RESEARCH ARTICLE

INDONESIAN JOURNAL OF CANCER

Performance of Pre-Operative IOTA Three-Step Algorithm in Detecting Ovarian Carcinoma in a Referral Center in Indonesia

Andi Kurniadi [1*], Wiryawan Permadi [1], Aria Yusti Kusuma [1], Jessica Kireina [1], Mia Yasmina Andarini [2], Gatot Nyarumenteng Adhipurnawan Winarno [1], Ali Budi Harsono [1]

[1] Department of Obstetrics and Gynecology, Universitas Padjadjaran, Bandung, Indonesia

[2] Faculty of Medicine, Universitas Islam Bandung, Bandung, Indonesia

ARTICLE INFO

Received : 14 March 2023
Reviewed : 15 May 2023
Accepted : 04 July 2023

Keywords:
adnexal mass, ADNEX model, diagnosis, simple descriptors, simple rules

**Corresponding author:*
Andi Kurniadi
Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia
andi.kurniadi@unpad.ac.id

ABSTRACT

Background: To assess the diagnostic performance of a three-step algorithm using the International Ovarian Tumor Analysis (IOTA) Group 'simple rules', 'simple descriptors', and Assessment of Different NEoplasias in the adneXa (ADNEX) model for discriminating benign and malignant adnexal masses.

Methods: This was a retrospective observational study, performed at a tertiary-care university hospital, on women diagnosed with adnexal mass on ultrasonography from January 2021 and February 2022. The examiner first classified the mass using 'simple descriptors' (first step) and, if not possible, using 'simple rules' (second step). For inconclusive masses, an assessment using the ADNEX model was done as the third step. All masses were managed surgically. Histopathology results were used as the reference standard.

Results: One hundred and forty-one women were included (median age of 48 years). Histopathology results showed 104 (73.76%) mass to be malignant, and 37 (26.24%) mass to be benign. Twelve (8.51%) of 141 masses could be classified using simple descriptors, 89 (63.12%) masses were classified using simple rules, and 40 (28.37%) masses were classified using the ADNEX model. Overall accuracy, sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio of the three-step algorithm were 89.36%, 94.23%, 75.68%, 91.59%, 82.35%, 3.87, and 0.08 respectively.

Conclusions: The IOTA three-step algorithm, based on the sequential use of simple descriptors, simple rules, and ADNEX model, performs well for classifying adnexal masses as benign or malignant.

INTRODUCTION

Ovarian cancer is the most lethal gynecologic cancer [1]. It is the fifth leading cause of cancer-related death in women worldwide [2]. In Indonesia, ovarian cancer is the third most prevalent cancer in women, accounting for 7.84% of the total cancers in women [3]. Therefore, early diagnosis when the tumor is small and still confined to the ovary is the most important prognostic factor.

Correct characterization of adnexal masses is essential to provide appropriate therapy [4]. Nowadays, ultrasound is considered the main imaging modality for adnexal masses assessment. Several studies have shown that subjective examination by a trained ultrasound examiner provides good diagnostic performance for adnexal masses characterization. Due to the scarce number of trained examiners, many scoring systems have been developed, but unfortunately, most of them are often too complicated [5–7]. The International Ovarian Tumor Analysis (IOTA) group proposed a simple approach for ovarian tumor screening that is based on ultrasonography features, called 'Simple Descriptors' and 'Simple Rules' [8,9]. The simple descriptors were developed based on senior examiners' experiences. When these descriptors did not apply to an ovarian tumor, the 'Simple Rules' were used [10]. The 'Simple Rules' have been validated to perform well even in the hands of less-experienced examiners [11].

In 2014, the IOTA group developed the Assessment of Different NEoplasias in the adneXa (ADNEX) model. This model uses three clinical variables including CA-125 levels, and six ultrasound variables. The output of this model is the percentage of probability of a tumor being malignant, with a cut-off number to declare a tumor as malignant or benign, so that the diagnosis of an ovarian tumor can be more certain because there are no inconclusive results in the ADNEX model [12]. The concept was after the two-step approach, residual masses where neither simple descriptors nor rules were applicable could be assessed by expert examiners using the ADNEX model as the final step [10]. This three-step strategy enables initial assessment of adnexal mass to be carried out by a non-expert examiner therefore allowing a more effective utilization of resources. However, this three-step strategy needs to be validated in various settings [7]. The purpose of this study is to evaluate the performance of the three-step IOTA strategy compared with histopathological results as the gold standard diagnosis in a referral center in Indonesia.

