Regional study into the performance and cost-effectiveness of simple ultrasound-based rules compared to the currently used Risk of Malignancy Index (RMI) in the diagnosis of ovarian cancer.

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This study is performed to compare the diagnostic performance and cost-effectiveness of different methods in the preoperative characterization of ovarian masses: RMI compared toa) simple ultrasound-based rules as a first step test and subjective...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Reproductive neoplasms female malignant and unspecified
Study type	Observational invasive

Summary

ID

NL-OMON41648

Source
ToetsingOnline

Brief title
Simple Ultrasound Based ruleS to differentiate OvariaN Cysts (SUBSONiC).

Condition

- Reproductive neoplasms female malignant and unspecified
- Ovarian and fallopian tube disorders

Synonym
ovarian cancer, ovarian carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Diagnosis, Ovarian cancer, Risk of Malignancy Index, Ultrasound

Outcome measures

Primary outcome

The main study parameters are:

1. Sensitivity;

2. Specificity;

3. Positive and negative predictive values; and

3. Positive and negative likelihood ratios

for the correct differentiation between malignant and benign adnexal masses.

The diagnosis is based on histology (gold standard) and, in case of a

malignancy, the surgical stage.

Based on the results of these study parameters a cost-effectiveness and budget

impact analysis will be performed.

Secondary outcome

Not applicable.

Study description

Background summary

Ovarian cancer is the second most common gynecologic malignancy and in 2008 it

was the seventh leading cause of cancer deaths in women worldwide.
The success of treatment depends on early diagnosis. However in an early stage ovarian cancer does not cause many symptoms and therefore approximately two-thirds of the patients are diagnosed in International Federation of Gynecology and Obstetrics (FIGO) Stage III-IV. Patients diagnosed in FIGO stage I-IIb have a five-year survival of 75-100%, while patients diagnosed in a higher stadium, FIGO stage III or IV, have a five-year survival of only 20-60%. The diagnostic evaluation of woman with an adnexal mass consists of a thorough anamnesis and physical examination followed by ultrasound imaging and laboratory studies for tumor markers. However, the definitive diagnosis can only be made by histopathological diagnosis of the mass following surgery.

Estimating the risk of malignancy is essential in the management of adnexal masses. In case of malignancy comprehensive surgical staging and cytoreductive (debulking) surgery is necessary and patients should be treated by a gynecologic oncologist in order to get optimal surgical management which is associated with a better median survival. However, when a malignancy is not suspected, in clinical practice the mass can be managed conservatively or with laparoscopy, if the mass is not too big. This will limit the morbidity and will avoid unnecessary costs: laparoscopic staging offers lower estimated blood loss, shorter hospital stay, and fewer postoperative complications with an improved quality of life and faster return of normal functioning. Because of these advantages of laparoscopy over laparotomy overtreatment will take place when a benign mass is mistaken for a malignant mass. Consequently, the morbidity, fear and cost price will increase. On the other hand, if a malignant mass is not identified as such and is treated as a benign mass, a laparoscopy can induce spillage of cyst fluid, which will deteriorate the prognosis of the patient.

There are several methods to distinguish benign from malignant adnexal masses. The commonly most used method in clinical practice is the Risk of Malignancy Index (RMI). The RMI is a scoring system that is recommended by many national guidelines in the differential diagnosis of ovarian masses, including the national guideline in the Netherlands. The advantage of the RMI is that it is easy to use, because of its simplicity. This scoring system combines serum CA125, ultrasound and menopausal status into an index score used to predict the risk of ovarian cancer before surgery. In clinical practice a cut-off value of 200 is usually used to determine if one has a high risk of having ovarian cancer.
The formula of this scoring system is U x M x serum CA125, where U is the ultrasound score, M is the menopausal status of the patient (premenopausal or postmenopausal) and the level of serum CA125 is measured in U/ml. The ultrasound score is based on five characteristics; multilocular cyst, evidence of solid areas, evidence of metastases, presence of ascites, and bilateral lesions. There are three different RMI formulas (RMI-I, RMI-II, and RMI-III) that differ according to the points attributed to the different ultrasound variables and the menopausal status of the patient. In the Netherlands RMI-III

is the algorithm of choice to differentiate between benign and malignant disease. The reported sensitivity and specificity of RMI at a cut-off value of 200 are 75-80% and 85-90%, respectively.

Recently, another method was proposed to distinguish benign from malignant adnexal masses by only using the morphological features of the mass. This method is called *simple ultrasound-based rules* (simple rules) and uses different morphological ultrasound features of adnexal masses (without including menopausal status or serum CA125 measurement). This method was described by Timmerman et al. (2008) in order to derive simple and clinically useful ultrasound-based rules to discriminate between benign and malignant adnexal masses. Ten simple rules that have high sensitivity and specificity and are applicable to a large number of tumors have been chosen; five simple ultrasound-based rules to predict malignancy (M-rules) and five rules to predict a benign tumor (B-rules).
If one or more M-rules are met and none of the B-rules, the mass is classified as malignant. On the other hand, if one or more B-rules are met in the absence of M-rules, the mass is classified as benign. If both or none of the M- and B-rules are met the test is inconclusive. This is the case in about 20% of the patients. Recent reports show that simple ultrasound based rules might be superior to the RMI.

