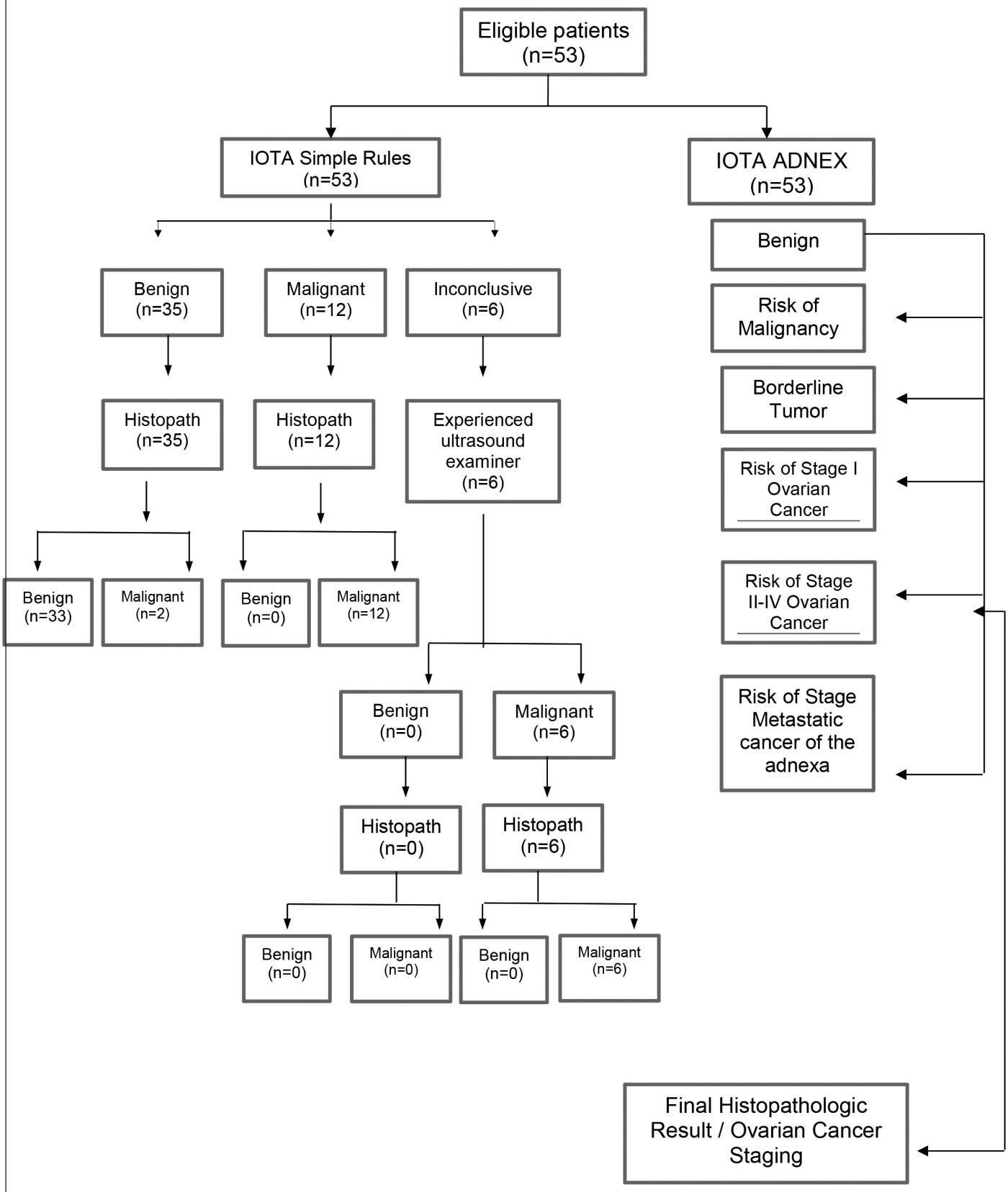
All data were encoded and tallied in Microsoft Excel (Microsoft Excel, IBM Corporation, California). Analysis of data were performed with IBM SPSS statistics v20 (IBM Corp, Los Angeles, CA, USA) and MedCalc v16.1 (MedCalc Software, Mariakerke, Belgium).

