TECHBRIEF

HORIZON SCANNING REPORT

Risk of Ovarian Cancer Algorithm (ROCA) Using Serial CA 125

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TechBrief

RISK OF OVARIAN CANCER ALGORITHM (ROCA) USING SERIAL CA 125

INTRODUCTION

Ovarian cancer is the seventh most common cancer in women worldwide (18 most common cancer overall), with 239,000 new cases diagnosed in 2012.[1] In United States of America (USA), the 5-year relative survival for all types of ovarian cancer is 45%.[2] Similar survival rate is observed in United Kingdom (UK). Women diagnosed when they are younger than 65 do better than older women. If ovarian cancer is found (and treated) before the cancer has spread outside the ovary (stages IA and IB), the 5-year relative survival rate is 92%. However, only 15% of all ovarian cancers are found at this early stage.[2]

In Malaysia, ovarian cancer is the 4th most common cancer reported among Malaysian female. There were 658 cases diagnosed in 2007 giving age-standardised rate of 7.8. About 48% were diagnosed at stage I and II.[3]

One approach to early detection of ovarian cancer is to screen women at risk for the disease before the onset of symptoms. Several methods of screening for ovarian cancer have been investigated, including transvaginal sonography (TVS) and serum CA-125.

The United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS), a randomised controlled trial of more than 200,000 women was started in 2001 to assess the Risk of Ovarian Cancer Algorithm (ROCA) as a screening tool to improve the yield of ovarian screening.

THE TECHNOLOGY

The Risk of Ovarian Cancer Algorithm also known as ROCA is used in the UKCTOCS. The algorithm incorporates a woman's age, her serum CA125 value (and changes in this value over time), and a pelvic ultrasound in selected women deemed to be high risk. Two screening tests were used. The first was measurement of serum CA125. The other screening test was transvaginal ultrasound or where this was not acceptable to a participant, transabdominal scan of the pelvis was performed.[4]

Level 1

In the Level 1 screen, women underwent venepuncture and serum CA125 measurement. The assay results were uploaded directly into the trial management system which calculated the risk of ovarian cancer.

Possible outcomes:

- Normal risk of ovarian cancer score: women returned to annual screening
- Intermediate risk of ovarian cancer score: women were recalled for a repeat CA-125 in 12 weeks after the screen. The risk is recalculated and triaged as Level 1 screen. Any women whose risk of ovarian cancer remained intermediate after three CA125 tests were referred for a Level 2 screen

- Elevated risk of ovarian cancer score: women were recalled for a level 2 screen in 6-8 weeks with earlier screens arranged where there was a high index of suspicion

Level 2

Level 2 screening involved venepuncture for repeat CA125 assay and a transvaginal ultrasound scan (TVS). The results of the Level 2 triggered three possible courses of action as below:

- Women with normal TVS and normal or intermediate risk of ovarian cancer returned to annual screening,
- Women with normal TVS but an elevated risk of ovarian cancer or an unsatisfactory scan irrespective of risk, underwent repeat level 2 screen in 6 weeks and were triaged again in the basis of the results to annual screening or clinical assessment.
- Women with abnormal TVS were referred for clinical assessment, irrespective of their risk of ovarian cancer status

Clinical assessment was undertaken by a designated clinician and include clinical evaluation and investigations as appropriate. Women with a risk of ovarian cancer (ROC) of more than 1 in 5 (severe risk) were recommended to have surgery irrespective of scan findings.[4, 5]

PATIENT GROUP AND INDICATION

Post –menopausal women aged between 50 to 74 years old.

CURRENT PRACTICE

Currently there is no screening test reliable enough to be used to pick up ovarian cancer at an early stage. The two tests that have been evaluated most extensively were CA 125 and transvaginal ultrasound (TVS).

CA125

CA125 is a high molecular weight, well surface glycoprotein which is encoded in MUC 16 gene. Serum CA125 is measured by radioimmunoassay, and is highly reproducible with minimal intra-assay variability. CA125 results ≥ 35 U/mL is considered as abnormal.[6]

Elevated concentrations can occur in healthy premenopausal women during menses, in pregnancy, in non-malignant gynaecologic diseases and uterine leiomyoma. High serum concentrations may also occur in several non-malignant non-gynaecologic diseases, such as peritoneal, pleural, and musculoskeletal inflammatory disorders as well as pelvic inflammatory diseases. Additionally elevated concentrations may also occur in most type of adenocarcinomas.[7]

In women with ovarian cancer, only 80% have raised CA125 and only 50% of women with early stage of ovarian cancer have raised CA125.[6, 7]

TVS

TVS using a 5- to 7.5-mHz vaginal probe to generate images of the ovary was initially reported as a method for ovarian cancer screening by Higgins.[6] It gives better picture of the ovary, however, there was no clear evidence that TVS can pick up cancer early.

