Risk of complications in patients with conservatively managed ovarian tumours (IOTA5): a 2-year interim analysis of a multicentre, prospective, cohort study

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Summary

Background Ovarian tumours are usually surgically removed because of the presumed risk of complications. Few large prospective studies on long-term follow-up of adnexal masses exist. We aimed to estimate the cumulative incidence of cyst complications and malignancy during the first 2 years of follow-up after adnexal masses have been classified as benign by use of ultrasonography.

Methods In the international, prospective, cohort International Ovarian Tumor Analysis Phase 5 (IOTA5) study, patients aged 18 years or older with at least one adnexal mass who had been selected for surgery or conservative management after ultrasound assessment were recruited consecutively from 36 cancer and non-cancer centres in 14 countries. Follow-up of patients managed conservatively is ongoing at present. In this 2-year interim analysis, we analysed patients who were selected for conservative management of an adnexal mass judged to be benign on ultrasound on the basis of subjective assessment of ultrasound images. Conservative management included ultrasound and clinical follow-up at intervals of 3 months and 6 months, and then every 12 months thereafter. The main outcomes of this 2-year interim analysis were cumulative incidence of spontaneous resolution of the mass, torsion or cyst rupture, or borderline or invasive malignancy confirmed surgically in patients with a newly diagnosed adnexal mass. IOTA5 is registered with ClinicalTrials.gov, number NCT01698632, and the central Ethics Committee and the Belgian Federal Agency for Medicines and Health Products, number S51375/B32220095331, and is ongoing.

Findings Between Jan 1, 2012, and March 1, 2015, 8519 patients were recruited to IOTA5. 3144 (37%) patients selected for conservative management were eligible for inclusion in our analysis, of whom 221 (7%) had no follow-up data and 336 (11%) were operated on before a planned follow-up scan was done. Of 2587 (82%) patients with follow-up data, 668 (26%) had a mass that was already in follow-up at recruitment, and 1919 (74%) presented with a new mass at recruitment (ie, not already in follow-up in the centre before recruitment). Median follow-up of patients with new masses was 27 months (IQR 14–38). The cumulative incidence of spontaneous resolution within 2 years of follow-up among those with a new mass at recruitment (n=1919) was 20·2% (95% CI 18·4–22·1), and of finding invasive malignancy at surgery was 0·4% (95% CI 0·1–0·6), 0·3% (<0·1–0·5) for a borderline tumour, 0·4% (0·1–0·7) for torsion, and 0·2% (<0·1–0·4) for cyst rupture.

Interpretation Our results suggest that the risk of malignancy and acute complications is low if adnexal masses with benign ultrasound morphology are managed conservatively, which could be of value when counselling patients, and supports conservative management of adnexal masses classified as benign by use of ultrasound.

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Introduction

The management of adnexal masses is an important clinical problem. More than 200 000 women are estimated to undergo exploratory surgery for a pelvic mass in the USA each year, and 22 240 patients are expected to be diagnosed with ovarian cancer in 2018.[1,2] Because of the widespread use of diagnostic imaging, including ultrasound, adnexal masses are often detected incidentally and most of them prove to be benign.[3,4] Most women with an adnexal mass undergo surgery. The probable reason for this liberal use of surgery is a concern that an adnexal mass could prove to be malignant or undergo malignant transformation if left in situ. A further issue is the presumed risk of torsion or rupture of the mass. Women are likely to benefit from surgical removal of an adnexal mass if they have bothersome symptoms, or from being referred to a gynaecological oncologist for evaluation before surgery if malignancy is suspected.[5] However, surgical interventions for asymptomatic patients with benign adnexal masses are

Research in context

Evidence before this study

We searched MEDLINE for articles on conservative management of adnexal (tubal and ovarian) masses, published between Jan 1, 1989, and June 30, 2018, using the keywords ("ultraso*[Title/Abstract]" OR "sonograph*[Title/Abstract]") AND ("ovarian[Title/Abstract]" OR "adnexal[Title/Abstract]") AND ("expectant[Title/Abstract]" OR "conservative[Title/Abstract]" OR "natural history[Title/Abstract]" OR "follow-up[Title/Abstract]"). Of 28 publications containing information on ultrasound follow-up of adnexal lesions presumed to be benign in non-pregnant adult women, eight were prospective cohort studies within ovarian or endometrial cancer screening projects, of which six comprised postmenopausal women or women aged at least 50 years, and seven included only adnexal lesions of a restricted size or a selected tumour type. Three studies were diagnostic accuracy studies, in which adnexal masses were classified as benign if they showed no signs of malignancy after 12 months of follow-up. The screening studies and diagnostic accuracy studies were not designed to study the natural history of adnexal masses during follow-up but mainly report on malignant outcome. One study was a randomised, controlled trial comparing resolution of simple cysts within 6 months between cyst puncture and expectant management. Of the remaining 16 studies, eight were retrospective and eight were prospective. Of the prospective studies, all were single-centre studies on small cohorts of selected patients (eg, only patients with unilocular cysts of a defined size, only patients with dermoid cysts, only premenopausal women, or only postmenopausal women). Cumulative incidence of complications was not reported in any of the studies.

Added value of this study

In this 2-year interim analysis of the prospective IOTA5 study, we describe the outcomes during the first 2 years of follow-up of 1919 newly diagnosed adnexal masses with benign ultrasound morphology (823 masses in postmenopausal patients). To our knowledge, this is the first multicentre prospective study in this area, and it has the largest number of patients in a study of conservative management of adnexal masses so far. When describing the outcome, we accounted for time in follow-up (ie, results need to be reported in terms of cumulative incidences), and our study, to our knowledge, is the first to do so to date. Our results show that the risk of complications in conservatively managed adnexal masses is very low. The 2-year cumulative incidence of spontaneous resolution was 20·2% and for surgical intervention was 16·1%. The cumulative incidence of complications confirmed at surgery or by histology in terms of malignancy was 0·4%, borderline tumour was 0·3%, torsion was 0·4%, and cyst rupture was 0·2%.