METHODS

This was a retrospective observational study, performed at a tertiary-care university hospital in Indonesia, on women diagnosed with ovarian mass from January 2021 until February 2022. This study included all patients with ovarian masses who were examined using IOTA algorithm and underwent surgery along with histopathological examination. We excluded those with incomplete patient case notes. There were a total of 205 patients with an ultrasound diagnosis of ovarian mass. However, only 141 patients met the eligible criteria.

The examiner first classifies the masses using 'simple descriptors' (first step), and if not applicable, the examiner would then use the 'simple rules' (second step). Then, masses with inconclusive results would be assessed by an expert examiner using the ADNEX model as the third step (**Table 1**).

A tumor was defined as malignant if it meets one of the following criteria: malignant criteria (MD1/MD2) without benign criteria (BD1-BD4) in simple descriptors, malignant criteria (M1-M5) without benign criteria (B1-B5) in simple rules, or a score above the 80% cut-off on the ADNEX model. All masses were managed surgically. Post-operative histopathological result was used as the gold standard for comparison.

A customized spreadsheet was utilized to tabulate patients' data and analysis was performed using SPSS software for Mac (version 25.0; SPSS, Inc., Chicago, IL). Descriptive statistics were conducted as appropriate. The normality test was performed using the Shapiro-Wilk test. Analytical statistics were done using an independent t-test or Mann-Whitney U test as required.

RESULTS

We enrolled 141 patients. Based on histopathological examinations, 104 patients (73.76%) had malignant tumors and 37 patients (26.24%) had benign tumors. The high number of malignant tumors in this study was probably because the samples came from Dr. Hasan Sadikin Bandung Hospital, a major referral hospital in Indonesia.

The mean age of the patients in this study was 46±14 years old. Patients with malignant tumors were significantly older than those with benign tumors (40.7±14 Vs 47.6±13.6, p=0.009). Referring to the post-operative histopathological results, around 75.68% of patients with benign tumors and 94.23% of patients with malignant tumors were detected accurately using IOTA algorithm (**Table 2**).

Table 3 shows the diagnostic performance of the three-step IOTA algorithm, with an overall accuracy of 89.36%. Each step in the algorithm contributed differently to the sensitivity and specificity. The simple descriptors could be applied to 12 masses (8.5%) and all those 12 masses were declared malignant by the simple descriptor. Eleven masses were true positive with only one mass showing a false positive result. Simple rules could be

Table 1. ADNEX Model

Age of the patient at examination? (years)
Oncology center (referral center for gyn-oncol)? (yes/no)
Maximal diameter of the lesion? (mm)
Maximal diameter of the largest solid part? (mm)
More than 10 locules? (yes/no)
Number of papillations (papillary projection)? (none/one/two/three/more than three)
Acoustic shadows present? (yes/no)
Ascites (fluid outside pelvis) present? (yes/no)
Serum CA-125? (U/ml)

P-ISSN: 1978-3744 E-ISSN: 2355-6811

Table 2. Comparison of IOTA Algorithm and Histopathological Examination Results

		Histopathological examination		Total
		Malignant	Benign	
IOTA Algorithm	Malignant	98 (94.23%)	9 (24.32%)	107
	Benign	6 (5.77%)	28 (75.68%)	34
Total		104	37	

Table 3. Diagnostic Performance of Three-Steps IOTA Algorithm

Diagnostic Index	Sensitivity	Specificity	PPV	NPV	PLR	NLR	Accuracy
SD (n = 12)	100%	0%	91.67%	-	1	-	91.67%
SR (n = 89)	100%	63.16%	90.91%	100%	2.71	0	92.13%
ADNEX Model (n=40)	73.91%	94.12%	94.44%	72.73%	12.57	0.28	82.50%
SD + SR (n=101)	100%	60%	91.01%	100%	2.50	0	92.08%
SD + SR + ADNEX Model (n = 141)	94.23%	75.68%	91.59%	82.35%	3.87	0.08	89.36%

