International Ovarian Tumour Analysis (IOTA) Phase 5

A multicentre study to examine the short and long term outcomes of the conservative management of benign-looking adnexal masses and the pre-operative characterisation of ovarian tumours

STUDY CO-ORDINATORS

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Summary

The medium to long term behaviour of benign-looking adnexal masses that do not undergo surgery is unknown. It is possible for these masses to undergo malignant transformation, rupture or torsion. Furthermore they may undergo changes in volume and/or morphology that may or may not predict any of these behaviours. To date, no research has rigorously investigated the long-term behaviour of such masses. Consequently, there are no evidence-based guidelines on the optimal management of the majority of adnexal tumours. It is therefore not surprising that clinical practice is highly variable, with some clinicians preferring to operate on virtually any mass. When a clinician decides not to operate, the time intervals selected for follow up scans is often arbitrarily chosen. On the other hand, we do have some convincing data to suggest that simple cysts are rarely malignant and so it is generally thought that operating on these common tumours is probably not necessary and simply increases costs and morbidity. Developing new insights into the natural history of benign looking conservatively managed ovarian

masses would potentially change the management of thousands of women, by avoiding surgery or even further surveillance for some and detecting cancer earlier or even preventing it for others.
In this international multicentre study IOTA phase 5 we aim to develop the optimal evidence-based algorithm for the management of all adnexal tumours in order to improve the detection of ovarian cancer while at the same time reducing the number of unnecessary operations. At least three thousand patients with an adnexal mass will undergo an ultrasound examination and if no operation is needed they will be followed up for at least 5 years. At each visit the investigator will assess the tumour and decide whether surgery is necessary based on the available information and local protocols. Survival and logistic regression analysis will be used to develop decision aids to assist clinicians in making decisions regarding surgery and follow up.

Relation with other IOTA studies

The **IOTA study (International Ovarian Tumour Analysis)** is a multicentre collaborative project for the pre-operative characterisation of ovarian tumours..

IOTA phase 1: The **first phase** of IOTA was conducted between 1999 and 2002. Several new mathematical models were developed based on the prospectively collected data of 1066 patients with a persisting adnexal tumour from 9 European centres (1). Between 2002 and 2005 three centres continued the prospective collection in order to be able to perform an internal validation of mathematical models developed in IOTA phase 1. In this so-called IOTA **phase 1b** study a dataset of 507 new patients was prospectively collected in 3 out of the 9 original IOTA centres (2). All models proved to perform excellently with areas under the ROC curves of more than 0.94.

IOTA phase 2: The **second phase** of IOTA consisted of an external validation of the models and this was conducted between 2005 and 2007. The diagnostic algorithms were prospectively validated on 1938 patients with adnexal tumours in 19 centres in Belgium, Italy, UK, Sweden, Poland, Czech Republic, Canada, and China (3). A first analysis showed that overall performance of the logistic regression models was excellent (area under the ROC curve 0.94). We concluded that a subgroup of "uncertain" tumours needs a reliable second stage test in order to help even experienced ultrasound examiners.

IOTA phase 3: The **third phase** of the IOTA study started in 2010.
The aim was to validate the added value of mathematical models as new diagnostic tool in the prediction of ovarian cancer in clinical practice in centres that were involved in IOTA phase 1 or 2. It is a temporal validation of IOTA mathematical models as a first stage examination. However in cases where the prediction is unreliable, we aim to further improve the predictive performance of this diagnostic tool with second stage tests, such as new sets of tumor markers, proteomics and three-dimensional Power Doppler ultrasonography.

IOTA phase 4: Randomised controlled trial in 7 London hospitals. Clinical implementation of IOTA logistic regression models LR2 vs. the routinely used Risk of Malignancy Index. Assessment of efficacy, referral pattern and costs.

Introduction

There is very little evidence on which to base a recommendation on how apparently benign looking adnexal masses should be managed. Because the natural history of such adnexal masses is not known, and because of the fear of "missing" ovarian cancer, many adnexal masses are currently surgically removed, even if they do not manifest any signs of malignancy. This is not optimal, because every surgical procedure is associated with risks of both short-term and long-term complications, for example pulmonary embolism, deep vein thrombosis, and bowel perforation or obstruction (4). Furthermore we do not know if benign ovarian lesions impact on fertility, although we know that surgery on ovaries may cause adhesions, which in turn may cause infertility, chronic pelvic pain and bowel obstruction. We do not know the frequency of these complications, nor do we know how often benign adnexal masses are associated with complications such as torsion if they are not removed. There is some evidence, however, that expectant management of presumed ovarian dermoid cysts less than 6 cm is safe and does not seem to interfere with pregnancy or delivery (5-7). The available data also suggest that expectant management of simple cysts less than 5 cm in post-menopausal women is a safe strategy (8,9).

On the other hand ovarian cancer is associated with a high mortality rate and significant morbidity. It is the fifth leading cause of cancer-related deaths (10). The lifetime risk of developing ovarian cancer is around 1 in 50 to 1 in 70 (11,12). Every year more than 200,000 new cases are diagnosed worldwide. The disease has a poor prognosis, with five-year relative survival strongly depending on disease stage (12,13). For example, Cancer Research UK reports survival rates of 73% for stage I versus 16% for stage IV ovarian cancer.