Implications of all the available evidence

Our study provides evidence that management of adnexal masses with benign ultrasound morphology expectantly could be safe. Our results could lead to a paradigm shift in recommended management of benign adnexal masses resulting in less surgery. The benefit thereof would be fewer severe surgical complications and associated patient discomfort and lower health costs than are associated with current practices.

expensive and have associated complications. The reported frequency of severe surgical complications for benign adnexal masses that are incidentally detected varies from 3·5% to as high as 15%.[4,6] Conservative management might be an alternative for asymptomatic adnexal masses that are benign, but few large studies describing long-term follow-up exist, and so the natural history of adnexal masses left in situ is largely unknown. This paucity of knowledge makes the clinical management of adnexal masses in women who are asymptomatic or who have minimal symptoms challenging.

By contrast with MRI and CT, ultrasonography is cheap, relatively harmless, accessible, requires no preparation of patients, and has no contraindications. Both subjective assessment of ultrasound images and use of International Ovarian Tumor Analysis (IOTA) ultrasound algorithms are excellent methods to discriminate between benign and malignant adnexal masses.[7–9] As such, ultrasound could be the preferred method for following up patients with an adnexal mass that is judged to not require surgery. To date, however, whether a benign appearance on ultrasound means the adnexal mass is safe to manage conservatively is unknown.

The primary aim of the IOTA phase 5 (IOTA5) study is to estimate the risk of adverse events (including a diagnosis of malignancy, cyst rupture, or torsion) during ultrasound follow-up of adnexal masses with benign ultrasound morphology in patients with no or minimal symptoms. Here, we report outcomes during the first 2 years of ultrasound follow-up of patients selected for conservative management in the IOTA5 study.

Methods

Study design and participants

In the IOTA5 study, an international prospective cohort study, patients with an adnexal mass who had been selected for surgery or conservative management after ultrasound assessment were consecutively recruited from 36 centres in 14 countries. The contributing centres were either oncology referral centres (tertiary centres with a specific gynaecological oncology unit) or other types of centre. Patients were eligible if they were aged at least 18 years at recruitment, and presented with at least

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See Online for appendix

For **IOTA** test see https://www.iotagroup.org

one adnexal mass (ovarian, paraovarian, or tubal) on ultrasound examination. Exclusion criteria were lesions presumed to be physiological if smaller than 3 cm in largest diameter, and denial or withdrawal of informed consent. Pregnancy was not an exclusion criterion. Patients could be recruited into the study even if they had an adnexal mass that was already being followed up at the recruitment centre. If so, the time in follow-up before inclusion was recorded. Local clinicians examined the patient by use of a standardised research protocol.

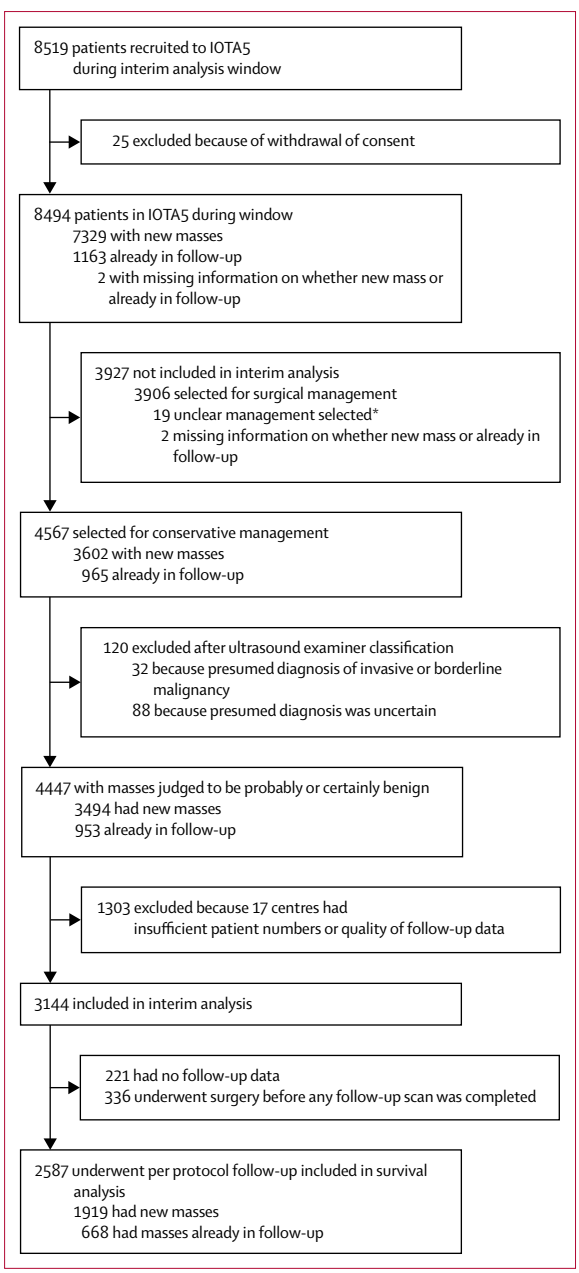

Figure 1: **Study profile**
*Ultrasound examiner forgot to enter selected management onto the IOTA5 electronic form.

We obtained approval from the ethics committee of the University Hospitals Leuven (Leuven, Belgium) as the coordinating centre (B32220095331/S51375), and the local ethics committee of each contributing centre. Patients were required to provide written or oral informed consent.

The study will continue at least until each conservatively managed patient has been followed up for at least 5 years. The primary aim of the IOTA5 study is to estimate the risk of adverse events during follow-up of adnexal masses with benign ultrasound morphology by use of ultrasound. Because of the lack of evidence in the literature, an interim analysis of the study was desirable to estimate the incidence of complications during follow-up. Most false-negative results should be detected within 1 year of follow-up. Malignant transformations could become more frequent during the second year of follow-up, therefore, we did this interim analysis at the 2-year timepoint. The protocol for IOTA5 is available in the appendix (p 20).

