Assessment of Diagnostic Accuracy of IOTA - ADNEX model in Detecting the Risk of Malignancy in Ovarian Carcinomas

Abstract

Background : Ovarian cancer has become a major public health issue which stood in 10th rank of mortality within India. 2.4 % is the annual new cases of ovarian cancer in overall India. In 2008 it was the seventh leading cause of cancer deaths in women worldwide. 70% of cases are diagnosed with poor prognosis at an advanced stage. Ovarian malignancy death rate is of 70% within 2 yrs and 90% within five years. **I**t's a tough task for a gynecologist to identify ovarian cancer correctly .Ovarian malignancy is initially detected as adnexal mass. Exploratory laparotomy or laparoscopy with histopathology is a specific diagnostic procedure for adnexal mass. This study aims to study and analyse the diagnostic accuracy of IOTA - ADNEX model in detecting the risk of malignancy in ovarian carcinomas.

Objectives- To make pre-operative diagnosis of adnexal masses and conserve the in menstruating women with less aggressive management .

Methodology: This prospective study will be conducted in Obstetrics & Gynaecology department of AVBRH, Wardha from September 2020 to July 2022. This will be conducted on 50 females presenting with adnexal mass. Patients will undergo transvaginal ultrasonography with HERA W10 ultra sound system with an endovaginal EA2-11B probe. The ultra sound evaluation we will include IOTA –ADNEX Model. The mass with the most complex structure will be chosen for analysis for ultrasound imaging to know the chances of being malignant .

Expected results: Positive correlation between the IOTA –ADNEX model and histopathological report .

Conclusion: IOTA-ADNEX model to be incorporated for ovarian malignancy diagnostic protocol.

Keywords: IOTA-ADNEX model, Malignancy, Ovarian, Malignancy, Histopathology, Early Detection.

INTRODUCTION-

With more than 8,00,000 new cases occurring annually, cancer has become a major public health issue which stood in 10th rank of mortality within India (1). 2.4 % is the annual new

cases of ovarian cancer in overall India (2).In 2008 it was the seventh leading cause of cancer deaths in women worldwide (3).70% of cases are diagnosed with poor prognosis(4) at an advanced stage. Ovarian malignancy death rate is of 70% within 2 yrs and 90% within five years(5).

Till date researchers invented numerous screening methods however they have been ineffective(6) due to insufficient results. Because of its bizarre & nonspecific symptoms(7) its a tough task for a gynecologist to identify ovarian cancer correctly .Ovarian malignancy is initially detected as adnexal mass(5).

Exploratory laparotomy or laparoscopy with histopathology is a specific diagnostic procedure for adnexal mass .

Referral of such patients to Multidisciplinary Cancer team in a tertiary hospital with experienced gynecologic oncology surgeons to perform specialized surgical procedures to increase life span of the ovarian cancer patients by knowing high risk of malignancy in said mass.

In local hospitals, most women present with adnexal mass and nonspecific symptoms. Its important to ascertain is it necessary to perform a surgery and if if so its variant, pro's & con's of surgery in preoperative duration(8),(9),(10).Earlier information of ovarian tumour either it is malignant or benign will lead to appropriate management of patients(5) . Implementing a methodology for better preoperative pelvic mass evaluation will help more women obtain first-line treatment from efficiently trained and skilled staff. Unfortunately, there is no established population based screening program for the disease. (11),(12)For such referrals, sensitive and specific efficient techniques for diagnosis of an ovarian tumour are needed.(13)Various mathematical models, software programs and scoring systems, which depend on Serum Cancer antigen 125 ,ultrasonographic findings, Doppler MRI and Computerized tomography were suggested to attain better discrimination for malignant ovarian tumours.

Serum CA-125 , an ovarian cancer tumor marker where 85% of epithelial ovarian cancer has an evidence of rise of its concentration more than 35 U/ml with 83% sensitivity and 39.3% specificity only (10),(14).

