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Short Title: RCT of two management protocols for asymptomatic adnexal tumours

A randomised controlled trial comparing surgical intervention rates between two protocols for the management of asymptomatic adnexal tumours in postmenopausal women: A study protocol

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Abstract

Introduction:
Detection of asymptomatic adnexal tumours in postmenopausal women has increased due to wider use of diagnostic ultrasound and imaging quality improvements. Reliable methods to differentiate between benign and malignant tumours are required to avoid delays in treating ovarian cancer and to prevent unnecessary interventions for benign lesions. In the UK the Royal College of Obstetricians and Gynaecologists (RCOG) has issued guidance for the management of adnexal cysts in postmenopausal women, which is considered standard in routine clinical practice. The protocol uses the Risk of Malignancy Index (RMI) calculation. This protocol has a relatively high intervention rate in order to avoid a delay in a cancer diagnosis. The Simple Rules Protocol designed by International Ovarian Tumour Analysis Group (IOTA) reports a low false positive rate in the diagnosis of ovarian cancer without a loss of sensitivity and therefore has the potential to reduce unnecessary interventions in asymptomatic postmenopausal women with benign cysts.

Methods and analysis:
140 postmenopausal women aged 40-80, with incidentally detected adnexal tumours on ultrasound scan will be recruited to this study. They will be randomly allocated, to be assessed and managed according to either of the two protocols under investigation. In both arms of the study the tumours will be classified into three groups: high, intermediate or low risk of malignancy. Women with high risk of malignancy will be referred for surgery in a tertiary cancer centre, women with low risk tumours will be managed expectantly, whilst those with intermediate risk findings will be operated on in their local hospital units. Analysis will be on an intention to treat basis.

Ethics and dissemination:

Research ethical approval was granted by the North London Research Ethical Committee 2 (10/H0724/48). Trial results will be published according to the CONSORT statement.

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Adnexal tumours, Ovarian cysts, Postmenopausal, RMI, RCOG, IOTA Simple Rules, Management protocols

Introduction

Wider and more liberal use of diagnostic ultrasound in gynaecological clinics has resulted in the detection of adnexal tumours in a large number of asymptomatic postmenopausal women. There has also been an increase in the use of other imaging modalities such at CT and MRI to assess a variety of medical complaints resulting in incidental detection and adnexal tumours. Any adnexal cyst detected in menopause has a potential of being malignant.

In the United Kingdom the Royal College of Obstetricians and Gynaecologists (RCOG) has issued a guideline for the management of cysts in postmenopausal women, which is widely used in the routine clinical practice.[1] According to this protocol all adnexal cysts/tumours are categorised as high, intermediate and low risk of being malignant. This categorisation is based on the Risk of Malignancy Index (RMI) calculation [2] This model calculates a score which is the product of the value of the CA 125 (U/ml), a score for menopausal status (1 if pre-menopausal and 3 if postmenopausal) and a greyscale ultrasound score of 0, 1 or 3 where 1 score is given each for bilaterality, ascites, multilocular, solid areas and intra-abdominal metastases. In the original study by Jacobs, a score of >200 gave a sensitivity of 85% and a specificity of 97% for the diagnosis of ovarian cancer. A recent systematic review of 16 studies assessing the diagnostic performance of RMI showed that the test had an overall sensitivity of 78% (95% CI 71– 85%) and a specificity of 87% (95% CI 83–91%). [3]

The RMI has the advantage of being simple and widely used. Its disadvantage though is that it includes a blood test for CA125, which adds to the cost. In addition the diagnosis is delayed until the result of blood test is available. The absolute value of the RMI and the level of CA125 in serum are used to determine the management plan. Simple unilateral adnexal cysts of <5cm with an RMI of < 25 and where the CA 125 is < 30u/ml are considered low risk. For cysts with an RMI<25 but where the CA 125 ≥ 30u/ml, the cyst is ≥ 5cm or the cyst has septations or solid areas then these are considered of intermediate risk. Those with a RMI of 25 – 250 are also considered to be of indeterminate risk. Adnexal tumours with a RMI >250 are classified as high risk.[1] (Flowchart) As the main aim of this protocol is to minimise the risk of delaying interventions in women with ovarian cancer, the overall intervention rates are relatively high and many women with benign lesions are treated by surgery.