Procedures

The ultrasound examiners (DT, LV, ACT, TB, WF, CL, PS, CVH, ED, RF, EE, MJdSB, DF, MJK, VC, JLA, FPGL, FB, LH, MEC, SG, ND, LJ, JK, and AC) who recruited participants collected clinical information and did a transvaginal ultrasound examination using the standardised research protocol (appendix pp 25–35). They used grey scale and colour or power Doppler ultrasound to characterise the morphology and vascularisation of the adnexal mass and described the ultrasound results using IOTA terminology.[10] We had no requirements about level of experience of the ultrasound examiners, but all examiners had passed the IOTA certification test and were required to submit five representative ultrasound images for approval of image quality before they could recruit patients. Ultrasound examiners classified each mass using subjective assessment of the ultrasound images as benign, borderline, or malignant, and specified the degree of certainty with which the diagnosis was made (certain, probable, or uncertain). The presumed histology was also registered (simple, para-ovarian, or salpingeal cyst; serous cystadenoma or cystadenofibroma; endometrioma; teratoma; functional cyst; fibroma or fibrothecoma; hydrosalpinx; mucinous cystadenoma or cystadenofibroma; abscess, salpingitis, or pelvic inflammatory disease; inclusion or peritoneal cyst; rare benign tumour; or not possible to suggest a specific histology). Ultrasound diagnoses were based on knowledge of the typical ultrasound appearance of benign, borderline, and malignant lesions and that of different types of specific adnexal pathology.[11] When the examiner detected multiple masses, the mass with the most complex ultrasound morphology was defined as the dominant mass. If multiple masses had similar morphology, the largest mass or the one best accessible with ultrasound

was denoted as dominant. The dominant mass was used for outcome assessment. The ultrasound examiner suggested surgery or conservative management based on the ultrasound diagnosis (benign or malignant, and borderline tumours considered malignant) and the patient's symptoms. Conservative management included ultrasound and clinical follow-up at intervals of 3 months, 6 months, and then every 12 months thereafter. At each follow-up visit, clinical information including symptoms was collected and a transvaginal ultrasound examination was done according to the research protocol. The transvaginal ultrasound followed the same protocol as the scan at recruitment. The examination included scanning of the uterus, both adnexa, and the whole pelvis outside these organs, supplemented with an abdominal scan if needed. Data were collected on a number of predefined ultrasound variables and a final diagnosis was made by use of pattern recognition (appendix pp 26–35).[11] In this analysis, we include masses that were judged to be probably or certainly benign on the basis of subjective evaluation of the ultrasound images and that were selected for conservative management by the ultrasound examiner. Ultimately, the treating clinician decided on the management plan.

We collected patient-level data using a secure electronic platform developed for the study (IOTA5 Study Screen; astraia software, Munich, Germany). Patients automatically received a unique identifier at enrolment. We encrypted all data communication to ensure data security. Data cleaning was done by a team of biostatisticians (BVC and BDC) and expert ultrasound examiners (DT, WF, and CL), which included sending queries to participating centres to retrieve missing information. Patients and managing clinicians were contacted by telephone using a standardised questionnaire (appendix p 13) to accrue missing information.

Follow-up continued until one of three outcomes was observed: spontaneous resolution (the examiner could no longer visualise the mass in the absence of any surgical intervention), surgical removal of the mass, or death due to any cause. The indication for surgery was based on local practice. We classified the reason for surgery into the following three groups: suspicion of malignancy; pain; or patient request, fertility concerns, or opportunistic or prophylactic removal (appendix p 2). We classified the findings at surgery into the following six groups: invasive malignancy; borderline tumour; torsion; cyst rupture; minor mass complications (inflammation or infection, or adhesions); or no mass complications (appendix p 2). Histological examinations were done at the local centre. We did not use central review of pathological samples because we previously observed little difference in reported outcomes between local and central pathology reports.[12] We classified malignant tumours according to the criteria recommended by the International Federation of Gynaecology and Obstetrics.[13]

	n	Without follow-up information	Operated on before any follow-up scan	Included in analysis
Malmo, Sweden	674	16 (2%)	67 (10%)	591 (88%)
Leuven, Belgium	377	12 (3%)	14 (4%)	351 (93%)
Rome, Italy	316	40 (13%)	44 (14%)	232 (73%)
Genk, Belgium	245	24 (10%)	43 (18%)	178 (73%)
Athens, Greece	211	24 (11%)	97 (46%)	90 (43%)
Monza, Italy	209	32 (15%)	10 (5%)	167 (80%)
Stockholm, Sweden	166	4 (2%)	16 (10%)	146 (88%)
Lisbon, Portugal	140	0	8 (6%)	132 (94%)
Milan, Italy	125	9 (7%)	0	116 (93%)
Katowice, Poland	98	10 (10%)	8 (8%)	80 (82%)
Pamplona, Spain	95	19 (20%)	10 (10%)	66 (69%)
London, UK	83	2 (2%)	2 (2%)	79 (95%)
Milan 2, Italy	82	2 (2%)	3 (4%)	77 (94%)
Milan 3, Italy	82	7 (8%)	1 (1%)	74 (90%)
Florence, Italy	62	7 (11%)	4 (6%)	51 (82%)
Trieste, Italy	59	0	4 (7%)	55 (93%)
Tampa, USA	58	6 (10%)	0	52 (90%)
Cagliari, Italy	42	4 (9%)	2 (5%)	36 (86%)
Nottingham, UK	20	3 (15%)	3 (15%)	14 (70%)
Total	3144	221 (7%)	336 (11%)	2587 (82%)

Data are n or n (%).

Table 1: **Patients in IOTA5 with a mass judged to be benign by ultrasound assessment and selected for conservative management included in 2-year interim analysis by site**

Outcomes

The main outcomes of this interim analysis were incidence of spontaneous resolution of the mass, surgical confirmation of torsion or cyst rupture, and surgical confirmation of invasive malignancy or a borderline tumour within 2 years of study entry in patients with a newly diagnosed mass (not already in follow-up in the centre before recruitment) among participants selected for conservative management of an adnexal mass judged to be benign on ultrasound.