New diagnostic strategies to decrease mortality are needed, as treatment advances have not decreased mortality over the past 20 years (14). Effective screening programmes may help, but current candidate tests remain unsatisfactory (15). A crucial issue is that ovarian cancer is typically asymptomatic in its early stages. Screening algorithms have generally resulted in high sensitivity at the cost of a large number of false positives. As a result a large number of surgical interventions are made in order to find relatively few cancers. However although one study has suggested that there is no benefit in removing benign ovarian tumors (16), there are no conclusive data to inform us regarding the long term behaviour of presumed benign ovarian cysts left in situ. Should benign cysts have malignant potential, then a policy of removing such masses may have a significant impact on mortality from this disease.
Research directed towards the use of diagnostic tests and models to predict malignancy in ovarian tumours has focused on masses that have been subsequently surgically removed in order to provide a clear histological end point. Clinicians decide whether to operate on an ovarian mass depending on a number of factors. These may include the subjective characterisation of the mass using ultrasound, the use of simple models such as the risk of malignancy index, the age of the patient, the serum CA 125 level and the presence or absence of symptoms such as pain. The management of cysts that are not removed surgically is not evidence based and often subject to wide variation. In the absence of rigorous follow up data, we do not know how many false negative results for cancer are associated with these cysts, or if they sometimes undergo malignant transformation. We will only gain this knowledge by long term systematic follow up of a large cohort of ovarian cysts.

A number of studies have focused on the prediction of malignancy in surgically removed masses (for overviews, see references 2,17-19). There is strong scientific evidence that subjective evaluation of a mass using ultrasound by an experienced examiner is a very good method for discriminating between benign and malignant adnexal masses (2,3,20-21), and that a correct histological diagnosis can be suggested on the basis of ultrasound findings in many cases (22,23). We have previously established the International Ovarian Tumor Analysis (IOTA) group to develop and validate prediction models based on large, multi-centre datasets with standardised definitions and data collection procedures (25). The aim was

to develop robust models to predict malignancy that performed well, and were widely generalisable. In doing so we aimed to overcome the shortcomings of earlier studies such as small sample sizes, single centre recruitment, and lack of standardised data collection. These models (1, 25-27) successfully passed temporal and external validation (2,3,28). Following these validation studies, we selected two logistic regression models for further study. The first (LR1) is a model with 12 predictors, the second (LR2) contains only six predictors. Even in postmenopausal women conservative management and sonographic follow up of incidental unilocular and multilocular cysts <7cm may be a valuable option (29).

Objectives

The general aim of this study is the development of the optimal algorithm for the management of all adnexal masses. This can be broken down into different specific objectives: 1) to study the occurrence of complications such as rupture, torsion, or malignancy in patients with benign looking conservatively treated masses; 2) to test the published IOTA diagnostic models for predicting that a mass is malignant at first visit or benign (either on the basis of histology following surgery or by the absence of malignant features on an ultrasound scan one year after the initial visit), and to predict complications (e.g. ocurrence of malignancy and other) during long-term follow-up; 3) to investigate factors that may be related to the need for surgery during long-term follow up; 4) to study the natural history of conservatively treated benign looking masses and to establish descriptive curves of the longitudinal changes seen in parameters from conservatively managed benign tumors (e.g. change in diameter, size of any solid component, number of papillations, or color score). We hope these curves will allow us to determine if any particular growth pattern is associated with complications or malignancy

Related to these four objectives, we aim to carry out the following analyses: 1) descriptive analysis of complications overall and by participating center (anonymised) and overall Kaplan-Meier curves for the need for surgery among benign looking masses; 2) estimation of discriminatory ability of LR1 for malignancy at the initial visit using the c-index and ROC curves and for complications during long-term follow-up using the hazard ratio and c-index within the context of survival analysis; 3) survival analysis to investigate predictors of the need for surgery during long-term follow-up of non-operated masses; 4) the development of longitudinal curves of the changes seen in the characteristics of non-operated masses using longitudinal analysis techniques such as mixed models and functional linear discriminant analysis (FLDA).

Methods

Study design

International multicenter prospective observational cohort study

Eligible for inclusion

- Any woman at least 18 years old with an adnexal mass.
- Any mass with benign ultrasound morphology may be suitable for conservative management.
- Pregnant patients can be included, but their data will be analysed separately.

Exclusion Criteria

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- Cysts that are deemed to be clearly physiological and less than 3 cm in maximum diameter are not eligible for inclusion.
- Any cyst with features of malignancy is excluded from the conservative management
- The denial or withdrawal of oral informed consent

Official approval by the Ethics Committee

The multicentre project IOTA phase 5 will be submitted to the Ethics Committee of the University Hospitals Leuven as main investigating centre as well as in each participating centre.
The study will be performed in accordance with generally accepted standards of Good Clinical Practice and the investigators will adhere to all applicable laws and regulations governing the conduct of clinical trials, including but not limited to the ICH Harmonized Tripartite Guidelines for Good Clinical Practice and the Declaration of Helsinki (2008).

Insurance policy
This multicentre international study is initiated by the University Hospitals Leuven, Belgium. Each participating centre outside Belgium is fully responsible for patient care within its own hospital in agreement with local laws. Each centre is also responsible for all legal aspects of patient care and for its own insurance for all matters related to this study.