Gynecologic ultrasonography (US) is a valuable tool to detect ovarian mass presence , distinguishing among benign and malignant tumors, establishing the ovarian tumors management plan (15).There are two primary explanations why using Ultra sonographic imaging are used to differentiate ovarian tumors from benign to malignant. The first accurate identification of tumors that are benign and malignant allows doctors to get an idea regarding plan of action : either medical or surgical management , method of surgery , open or minimally invasive or other extended researches , tumor marker & radio imaging like CT , or MRI (15). Next, among gynecological tumors ovarian cancer is not that prevalent , but it is a deadly illness with high levels of recurrence(15). The majority of the patients have an advanced stage survival rate of less than 30 percent for five years at the time of diagnosis. 92.4 % is average 5-year survival of early-stage cancer (15), therefore preliminary diagnosis by US increases the survival rate of a patient. This will give the most easiest follow-up or the most beneficial care in low expense to the patient .

For the differentiation of LR1, LR2(15) and simple rules(15) have been introduced by IOTA group since 2005 ,which reported that the diagnostic performance of these predictive models is superior than that of preexisting systems(15) . In 2014, a new better performance model was developed in this group (15) , namely -adnex (ADNEX) model in view of evaluation of adnex into different tumours .3 clinical features and six US are used in this model to suspect the probability of adnexal masses malignancy. With IOTA-ADNEX model , perceptive efficiency of ovarian tumors was greater to existing current models [27-28] through various external validation studies. However, in terms of characterizing ovary tumors, there have been few prospective studies weighing the differences of this model and gynecologic experts .

The ADNEX model was designed and validated with the information from the IOTA phase 1-3 datasets, comprising of prospectively gathered patients presenting with adnex mass who were referred for an ultrasonographic examination to one of the participating centers (16) .If a female presented with a minimum one adnexal mass which is a non-physiological cyst & been selected for surgical care by the managing clinician following local guide lines were eligible for inclusion criteria.

10% of cut-off value was the calculated specificity for differentiating ovarian tumors in accuracy of IOTA-ADNEX Model for its validation .For operable group it shows 0.816 (95% CI: 0.680–0.912) and 0.795 (95% CI: 0.647–0.902) with significant difference ($p = 0.005$ in all participants and $p = 0.017$ in operable group) (16) and S_N 0.9 (95% CI: 0.555–0.998) in all participants and the operable group. Later the accuracy of the ADNEX Model will be confirmed by the histopathology reports of that particular mass.

RATIONALE

This study is used to detect risk & differentiate among benign and malignant with IOTA-ADNEX Model and formulate management better prognosis depending on the type of tumour.

AIM AND OBJECTIVES

Aim-

To analyse diagnostic accuracy of IOTA - ADNEX model in detecting the risk of malignancy in ovarian carcinomas.

Objective-

- Pre-operative diagnosis of adnexal masses before surgery.
- To conserve the fertility by decreasing morbidity and mortality associated with adnexal pathology in menstruating women (in cases of borderline tumours and stage I cancer) with less aggressive management .

METHODS:

Study design: Cross sectional study

Setting: The study will be conducted in Department of Obstetrics & Gynaecology , Acharya Vinoba Bhave Hospital of Wardha district in Central Maharashtra, India for 2 years from September 2020 to July 2022 with approval of IEC . The hospital is the largest in the region and caters to the medical needs of the population residing in Wardha.
SAMPLE SIZE: 50 depending on **prevalence** of ovarian carcinoma in Wardha, India.
Sample size formula based on prevalence of ovarian carcinoma in India

$n=Z\alpha/2^2 .P(1-P)/d^2$
Where:
Zα/2 is the level of significance at 5% i.e 95%
Confidence interval =1.96
P= *Prevalence of ovarian carcinoma in Wardha=6.6%=0.066*
D=Desired error of margin =7%=0.07
$n=1.96^2$ x 0.066 x (1-0.059)/0.07^2
n=48.32

n= 50 patients needed in study

Participants:

Inclusion criteria

1.Females presenting with adnexal mass
2.Willing to take treatment
3.Willing for Trans Vaginal Ultrasonography
Exclusion criteria
1. Women who have already been diagnosed with malignancy and have received chemotherapy.
2. Those not giving consent.
3.Patients not willing for surgery within 120 days

METHODOLOGY
Firstly, the whole procedure is explained in their own language and written informed consent will be taken from the each patient presenting with the adnexal mass to the hospital. Peripheral venous blood will be sent to lab to measure CA-125 ,an ovarian tumour marker, which is a routine investigation sent for a adnexal mass patient. Then patient will undergo transvaginal ultrasonography with HERA W10 ultra sound system with an endovaginal EA2-11B probe . Here in ultra sound evaluation we will include IOTA –ADNEX Model which includes age, referral center , maximum diameter of adnexal lesion & largest solid part , no. of locules , acoustic shadows in the mass , presence of ascitic fluid & serum CA 125 levels**.** In case if a patient presents with several masses, the mass with the most complex structure will be chosen for analysis for ultrasound imaging to know the chances of being malignant .with all these parameters the ADNEX score is calculated. If there is more than one mass with identical morphology , the largest or the most widely accessible mass will be used.