Statistical analysis

We present descriptive statistics separately for participants without any information (ie, those lost to follow-up before any follow-up scan was done) and for those with information after recruitment (ie, with follow-up scans or who underwent surgery before a follow-up scan was done) to check for differences in background information between these groups

Because no accurate estimates of the three outcomes of conservative management could be found in the literature, we aimed to collect data for at least 3000 patients with an adnexal mass and at least 1000 patients with an adnexal mass managed conservatively in the IOTA5 study (for the study protocol see appendix p 20). For a study centre to be included in our analysis, we required them to have recruited at least 50 patients, and have good quality follow-up data for at least 70% of the recruited patients. We

	All patients (n=3144)	New masses (n=2410)*	New masses with follow-up (n=1919)	Masses already in follow-up (n=734)*†
Patient age at recruitment, years				
Median	48 (37–63)	47 (35–61)	48 (36–62)	55 (42–67)
Range	18–98	18–98	18–98	18–93
Postmenopausal	1429 (45%)	1001 (42%)	823 (43%)	428 (58%)
Gynaecological symptoms during the year preceding inclusion	1760 (56%)	1358 (56%)	1069 (56%)	402 (55%)
Time in follow-up at recruitment, months				
Median	NA	NA	NA	18 (6–36)
Range	NA	NA	NA	<1–266
Tumour type using IOTA terminology[10]				
Unilocular	1912 (61%)	1474 (61%)	1149 (60%)	438 (60%)
Unilocular—solid	138 (4%)	97 (4%)	79 (4%)	41 (6%)
Multilocular	788 (25%)	601 (25%)	505 (26%)	187 (25%)
Multilocular—solid	122 (4%)	96 (4%)	80 (4%)	26 (4%)
Solid	184 (6%)	142 (6%)	106 (6%)	42 (6%)
Presence of solid components	444 (14%)	335 (14%)	265 (14%)	109 (15%)
Maximum diameter of lesion, mm				
Median	41 (30–55)	42 (30–56)	41 (30–54)	40 (29–53)
Range	5–456	7–456	7–216	5–157
Bilateral masses	359 (11%)	269 (11%)	212 (11%)	90 (12%)
Ultrasound examiner´s subjective impression				
Certainly benign	2282 (73%)	1716 (71%)	1336 (70%)	566 (77%)
Probably benign	862 (27%)	694 (29%)	583 (30%)	168 (23%)
Ultrasound examiner´s presumed diagnosis				
Simple, para-ovarian, or salpingeal cyst	762 (24%)	583 (24%)	480 (25%)	179 (24%)
Serous cystadenoma or cystadenofibroma	744 (24%)	511 (21%)	428 (22%)	233 (32%)
Endometrioma	591 (19%)	458 (19%)	331 (17%)	133 (18%)
Teratoma	347 (11%)	268 (11%)	195 (10%)	79 (11%)
Functional cyst	182 (6%)	177 (7%)	158 (8%)	5 (1%)
Fibroma or fibrothecoma	158 (5%)	116 (5%)	92 (5%)	42 (6%)
Hydrosalpinx	128 (4%)	104 (4%)	85 (4%)	24 (3%)
Mucinous cystadenoma or cystadenofibroma	105 (3%)	84 (3%)	67 (3%)	21 (3%)
Abscess, salpingitis, or pelvic inflammatory disease	37 (1%)	34 (1%)	21 (1%)	3 (<1%)
Inclusion or peritoneal cyst	36 (1%)	26 (1%)	20 (1%)	10 (1%)
Rare benign tumour	3 (<1%)	2 (<1%)	1 (<1%)	1 (<1%)
Not possible to suggest a specific histology	51 (2%)	47 (2%)	41 (2%)	4 (<1%)
Operated on before any follow-up scan	336 (11%)	314 (13%)	0	22 (3%)
Outcome events observed within 24 months after inclusion‡				
Spontaneous resolution	406	374	374	32
Surgery performed	685	598	288	87
Invasive malignancy	11	8	7	3
Borderline tumour	9	7	5	2
Torsion	16	14	7	2
Cyst rupture	12	10	4	2
Minor mass complications§	113	97	47	16
No mass complications	524	462	218	62
Death, any cause	27	20	20	7

Data are median (IQR) or n (%), unless otherwise specified. Baseline characteristics for all patients with new masses, with and without follow-up data are shown in the appendix (p 5). IOTA=International Ovarian Tumour Analysis. NA=not applicable. *Includes patients without follow-up after inclusion in the study. †This number includes 668 patients undergoing follow-up as stated by the protocol, and patients undergoing surgery before follow-up in the framework of the study (n=22), and patients without any follow-up information after inclusion into the study (n=44). ‡The number of cases with specific outcomes are presented here, proportions are not included for these variables because follow-up time was not taken into account. §Includes inflammation or infection, or adhesions.

Table 2: **Baseline characteristics**

defined good follow-up data as a recorded study outcome or a last follow-up visit 10 months or later after inlcusion. The 70% cutoff was chosen arbitrarily, because it seemed reasonable (appendix pp 3, 4).

We calculated the follow-up time from recruitment visit until one of the three outcomes occurred. In the absence of an outcome we calculated follow-up time until the last visit and included these patients as censored observations in the analysis. We estimated median follow-up using the reverse Kaplan-Meier method.[14] We analysed follow-up data using cumulative incidence curves in the context of competing-risks survival analysis.[15] Cumulative incidence curves for a specific outcome classified other outcomes as competing events. We summarised cumulative incidence curves by reporting the estimated cumulative incidence with 95% CIs at 12 months and 24 months of follow-up.

Some participants underwent surgery before they had a follow-up scan, even though the ultrasound examiner had suggested conservative management. We did not include these patients in the survival analysis but we describe the reason for surgery and the histological outcome for them separately. Some participants did not have any information after their initial visit and so we did not include them in the survival analysis.

Our main analysis is the survival analysis of only patients with a new mass (a mass that was not already in follow-up in the centre before recruitment). This analysis provides the most correct estimates of cumulative incidences by avoiding survival bias because patients with masses already in follow-up before recruitment are a selected group and probably have a higher proportion of benign and stable tumours. We made this assumption because if any patients had malignant tumours that were misdiagnosed as benign or rapidly growing tumours or tumours that became symptomatic during follow-up, they would have been diagnosed and surgically removed, leaving only the more indolent tumours for continued follow-up. To provide transparent reporting of all data in our study, we also show the results of the survival analysis including those patients already in follow-up at inclusion.