Financial Support

The IOTA phase 3 project is supported by an Applied Biomedical Research grant (Toegepast Biomedisch Onderzoek, TBM) from the Flanders Institute for Scientific and Technological Research: IWT Flanders, Belgium (IWT-TBM 070706). This grant covers costs of central data collection, proteomic analysis, analysis of new tumour markers and statistical analyses. For IOTA phase 5 we received a research grant for a doctoral researcher by the Flemish Fund for Scientific Research (FWO Vlaanderen 06260, IOTA5).

There is no financial compensation for principal investigators nor patients.

Definition of benign ultrasound morphology
This is defined on the basis of subjective assessment of ultrasound findings by an experienced ultrasound examiner. Only lesions where the ultrasound examiner is certain or almost certain that the lesion is benign can be managed conservatively. The management of benign masses will be decided according to local protocols.

Number of study patients and recruitment period
This is an observational study and therefore a sample size cannot be calculated. We aim to collect at least 3000 women with an adnexal mass and at least 1000 women with an adnexal mass managed conservatively. We plan an initial recruitment period of eighteen months. Patients will be followed up for at least 5 years, unless surgical intervention is necessary.

Follow-up

Ultrasound (and clinical) follow up will be organised by the ultrasound examiner who entered the patient into the study. Follow-up will be after 3 months (maximal range 1-4 months), 6 months (maximal range 4-8 months) and then every 12 months (maximal range 10-14 months).

Although measurement of serum CA 125 levels is encouraged, it is not mandatory for inclusion in the study. If CA125 is measured it should be recorded in the study screen and preferably measured on each visit.

Duration of follow-up

A yearly analysis will be carried out in order to evaluate acute complications. The duration of follow up will be for at least 5 years and is not limited as long as the patient is compliant with the study and the study is ongoing.

Departments (e.g. radiology departments) that are not involved with clinical decision making about plans for follow up or surgery cannot participate in the full IOTA 5 study. In these centres data can be prospectively collected as an observational study. Only patients with appropriate outcome measures (i.e. follow up ultrasonography after one or more years or patients with complete details of clinical history or surgical procedures) will be included in any statistical analysis.

Collection of clinical data

Family history: Number of first degree relatives with ovarian cancer (0-...)

Medical history:

Personal history of ovarian cancer and breast cancer
Age (years)
Previous hysterectomy (yes/no)
Previous oophorectomy (yes/no)
Contraception (drop down list) (None/oral combined contraceptive pill/progestogen only pill/ patch/vaginal ring/Mirena coil/copper IUD)
Hormonal therapy (yes, no).

Is the patient currently wishing to conceive? (yes/no)
Menopausal status (pre- or postmenopausal)
History of subfertility? Yes/no
History of ovarian stimulation for subfertility? Yes/no

<u>For ALL patients before menopause two extra questions pop up:</u>

Patient is currently pregnant? (No/Yes)

Patient became pregnant during the last year? (No/Yes)

- If Yes: Outcome of pregnancy (it should be possible to enter more than one date, should there be more than one pregnancy during follow-up):

- Ongoing pregnancy
- Miscarriage; date: …
- Ectopic; date: …
- Termination; date: …
- Delivery; date: …
- Complications from the lesion during pregnancy? No/Yes (pop up list):
  - Acute pain
  - Chronic pain
  - Suspected torsion
  - Infection
  - Haemorrhage related to the cyst
  - Cyst rupture
  - Required surgery
  - Other, please specify: ….
- Complications from the lesion during delivery? No/Yes (pop up list):
  - Acute pain
  - Suspected torsion
  - Haemorrhage
  - Cyst rupture
  - Obstructed labour
  - Malpresentation (e.g. breech or unstable lie)
  - Other, please specify: ……..

Ultrasound examination

A standardized ultrasound examination following the IOTA protocol is carried out.

All ultrasound variables are included in the dedicated software. In the database 0 always means NO and 1 always means YES.

The adnexal lesion is that part of an ovary or of an adnexal mass that is judged by ultrasonography to be not consistent with normal physiology. This can be a persistent unilocular cyst, surrounded by normal looking ovarian stroma with some follicles. In this case the whole ovary containing the cyst is the 'ovary', whereas the unilocular cyst is the 'lesion'. Both are measured and the cyst is described as being 'unilocular' and not 'unilocular-solid'. In other cases the lesion is separate from the ovary (e.g. hydrosalpinx). Again, both ovary and lesion are measured separately. In other cases no normal ovarian stroma is seen. In these cases the lesion and the ovary are undistinguishable and the measurement of lesion and ovary will be the same.

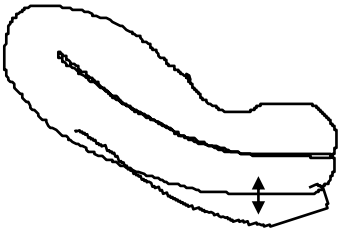
Measurements (in mm): The ovary in two perpendicular planes

The lesion in two perpendicular planes

The volume of the tumor is calculated from the three diameters in two perpendicular planes

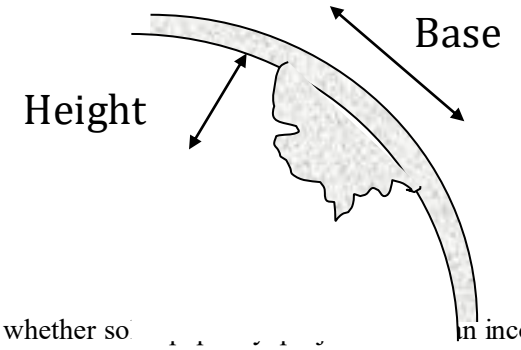
- The presence of ascites (*i.e. fluid outside* the pouch of Douglas) is noted (yes/no).

