Risk of Ovarian Malignancy Algorithm (ROMA) Versus Risk of Malignancy Index (RMI) for prediction of malignancy in women presenting with Ovarian Tumours

Thesis

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IBS ..... Irritable Bowel Syndrome

ICON ..... International Collaborative Ovarian Neoplasm group

IDS ..... Interval Debulking Surgery

IOTA ..... International Ovarian Tumor Analysis group

LDH ..... Lactate Dehydrogenase

MRI ..... Magnetic Resonance Imaging

NICE ..... National Institute for Health & Clinical Excellence

PET ..... Positron Emission Tomography

PSM ..... Port Site Metastasis

RMI ..... Risk of Malignancy Index

ROC curve Receiver-operating characteristic curve

ROMA ..... Risk of Ovarian Malignancy Algorithm

SCST ..... Sex-Cord Stromal Tumors

SE ..... Standard Error

TAH BSO . Total Abdominal Hysterectomy Bilateral Salpingoopherectomy

WFDC ..... Whey acidic Four-Disulfide Core

WHO ..... World Health Organization

List of Abbreviations

ACOG ..... American College for Obstetricians & Gynecologists

AFP ..... Alpha Feto-protein

AUC ..... Area Under the Curve

BRCA1 ..... Breast Cancer susceptibility gene 1

BRCA2 ..... Breast Cancer susceptibility gene 2

CA125 ..... Cancer (or Carbohydrate) Antigen 125

CA19.9 ..... Cancer (or Carbohydrate) Antigen 19.9

CBC ..... Complete Blood Count

CEA ..... Carcino-Embryonic Antigen

CT ..... Computed Tomography

DHEAS ..... Dehydroepiandrosterone Sulphate

EOC ..... Epithelial Ovarian Cancer

FDA ..... Food & Drug Administration

FIGO ..... International Federation of Gynocology & Obstetrics

GOG ..... Gynecology Oncology Group

hCG ..... Human Chorionic Gonadotrophin

HE4 ..... Human Epididymis protein type 4

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Introduction

Ovarian cancer accounts for 3.7% of all cancers in women and is the seventh leading cause of cancer-related deaths among women worldwide ***(GLOBOCAN 2008)***. The outcome for women with ovarian cancer is generally poor, with an overall 5-year survival rate of less than 35%, due to the advanced stage at time of presentation ***(Rossing et al., 2010).***

Early prediction of malignancy in patients presenting with ovarian mass is very important;as mean survival time for women with ovarian malignancy is significantly improved when managed within a specialised gynaecological oncology service ***(Vernooij et al., 2007)***.

Different tools have been used for prediction of malignancy in ovarian masses; such as tumor markers, ultrasound findings, or other malignancy indices combining more than one variable. CA-125 is the most frequently used biomarker for ovarian cancer detection ***(Suh et al., 2010)***. The major limitation of CA125 is that it may be high in benign diseases, such as endometriosis, ovarian cysts, and pelvic inflammatory diseases ***(Yamamoto et al., 2009)***. In 1990, ***Jacobs et al.*** originally developed the Risk of Malignancy Index (RMI)as a simple scoring method based on menopausal status, ultrasound findings, and the serum CA125 level; giving

significantly better results than the use of a single parameter. Recently, the HE4 protein was suggested as predictor for ovarian cancers, especially elevated in serous and endometrioid histology ***(Hellstrom et al., 2003; Galgano et al., 2006; Huhtinen et al., 2009).*** Studies suggest that HE4 has a similar sensitivity to CA 125, but an increased specificity ***(Escudero et al., 2011; Anastasi et al., 2010).*** In subsequent study, the combination of HE4 and CA125 was a more accurate predictor of malignancy than either marker alone ***(Moore et al., 2008)***. The combination of these two markers; the Risk of Ovarian Malignancy Algorithm (ROMA) was first used by Moore et al, together with the menopausal state accurately classifies women with ovarian masses into high and low risk for ovarian malignancy ***(Moore et al., 2009)***.

The aim of this study is to compare the performance of ROMA versus that of RMI in predicting malignant ovarian masses.

Aim of the Work

The aim of this study is to compare the performance of Risk of Ovarian Malignancy Algorithm (ROMA) versus that of Risk of Malignancy Index (RMI) in predicting malignant ovarian masses.

Chapter One
Management of Ovarian Cancer

Overview:

Ovarian cancer accounts for 3.7% of all cancers in women and is the seventh leading cause of cancer-related deaths among women worldwide ***(GLOBOCAN 2008)***. In the United States, ovarian cancer is the 5th leading cause of cancer-related deaths among women ***(Siegel et al., 2013)***. The outcome for women with ovarian cancer is generally poor, with an overall 5-year survival rate of less than 35%, due to the advanced stage at time of presentation ***(Rossing et al., 2010).***

The symptoms of ovarian cancer are usually non-specific; however, there are a number of symptoms that do suggest ovarian cancer if they are experienced frequently and/or last a long time ***(Goff et al., 2012).***

Women presenting with ovarian mass need to be triaged into either benign or malignant cases ***(Canis et al., 2000).*** The underlying management rationale is to minimise patient morbidity by ***(Green-top guideline 62)****:*

- Conservative management where possible

- Use of laparoscopic techniques where appropriate, thus avoiding laparotomy where possible
- Referral to a gynaecological oncologist where appropriate.

Mean survival time for women with ovarian malignancy is significantly improved when managed within a specialised gynaecological oncology service; that's why early diagnosis and referral is important ***(Vernooij et al., 2007)***.

Risk Factors:

Numerous reproductive, environmental, and genetic risk factors have been associated with the development of ovarian cancer.

An important risk factor for **epithelial ovarian cancer** is a family history of the disease; with at least one first degree relative with ovarian cancer ***(Stratton et al., 1998)***. It should be mentioned, however, that familial ovarian cancers make up a relatively small proportion of total ovarian cancer cases with only 5% to 10% of ovarian cancer patients report having a positive family history of the disease ***(Berchuck et al., 1999).***

Ovarian cancer has been associated with familial autosomal dominant syndromes; the commonest are BRCA1 & BRCA2 mutation syndromes ***(Schorge et al., 2008; Van Nagell et al., 2008)***. Others include: *Lynch syndrome type II;* characterized by a predominance of early-onset proximal colon cancer in association with cancers of the endometrium and ovary ***(Lindor et al., 2008)***.

The overall incidence of ovarian cancer rises with **increasing age** up to the mid-70s before declining slightly among women beyond 80 years ***(Goodman et al., 2003).***

Nulliparity is associated with long periods of repetitive ovulation, and women without children have double the risk of