Finally we did prespecified subgroup analyses for the variables of tumour type (unilocular, unilocular–solid, multilocular, multilocular–solid, and solid), presumed diagnosis, subjective assessment (certainly benign, probably benign), lesion size (median split method and description on the cumulative incidence at cutoffs of 3 cm, 4 cm, 5 cm, 7 cm, and 10 cm), and menopausal status at recruitment. If menopausal status was uncertain (eg, because of hysterectomy), we classified patients aged 50 years or older as postmenopausal. We report cumulative incidences at 12 months and 24 months for menopausal status, and only at 24 months for the other subgroup analyses.

We did our statistical analysis using R (version 3.4.4). IOTA 5 is registered with ClinicalTrials.gov (NCT01698632), and the central Ethics Committee and the Belgian Federal Agency for Medicines and Health Products (S51375/B32220095331).

	n (%)	Reason for surgery			Time between recruitment scan and surgery,† months
		Suspicion of malignancy	Pain	Other*	
Major mass complications					
Primary invasive stage III	1 (<1%)	0	0	1	2
Borderline stage I	2 (1%)	0	0	2	2 and 3
Benign histology with torsion	7 (2%)	0	6	1	1 (0–3)
Benign histology with rupture	6 (2%)	0	2	4	3 (0–7)
No major mass complications					
Endometrioma	75 (24%)	2	48	25	2 (1–4)
Simple or parasalpingeal cyst	67 (21%)	1	19	47	1 (0–3)
Serous cystadenoma	48 (15%)	4	9	35	2 (1–3)
Teratoma	46 (15%)	1	9	36	3 (1–5)
Mucinous cystadenoma	16 (5%)	2	6	8	2 (2–4)
Hydrosalpinx or salpingitis	14 (4%)	0	9	5	1 (0–2)
Physiological cyst	13 (4%)	1	0	12	1 (0–2)
Fibroma	12 (4%)	1	2	9	1 (1–2)
Abscess	3 (1%)	0	2	1	0, 3, and 14
Peritoneal pseudocyst	2 (1%)	0	1	1	0 and 5
Rare benign or no specific histology	2 (1%)	1	0	1	0 and 6
All	314 (100%)	13	113	188	2 (0–3)

Data are n and median (IQR), unless otherwise stated. *Includes patient request, fertility concerns, and opportunistic or prophylactic removal. †For three or fewer cases, the individual numbers are shown, and for four or more cases, median (IQR) are shown.

Table 3: **Reason for surgery and histological or surgical findings in patients who were operated on before a follow-up visit**

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or the writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Jan 1, 2012, and March 1, 2015, 8519 patients were recruited into IOTA5, of whom 25 (<1%) were excluded from our analysis because they withdrew their consent (figure 1). The ultrasound examiners suggested conservative management for 4567 (54%) patients, of whom 4447 (97%) were judged to have a mass that was probably or certainly benign (appendix pp 3, 4). Of those suggested for conservative management, 3602 (79%) had a new mass, of whom 3494 (97%) were judged to have a mass that was probably or certainly benign. For our primary analysis, we excluded 17 centres because they recruited too few patients (ie, n<50) or provided follow-up data of insufficient quality (appendix pp 3, 4).

Of the 3144 patients who were being managed conservatively in the remaining 19 centres (figure 1;

	All masses (n=2587)		New masses (n=1919)	
	12 months	24 months	12 months	24 months
Study endpoint event				
Spontaneous resolution of cyst	13·2% (11·8–14·5)	16·3% (14·8–17·7)	16·5% (14·8–18·2)	20·2% (18·4–22·1)
Surgery performed	9·0% (7·9–10·2)	14·6% (13·2–16·0)	10·3% (8·9–11·7)	16·1% (14·3–17·7)
Death, any cause	0·5% (0·2–0·7)	1·1% (0·7–1·6)	0·5% (0·2–0·8)	1·2% (0·6–1·7)
Surgery by indication				
Suspicion of malignancy	1·4% (0·9–1·8)	2·1% (1·6–2·7)	1·4% (0·9–2·0)	2·0% (1·3–2·6)
Pain	2·6% (1·9–3·2)	4·2% (3·4–5·0)	2·6% (1·9–3·4)	4·5% (3·5–5·5)
Patient request, fertility concerns, or opportunistic or prophylactic removal	5·1% (4·2–6·0)	8·2% (7·1–9·3)	6·2% (5·1–7·3)	9·5% (8·2–10·9)
Surgery by outcome				
Invasive malignancy	0·3% (0·1–0·5)	0·4% (0·2–0·7)	0·4% (0·1–0·6)	0·4% (0·1–0·6)
Borderline tumour	0·2% (<0·1–0·4)	0·3% (0·1–0·5)	0·2% (<0·1–0·4)	0·3% (<0·1–0·5)
Torsion	0·2% (<0·1–0·4)	0·3% (0·1–0·6)	0·3% (<0·1–0·5)	0·4% (0·1–0·7)
Cyst rupture	0·2% (<0·1–0·4)	0·2% (<0·1–0·4)	0·2% (<0·1–0·3)	0·2% (<0·1–0·4)
Minor mass complications*	1·2% (0·7–1·6)	2·4% (1·8–3·0)	1·2% (0·7–1·7)	2·7% (1·9–3·4)
No mass complications	7·0% (6·0–8·0)	10·9% (9·6–12·1)	8·1% (6·8–9·3)	12·1% (10·6–13·6)
Probability of being in follow-up†	77·3% (75·6–78·9)	68·0% (66·1–69·8)	72·7% (70·6–74·6)	62·5% (60·2–64·7)

Data are cumulative incidence (95% CI). *Includes inflammation or infection, or adhesions. †The probability of being in follow-up at 12 months or 24 months is the estimated probability of not having a study outcome (spontaneous resolution, surgery, or death of any cause) after 12 months or 24 months of conservative management—ie, 100 minus the sum of the cumulative incidences of each study outcome.