There was good evidence to indicate that screening for ovarian cancer with single threshold serum marker CA-125 and TVU

does not result in a decrease in ovarian cancer mortality, after a median follow-up of 12.4 years.[8]

EFFICACY AND SAFETY

The UKTOCS study was carried out since 2001 involving 202,638 post-menopausal women from 13 regional trial centres within National Health Service Trusts in England, Wales and Northern Ireland.[4, 5] The aim of the RCT was to provide definitive data on the effect of ovarian cancer screening on mortality, as well as comprehensively addressing the cost, acceptance, physical and psychosocial morbidity and performance characteristics of multimodal screening (MMS) and ultrasound-based screening (USS).[4]

The subjects were randomised to three groups; MMS, USS and controls (no screening). The mean follow up was 14 years.[5]

A prospective single arm study was carried out in the United States of America from 2001 until 2011 to evaluate ROCA. A total of 4051 participants with a total number of screen years of 16,832 years were included.[9]

Efficacy

Sensitivity and specificity

In the UKTOCS study, the combined methods showed 82.8% (95%CI 76.6,87.9) sensitivity and 99.8% (95%CI 99.8,99.9) specificity for ovarian and fallopian tube cancers. As for invasive epithelial ovarian, tubal and primary peritoneal malignancies, the sensitivity was 85.8% (95%CI 79.3,90.9) and the specificity was 99.8% (95% CI 99.8,99.8).[5]

In the prospective single arm study, of 117 women who were triage to undergo a TVS and referral to a gynecologic oncologist, 82 women had a normal TVS, 11 had benign ovarian findings, 10 had suspicious ovarian findings, and 14 did not have a TVS done (4 had recurrence of a previously diagnosed cancer, six patients declined, one patient was unable to undergo TVS due to vaginal stenosis but had transabdominal ultrasound, in three women, TVS were not performed based on judgement of the physician.[9]

All 10 patients with suspicious ovarian findings on TVS underwent surgery. Three patients had benign cystadenomas, two patients had stage 1 ovarian serous tumours of low malignant potential (LMP), four patients had early-stage high grade invasive ovarian cancers and one patient was ultimately found to have endometrial cancer, providing a positive predictive value of 40% (95% CI 12.2%, 73.8%). The specificity was 99.9% (95% CI 99.7, 100%).[9]

Mortality

The follow up of UKTOCS study ended on 31 December 2014. The mortality outcome was analysed and published in March 2016. The final cohort eligible for analysis consisted of 202,546 (>99.9%). Of the 3310 women investigated, 1282 (41%) women were confirmed on outcomes review to have ovarian cancers. Of the primary peritoneal cancers, 81% (13 of 16) were screen detected with MMS and 30% were with USS. A higher proportion of invasive epithelial ovaries and peritoneal cancer diagnosed with low volume disease (Stage I, II and IIIa) in the MMS group (119 [40%] of 229; p<0.0001) than in the no screening group (149 [26%] of 574) but not in the USS group (62 [24%] of 259; p=0.57).[10]

About 649 (0.32% women had died of ovarian cancer; 347 (0.34%) in the no screening group, 148 (0.29%) in the MMS group, and 154 (0.30%) in the USS group. The mortality reduction over years 0-14 with the Cox model was 15% (95% CI -3, 30) in the MMS group and 11% (95%CI -7, 27) in the USS group. Further analysis showed that in the MMS group, the mortality effect was made up of 8% (95% CI -20, 31) in years 0 - 7 and 23% (95% CI 1, 46) in years 7 – 14 and in the USS group, 2% (95% CI -27, 26) in years 0 - 7 and 21% (95% CI -2, 42) in years 7 – 14. The data was re-analysed by excluding prevalent cases which comprised of 63 cases (19%) from 338 cases in MMS group and 116 cases (18%) from 630 cases in the no screening group. The mortality reduction was increased (p=0.021) with an average reduction of 20% (95% CI -2, 40) and a reduction of 8% (-27, 43) in years 0 – 7 and 28% (95% CI -3, 49) in years 7 – 14 in favour of MMS. At censorship with a maximum follow-up of 13.6 years, the preliminary number needed to screen to prevent one death from ovarian cancer was 641 (95% CI 375, 1934).[10]