Non-parametric analysis using age, menopausal status, family history of ovarian cancer, laterally and types of tumor, proportion of solid tissues, number of locules, number of papillary projections, and etc. were represented by frequency and percentage (for patient demographics and sonographic features according tumor type in patients with adnexal mass). Incidence of pathology (benign, borderline, malignant) were likewise reported. In this study, for statistical purposes, borderline tumors were considered malignant.

Diagnostic accuracy of IOTA Simple Rules and IOTA ADNEX Model were reported using sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy.

Receiver–operating characteristics (ROC) curves were derived for the ADNEX model and summarized by calculating the area under the curve (AUC) with 95%CI using exact methods based on the binomial distribution. The method described by DeLong et al.[19] was used to calculate statistical significance of differences between AUCs.

Schematic Diagram



RESULTS AND DISCUSSION

Between May 2017 and March 2018 a total of 167 patients with adnexal masses were scanned in the Women's Clinic Section of Obstetic and Gynecologic Ultrasound of Dr. Jose Fabella Memorial Hospital. Among those, 62 patients were surgically intervened and the final cohort consisted of 53 patients who met the inclusion criteria.

The median interval between ultrasound examination and gathering the histopathology results was twenty one (21) days.

Descriptive statistics for patient demographics and data for the ultrasound features used in the different models according to tumor type are shown below.

Among the 53 subjects included in this study final histopatological diagnosis were as follows: 33 (62.26%)

Table 4. Descriptive statistics for patient's characteristics and ultrasound features according to tumor type in 53 patients with adnexal mass

Variable	Benign (n=33)	Borderline (n=10)	Stage I (n=4)	Stage II-IV (n=6)	Metastatic (n=0)
Age (years)	35.15	48.14	49.66	52.16	0
CA-125 (U/mL)	57.03	82.88	96.33	3,630.36	0
Menopausal Status					
Premenopausal	31	4	2	5	0
Postmenopausal	1	3	4	3	0
Family history of Ovarian Cancer	18	2	3	5	0
Laterality of Tumor					
Unilateral	29	9	4	4	0
Bilateral	5	1	0	2	0
Maximum diameter of lesion (mm)	173.62	246.64	177.25	145.7	0
Type of Tumor					
Unilocular	18	2	0	0	0
Multilocular	15	7	4	3	0
Unilocular-solid	0	0	0	0	0
Multilocular-solid	0	0	0	1	0
Solid	0	0	0	1	0
Unclassifiable	0	0	0	0	0
Presence of Solid Tissue	0	1	0	2	0
Maximum Diameter of Solid Tissue (mm)	0	32.23	47.93	95.3	0
Proportion of solid tissue (%)	0	13.82	31.46	64.96	0
Number of locules					
0	0	0	0	2	0
1-4	18	2	0	0	0
5-10	4	0	1	0	0
>10	11	8	3	4	0
Number of Papillary Projections					
0	33	4	0	2	0
1	0	3	0	0	0
2	0	0	0	0	0
3	0	0	0	1	0
>3	0	3	4	3	0
Blood Flow in papillary projections: color Doppler score					
1	33	1	1	1	0
2	0	5	1	0	0
3	0	0	0	0	0
4	0	4	2	5	0
Irregular Cyst Wall	0	2	1	6	0
Metastases	0	0	0	0	0
Acoustic Shadow	0	0	0	0	0
Ascites	0	3	0	6	0

were benign, 10 (18.87%) were Borderline tumor, 4 (7.55%) were Stage I Ovarian Cancer, 6 (11.32%) were Stage II-IV Ovarian Cancer and 0 (0%) for Metastatic.

Among the 33 total benign cases five histologic types were obtained: endometrial cysts (28.30%), mucinous cystadenoma (16.98%), mature cystic teratoma (9.43%), serous cystadenoma (5.63%) and a mixed histologic type seromucinous cyst (1.88%).

Among the 10 borderline tumors, there are only two histologic types obtained: 9 (16.98%) mucinous type and 1 (1.88%) serous type.