Table 4: **Cumulative incidence of study outcomes at 12 and 24 months**

table 1), 734 (23%) patients had a previous mass and were already being followed-up in the recruitment centre before inclusion, and 2410 (77%) had a new mass (table 2). Median age of all remaining participants was 48 years (IQR 37–63), 1429 (45%) were postmenopausal, 1912 (61%) had a dominant mass that was a unilocular cyst (one cyst locule, no solid components), and 444 (14%) had a dominant mass containing solid components (table 2). We had no follow-up information after the recruitment visit for 221 (7%) of 3144 patients, of whom 177 (80%) had a new mass (appendix p 5). No substantial differences were seen between the baseline demographic and histological characteristics of patients with new masses who did and did not have follow-up data (appendix p 5). Even though conservative management was suggested, 336 (11%) of 3144 patients underwent surgery before a follow-up visit, of whom 314 (93%) had a newly diagnosed mass (table 1). Of these 314 patients, 13 (4%) were operated on because of suspicion of malignancy by the managing clinician and 113 (36%) because of pain (table 3). Median time between recruitment scan and surgery was 2 months (IQR 0–3). At surgery, stage III primary ovarian cancer was found in one (<1%) patient, stage I borderline tumours in two (1%) patients, torsion in seven (2%) patients, and cyst rupture in six (2%) patients.

For the 1919 patients with a new mass at recruitment and who received per-protocol follow-up, median follow-up was 27 months (IQR 14–38). A histogram showing the follow-up time at all patient visits is in the appendix (p 11). For patients with new masses, the 2-year cumulative incidence of spontaneous resolution was 20·2% (95% CI 18·4–22·1), of any surgical intervention was 16·1% (14·3–17·7), of surgical intervention because of suspected malignancy was 2·0% (1·3–2·6), and of death due to any cause was 1·2% (0·6–1·7; table 4; figure 2; appendix p 12).

The 2-year cumulative incidence of finding an invasive malignancy in patients with new massess was 0·4% (95% CI 0·1–0·6), a borderline tumour was 0·3% (<0·1–0·5), torsion was 0·4% (0·1–0·7), and cyst rupture was 0·2% (<0·1–0·4; table 4; figure 3). Among these 1919 patients, we observed the following complications within 24 months of follow-up: seven (<1%) invasive malignancies (three stage I, two stage III, and two secondary metastatic tumours), five (<1%) borderline tumours, seven (<1%) cases of torsion, and four (<1%) of cyst ruptures. Six (50%) of 12 malignancies were diagnosed with surgery within 3 months after inclusion, three (25%) 4–6 months after inclusion, two (17%) 11 months after inclusion, and one (8%) 20 months after inclusion (appendix pp 6, 7). Four of the ovarian cancers were type I (three stage I and one stage III), and one was a type II ovarian cancer (stage III; appendix pp 6, 7).

The cumulative incidences of outcomes at 12 months and 24 months for patients at all centres, including the 17 centres excluded because they recruited too few patients or provided follow-up data of insufficient quality, are shown in the appendix (p 10). For all 36 centres, the 2-year cumulative incidence was 18·9% (95% CI 17·3–20·5) for spontaneous resolution, 15·1% (13·6–16·6) for surgery, and 0·3% (0·1–0·5) for finding an invasive

malignancy. These results are not substantially different from the main analysis.

For the prespecified subgroup analysis of outcomes by menopausal status, we defined patients as premenopausal (n=1096) and postmenopausal (n=823). Among premenopausal patients, the 2-year cumulative incidence was 29·8% (95% CI 27·0–32·6) for spontaneous resolution and 18·7% (16·3-21·1) for surgery; whereas in postmenopausal patients, the 2-year cumulative incidence was 7·5% (5·6–9·3) for spontaneous resolution and 12·6% (10·2–14·9) for surgery. 192 (18%) of 1096 premenopausal patients and 96 (11%) of 823 postmenopausal patients underwent surgery during the first 2 years of follow-up. The cumulative incidence for finding an invasive malignancy was 0·1% (95% CI <0·1–0·3) in premenopausal patients and 0·7% (0·1–1·3) in postmenopausal patients. The subgroup analysis for premenopausal and postmenopausal patients who presented with a new mass is in the appendix (p 8).

The results of the other subgroup analyses are shown in the appendix (p 9). The cumulative incidence at 2 years of spontaneous resolution was high for masses presumed to be functional cysts (83·2%, 95% CI 75·8–88·4) but low for masses presumed to be teratomas (2·2%, <0·1–4·3), fibromas or fibrothecomas (2·6%, <0·1–6·0), and mucinous cystadenomas or cystadenofibromas (4·7%, <0·1–9·8). Furthermore, the cumulative incidence at 2 years of surgery and of torsion increased with increasing size of the mass. Teratoma was the presumed diagnosis with the highest cumulative incidence of torsion at 2 years (1·3%, <0·1–3·0).

Discussion

In this interim analysis, in patients selected for conservative management of an adnexal mass with benign ultrasound morphology, the 2-year cumulative incidence of spontaneous resolution was 20·2% and surgical intervention was 16·1%, and the 2-year cumulative incidence of major complications, including invasive malignancy, torsion, and cyst rupture, were each less than 0·5%; and of minor mass complications was 2·7%. To our knowledge, IOTA5 is the largest prospective study describing the outcome of consecutively recruited participants with conservatively managed adnexal masses. By contrast with most other prospective cohort studies,[16–23] we report results for all patients, including those who underwent surgery before a follow-up visit despite having been recommended for conservative management. Many ultrasound centres and operators from different countries with different levels of experience participated, which increases the likelihood that our results are generalisable. We applied thorough data cleaning to make our data more reliable, and we present our results as cumulative incidences based on survival analysis. To our knowledge, no previous studies have presented their data using this statistical method, the benefit of which is that the analysis takes into account all available follow-up data and the evolution over time of the numbers at risk by applying censoring.