- Fluid in the pouch of Douglas is measured in the sagittal plane (the largest anteroposterior diameter is given).
  (see Figure)



- An incomplete septum (as seen in hydrosalpinges) is defined as a thin strand of tissue running across the cyst cavity from one internal surface to the contralateral side, butis not complete in some scanning planes. If a cyst only has incomplete septa, it is unilocular, despite the fact that in certain sections the cyst appears to be multilocular.
- Solid means echogenicity suggesting the presence of tissue (e.g. the myometrium, the ovarian stroma, myomas, fibromas). Blood clots and the presence of solid tissue can be distinguished by looking for internal movement when gently pushing the structure with the transducer. The presence of blood flow (with the appropriate color Doppler settings) is diagnostic for solid tissue. The absence of flow is not definitive . In cases of doubt the lesion should be classified as solid.

- Solid papillary projections are defined as any solid projections into the cyst cavity from the cyst wall greater than or equal to 3 mm in height

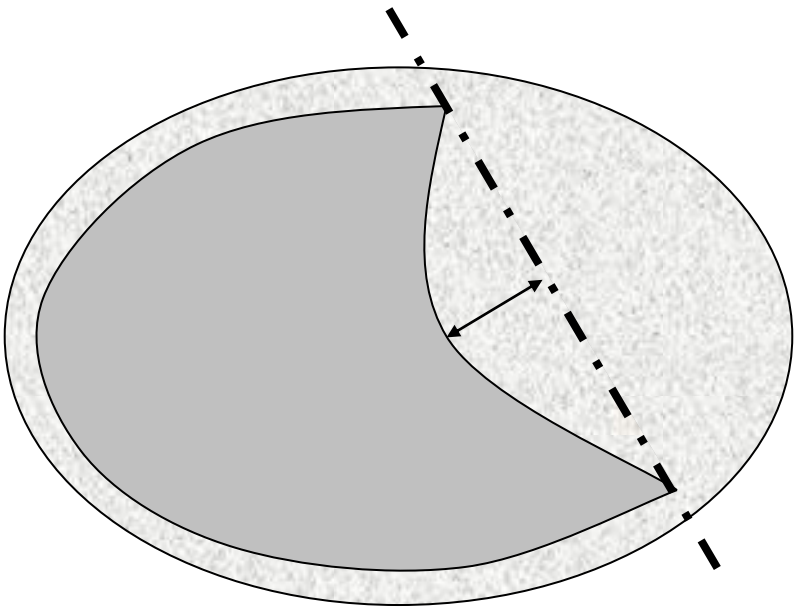


If it is unsure whether so [illegible] n incomplete septum are present, the 'worse case scenario' is used. E.g. 'cogwheel excrescences' and 'beads-on-a-string' (as seen in hydrosalpinges) should be classified as papillary excrescences if their height is greater than or equal to 3 mm. The 'white ball' in a dermoid (i.e. Rokitansky node), should not be classified as a solid papillary projection.

The 'sludge' on the internal walls of endometriotic cysts is not regarded as a papillary projection. In these cases the internal walls are usually 'irregular'.

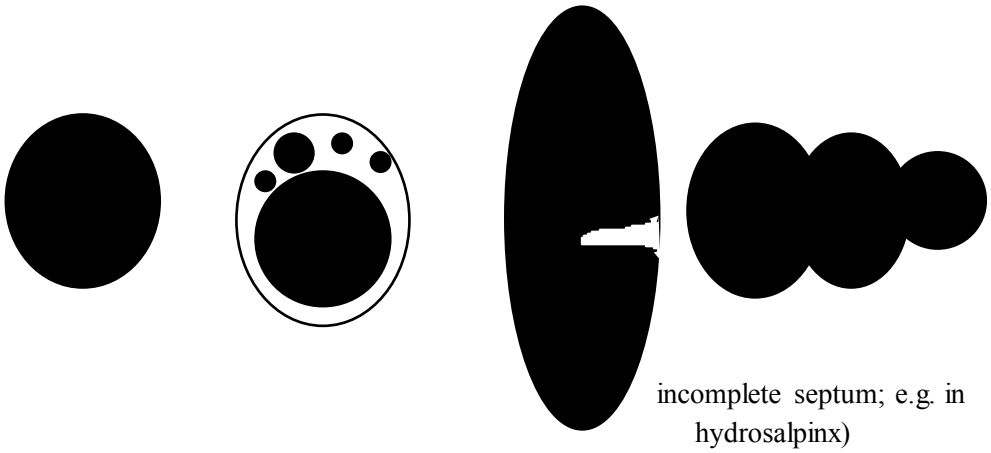
- The number of separate papillary projections is noted (1/2/3/more).
- The presence of flow within some of these projections is noted (yes/no).
- Solid papillary projections are described as being 'smooth' or 'irregular' (e.g. cauliflower-like).