In recent years the International Ovarian Tumour Analysis (IOTA) collaboration has developed several novel diagnostic models with the aim of improving non-invasive diagnosis of ovarian cancer. In 2008 the collaboration proposed use of 'Simple Rules' to assess tumours.[4] The 'Simple Rules' are based on a structured approach to morphological analysis of ovarian tumours on ultrasound scan. It enables discrimination between benign and malignant lesions without the need to measure tumour markers.

Ultrasound scan 'Simple Rules' use 10 rules to assess adnexal tumours. There are five rules to predict malignancy (M-rules): (1) irregular solid tumour; (2) presence of ascites; (3) at least four papillary structures; (4) irregular multilocular–solid tumour with a largest diameter of at least 100 mm; and (5) very high colour content on colour Doppler examination (colour score 4). There are five rules to suggest a benign tumour (B-rules): (1) unilocular cyst; (2) presence of solid components where the largest solid component is <7 mm in largest diameter; (3) acoustic shadows; (4) smooth multilocular tumour less than 100 mm in largest diameter; and (5) no detectable blood flow on Doppler examination (colour score 1).

If one or more M-rules apply in the absence of a B-rule, the mass is classified as malignant. If one or more B-rules apply in the absence of an M-rule, the mass is classified as benign. If no rule applies or both M and B rules apply, the mass cannot be classified and defined as indeterminate.

These ten rules were applicable to 76% (937/1233) of all tumours in the study, where they resulted in a sensitivity of 93%, specificity of 90%, positive likelihood ratio (LR+) of 9.45 and negative likelihood ratio (LR−) of 0.08. [4] When prospectively tested the rules were applicable in 76% (386/507) of the tumours, where they had a sensitivity of 95% (106/112), a specificity of 91% (249/274), LR+ of 10.37, and LR− of 0.06. The 'Simple Rules' were subsequently tested prospectively. [5] The rules were applicable in 77% of the 1938 women with a sensitivity of 92% (95% confidence interval 89% to 94%) and specificity of 96% (94% to 97%).

The Simple Rules Model is particularly suitable for the use in standard clinical practice and, similar to the RMI, also divides the cysts into high, intermediate and low risk categories. There is some evidence, albeit limited, that the Simple Rules model may be superior to the RMI in terms of sensitivity and specificity.[2,5,6] Successful use of Simple Rules require more skilled ultrasound operators, but there in no need for additional blood tests and the results are available instantly.

Methods and analysis

The aim of this study is to assess the difference in the intervention rates between two different protocols for the management of incidentally detected adnexal tumours in postmenopausal women.

This is a prospective randomised controlled trial that will take place at the University College London Hospital gynaecology clinic. Women will be randomised into two groups. The first group will be assessed and managed in accordance with the current Royal College of Obstetricians and Gynaecologists protocol for the management of cysts in postmenopausal women. [1] The second group of women will be assessed using the "Simple Rules". [4]

Inclusion criteria

All postmenopausal women aged 40-80 who are referred for an asymptomatic adnexal tumour or those found to have one at the time of their visit to the Gynaecology unit will be invited to take a part of the study. Postmenopausal women are defined as those who have had one year of spontaneous amenorrhoea above the age of 40 where no illness or medication may have caused the amenorrhoea or those at or above the age of 50 who have had a hysterectomy. Women will be judged to be asymptomatic if they did not present with pain localised to the area of the tumour or the lower pelvis.

Women who present with pelvic pain that could be attributed to the tumour and those who are younger than 40 or older than 80 years of age will be excluded. Women who are unable to consent and those with simple unilateral unilocular cysts <2cm in size will also be excluded as the RCOG guideline stipulates these women do not require follow up.