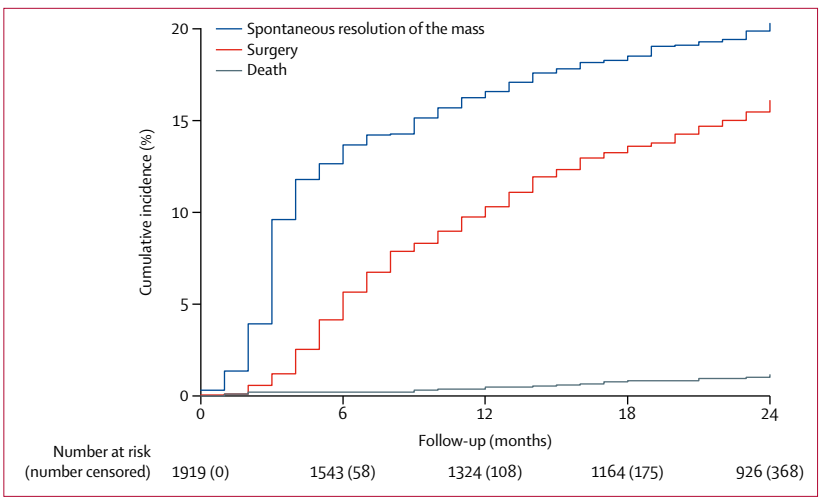

Figure 2: **Cumulative incidence curves of spontaneous resolution of mass, surgery performed, or death**
This figure is based on patients who presented with a new mass and who actually received follow-up (n=1919).

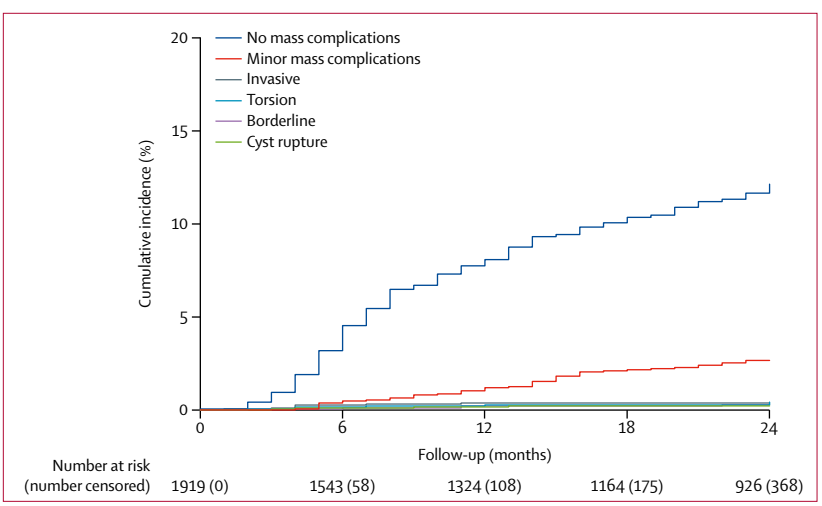

Figure 3: **Cumulative incidence of outcomes found during surgery, stratified by surgical outcome**
Includes patients who presented with a new mass and who actually received follow-up (n=1919).

Some patients who were selected for conservative management were excluded or censored in the survival analysis because of loss to follow-up; however, loss to follow-up reflects clinical reality. For example, some of the patients referred to a study site for a second opinion who were selected for follow-up thereafter opted for management at their primary centre because of travel distances or other logistical problems, while others moved to another city or country. We made great efforts to minimise loss to follow-up, including several rounds of queries to study sites and managing clinicians, structured telephone interviews with patients, and we only included centres with sufficient quantity and quality of follow-up data in our primary analysis. We do not believe that loss to follow-up resulted in major bias because we saw no

important differences in patient or tumour characteristics between patients with and without follow-up information.

The low cumulative incidence of complications we observed suggests that conservative management of adnexal masses with a benign ultrasound appearance with clinical and ultrasound follow-up could be a safe management option, in terms of complications during the first 2 years of follow-up. By contrast with most previously published studies on follow-up of adnexal masses,[16–31] our study is prospective, large, comprised multiple centres, had very broad inclusion criteria, and, to our knowledge, is the only study that has used survival analysis to estimate the incidence of complications. This study provides the most solid evidence to date of the natural history of adnexal masses left in situ.

Our results are not directly comparable with those in the published literature because of differences in inclusion criteria, follow-up time, and outcomes assessed. Nevertheless, in agreement with our results, torsion of an adnexal lesion during follow-up is rare in published studies.[16,17,21,24,27,28] To our knowledge, no published study has reported on the incidence of cyst rupture. The results of our subgroup analysis in pre-menopausal patients are similar to those in the largest single-centre study published so far in a similar population.[17] Among 166 premenopausal patients with 192 masses who were followed up over a median of 4 years, 74 (39%) masses resolved spontaneously, and 40 (21%) were surgically removed because of changes in morphology or size (n=22), patient request (n=13), appearance of a new tumour (n=4), and symptoms (n=1). In the surgical group, the authors found one borderline tumour and one stage IA mucinous adenocarcinoma.[17] After at least 1 year of follow-up in 134 postmenopausal patients, Valentin and Akrawi[18] reported that 39 (29%) patients had spontaneous resolution of their mass and that 12 (9%) underwent surgery. The discrepancy between the results of this study and ours might be explained at least partly by differences in the size of the lesions (only 9% of cysts in Valentin and Akrawi's study were at least 50 mm in diameter) and ultrasound morphology of the masses (76% of their masses were unilocular cysts). The difference in the incidence of surgery between premenopausal and postmenopausal patients observed in our study might be explained by differences in indications for surgery between these two populations. Premenopausal patients undergo surgery more often because of pain than postmenopausal patients do. Premenopausal patients often have endometriomas that cause pain, whereas endometriomas are rarely associated with symptoms in postmenopausal patients. The most common indication for surgery during follow-up was patient request, fertility concerns, or opportunistic or prophylactic removal. Because operative risks are generally higher in older women than in younger women, postmenopausal women are less prone to undergo surgery than premenopausal women and doctors are more reluctant to perform surgery on older women than on younger women.