Among the 10 malignant tumors, five histologic types were obtained: adult granulosa cell tumor (7.54 %), mucinous cystadenocarcinoma (3.77%), high grade papillary serous carcinoma (3.77), high grade serous carcinoma (1.89%) and clear cell adenocarcinoma (1.89%).

Table 5. Distribution of the final pathological diagnosis of the adnexal masses

DIAGNOSTIC CATEGORIES	FINAL DIAGNOSES	NO.	%
BENIGN TUMORS	ENDOMETRIOTIC CYSTS	15	28.30188
	SEROMUCINOUS CYSTS	1	1.88679
	SEROUS CYSTADENOMA	3	5.66037
	MUCINOUS CYSTADENOMA	9	16.98113
	MATURE CYSTIC TERATOMA	5	9.43396
BORDERLINE TUMORS	MUCINOUS BORDERLINE	9	16.98113
	SEROUS BORDERLINE	1	1.88679
MALIGNANT TUMORS	ADULT GRANULOSA CELL TUMOR	4	7.54716
	CLEAR CELL ADENOCARCINOMA	1	1.88679
	SEROUS CARCINOMA, HIGH GRADE	1	1.88679
	MUCINOUS CYSTADENOCARCINOMA	2	3.77358
	HIGH GRADE PAPILLARY SEROUS CARCINOMA	2	3.77358
TOTAL		**53**	**100**

The IOTA Simple rules was used to classify the 53 adnexal masses as benign, malignant and inconclusive results. Using the IOTA Simple rules, 35 adnexal masses classified as benign (94.28 %) are truly benign by histopathologic diagnosis. There were 2 tumors classified as benign but came out to be malignant upon obtaining the histopath (5.72%), these turned out to be borderline ovarian cancer. All 12 classified malignant tumors were truly malignant. There were 6 inconclusive results, re-classified as malignant by an expert opinion (senior sonologist) and obtained 100% malignant histologic types: Five (5) were borderline mucinous tumors (83.33%) and one (1) Granulosa cell tumor (16.66%).

Table 6. Classifications of adnexal masses in comparison to final histopathologic diagnosis using IOTA Simple Rules

IOTA SIMPLE RULES	PATHOLOGIC DIAGNOSIS		TOTAL
	MALIGNANT MASSES	BENIGN MASSES	
MALIGNANT	12	0	12
BENIGN	2	33	35
*UNCLASSIFIED (ASSIGNED MALIGNANT BY AN EXPERT)	6	0	6
TOTAL	**20**	**33**	**53**

Table 7. Re-classification of all unclassified by an expert sinologist (For statistical purposes, borderline tumors were considered malignant) *all unclassified tumors were reclassified as malignant

IOTA SIMPLE RULES	PATHOLOGIC DIAGNOSIS		TOTAL
	MALIGNANT MASSES	BENIGN MASSES	
MALIGNANT	18	0	18
BENIGN	2	33	35
TOTAL	**20**	**33**	**53**

Table 8. Distribution of 6 Inconclusive Tumors According to Final Histopathological diagnosis

DIAGNOSTIC CATEGORIES	FINAL DIAGNOSES	NO.	%
Inconclusive tumors	Borderline mucinous cyst tumors	5	83.33333
	Granulosa Cell Tumor	1	16.66666
TOTAL		**6**	**100**

In this study, we were able to prove that by subjective opinion from an expert sonographer in reclassifying tumors that are unclassified by IOTA simple rules approximates 100% accuracy.

In this study, IOTA Simple Rules obtained a sensitivity of 90%, specificity of 100%, positive predictive value of 100%, negative predictive value of 94% and accuracy of 96%. Due to high statistically significant values obtained by IOTA Simple rules, its use is validated and is encouraged to be a standard of use in scoring adnexal masses.