IOTA-ADNEX MODEL

1. *Age of patient at examination(years)*

2. *Oncology center (referral center for gyn-oncol)? Yes or No*

3 . Maximal diameter of the LESION (mm)

4.Maximal diameter of the largest solid part (mm)

5 .More than 10 locules?

6 . No. of papillations (papillary projections)

7. Acoustic shadows present? Yes or No

8. Ascites (fluid outside pelvis) present ? Yes or No

9 .Serum CA-125 (U/ml)

The sonographic results are given in the graphical form with percentage as below and risk will be calculated as whether-
Chance of benign tumor
Risk of malignancy
Risk of border line
Risk stage I ovarian cancer
Risk stage II-IV ovarian cancer
Risk metastatic cancer to the adnex

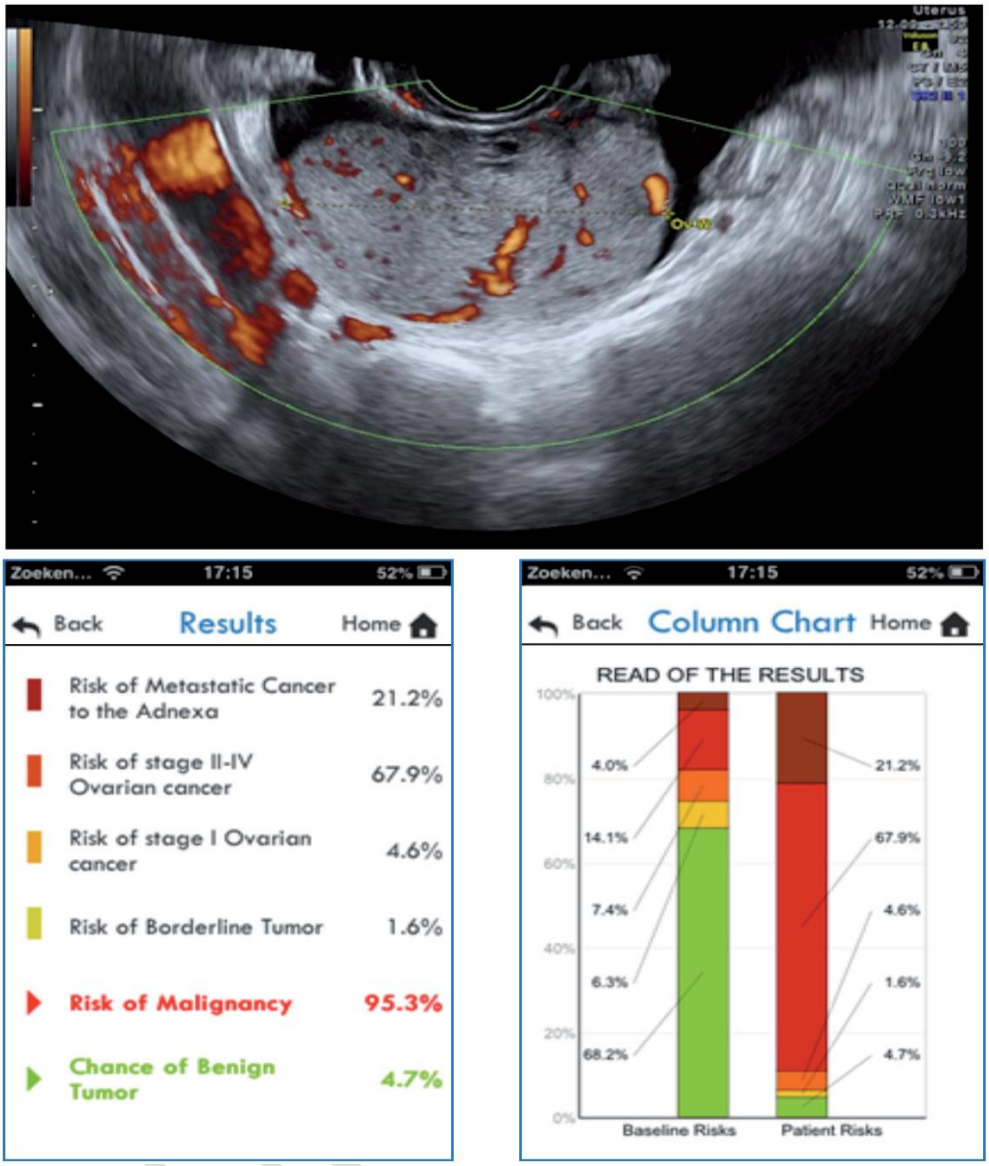

Fig.1: Example of graphical representation of IOTA-ADNEX MODEL TOOL

*The risk percentage will be given in terms of patient specific risk ,relative risk & baseline risk
*Based on the Two step clinical approach,if the patients specific risk of malignancy is less than 10% (cut off) it is considered as benign and if above 10% it is considered as malignant .
*Patient will be taken for surgery accordingly in case of both benign and malignant.
*Intra op findings of the mass to be noted to differentiate the specimen by its features and the specimen will be send to histopathology .
*After knowing the pathological diagnosis by histopathology report which is gold standard ,will be compared with the IOTA ADNEX MODEL tool's malignancy risk prediction , of the presenting mass calculated beforehand.

