# Rischio di torsione, rottura e cancerizzazione delle cisti benigne non rimosse

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# Epidemiology of ovarian masses

1. Widespread use of imaging techniques → large number of ovarian masses incidentally detected (vast majority benign)
2. 200,000 women/year undergo surgery for a pelvic mass in the USA
3. 22,240 ovarian cancers/year
4. Many women undergo unnecessary surgery because of fear of cancerization, rupture, torsion

# Prevalence and types of cysts

UKCTOCS randomized controlled trial

48053 postmenopausal women, annual TVS:

- 4367 women had an ovarian abnormality
- 5.3% unilocular cysts
- 2.3% multilocular cysts
- 0.7% unilocular-solid
- 0.7% multilocular-solid
- 0.2% solid tumors

Sharma et al., UOG 2012

# US findings in a large unselected population

*(Smith-Bindman, JAMA, 2019)*

To quantify the risk of ovarian cancer based on US characteristics of ovarian masses

72093 women > 18 years

118778 TVS (jan 1997-dec 2008)

Follow up until December 2011 (minimum 3 years)

- → Normal ovaries, ovaries not identified
- → Simple cysts >10 mm
- → Complex cysts (multiple septations, thick septa, papillary projections, solid components…)
- → Solid masses

# US findings in a large unselected population

*(Smith-Bindman, JAMA, 2019)*

72093 women overall

Prevalence of simple cysts:

- 24% younger than 50 yrs
- 13% older than 50 yrs

(the estimated number of patients with simple cysts decreased with cyst size)

Prevalence of complex cysts:

- 8% younger than 50 yrs
- 5% older than 50 yrs

# Behaviour of ovarian cysts during menopause – one year after TVS

To evaluate occurrence and natural history of simple cysts during menopause: PLCO screening trial (55-74 years)

- 14% had at least a simple cyst
- The one-year incidence of new simple cyst: 8%
- 32% had no cyst one year later
- 8% of pts with a simple cyst showed multiple simple cyst one year later
- Simple cysts did not increase incidence of invasive ovarian cancer

Graenlee et al., Am J Obstet Gynecol 2010

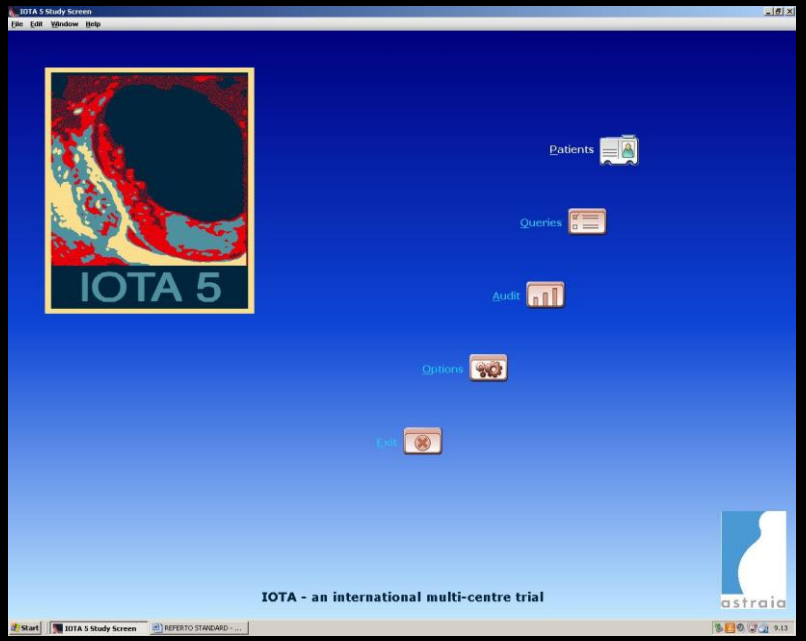
# What to do with benign looking masses?