Interventions

All women will have an initial ultrasound scan. Those randomised to the RCOG/RMI group will also have a blood test taken for the measurement of serum CA125. The tumours will be classified as low, intermediate and high risk as previously described (flowchart) In the Simple Rules group, adnexal tumours will be classified as low risk if one or more B-rules apply in the absence of an M-rule. If one or more M-rules apply in the absence of a B-rule, the mass will be classified as high risk. If no rules apply or if both M and B rules apply, the tumour will be classified as intermediate risk.

Women with tumours classified as high risk of malignancy on either protocol, will be referred to the Gynaecological Oncology team. Tumours found to be of intermediate risk will be offered surgery by the general gynaecology team. All asymptomatic women diagnosed with low risk tumours will be managed conservatively and have 4 monthly scans for 1 year observing for any changes in the tumour size or morphology. Should the characteristics of the tumour change prompting its reclassification into intermediate or high risk category the management plan will be modified accordingly.

Randomisation

A statistician using a Stata 12.1 ® (Stata Corp., College Station, TX, USA) will generate the blocked randomisation list with varying block sizes. The randomisation numbers will be placed in sealed, opaque, numbered envelopes and kept in a box locked in a filing cabinet. This randomisation ensures allocation concealment. When a patient consents, a clinic nurse who is not part of the research team will access the next envelope and give it to the recruiting doctor.

Outcome measures

The primary outcome is the rate of surgical intervention. Secondary outcomes include the sensitivities, number of staging procedures number of surgical complications and number of delayed diagnoses of ovarian cancer (invasive as well as borderline tumours) or the false negative rate.

Data Collection and Statistical analysis

The data is collected on a pre-designed proforma, which is then filed. This is transferred to a Microsoft Excel database in preparation for analysis. A Chi-square test or Fisher's exact test will be used will be used to assess significant differences in the intervention rates between the two management protocols.

Analysis will be on an intention to treat basis of all patients who fit the inclusion criteria. The researchers will do the analysis with the statistician at the midpoint and at the end.

Pilot Study and Sample Size

A preliminary prospective audit of 67 patients was done. These patients were aged 47 to 90 years. Using RMI/RCOG group protocol 41/67 [61.2% (95% CI 48.5 to 72.9)] were classified as requiring a surgical intervention compared to 5/67[7.5% (95%CI;2.5 to 16.6)] when the 'Simple Rules' protocol was used. The women with the final diagnosis of ovarian cancer were classified as high (n=1) or intermediate (n=1) risk by both protocols and they both had surgery performed by the gynaecological oncology team. We will assume that some patients offered conservative management will choose to still have surgery and that some patients who are offered surgery will choose not have an operation.

A significant improvement of surgical rates is considered to be a 50% reduction without a significant difference in the number of women with a delayed diagnosis of ovarian cancer. Therefore, if use of the 'Simple Rules' halves the intervention rate from 60% to 30% and assuming a 5% significance level and 90% power, 63 patients would be required in each group. Allowing for a 10% drop out rate, 140 patients will be needed. The sample size was calculated by use of Stata 12.1 ® (Stata Corp., College Station, TX, USA) as provided by evidence from Machin et al. [7] There was a 3% incidence of ovarian cancer in our pilot study population so we would expect to find 4 cancer diagnoses in the study population.

Discussion

Most asymptomatic adnexal tumours detected on ultrasound scan are benign. In these women, an operation to remove the cyst is unlikely to be beneficial and may do harm. By avoiding surgery women are not exposed to surgical and anaesthetic complications and their care is likely to be more cost-effective. Postmenopausal women are also more likely to suffer from chronic medical problems such as diabetes and high blood pressure, which increase operative and anaesthetic risks. Women with presumed benign cysts will be observed over the following year in 3-4 monthly intervals in order to detect any change in appearance or increase in size,

which would be suspicious of malignancy. Any suspicion of malignant change would trigger a surgical intervention.

We will record sensitivities of both protocols for the detection of ovarian cancer. Although our audit showed that all cases of ovarian malignancies were correctly classified by both protocols, it is important to confirm this observation in a larger prospective study. We do expect, however, that the specificity of the 'Simple Rules' protocol will be higher, which should translate into lower intervention rates.