An analysis was carried out to ascertain whether the use of ROCA could have favourably affected the outcome of Prostate, Lung, Colorectal and Ovarian (PLCO) trial. The trial reported no mortality benefit of annual screening with CA 125 and TVS. Best case and stage shift scenario using ROCA was used, however the results showed no significant changes in the mortality with RR of 0.90(95% CI 0.69, 1.17) and 0.95 (95% CI 0.74, 1.23) respectively.[11]

Safety

The ROCA test is currently being produced by Abcodia. It has received CE marked and is available in the private healthcare market in the U.K. and in selected U.S. markets.

Psychological impact

The psychological sequelae associated with abnormal screening was evaluated in the UKTOCS.[12] About 91.6% (185,693/201,638) women participated in the psychological substudy. All women completed questionnaires prior to randomisation. Women in MMS and USS groups with abnormal results after annual screening were sent psychological questionnaires (Spielberger State/trait Anxiety Inventory (STAI) and the General Health Questionnaire 12 (GHQ-12)) following each abnormal screening and thereafter annually, during their time in the study (for a maximum of seven years). Women from MMS and USS groups who experienced any abnormal screens formed the event sample (ES), n= 24,743. Women from each group were randomly selected to be followed up for the whole of their time in study formed the random sample group (RS), n=1455. The results showed that screening did not raise anxiety but psychological morbidity was elevated by more intense repeat testing following abnormal annual screens and in women after surgical treatment of ovarian cancer at both six weeks (OR 16.2, 95% CI 9.19, 28.54) and six months following surgery (OR 3.32, 95%CI 1.91, 5.77).[12]

Psychosocial factors associated with withdrawal from the UKTOCS after one episode of repeat screening were evaluated. About 16% of women requiring a repeat screening test in addition to annual screening withdrew from the study. The percentage of withdrawal was 12.9% (1560/1273) in MMS group and 20.1% (1939/9660) in USS group. The estimated relative risk of withdrawal was 1.46 (95% CI 1.36, 1.56) for the USS vs MMS arm. High anxiety

trait and increased psychological morbidity significantly influenced withdrawal even when age, screening centre and the group were taken into account. The risk of withdrawal, decreased significantly the longer the woman stayed in UKCTOCS, irrespective of the number of screens and intensity in the preceding year.[13]

False positive screening and unnecessary surgery

Benign adnexal pathology or normal adnexa was noted in 488 (1.0%) women in the MMS group and 1634 (3.2%) women in the USS group who had screen positive surgery. This translated to 14 false positive surgeries per 10,000 screens in the MMS group and 50 false positive surgeries per 10,000 screens in the USS group.

ESTIMATED COST

The cost of a single CA125 test ranged from RM25 – RM50. As for pelvic ultrasound the cost ranged from RM150 - RM300. As ROCA is currently distributed by Abcodia, the package of test in UK is approximately £150.

The cost-effectiveness study on ROCA is not available yet. However, Havrilesky et al. has developed an ovarian cancer natural history model which incorporated disease heterogeneity published in 2011. Data from UKTOCS has been used to validate the model. The analysis suggested that reductions in ovarian cancer mortality using available screening technologies on an annual basis are likely to be modest.[14]

ORGANIZATIONAL ISSUES

In order for a screening to be effective, it needs a clear pathway for all procedures required. A clear referral system should be in place before it is being implemented.

In this screening program, serial CA125 measurement is required, the laboratory has to be ready to cope with the workload. As for TVS, currently it is available in some health clinics and at Obstetric and Gynecology Clinic in the hospitals.

There may be some issues on the acceptability of TVS. Patients should be explained clearly on the procedure, before alternative transabdominal ultrasound is perform.

POTENTIAL IMPACT

ROCA uses serial CA125 measurements to measure change over time to obtain a better picture of the individual's risk of developing ovarian cancer.

The long term study showed good sensitivity and specificity. The initial mortality result is promising, however, more data is required to ensure the actual impact of the screening method. In terms of safety, psychological morbidity may be elevated by more intense repeat testing following abnormal annual screens and in women after surgical treatment of ovarian cancer. The false positive surgeries due to ROCA are less compared to the USS.

Cost effectiveness study is required to ensure the value of this screening method .

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