SD: simple descriptors. SR: simple rules. PPV: positive predictive value. NPV: negative predictive value. PLR: positive likelihood ratio. NLR: negative likelihood ratio.

applied to 89 of the residual masses that could not be classified with SD. Overall, the combination of SD and SR was able to characterize 71.6% of the masses. With SD and SR applied, the sensitivity, specificity, and accuracy were as follows: 100%, 60%, and 92,08%. When both SD and SR were inconclusive (28.4%), the masses were benign in 17 (42.5%) and malignant in 23 (57.5%) cases. When ADNEX model was used to characterize these 40 cases, there were 6 false negative and 1 false positive test results giving a sensitivity and specificity of 73.91% and 94.12%, respectively (**Table 3**).

DISCUSSION

This study aims to evaluate the accuracy of a three-step IOTA algorithm which has never been done before. In this study, all patients were subjected to histopathological examination so we eliminated verification bias.

We found that patients with malignant tumors were significantly older than those with benign tumors (40.7±14 Vs 47.6±13.6, p=0.009). This finding is in line with previous theories and literature. Ovarian cancer is a disease known to correlate with age and is often found in postmenopausal women. Ovarian cancer incidence is higher in women over 65 years of age. Previous studies stated that the median age at diagnosis is around 50-79 years [13,14]. In ovarian cancer, older age is associated with more advanced stages and a lower survival rate [13,15].

We found that the three-step IOTA algorithm has a really good sensitivity, but not as good specificity. The first and second steps of IOTA algorithm (simple descriptors and simple rules) have good sensitivity compared to the third step (100% and 100% Vs 73.91%). On the contrary, the third step of IOTA algorithm has better specificity (0% and 63.16% Vs 94.12%). In this study, the ADNEX model has a sensitivity of 73.91% and a specificity of 94.12% with a cut-off as high as 80%. This result is similar to a study by Viora et al. [11] that showed a sensitivity of 71.5% and specificity of 93.5% but with a lower cut-off than our study (50%). A meta-analysis conducted by Huang et al. [16] found that the pooled sensitivity and specificity for ADNEX model were 92% and 82% respectively. With this study, we proved that the ADNEX model has good diagnostic performance and therefore might be a reliable strategy for better classifying ovarian masses. Our study proved that the ADNEX model performance in a tertiary hospital where a variegated population is referred to from different backgrounds is comparable to the original study [17].

The results of our study could be influenced by the high prevalence of malignant tumors in the sample (73.76%). Since the samples come from a tertiary hospital which is also a referral center, these results can be influenced by the referral filter effect. By definition, prevalence does not influence sensitivity or specificity. Sensitivity is calculated in people who have the disease, while specificity is calculated in people without the disease. Therefore, changing the proportion of people with and without the disease studied should not lead to systematic differences. However, one study found a significant relationship between prevalence with both sensitivity and specificity. Specificity is inversely related to the prevalence rate, while sensitivity is directly proportional to the prevalence rate. The association with specificity was stronger than that of sensitivity. Prevalence can cause a reader expectation, if the examiner knows that the prevalence of the disease in

P-ISSN: 1978-3744 E-ISSN: 2355-6811

the subjects studied is higher, then the examiner's intrinsic threshold can be lowered so that more subjects will have positive results [6].

Limitations of this study include the relatively small sample and that all the data were collected from a single referral center with a high prevalence of malignant tumors, thereby allowing bias. A larger study with a more diverse sample is needed to further confirm the results of our study.

CONCLUSIONS

The three-step IOTA algorithm performs well in classifying adnexal masses as benign or malignant. We recommend the use of this three-step algorithm in adnexal masses screening. This algorithm may aid in triaging cases of ovarian tumors and assist in determining the appropriate management for each patient

DECLARATIONS

Competing interest

The authors declare no competing interest in this study.

Ethics Approval

This study was approved by Research Ethics Committee Hasan Sadikin Hospital, Bandung under the following registration number: LB.02.01/X.6.5/368/2020.

Acknowledgment

None.