In some cases it is difficult to judge whether it is a papillary projection and from which point to measure the projection. In these cases it may be helpful to use an imaginary line as shown in the following schematic drawing:



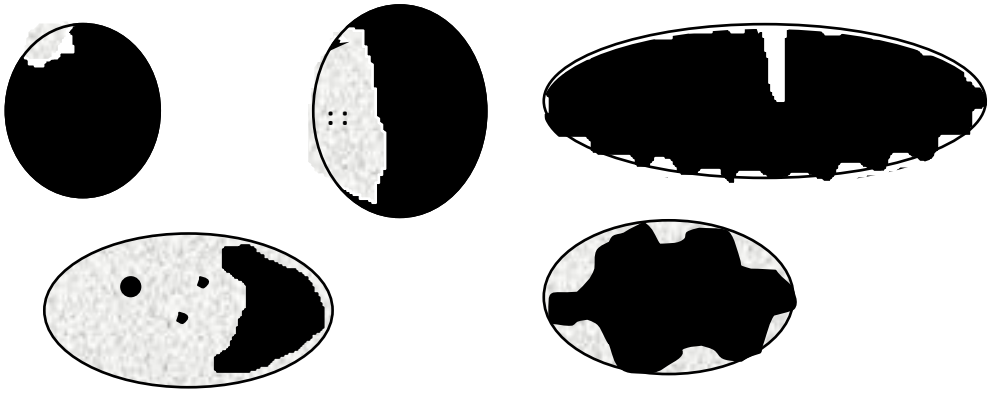
All lesions are qualitatively classified into one of 5 categories:

1. unilocular (a unilocular cyst without septa and without solid parts or papillary structures). Normal ovarian stroma is not regarded as 'solid' (e.g. a peritoneal cyst, containing a normal ovary, is unilocular and not unilocular-solid).

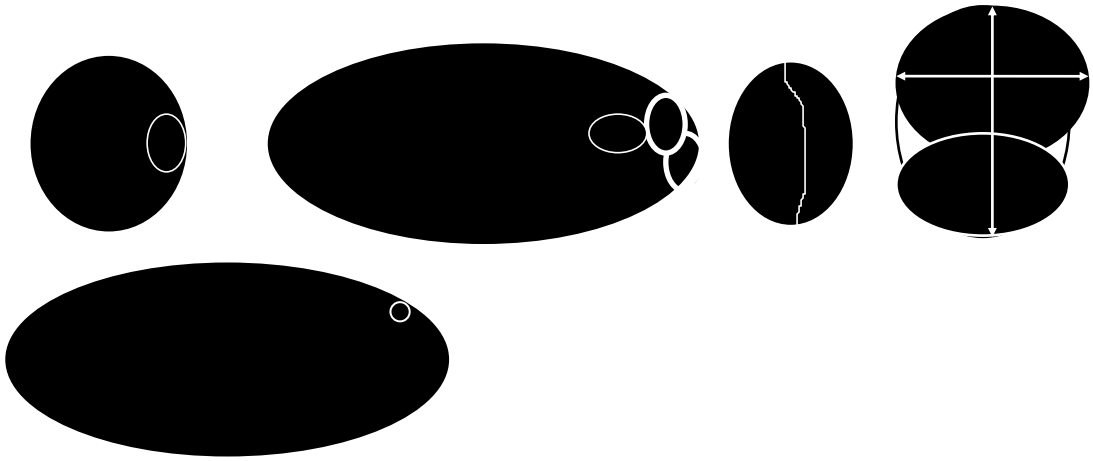


incomplete septum; e.g. in hydrosalpinx)

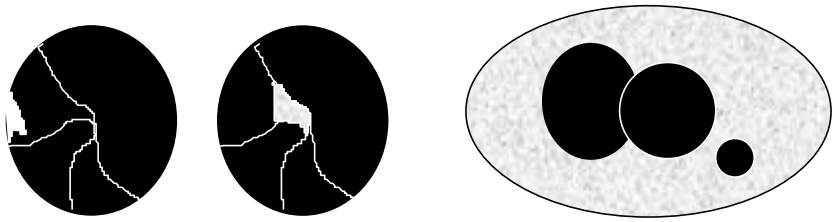
2. unilocular cyst with solid component (a unilocular cyst with a measurable solid component or at least one papillary structure). This category may include pyo- or hydrosalpinges with the so-called 'beads-on-a-string' or 'cogwheel' appearance if ≥ 3 mm. If the solid part contains very small cysts the mass might be unilocular-solid (see below).



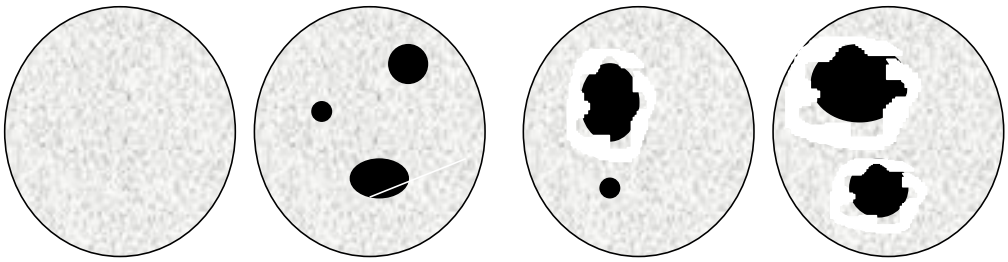
3. multilocular (a cyst with at least one septum but no measurable solid components or papillary projections). The 'lesion' is measured as indicated by the arrows.



4. multilocular with solid component (a multilocular cyst with a measurable solid component or at least one papillary structure)



5. solid (a tumour where the solid components comprise 80% or more of the tumour when assessed in a two-dimensional section).