In adnexal masses for which the simple ultrasound rules yield an inconclusive result, subjective assessment of Gray-scale and color Doppler ultrasound images by an experienced ultrasound examiner can be used as a second stage test to achieve an optimal diagnostic performance. This subjective assessment is also called *pattern recognition*. The downside of subjective assessment is that it is experience dependent: the more experienced the ultrasound examiner the better subjective assessment will work.
Nevertheless, subjective assessment by experienced examiners is generally expected to be the best way to classify adnexal masses prior to surgery. Several reports have demonstrated that subjective assessment is superior to the use of scoring systems and mathematical models, such as the Risk of Malignancy Index or simple ultrasound based rules, when classifying adnexal masses as benign or malignant. Unfortunately, the expertise of experienced ultrasound examiners is not easily transferred to less experienced examiners. This is why many national guidelines concerning the management of ovarian masses still advocate the use of the RMI in the classification of adnexal masses and therefore the RMI is still the most commonly used model in clinical practice. This problem could be circumvented by using subjective assessment in a two-stage test, where simple rules are used as a first stage test and subjective assessment as a second stage test for the diagnosis in difficult cases.

Another option is to use Diffusion Weighted - Magnetic Resonance Imaging (DW-MRI) as a second stage test, when the simple rules yield an inconclusive result. The test holds as an advantage that a full body MRI can not only

distinguish a benign from a malignant mass, but can also detect possible metastasis in case of a malignancy. Furthermore, MRI can be used for the detection of inoperable tumors and therefore help to select patients who might be more appropriately managed by neoadjuvant chemotherapy. The use of MRI - when interpret by specialized radiologists- also seems to be superior to RMI in the preoperative identification of adnexal masses.

Rationale
The objective of this study is to test the hypothesis that the simple rules supplemented -if necessary- with either subjective assessment by an expert sonographer or DW-MRI, will give better diagnostic accuracy and cost-effectiveness than the RMI and therefore will improve the management of women with adnexal masses. Furthermore, we estimate that the two-step triage test has a potential cost saving effect of approximately ¤ 1,3 million a year in The Netherlands.
Since the RMI is now widely used, any result in favor of the triage test has the potential to alter future clinical practice. The information gained with this study can be used to update or construct new national and international guidelines.
Since in different hospitals different levels of expertise are present for either ultrasound or DW-MRI, the decision was made to compare both subjective assessment by an expert sonographer and DW-MRI with the current standard (RMI). In the event of a positive study (difference in accuracy to the disadvantage of the RMI), either simple rules in combination with subjective assessment, or simple rules in combination with DW-MRI can be used depending on the expertise present in each hospital or region.

Study objective

This study is performed to compare the diagnostic performance and cost-effectiveness of different methods in the preoperative characterization of ovarian masses: RMI compared to
a) simple ultrasound-based rules as a first step test and subjective assessment by an experience ultrasound examiner in those cases the simple rules yield an inconclusive result; and
b) simple ultrasound-based rules as a first step test and DW-MRI in those cases the simple rules yield an inconclusive result.

Secondary Objective(s):
• To perform a subgroup-analysis for premenopausal and postmenopausal women for the above mentioned comparisons;
• To perform a subgroup-analysis to compare the diagnostic accuracy of subjective assessment by an experience ultrasound examiner and DW-MRI for those cases where the simple ultrasound-based rules were inconclusive.
• To assess interobserver-agreement in the interpretation of Simple Rules between the primary ultrasound and the expert ultrasound.
• To assess interobserver-agreement in the subjective assessment between the

primary ultrasound and the expert ultrasound.
• To assess interobserver-agreement in the interpretation of DW-MRI images between radiologists.
• To perform translational research and validate new biomarkers in the diagnosis of ovarian cancer.

Study design

A prospective multicenter cohort study.

Study burden and risks

The burden of patients participating in the study is very low. About 80% of all patients (in which the simple rules are sufficient for making the diagnosis) do not have to undergo additional tests, neither are any other additional actions taken.
About 20% of all participants (in which the simple rules yield an inconclusive result) will be asked to visit the MUMC+ for either a DW-MRI (patients included in Maastricht) or both an extra ultrasound performed by an expert and a DW-MRI (all other patients). These participants will also be asked to give a blood sample. The extra time spent by this group of participants is minimal (approximately 2.5 hours plus time needed to travel to Maastricht) .

The risks of participation are negligible.
Risks of venipuncture are hematoma, pain, bleeding, and in immune compromised patients there is a very small risk of infection.
Risks of an DW-MRI are claustrophobia and self inflicted injuries due to this claustrophobia, bleeding or burns in case of presence of metal objects, dizziness and balance disorders.

In summary, the burden and risks of participation are very small.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Female patients;
Diagnosed in one of the participating centers with at least one pelvic mass that is suspected to be of ovarian origin;
Patients who are to undergo surgery in order to obtain a final histological diagnosis;
Patients are 18 years of age or older.

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
• Pregnant patients;
• Patients aged under 18 years;
• Patients in whom the surgery does not take place, or takes place more than 120 days after RMI and simple ultrasound-based rules are performed;
• Patients with a prior bilateral oophorectomy (removal of both ovaries);
• Patients with insufficient or missing data;
• Patients who do not give or are incapable of giving an informed consent;
• Patients who are not able or willing to travel to the center hospital (MUMC+ at Maastricht) for additional diagnostic procedures.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	24-10-2014
Enrollment:	270
Type:	Actual

Ethics review

Approved WMO Date:	02-07-2014
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO Date:	05-09-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL44181.068.13

Study results

Date completed: 05-10-2015

Actual enrolment: 55

Summary results
Trial ended prematurely