Table 9. Comparison of results of present study with the previously published data

AUTHOR AND YEAR OF STUDY	NO. OF PATIENTS	SENSITIVITY (%)	SPECIFICITY (%)
TIMMERMAN D ET AL (2008)	507	95	91
TIMMERMAN D ET AL (2010)	1938	92	96
FATHALLLAH K ET AL (2011)	122	73	97
HARTMAN CA ET AL (2012)	103	91	87
SAYASNEH A ET AL (2013)	255	87	98
ALCAZAR JL ET AL (2013)	340	88	97
NUNES N ET AL (2012)	303	96	89
SUGANDHA ET AL (2017)	50	92	85
PRESENT STUDY	**53**	**90**	**100**

Table 10. IOTA Simple Rules Sensitivity, Specificity, Positive Predictive value, Negative Predictive Value and Accuracy in predicting a benign versus a malignant tumor

IOTA SIMPLE RULES	PATHOLOGIC DIAGNOSIS		SENSITIVITY	SPECIFICITY	PPV	NPV	Accuracy
	MALIGNANT	BENIGN					
MALIGNANT	18	0	90%	100%	100%	94%	96%
BENIGN	2	33					

In the IOTA ADNEX model, by following the standard cut-off of ≥10% in predicting the risk of benignity and malignancy, regardless of the cancer subtypes, yielded a 100% sensitivity and specificity.

Table 11. IOTA ADNEX Model Sensitivity, Specificity, Positive Predictive value, Negative Predictive Value and Accuracy in predicting a benign versus a malignant tumor

IOTA ADNEX MODEL	PATHOLOGIC DIAGNOSIS		SENSITIVITY	SPECIFICITY	PPV	NPV	Accuracy
	MALIGNANT	BENIGN					
MALIGNANT	20	0	100%	100%	100%	100%	100%
BENIGN	0	33					

Using the baseline risks assessment proposed by the ADNEX Model cut off point, it showed a 96.88% sensitivity and 90.48 % specificity for identifying malignant adnexal masses; 86.84% sensitivity and 100 % specificity for risk of borderline tumor; 91.67% sensitivity and 100 % specificity for risk of Stage 1 ovarian cancer; 78.57% sensitivity and 100 % specificity for risk of Stage 2-4 ovarian cancer; and 74.42 % sensitivity and 90 % specificity for risk of metastatic cancer.

Table 12. IOTA ADNEX Model Sensitivity, Specificity, Positive Predictive value, Negative Predictive Value in predicting a benign versus a malignant tumor as per staging

	Sensitivity	Specificity	PPV	NPV	LR-	LR+
Benign Tumor	**0%**	**13.16%**		**25.00%**	**7.6**	**0**
	(0% to 21.80%)	(4.41% to 28.09%)		(12.84% to 43%)	(3.36 to 17.20)	(3.13% to 20.66%)
Risk of Malignancy	**96.88%**	**90.48%**	**93.94%%**	**95.00%**	**10.17**	**0.03**
	(83.78% to 99.92%0	(69.62% to 98.83%)	(80.55% to 98.31%)	(73.31% to 99.24%)	(2.72 to 38.07)	(0.00 to 0.24)
Risk of Borderline Tumor	**86.84%**	**100%**	**100%**	**75.00%**		**0.13**
	(71.91% to 95.59%)	(78.20% to 100%)		(57% to 87.16%)		(0.06 to 0.30)
Risk of Stage 1 Ovarian Cancer	**91.67%**	**100.00%**	**100.00%**	**85.00%**		**0.08**
	(77.53% to 98.25%)	(80.49% to 100%)		(65.73% to 94.36%)		(0.03 to 0.25)
Risk of Sage 2-4 Ovarian Cancer	**78.57%**	**100%**	**100%**	**55%**		**0.21**
	(63.19% to 89.70%)	(71.51% to 100%)		(40.65% to 68.56%)		(0.12 to 0.38)
Risk of Metastatic Cancer	**74.42%**	**90%**	**96.97%**	**45%**	**7.44**	**0.28**
	(58.83% to 86.48%)	(55.50% to 99.75%)	(83.17% to 99.52%)	(32.07% to 58.65%)	(1.15 to 48.17)	(0.16 to 0.49)

The area under the curve for the overall difference among benign and malignant tumors was 0.880 (95% CI, 0.751-1.0). AUCs for discrimination between different tumor subgroups ranged between 0.873-0.981. With the values obtained from the AUC (greater than 0.80) it can be surmised that the diagnostic model being tested (IOTA ADNEX Model) has a good accuracy.