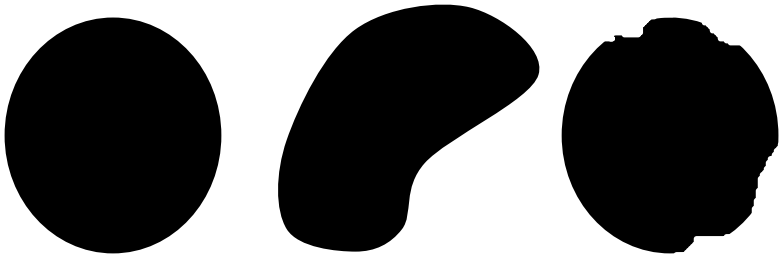


(solid tumour with an irregular cyst wall)

A solid tumour may contain papillary projections protruding into the small cysts.

Quantitative assessment of morphology

- In cystic-solid tumours the largest solid component is measured separately (in three perpendicular planes). The solid component is noted as being smooth or irregular (e.g. cauliflower-like). In some cases a solid papillary projection is the largest solid component and thus the papillary projection is recorded both as papillary projection and as solid component.
- The internal wall is also noted as being smooth or irregular.

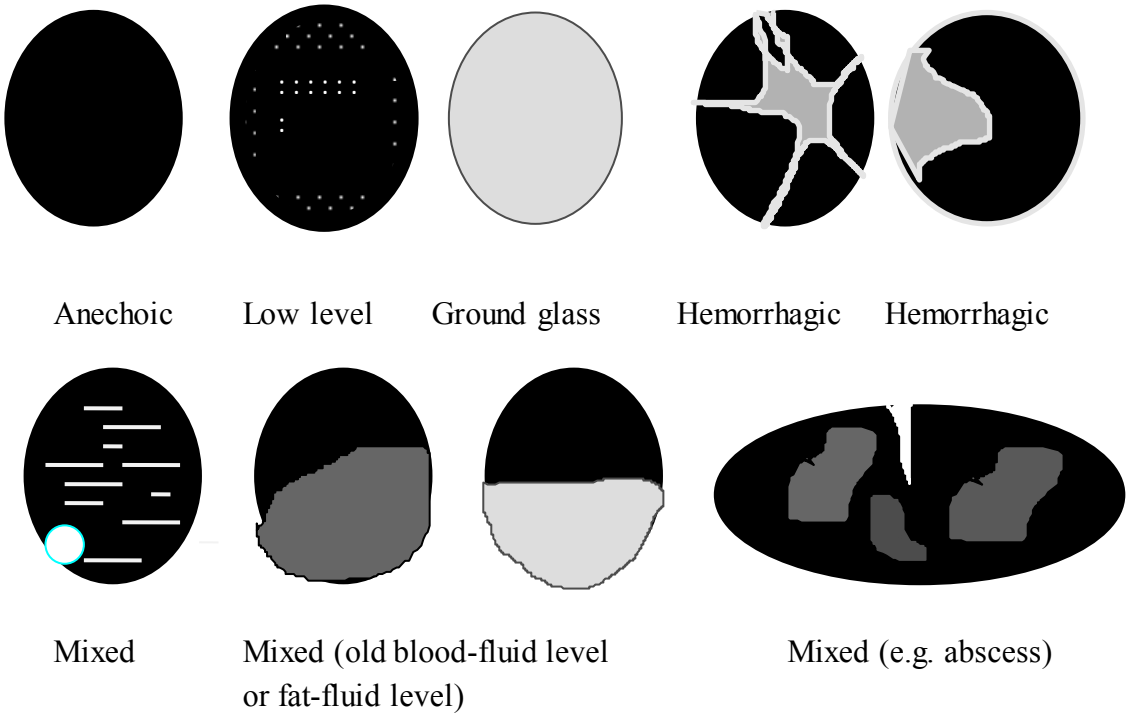


Smooth Smooth Irregular

If there is a solid papillary projection, then the wall is irregular by definition.

- The external wall of tumors are not examined unless they are solid.
- In cases of solid tumours the description of the internal wall being smooth or irregular is usually not applicable but the outline of the tumour is described as smooth or irregular.
- If there is any irregularity in either the inner wall of any cyst or in the outer wall of a solid tumour or on the surface or echogenicity of a solid component, the lesion is described as 'irregular'.

- The dominant feature of the cystic contents is described as anechoic (black), low-level echogenic (homogeneous low level echogenic as seen in mucinous tumours), 'ground glass' appearance (homogeneously dispersed echogenic cystic contents, as often seen in endometriotic cysts), hemorrhagic (with internal thread-like structures, representing fibrin strands; it is possible to describe the echogenicity as star-shaped, cobweb-like or jelly-like) or mixed echogenic (as often seen in teratomas) (see images attached).