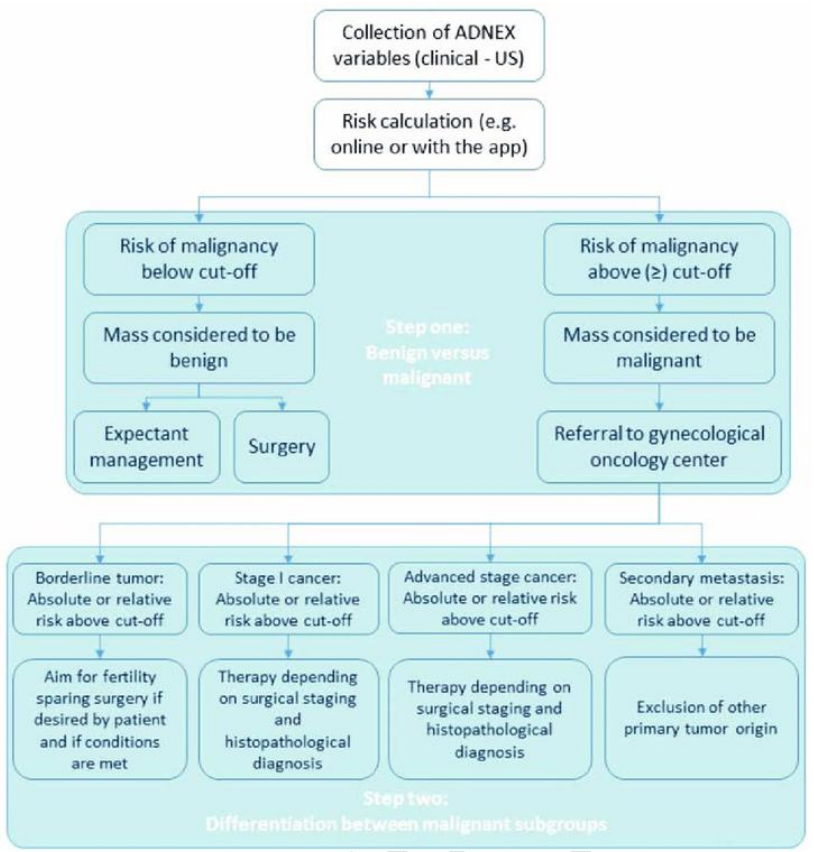

Fig.2: Flow chart showing 2 step model

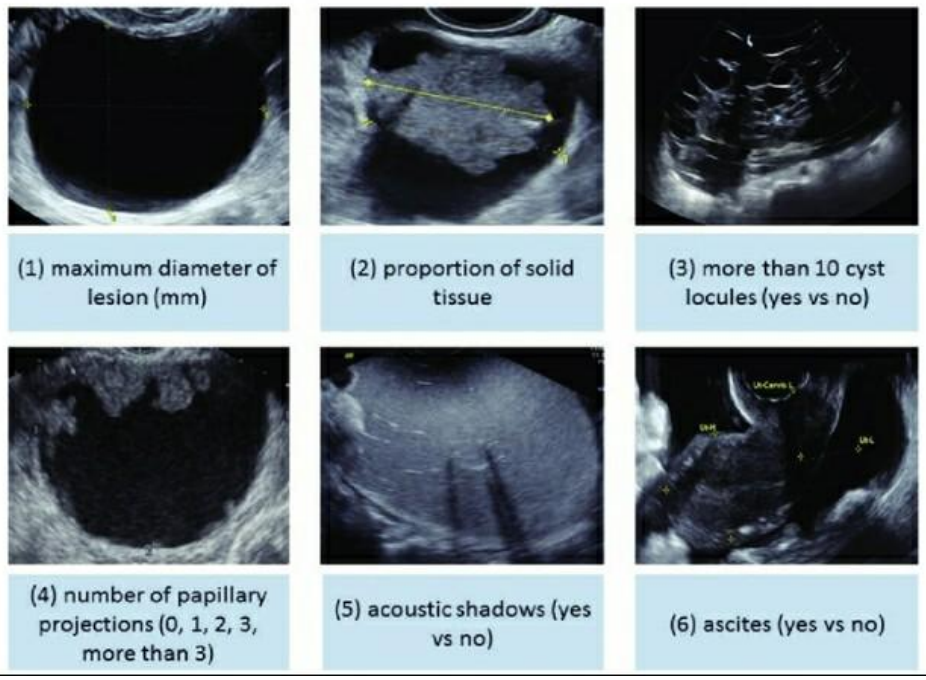

Fig. 3: Diagram showing the ultrasound parameters to be evaluated

Discussion:

With IOTA ADNEX model validation studies have attempted to find the ideal numerical value of malignancy risk . RMI is used in national guidelines of RCOG to differentiate ovarian tumors. RMI had lesser accuracy compared to mathematical models or SR or LR2, especially with low S_N in a recent review article, . Moreover, differentiating adnexal masses from benign and malignant subjective assessment is better than RMI or ROMA(15).

The benefit of usage of IOTA-ADNEX model in differentiating ovarian tumors has been concluded in various studies compared to different methods ,like subjective evaluation. High negative predictive value, without including malignancy with high accuracy was the typical outcome of the ADNEX model in diagnosis of ovarian tumor characteristics .In addition . ADNEX model has good distinguishing accuracy against other tumors for stage II-IV ovarian malignancies(15).

As a screening tool for epithelial ovary tumors Serum CA-125 has been used most commonly since 198. This tumor marker has comparatively low S_S as its value is raised in other benign conditions too. Several gynecologists use imaging studies, including Ultra Sound, CT, or MRI to address this constraint(15, 16). Above all, Ultrasonography is a primary imaging modality, and for those who have inconclusive Ultra sound results CT or MRI is a solution .Detailed analysis proven that sonography itself offers excellent outcomes of preoperative ovarian tumors and benign or borderline/malignancies characteristic assessment compared to other radiological imaging .

The research carried out by Uma Devi et al,2009, Current status of gynecological care in India . This study concluded , over 70% of patients report low survival and high mortality rates for diagnosis and management in disease late stages.

The study carried out by Shintre et al, 20017, Effectiveness of Risk of Malignancy Index to Differentiate benign from Malignant Ovarian Masses-A Cross Sectional Study .Of the 64 cases ,RMI is around 200 in 14 cases & are malignant and benign on HPR & <200 in 44 cases in which 1 case was HPR malignant . The S_N was 93.3 percent, 1-S_N was 87.7percent, Positive Predictive Value was 70percent, and Negative Predictive Value was 97.7percent .This study concluded that in most cases , it is successful to distinguish benign and malignant ovarian lesions. In selecting the cases for conservative treatment or minimal invasive surgery ,RMI is also an easy scoring method with greater precision and high 'potential. And thus in preoperative assessment of ovarian masses, it can be measure of preference.