Thus, for the study population as a whole, among the two methods assessed, IOTA Adnex is more sensitive than Simple rules, 90% and 96.88% respectively. IOTA Simple rules is more specific than IOTA ADNEX, 100% and 90.48% respectively.

Furthermore, our study supports that subjective assessment via pattern recognition remains an irreplaceable tool and must always be correlated to the the different models mentioned in this study.

The limitations of this study include short time frame, limited number of subjects and was not conducted in an oncology center, in comparison to that of published original study.

The strength of our study counted on the meticulous and prospective collection of clinical and ultrasound data in line with IOTA nomenclature and measurement techniques, based on real-time ultrasound and being blinded to the histopathology results.

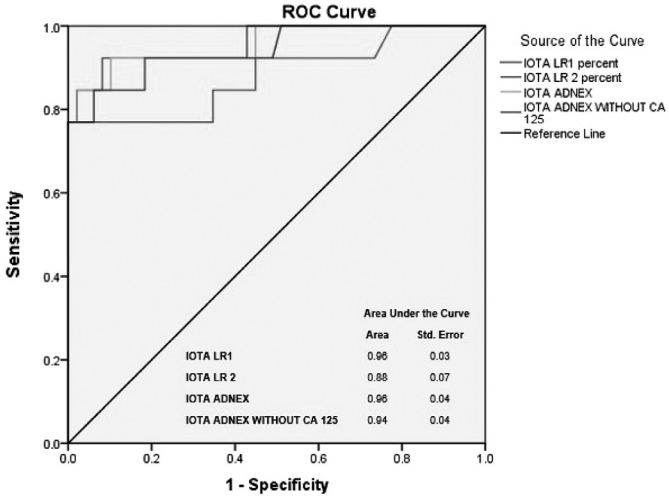


Figure 5. ROC Curve for ADNEX model

In conclusion, the IOTA Simple Rules and ADNEX Model have high sensitivity, specificity and accuracy in

Table 13. IOTA ADNEX Model Area under the curve with test result variables

	AUC	95% CI
Benign vs borderline	0.871	0.751 to 0.991
Benign vs Stage I	0.998	0.991 to 1.000
Benign vs Stage II-IV	0.927	0.858 to 0.997
Borderline vs Stage I	0.972	0.919 to 1.000
Borderline vs Stage II-IV	1.000	1.000 to 1.000
Stage I vs Stage II-IV	0.955	0.903 to 1.000

Area Under the Curve					
Test Result Variable(s)	**Area**	**Std. Error[a]**	**Asymptotic Sig.[b]**	**Asymptotic 95% Confidence Interval**	
				Lower Bound	**Upper Bound**
BenignTumor	.987	.013	.000	.961	1.000
Risk of Malignancy	.880	.066	.000	.751	1.000
Risk of Borderline	.937	.050	.000	.840	1.000
Risk Stage1	.977	.019	.000	.940	1.000
Risk Stage 234	.981	.017	.000	.948	1.000
Risk Metastatic Cancer	.873	.047	.000	.781	.965

The test result variable(s): RiskofMalignancy, RiskofBorderline, RiskStage1, RiskStage234, RiskMetastaticCancer has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.
a. Under the nonparametric assumption
b. Null hypothesis: true area = 0.5

Table 14. Comparison of the IOTA ADNEX and IOTA Simple Rules

Assessment method	SENSITIVITY	SPECIFICITY	PPV	NPV	Accuracy
IOTA Simple Rules	90%	100%	100%	94%	96%
ADNEX Model	100%	100%	100%	100%	100%

identifying benign versus malignant adnexal masses. However, ADNEX model has the advantage over IOTA simple rules in the differentiation between the various subtypes of malignancy among adnexal malignancies.

More guidance on future conferences on how to fully optimize the ADNEX model in our practice would be recommended. At the same time, data may be summed up and obtained from other oncology institutions to come up with improved statistical interpretation. Further analyses likewise are needed to determine the use of the IOTA ADNEX model by less experienced ultrasound examiners. ■

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