- The presence of acoustic shadows, defined as loss of acoustic echo behind a sound-absorbing structure, is noted as well. Solid tumours are identified by the appearance of the internal texture, by the absence of internal movement when moving the transducer or by colour Doppler imaging (presence of central flow).
- In solid tumours the dominant feature of any cystic contents is described only if it can be assessed.
- 'Ovarian crescent sign', defined as the presence of normal ovarian tissue adjacent to an adnexal tumour. ("absent" or "present", mandatory new variable for phase 3 and 5)
- Ultrasound evidence of metastases (e.g. "omental cake" or peritoneal tumoural implants). ("absent" or "present", mandatory new variable for phase 3 and 5)

Colour Doppler imaging and blood flow indices

Subsequently, the entire tumor is surveyed by CDI. The power, gain and pulse repetition frequency are initially adjusted for maximum sensitivity of low blood flow states. The lowest velocity signals are filtered out by gradually increasing the pulse repetition frequency and flow analysis is concentrated on the highest velocity signals. A subjective semiquantitative assessment of the amount of blood flow (area and colour scale) within the septa, cyst walls, or solid tumor areas is made: a score of 1 is given when no blood flow can be found in the lesion; a score of 2 is given when only a small amount of flow can be detected; 3 is given when moderate flow is present and 4 is given when the adnexal mass appears highly vascular with marked blood flow using colour Doppler (abundant flow). This colour score refers only to the colour Doppler image and not to Doppler shift spectrum. It is given for the tumour as a whole (not for a solid part or a septum only, but for the whole tumour). Multiple photographic prints are made of relevant structures and Doppler signals.

Quality control

Several informative images or volumes of all adnexal masses should be made. Preferably, these are stored digitally. Photographs or video are acceptable as well.

Subjective assessment

After ultrasonographic examination of the mass the investigator gives his subjective assessment of the mass:

A: Malignant or benign or borderline?

B: Probability of malignancy: 1 = benign
(=level of certainty) 2 = probably benign
3 = uncertain
4 = probably malignant
5 = malignant

C: Self impression: presumed histological diagnosis (e.g. dermoid, serous cystadenoma, endometrioma, abscess…)

Surgical intervention

Surgery is performed according to local protocols. The reason for surgery, e.g. symptoms (pain, discomfort or pressure symptoms), raised serum CA125 levels or changes in the morphology or volume of the mass is recorded in the study screen.

Study screen

An astraia study screen will be used which will permit the entry of **multiple scans** per patient.

All centres will receive the **IOTA 5 study screen**.

At initial set up centres can choose between the two options:

1. Full IOTA 5 study (with planning of appropriate follow up and conservative management whenever feasible).
2. Observational study only (e.g. in radiology departments that are not involved in management decisions)

Recorded variables (entered in the **astraia study screen**).

Patient data
(click one option from list below)

- New patient with diagnosis of adnexal mass
- New patient who was already in follow up in your centre for adnexal mass before she was enrolled to the IOTA 5 study. How many months in follow up? …
- Follow up scan of patient that is already enrolled to the IOTA 5 study before

Ultrasound

- Spontaneous resolution of the adnexal mass (no further details are entered)
- Adnexal mass present (fill in all variables below)

- 12 variables described in LR 1:
  - Age
  - personal history of ovarian cancer
  - personal history of breast cancer
  - Max diameter of lesion
  - Max diameter of solid component
  - Presence of ascites
  - Presence of blood flow within papillary projection
  - Irregular internal cyst walls
  - Presence of a purely solid tumour
  - Colour score (1/2/3/4)
  - Presence of acoustic shadows
  - Current hormonal therapy
  - Presence of pain during the examination

- as well as simple rules, RMI and other variables:
  - Type of tumour (unilocular/unilocular-solid/multilocular /multiloc-solid/solid)
  - Ovarian crescent sign
  - Cyst content
  - Incomplete septum
  - Mobility: mobile/reduced mobility/completely fixed
  - Number of locules
  - Number of papillations (0/1/2/3/more)
  - Size of ovary
  - Bilateral tumour
  - Evidence of metastases
  - Menopausal status: premenopausal/postmenopausal

- Serum CA 125 result (not mandatory)

- Symptoms during the last year before ultrasound scan (multiple options are possible)
  - Pelvic pain
  - Postmenopausal bleeding
  - increased abdominal size
  - persistent abdominal distention (bloating)
  - appetite loss
  - constipation
  - diarrhoea
  - urinary urgency
  - urinary frequency
  - weight changes
  - dyspareunia
  - Other: please specify: ….

- *For centres participating at the full IOTA 5 study only:* Suggested management recorded by examiner: "What type of management do you propose for this patient based on ultrasound and clinical data?"
  - Conservative management without follow up
  - Conservative management with follow up as specified in the protocol
  - Surgery by a gynaecologist or general surgeon
  - Surgery by an oncological surgeon

Current status of the patient (this new tab should come before the tab "Histology"). A fixed query could be made to automatically ask the investigator about the status of all patients that were not rescanned 55 weeks after their previous scan as soon as the investigator opens the IOTA 5 study screen.

- Lost to follow up (no other pop-up)
- Patient stopped participating to the study (please specify why : …..) (no other pop-up)
- Patient withdrew her consent (data cannot be used for statistical analysis and no reason is aked) (no other pop-up)
- Surgery performed (pop-up of fields about operation below)

<u>If Surgery</u>

- Date of operation:

- Type of operation: cystectomy or oophorectomy or staging etc
  - Laparotomy with vertical incision
  - Laparotomy with horizontal incision
  - Operative laparoscopy
  - Diagnostic laparoscopy
  - Primary chemotherapy

- Indication for operation (more than one possibility may be thicked)
    - Suspicion of malignancy based on ultrasound
    - Suspicion of malignancy based on other information if so what?
    - Malignancy cannot be excluded
    - Acute pain
    - Chronic pain
    - Suspected torsion
    - Fertility concerns
    - Patient request
    - Increase in size of the tumour
    - Change in morphology of the tumour
    - Increase in CA 125 level
    - Indicated by other imaging technique (CT, MRI…)
    - Other doctor recommended operation. Please specify the reason: …
    - "en passent" removal of the mass when patient was operated for another indication
    - Other: Specify: ….