The clinical challenge is to balance any possible benefit of removing presumably benign adnexal masses in women with no or minimal symptoms against the risks of surgery. The presumed benefit of removing masses with benign ultrasound morphology is prevention of a benign lesion becoming malignant and avoiding leaving a malignant lesion in situ because of misdiagnosis. However, in an observational study[32] in which almost all benign adnexal lesions that were detected at screening for ovarian cancer were surgically removed, after an average follow-up of 15 years, ovarian cancer mortality was not lower than would be expected in the general female population, taking into account age distribution and time in follow-up. Randomised trials on ovarian cancer screening, in which substantial numbers of benign lesions were surgically removed in the screened groups, have not shown a reduction in ovarian cancer mortality in the screened groups compared with the control groups.[4,6] The explanation for these findings is probably that ovarian borderline tumours and cancers that develop from benign lesions are type I tumours (low-grade serous, low-grade endometrioid, clear cell, and mucinous). These tumours develop slowly, have a good prognosis, and account for only a small proportion of ovarian cancer mortality. Type II tumours (high-grade serous and undifferentiated carcinomas, and malignant mixed mesodermal tumours) might arise from fallopian tube precursors and have aggressive behaviour and a less favourable prognosis.[33] In our study, of 1919 patients with a new adnexal mass who were managed conservatively, five (<1%) were diagnosed with ovarian cancer (three stage I and two stage III), five (<1%) with an ovarian borderline tumour, and two (<1%) with secondary metastases in the ovaries from another primary tumour. All but one of these malignancies (a borderline tumour) were surgically removed within 1 year of follow-up, and nine of them within the first 6 months. Four of the ovarian cancers were type I (three stage I and one stage III) and one was a type II ovarian cancer (stage III). The short time interval between recruitment of these patients and diagnosis of malignancy at surgery suggests that these cases might have been misdiagnosed initially. Moreover, retrospective review of the ultrasound images of the malignant lesions showed that many of them manifested ultrasound signs that suggested malignancy at inclusion and so were misdiagnosed as benign. We find it unlikely that the prognosis of the borderline tumours and stage I tumours was made worse by the delay in diagnosis. If, and to what extent, the prognosis of the two stage III ovarian cancers and two secondary cancers was affected is difficult to determine. Longer follow-up than in this study is needed to estimate the incidence of a change from benign to malignant ultrasound morphology in an

adnexal mass. The disadvantage of surgical removal of all adnexal masses is the risk of short-term and long-term surgical complications. Severe surgical complications (eg, injury to hollow viscus, deep vein thrombosis, pulmonary embolism, wound breakdown, bowel obstruction, and myocardial infarction) associated with removal of benign adnexal masses detected at screening for ovarian cancer in women aged 50–74 years have been reported with frequencies of 15·1% (163 of 1080)[4] and 3·5% (57 of 1634).[6] We do not have complete information on intraoperative and postoperative surgical complications for our own study population. If the published complication rates were applicable to our postmenopausal population, and if we had operated on all 823 postmenopausal patients with a new adnexal mass in our study, then we could speculare that 29–123 of them would most likely have suffered severe surgical complications. Instead, only 96 (12%) post-menopausal patients with new masses underwent surgery, which means that severe complications were probably avoided in 26–109 postmenopausal women. The complication rate associated with adnexal surgery in premenopausal women is not well known but is probably lower than in postmenopausal women. The risk of complications during and after surgery is closely related to comorbidity and disorders such as diabetes, heart disease, and lung disease. With increasing age the number of medical disorders increases, and at least 50% of people older than 80 years have three medical disorders.[34] In addition to intraoperative and post-operative complications, long-term complications of surgery can occur—eg, adhesion formation that can cause bowel obstruction, chronic pelvic pain, or fertility problems.

Because of the international, multicentre nature of our study and the consecutive recruitment of a large study population by ultrasound examiners with different levels of experience, our results could be generalisable to other patient populations. As many as 49·1% (3602 of 7329) of patients with a newly diagnosed adnexal mass were deemed suitable for conservative management at the first visit. However, the proportion of patients judged to be suitable for follow-up differed between the centres in our study, probably due to differences in patient characteristics and the level of experience of ultrasound examiners. Selection for conservative management is not only directed by the ultrasound morphology of an adnexal mass; rather, clinical reasons could dictate selection for conservative management—eg, a comorbidity that makes the patient unfit for surgery, or previous adnexal surgery resulting in reduced ovarian reserve in a premenopausal patient. Based on the results of this interim analysis with 2 years of follow-up, adnexal masses presumed to be benign on ultrasound seem suitable for ultrasound and clinical follow-up at intervals of 3 months, 6 months, and then every 12 months. Before management recommendations can be made, results from the extended follow-up of our participants who were conservatively managed are needed. Future research should also investigate whether the application of objective criteria or prediction models could improve safe selection of patients for follow-up.

Our results suggest that the risk of malignancy and acute complications is low if adnexal masses with benign ultrasound morphology are managed conservatively. Such knowledge could be of great value when counselling patients and supports conservative management of adnexal masses that are classified as benign by use of ultrasound. This information could lead to a reduction in the number of women who undergo surgery for benign adnexal pathology.

Contributors

DT, LV, ACT, TB, and BVC conceived and designed the study. DT, LV, ACT, TB, WF, CL, PS, CVH, ED, RF, EE, MJdSB, DF, MJK, VC, JLA, FPGL, FB, LH, MEC, SG, ND, LJ, JK, and AC enrolled patients and acquired data. DT, BVC, WF, CL, and BDC did the data cleaning. DT, LV, TB, BVC, BDC, and WF wrote the statistical analysis plan. BVC and BDC analysed the data, with support from LW and JYV. DT, LV, ACT, TB, BVC, WF, CL, BDC, LW, IV, and JYV interpreted the data. DT, LV, ACT, TB, BVC, WF, CL, BDC, LW, and JYV wrote the first draft of the manuscript, which was then critically reviewed and revised by the other authors. All authors approved the final version of the manuscript for submission. DT and BVC had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of interests

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