***The study carried out by Irshad et al*,**2013, Accuracy of Risk of Malignancy Index in post-menopausal women's preoperative diagnosis of ovarian cancer .RMI was found to be have S_N of 91.3% ,S_S of 76.9% , PPV of 87.5% and NPV of 83.3% This study concluded that the index is a straight forward form scoring which can be used in bed side practices , ovarian mass evaluation before surgery .

The research conducted out by van Calster *et al.,*2015 Practical guidance for applying the ADNEX model from the IOTA group to discriminate between benign and malignant tumors of

adnexal masses .This study shows few example of adnexal mass patients and their distinction between benign and malignancy by using IOTA-ADNEX Model .

The study carried out by Jeong et al.,2020 Validation of IOTA-ADNEX Model in Discriminating Characteristics of Adnexal Masses: A Comparison with Subjective Assessment
Results: Fifty-nine participants were eligible: 54 underwent surgery and 5 underwent follow-up computed tomography (CT), respectively. 49 (83.1%) and 10 (16.9%) participants were identified to be benign and malignant. The S_S of the ADNEX model is 0.816 in all participants (95 percent CI: 0.680–0.912) and 0.795 for surgical group (95 percent CI, 0.647–0.902) .Area under ADNEX model (0.924) did not vary from with the subjective evaluation (ROC:0.953 ; p = 0.391 in all participants, ROC: 0.951 , ; p = 0.in the surgical group; p = 0.407 in surgical group). The optimal cut-off point using the ADNEX model was 47.3 percent , with a specificity of 0.977 (95% CI: 0.880–0.999). In exclusion of benign ovarian tumors IOTA-ADNEX model was equivalent with gynecologic US experts is concluded by this study. As a result gynecologic beginners can reduce unnecessary surgery being familiar with this US software.
A number of related articles were reviewed. Gupta et. al. studied correlation of ki-67 labeling index in cervical intraepithelial neoplasia (17). Other related studies were reviewed (18-23).

Conclusion:

In conclusion, IOTA-ADNEX model should be incorporated into the model for predicting the in-hospital mortality for ovarian malignancy .Considering its diagnostic accuracy might be relatively modest, further studies should validate the ultrasonography usefulness of adnexal masses.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

REFERENCES:

1. Devi K. Current status of gynecological cancer care in India. J Gynecol Oncol. 2009 Jun 1;20.

2. 9.pdf [Internet]. [cited 2020 Dec 3]. Available from: https://www.ijhsr.org/IJHSR_Vol.7_Issue.5_May2017/9.pdf

3. Meys EM, Rutten IJ, Kruitwagen RF, Slangen BF, Bergmans MG, Mertens HJ, et al. Investigating the performance and cost-effectiveness of the simple ultrasound-based rules compared to the risk of malignancy index in the diagnosis of ovarian cancer (SUBSONiC-study): protocol of a prospective multicenter cohort study in the Netherlands. BMC Cancer [Internet]. 2015 Jun 26 [cited 2020 Dec 4];15. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4489120/

4. Irshad F, Irshad M, Naz M, Ikram M. Accuracy of “risk of malignancy index” in the preoperative diagnosis of Zovarian malignancy in post menopausal women. Rawal Med J. 2013 Jan 1;38:266–70.

5. Torres JCC, Derchain SFM, Faundes A, Gontijo RC, Martinez EZ, Andrade LALA. Risk-of-malignancy index in preoperative evaluation of clinically restricted ovarian cancer. Sao Paulo Med J Rev Paul Med. 2002 May 2;120(3):72–6.

6. Cohen JG, White M, Cruz A, Farias-Eisner R. In 2014, can we do better than CA125 in the early detection of ovarian cancer? World J Biol Chem. 2014 Aug 26;5(3):286–300.

7. Park J-W. Four Risk of Malignancy Indices in Evaluation of Pelvic Masses. J Minim Invasive Gynecol. 2014 Nov 1;21(6):S192.

8. Tingulstad S, Hagen B, Skjeldestad FE, Halvorsen T, Nustad K, Onsrud M. The risk-of-malignancy index to evaluate potential ovarian cancers in local hospitals. Obstet Gynecol. 1999 Mar;93(3):448–52.