If the study shows that the use of the 'Simple Rules' and conservative management could substantially reduce intervention rates without increasing the risk of delaying the diagnosis of ovarian cancer this could have a positive impact on clinical practice, increase patients' safety and result in significant savings for the health services.

Ethics and dissemination

Approval for this study was obtained from the North London Research Ethical Committee 2 (North REC 2), London, UK (10/H0724/48). Written informed consent is obtained from each patient fulfilling the inclusion criteria before randomisation. Women who refuse participation are recorded. There is a small risk to patients of a delayed diagnosis of ovarian cancer and there are also the risks of surgery for those who are offered surgical intervention.

Incident Reporting

Adverse events will be recorded from recruitment to the 1 year scan date for those who have conservative management or to 3 months post-operatively for those who have surgery. The chief investigator will be responsible for the reporting of all serious adverse events (SAE) or suspected unexpected serious adverse reactions (SUSAR) immediately or as soon as the trial personnel become aware of an event. The chief investigator will report all fatal or life-threatening events as soon as possible to the trial coordinating centre (TCC). This will be done not later than seven days after the chief investigator is first aware of the event. All events which are not fatal or life-threatening will also reported as soon as possible and not later than 15 days after the chief investigator is first aware of the reaction. The research and ethics committee (REC) also require a report of all SAEs and SUSARs within 15 days of the chief investigator being made aware. The principal investigator will also follow all SAEs and SUSARs through to outcome.

The results will be published once the study is complete

List of abbreviations

CA125	Cancer antigen 125
RCOG	Royal College of Obstetricians and Gynaecologists
RMI	Risk of Malignancy Index

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Authors' contributions

NN and DJ were responsible for the development of the study protocol and the application for ethical approval. NN drafted the paper and recruits patients. XF

recruits patients. MW provides supervision. DJ provides supervision and has contributed to the writing of the draft paper.

Authors' information
NN and XF are trainees in obstetrics and gynaecology. MW is a Professor of Womens Cancer at UCL and a consultant gynaecological oncology Consultant at UCLH. DJ is a gynaecology consultant and ultrasound expert who runs the early pregnancy and gynaecology clinic.

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This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests
The authors declare that they have no competing interests