REFERENCES

1. Curry SJ, Krist AH, Owens DK, et al. Screening for cervical cancer us preventive services task force recommendation statement. JAMA - J Am Med Assoc. American Medical Association; 2018 Aug 21;320(7):674–86.
2. Momenimovahed Z, Tiznobaik A, Taheri S, Salehiniya H. Ovarian cancer in the world: epidemiology and risk factors. Int J Womens Health. Dove Press; 2019;11:287.
3. Pusat Data dan Informasi Kementerian Kesehatan RI. Beban Kanker di Indonesia. 2019.
4. Westwood M, Ramaekers B, Lang S, et al. Risk scores to guide referral decisions for people with suspected ovarian cancer in secondary care: a systematic review and cost-effectiveness analysis. Health Technol Assess (Rockv). NIHR Journals Library; 2018 Aug 1;22(44):V–264.
5. American College of Obstetricians and Gynecologists Committee on Practice Bulletins. ACOG Practice Bulletin No. 83: Management of Adnexal Masses. Obstet Gynecol. 2007 Jul;110(1):201–14.
6. Sokalska A, Timmerman D, Testa AC, et al. Diagnostic accuracy of transvaginal ultrasound examination for assigning a specific diagnosis to adnexal masses. Ultrasound Obstet Gynecol. Ultrasound Obstet Gynecol; 2009 Oct;34(4):462–70.
7. Alcázar JL, Pascual MA, Graupera B, et al. External validation of IOTA simple descriptors and simple rules for classifying adnexal masses. Ultrasound Obstet Gynecol. 2016 Sep;48(3):397–402.
8. Timmerman D, Testa AC, Bourne T, et al. Simple ultrasound-based rules for the diagnosis of ovarian cancer. Ultrasound Obstet Gynecol. Ultrasound Obstet Gynecol; 2008 Jun;31(6):681–90.
9. Ameye L, Timmerman D, Valentin L, et al. Clinically oriented three-step strategy for assessment of adnexal pathology. Ultrasound Obstet Gynecol. 2012 Nov;40(5):582–91.
10. Sayasneh A, Kaijser J, Preisler J, et al. A multicenter prospective external validation of the diagnostic performance of IOTA simple descriptors and rules to characterize ovarian masses. Gynecol Oncol. 2013 Jul;130(1):140–6.
11. Viora E, Piovano E, Baima Poma C, et al. The ADNEX model to triage adnexal masses: An external validation study and comparison with the IOTA two-step strategy and subjective assessment by an experienced ultrasound operator. Eur J Obstet Gynecol Reprod Biol. 2020 Apr;247:207–11.
12. Gaurilcikas A, Gedgaudaite M, Cizauskas A, et al. Performance of the IOTA ADNEX Model on Selected Group of Patients with Borderline Ovarian Tumours. Medicina (B Aires). Multidisciplinary Digital Publishing Institute (MDPI); 2020 Dec 1;56(12):1–10.
13. Chan JK, Urban R, Cheung MK, et al. Ovarian cancer in younger vs older women: a population-based analysis. Br J Cancer. 2006 Nov 20;95(10):1314–20.
14. Zheng G, Yu H, Kanerva A, et al. Familial risks of ovarian cancer by age at diagnosis, proband type and histology. Akbari MR, editor. PLoS One. 2018 Oct 3;13(10):e0205000.
15. Poole EM, Merritt MA, Jordan SJ, et al. Hormonal and Reproductive Risk Factors for Epithelial Ovarian Cancer by Tumor Aggressiveness. Cancer Epidemiol Biomarkers Prev. 2013 Mar 1;22(3):429–37.
16. Huang X, Wang Z, Zhang M, Luo H. Diagnostic Accuracy of the ADNEX Model for Ovarian Cancer at the 15% Cut-Off Value: A Systematic Review and Meta-Analysis. Front Oncol. 2021 Jun 17;11.
17. Van Calster B, Van Hoorde K, Valentin L, et al. Evaluating the risk of ovarian cancer before surgery using the ADNEX model to differentiate between benign, borderline, early and advanced stage invasive, and secondary metastatic tumours: prospective multicentre diagnostic study. BMJ. 2014 Oct 15;349(oct07 3):g5920–g5920.