9. Kestane I, Senol T, Kahramanoglu I, Kestane D. The Use of Risk of Malignancy Index for Adnexal Masses. 2014;4(6):4.

10. Benjapibal M, Neungton C. Pre-operative prediction of serum CA125 level in women with ovarian masses. J Med Assoc Thail Chotmaihet Thangphaet. 2007 Oct;90(10):1986–91.

11. Bast RC, Skates S, Lokshin A, Moore RG. Differential diagnosis of a pelvic mass: improved algorithms and novel biomarkers. Int J Gynecol Cancer Off J Int Gynecol Cancer Soc. 2012 May;22 Suppl 1:S5-8.

12. Mohan L, Rao A, Ullal S, Krishna G. Accuracy of pelvic mass score in preoperative determination of malignancy in adnexal masses. J Clin Diagn Res. 2016 Nov 1;10(11):QC01–3.

13. Aktürk E, Karaca RE, Alanbay İ, Dede M, Karaşahin E, Yenen MC, et al. Comparison of four malignancy risk indices in the detection of malignant ovarian masses. J Gynecol Oncol. 2011 Sep;22(3):177–82.

14. Moolthiya W, Yuenyao P. The risk of malignancy index (RMI) in diagnosis of ovarian malignancy. Asian Pac J Cancer Prev APJCP. 2009;10(5):865–8.

15. jcm-09-02010.pdf(Review)- Adobe Document Cloud [Internet]. [cited 2020 Dec 3]. Available from: https://documentcloud.adobe.com/link/review?uri=urn:aaid:scds:US:001d3480-f42f-451c-a23f-4a49bc3c7c4b#pageNum=1

16. Van Calster B, Van Hoorde K, Froyman W, Kaijser J, Wynants L, Landolfo C, et al. Practical guidance for applying the ADNEX model from the IOTA group to discriminate between different subtypes of adnexal tumors. Facts Views Vis ObGyn. 2015;7(1):32–41.

17. Gupta, N., P. Dawande, S. Shukla, and A. Bhake. "Correlation of Ki-67 Labeling Index in Cervical Intraepithelial Neoplasia with Histomorphologic Grading System." *Journal of Datta Meghe Institute of Medical Sciences University* 14, no. 3 (2019): 162–65. https://doi.org/10.4103/jdmimsu.jdmimsu_44_19. 138.

18. Rashmi, S., S.N. Jajoo, and A. Belsare. "Assessment of Correlation between Clinical Examination and Investigations with Outcome in Cases of Abdominal Malignancy." International Journal of Pharmaceutical Research 11, no. 3 (2019): 1465–68. https://doi.org/10.31838/ijpr/2019.11.03.163.

19. Khatib MN, Gaidhane A, Gaidhane S, Quazi ZS. Ghrelin as a promising therapeutic option for cancer cachexia. Cellular Physiology and Biochemistry. 2018;48(5):2172–88. https://doi.org/10.1159/000492559

20. Manisha, S., N. Bagde, and D. Shrivastava. "Visual Inspection of Cervix with Acetic Acid: An Alternative to Cytology and Colposcopy in Early Screening of Cervical Cancer in Low-Resource Setup." Journal of Datta Meghe Institute of Medical Sciences University 12, no. 1 (2017): 32–34. https://doi.org/10.4103/jdmimsu.jdmimsu_19_17. 14.

21. Agarwal, A., N. Bhola, R. Kambala, and R.M. Borle. "Touch Imprint Cytology: Can It Serve as an Alternative to Frozen Section in Intraoperative Assessment of Cervical Metastasis in Oral Squamous Cell Carcinoma?" Journal of Oral and Maxillofacial Surgery 77, no. 5 (2019): 994–99. https://doi.org/10.1016/j.joms.2019.01.011.

22. Nagrale AV, Herd CR, Ganvir S, Ramteke G. Cyriax physiotherapy versus phonophoresis with supervised exercise in subjects with lateral epicondylalgia: a randomized clinical trial. Journal of Manual & Manipulative Therapy. 2009 Jul 1;17(3):171-8.

23. Bourne R, Steinmetz JD, Flaxman S, Briant PS, Taylor HR, Resnikoff S, Casson RJ, Abdoli A, Abu-Gharbieh E, Afshin A, Ahmadieh H. Trends in prevalence of blindness and distance and near vision impairment over 30 years: an analysis for the Global Burden of Disease Study. The Lancet Global Health. 2021 Feb 1;9(2):e130-43.