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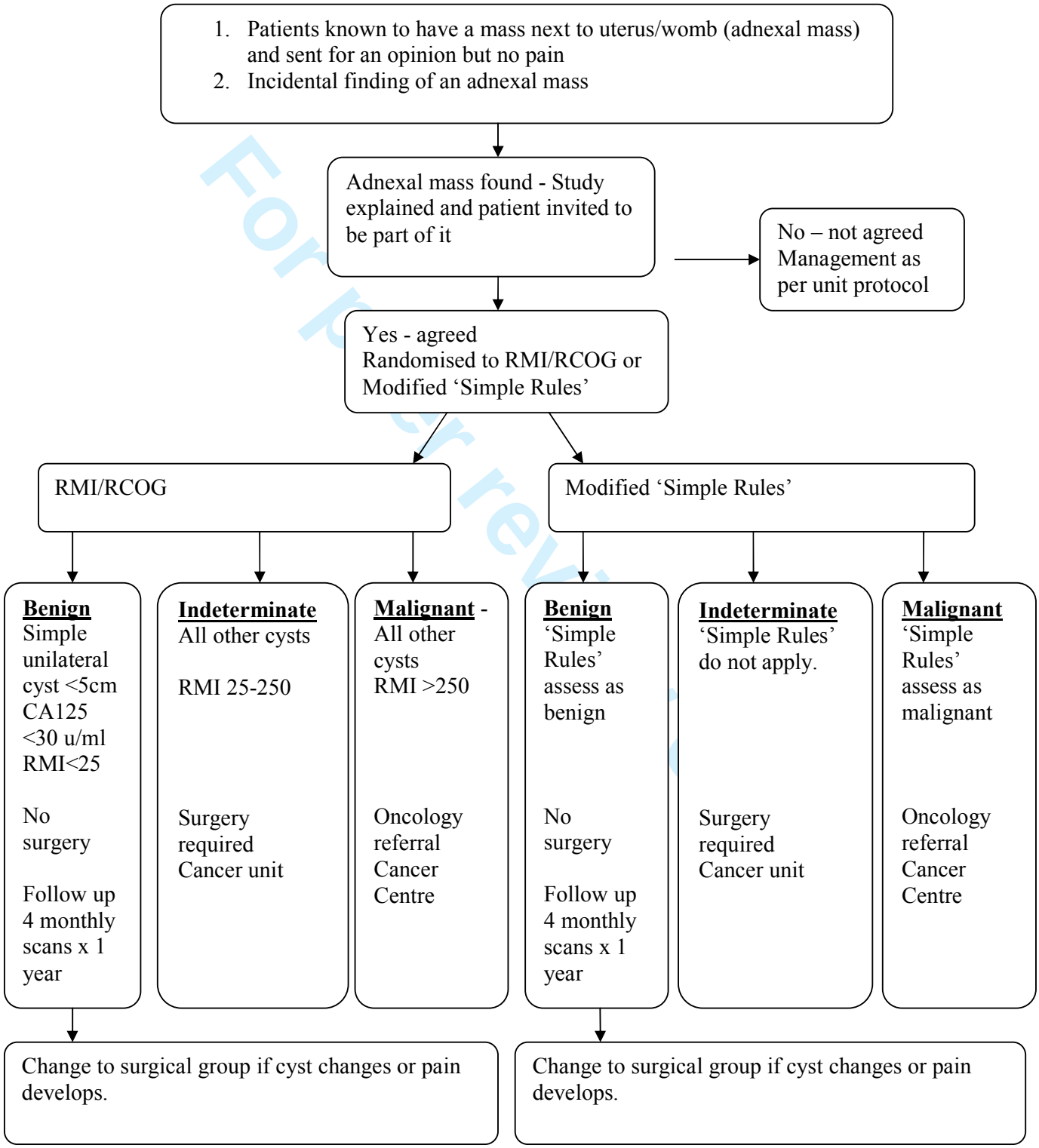
Article focus
- The primary objective is to assess the differences in surgical intervention rates between two different protocols for the management of incidentally detected adnexal tumours in postmenopausal women.
- Assessment of adnexal tumours using the Risk of Malignancy Index (RMI) calculation alongside the guidance from the Royal College of Obstetricians and Gynaecologists (RCOG) as compared with the Simple Rules as designed by the International Ovarian Tumour Analysis Group (IOTA).

Key messages
- Most asymptomatic adnexal tumours detected on ultrasound scan are benign. In these women, an operation to remove the cyst is unlikely to be beneficial and may do harm.
- A test, which can better discriminate between benign and malignant tumours, will afford women without a malignancy to decline surgery.

Strengths and limitations of this study
- This is the first randomized controlled trial to assess the RMI and the RCOG protocol against the Simple Rules protocol for the management of asymptomatic adnexal tumours in postmenopausal women.
- It is a single centre study, which can affect applicability of the results in other units.
- Both assessment and management protocols have high sensitivity rates with low false negative rates.

Flowchart


1. Patients known to have a mass next to uterus/womb (adnexal mass) and sent for an opinion but no pain
2. Incidental finding of an adnexal mass
Adnexal mass found - Study explained and patient invited to be part of it
No – not agreed Management as per unit protocol
Yes - agreed Randomised to RMI/RCOG or Modified 'Simple Rules'
RMI/RCOG
Modified 'Simple Rules'
Benign Simple unilateral cyst <5cm CA125 <30 u/ml RMI<25 No surgery Follow up 4 monthly scans x 1 year
Indeterminate All other cysts RMI 25-250 Surgery required Cancer unit
Malignant - All other cysts RMI >250 Oncology referral Cancer Centre
Benign 'Simple Rules' assess as benign No surgery Follow up 4 monthly scans x 1 year
Indeterminate 'Simple Rules' do not apply. Surgery required Cancer unit
Malignant 'Simple Rules' assess as malignant Oncology referral Cancer Centre
Change to surgical group if cyst changes or pain develops.
Change to surgical group if cyst changes or pain develops.