- Findings at operation (more than one option may be ticked)
    - No complications of the tumour
    - Torsion
    - Rupture
    - Inflammation/Infection
    - Adhesions
    - Bleeding from tumour
    - Metastatic cancer
    - Other complications of tumour: specify: ….
    - Other non-gynaecological pathology (e.g. appendicitis): specify: ….

- Complications during operation (within one week of surgery). (more than one option may be ticked) :
    - Conversion from laparoscopy to laparotomy
    - Bowel perforation
    - Bleeding requiring transfusion
    - Embolism, deep venous thrombosis
    - Wound Infection
    - Peritonitis
    - Other: Specify: ….

- Histological diagnosis (pop up list as before) with open text area ("Details")

<u>If follow up examination:</u>

- Complications of adnexal mass: no /yes
- If yes : date of first complication: ….

- And pop up list (you can select more than one):
    - Acute pain
    - Chronic pain
    - Suspected torsion
    - Infection
    - Haemorrhage
    - Rupture
    - Other, please specify: ….

- Death: date
- Death directly or indirectly relatd to adnexal mass?
- cause of death (

- Autopsy findings: specify: ….

Not needed for IOTA phase 5: second stage tests

Consent / information leaflet

Information leaflets are at the discretion of the participating centres.
Approval of the local Ethical Committee for clinical studies is necessary.

Serum tumour markers

Serum CA 125 measurements or other tumour markers are performed locally, using a CA 125 II immunoradiometric assay

Tissue collection

Preferably the whole tumour should be removed. However, representative biopsies may be sufficient (e.g. in advanced ovarian cancer or endometrioma).

Tumour classification

Tumours are classified according to the criteria recommended by the International Federation of Gynecology and Obstetrics (FIGO). In malignant tumours the degree of differentiation is included.

Statistical analysis

For the first objective, a descriptive analysis of complications on all data and stratified for participating center (anonymized) will be performed, as well as an overall Kaplan-Meier curve of 'complication free survival'. Complication free survival is defined as the time to the need for surgery during long-term follow-up. Patients that did not need surgery at the end of the follow-up period are right censored at the time of the last examination.

For the second objective, the discriminatory ability of LR1 and the polytomous model to detect malignancy at the initial visit will be assessed. To this end, the logit of the risk of malignancy given by LR1, logit(LR1), is used to predict malignancy using logistic regression, and the performance assessed with the odds ratio, the c-index and a ROC curve. Linearity of the effect of logit(LR1) will be assessed using spline functions. This analysis is planned one year after the end of the inclusion phase of the trial. Non-operated masses will be classified as benign at the initial visit if there is an absence of a clinical diagnosis of cancer after 1 year of follow up. In addition, the ability of LR1 to predict complications during long-term follow-up will be assessed. This will be done using Cox proportional hazards regression with the logit(LR1) as predictor of complication free survival. Performance will be assessed using the hazard ratio and the c-index within the context of survival analysis. Linearity of the effect of logit(LR1) will be investigated using Schoenfeld residuals.

For the third objective, a multivariable survival analysis will be undertaken using Cox proportional hazards regression or more complex alternatives based on support vector machines (30). The models will be penalized to prevent overfitting, given that not enough events (i.e., patients that need surgery during long term follow-up) are expected for the number of available predictor variables. Internal validation will be assessed through bootstrapping rather than a split of the data in training and test sets (31).

For the fourth objective, longitudinal normative curves will be derived of the changes seen in the characteristics of non-operated masses. Longitudinal analysis techniques such as mixed models, longitudinal support vector machines, and functional linear discriminant analysis (FLDA) (32-34).

Study supervision

Central supervision: the Steering Committee is responsible for the protocol, quality control, interim analyses of the data and final analysis and reporting of the study.

Local supervision: the Principal Investigators are responsible for the data collection in their centres.

Dirk Timmerman is responsible for the co-ordination of the overall IOTA project and the contact between the centres.

Sabine Van Huffel and Bart De Moor are responsible for the data management and the development of new algorithms, in collaboration with Ben Van Calster, Lieveke Ameye and Kirsten Van Hoorde.

Publication policy

The steering committee is responsible for publication of the data in scientific journals. As such the members are co-authors in all resulting clinically relevant papers, to which they made significant contributions. By the time of the final analysis the principal investigators

have to have contributed at least 50 cases to the study. They are co-authors, according to the number of patients they contributed to the study (depending on the journal's restriction of the number of co-authors) on condition that they contribute to writing the papers and read and approve the final version.

Purely mathematical papers without clinical relevance related to the study data are published by S. Van Huffel, B. De Moor and co-workers at ESAT with reference to the IOTA group and the inclusion of as many as possible of the clinical contributors.

The Katholieke Universiteit Leuven represented by its department K.U.LEUVEN RESEARCH & DEVELOPMENT, having its office in 3000 Leuven, Minderbroedersstraat 8A – box 5105, Belgium, VAT number BE 419.052.173 holds intellectual property rights that might result from the IOTA project.

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