Research Checklist
SPIRIT Checklist

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Methods: Assignment of interventions (for controlled trials)	√	5
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Methods: Monitoring	√	6-7
Ethics and dissemination	√	7
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Methods and analysis:
140 postmenopausal women aged 40-80, with incidentally detected adnexal tumours on ultrasound scan will be recruited to this study. They will be randomly allocated, to be assessed and managed according to either of the two protocols under investigation. In both arms of the study the tumours will be classified into three groups: high, intermediate or low risk of malignancy. Women with high risk of malignancy will be referred for management in a tertiary cancer centre, women with low risk tumours will be managed expectantly, whilst those with intermediate risk findings have surgery in their local hospital units. Analysis will be on an intention to treat basis.

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Interventions

All women will have an initial ultrasound scan. All examinations will be performed by level II ultrasound operators, who have been fully trained in the assessment of adnexal tumours using both the RMI and "Simple Rules" approach. Those randomised to the RCOG/RMI group will also have a blood test taken for the measurement of serum CA125. The tumours will be classified as low, intermediate and high risk as previously described (flowchart) In the Simple Rules group, adnexal tumours will be classified as low risk if one or more B-rules apply in the absence of an M-rule. If one or more M-rules apply in the absence of a B-rule, the mass will be classified as high risk. If no rules apply or if both M and B rules apply, the tumour will be classified as intermediate risk.

Women with tumours classified as high risk of malignancy by either protocol, will be referred to the Gynaecological Oncology team. Tumours found to be of intermediate risk will be offered surgery by the general gynaecology team. All asymptomatic women diagnosed with low risk tumours will be managed conservatively and have 4 monthly scans for 1 year observing for any changes in the tumour size or morphology. Should the characteristics of the tumour change prompting its reclassification into intermediate or high risk category the management plan will be modified accordingly. Following conclusion of the study all women who did not require an intervention will be offered yearly follow up ultrasound scans for a further four years.

Randomisation

A statistician using a Stata 12.1 ® (Stata Corp., College Station, TX, USA) will generate the blocked randomisation list with varying block sizes. The randomisation numbers will be placed in sealed, opaque, numbered envelopes and kept in a box locked in a filing cabinet. This randomisation ensures allocation

concealment. When a patient consents, a clinic nurse who is not part of the research team will access the next envelope and give it to the recruiting doctor.

Outcome measures

The primary outcome is the rate of surgical intervention. Secondary outcomes include the number of delayed diagnoses of ovarian cancer, number of staging surgical procedures and number of surgical complications.

Data Collection and Statistical analysis

The data is collected on a pre-designed proforma, which is then filed. This is transferred to a Microsoft Excel database in preparation for analysis. A Chi-square test or Fisher's exact test will be used will be used to assess significant differences in the intervention rates between the two management protocols.
Analysis will be on an intention to treat basis of all patients who fit the inclusion criteria. The researchers will do the analysis with the statistician at the midpoint and at the end.

Pilot Study and Sample Size

A preliminary prospective audit of 67 patients was done. These patients were aged 47 to 90 years. Using RMI/RCOG group protocol 41/67 [61.2% (95% CI 48.5 to 72.9)] were classified as requiring a surgical intervention compared to 5/67[7.5% (95%CI;2.5 to 16.6)] when the 'Simple Rules' protocol was used. The women with the final diagnosis of ovarian cancer were classified as high (n=1) or intermediate (n=1) risk by both protocols and they both had surgery performed by the gynaecological oncology team. We will assume that some patients offered conservative management will choose to still have surgery and that some patients who are offered surgery will choose not have an operation.

A significant improvement of surgical rates is considered to be a 50% reduction without a significant difference in the number of women with a delayed diagnosis of ovarian cancer. Therefore, if use of the 'Simple Rules' halves the intervention rate from 60% to 30% and assuming a 5% significance level and 90% power, 63 patients would be required in each group. Allowing for a 10% drop out rate, 140 patients will be needed. The sample size was calculated by use of Stata 12.1 ® (Stata Corp., College Station, TX, USA) as provided by evidence from Machin et al. [7] There was a 3% incidence of ovarian cancer in our pilot study population so we would expect to find 4 cancer diagnoses in the study population.

Discussion

Most asymptomatic adnexal tumours detected on ultrasound scan are benign. In these women, an operation to remove the cyst is unlikely to be beneficial and may do harm.

By avoiding surgery women are not exposed to surgical and anaesthetic complications and their care is likely to be more cost-effective. Recent trials have shown that unnecessary interventions in women with benign adnexal lesions lead to significant morbidity and mortality, which offsets the potential benefits of screening for ovarian cancers. [8] Postmenopausal women are also more likely to suffer from chronic medical problems such as diabetes and high blood pressure, which increase operative and anaesthetic risks. Women with presumed benign cysts will be observed over the following year in 3-4 monthly intervals in order to detect any change in appearance or increase in size, which would be suspicious of malignancy. Any suspicion of malignant change would trigger a surgical intervention.

We will record sensitivities of both protocols for the detection of ovarian cancer. Although our audit showed that all cases of ovarian malignancies were correctly classified by both protocols, it is important to confirm this observation in a larger prospective study. We do expect, however, that the specificity of the 'Simple Rules' protocol will be higher, which should translate into lower intervention rates.

If the study shows that the use of the 'Simple Rules' and conservative management could substantially reduce intervention rates without increasing the risk of delaying the diagnosis of ovarian cancer this could have a positive impact on clinical practice, increase patients' safety and result in significant savings for the health services.

Ethics and dissemination

Approval for this study was obtained from the North London Research Ethical Committee 2 (North REC 2), London, UK (10/H0724/48). Written informed consent is obtained from each patient fulfilling the inclusion criteria before randomisation. Women who refuse participation are recorded. There is a small risk to patients of a delayed diagnosis of ovarian cancer and there are also the risks of surgery for those who are offered surgical intervention.

Incident Reporting

Adverse events will be recorded from recruitment to the 1 year scan date for those who have conservative management or to 3 months post-operatively for those who have surgery. The chief investigator will be responsible for the reporting of all serious adverse events (SAE) or suspected unexpected serious adverse reactions (SUSAR) immediately or as soon as the trial personnel become aware of an event. The chief investigator will report all fatal or life-threatening events as soon as possible to the trial coordinating centre (TCC). This will be done not later than seven days after the chief investigator is first aware of the event. All events which are not fatal or life-threatening will also reported as soon as possible and not later than 15 days after the chief investigator is first aware of the reaction. The research and ethics committee (REC) also require a report of all SAEs and SUSARs within 15 days

of the chief investigator being made aware. The principal investigator will also follow all SAEs and SUSARs through to outcome.

The results will be published once the study is complete

List of abbreviations

CA125	Cancer antigen 125
RCOG	Royal College of Obstetricians and Gynaecologists
RMI	Risk of Malignancy Index

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Authors' contributions

NN and DJ conceived the idea and contibuted to the design along with MW. XF contributed to design and NN with XF are responsible for data aquisition. NN and DJ prepared the initial article draft and curculated it to the other authors XF and MW until all authors approved the final article for submission.

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Competing interests

The authors declare that they have no competing interests

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Article focus

- The primary objective is to assess the differences in surgical intervention rates between two different protocols for the management of incidentally detected adnexal tumours in postmenopausal women.
- Assessment of adnexal tumours using the Risk of Malignancy Index (RMI) calculation alongside the guidance from the Royal College of Obstetricians and Gynaecologists (RCOG) as compared with the Simple Rules as designed by the International Ovarian Tumour Analysis Group (IOTA).

Key messages

- Most asymptomatic adnexal tumours detected on ultrasound scan are benign. In these women, an operation to remove the cyst is unlikely to be beneficial and may do harm.
- A test, which can better discriminate between benign and malignant tumours will afford women without a malignancy to decline surgery.

Strengths and limitations of this study

- This is the first randomized controlled trial to assess the RMI and the RCOG protocol against the Simple Rules protocol for the management of asymptomatic adnexal tumours in postmenopausal women.
- It is a single centre study, which can affect applicability of the results in other units.
- Both assessment and management protocols have high sensitivity rates with low false negative rates.

Flowchart