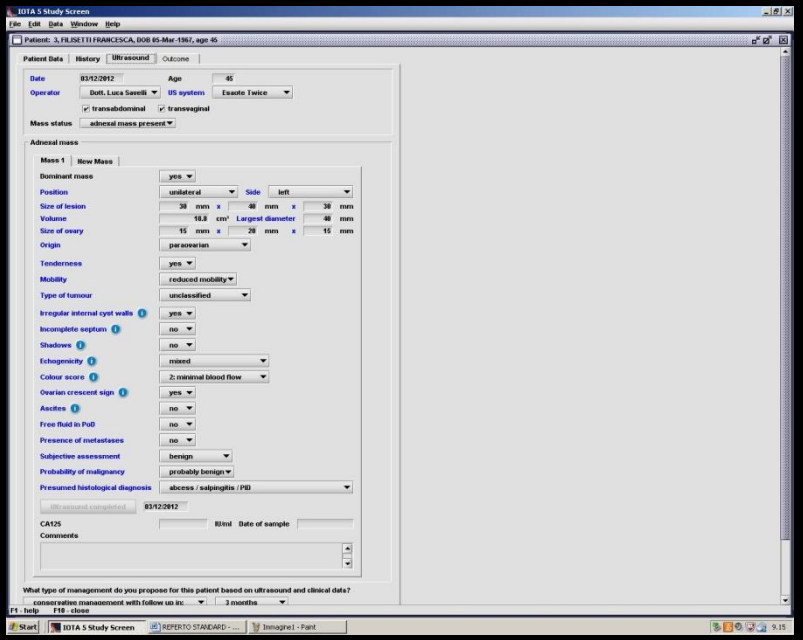
Rate of torsion, rupture
cancerization
of benign looking cysts

# IOTA 5: International prospective cohort study

36 centers , 14 countries

Collection of data in a single database



# IOTA 5: International prospective cohort study

Inclusion criteria:

Patients >18 yrs with at least one adnexal mass

Exclusion criteria:

lesions <3 cm presumed to be physiological

All US examiners passed IOTA certification test

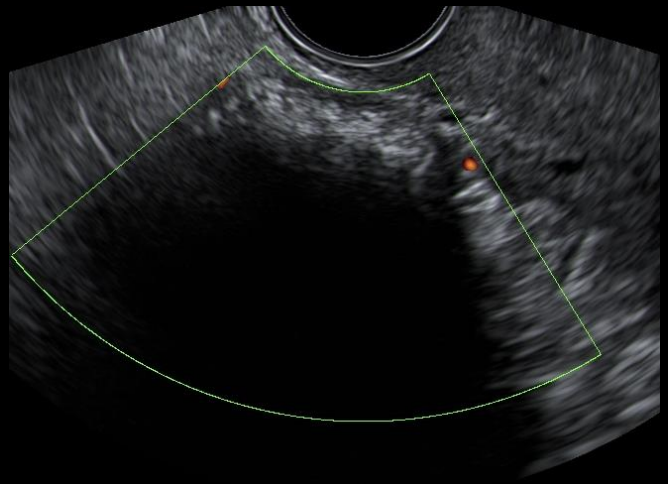
Masses subjectively classified as benign, BOT or malignant

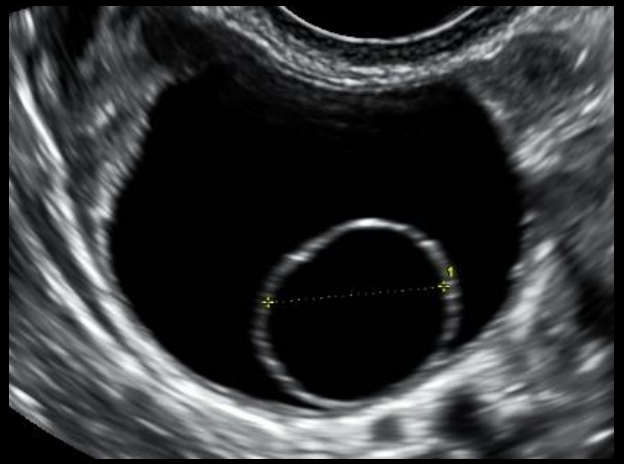
Degree of certainty recorded

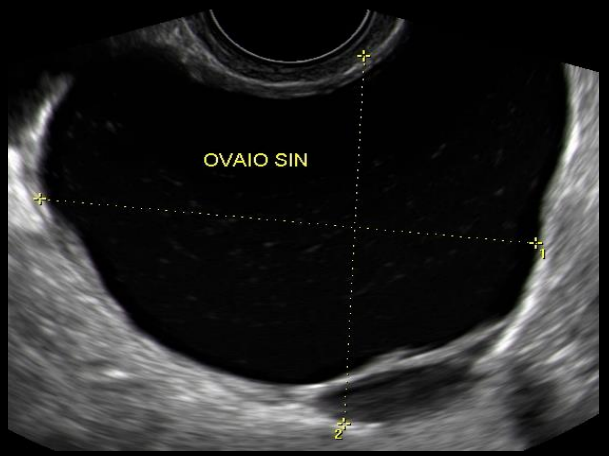
Presumed histology was registered

Examiners suggested management based on US & symptoms

# Examples of benign-looking masses occasionally detected








# IOTA 5: International prospective cohort study

Sonographic follow up continued until:

- spontaneous resolution of the mass
- surgical removal of the mass
- death of the patient

Reasons for surgery:

- suspicion of malignancy
- pain
- patient request
- fertility concerns
- opportunistic removal

# IOTA 5: International prospective cohort study

Findings at surgery classified as:

- invasive malignancy
- BOT
- torsion
- cyst rupture
- Minor mass complications (inflammation, infection, adhesions)
- No mass complications

Outcomes

- spontaneous resolution
- surgical confirmation of torsion or rupture

# Details of participating centers at recruitment

| Centre | Principal investigator | N total | Initial policy | | | Judged to be benign, initial policy conservative | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Unk | Surgery | Conservative | N | No FU information | Surgery without FU | Good FU information |
| Malmo, Sweden | Lil Valentin | 973 | 0 | 289 | 684 | 674 | 16 (2%) | 67 (10%) | 652 (97%) |
| Bologna, Italy | Luca Savelli | 917 | 0 | 360 | 557 | 540 | 111 (21%) | 31 (6%) | 315 (58%) |
| Rome, Italy | Antonia Carla Testa | 721 | 1 | 396 | 324 | 316 | 40 (13%) | 44 (14%) | 258 (82%) |
| Leuven, Belgium | Dirk Timmerman | 602 | 0 | 216 | 386 | 377 | 12 (3%) | 14 (4%) | 342 (91%) |
| Athens, Greece | Ekaterini Domali | 572 | 0 | 359 | 213 | 211 | 24 (11%) | 97 (46%) | 185 (88%) |
| Stockholm, Sweden | Elisabeth Epstein | 454 | 0 | 267 | 187 | 166 | 4 (2%) | 16 (10%) | 160 (96%) |
| Genk, Belgium | Caroline Van Holsbeke | 446 | 0 | 198 | 248 | 245 | 24 (10%) | 43 (18%) | 205 (84%) |
| Monza, Italy | Robert Fruscio | 430 | 0 | 200 | 230 | 209 | 32 (15%) | 10 (5%) | 165 (79%) |
| Milan, Italy | Dorella Franchi | 418 | 0 | 292 | 126 | 125 | 9 (7%) | 0 | 113 (90%) |
| Lublin, Poland | Artur Czekierdowski | 363 | 0 | 107 | 256 | 253 | 77 (30%) | 29 (11%) | 163 (64%) |
| Prague, Czech Republic | Daniela Fischerova | 347 | 0 | 185 | 162 | 160 | 64 (40%) | 3 (2%) | 75 (47%) |
| Cagliari, Italy | Stefano Guerriero | 182 | 0 | 140 | 42 | 42 | 4 (9%) | 2 (5%) | 36 (86%) |
| Krakow, Poland | Anna Knafel | 175 | 2 | 147 | 26 | 25 | 2 (8%) | 14 (56%) | 23 (92%) |
| Pamplona, Spain | Juan Luis Alcazar | 154 | 0 | 59 | 95 | 95 | 19 (20%) | 10 (10%) | 73 (77%) |
| Lisbon, Portugal | Maria José dos Santos Bernardo | 146 | 0 | 6 | 140 | 140 | 0 | 8 (6%) | 138 (99%) |
| Milan 2, Italy | Valentina Chiappa | 143 | 0 | 59 | 84 | 82 | 2 (2%) | 3 (4%) | 78 (95%) |
| Bari, Italy | Doriana Scardigno | 143 | 2 | 109 | 32 | 31 | 10 (32%) | 10 (32%) | 17 (55%) |
| Katowice, Poland | Marek Jerzy Kudla | 139 | 0 | 40 | 99 | 98 | 10 (10%) | 8 (8%) | 88 (90%) |
| Udine, Italy | Alberto Rossi | 117 | 0 | 115 | 2 | 2 | 0 | 2 (100%) | 2 (100%) |
| Milan 3, Italy | Francesco Paolo Giuseppe Leone | 114 | 0 | 32 | 82 | 82 | 7 (8%) | 1 (1%) | 73 (89%) |
| Trieste, Italy | Francesca Buonomo | 112 | 0 | 53 | 59 | 59 | 0 | 4 (7%) | 57 (97%) |
| London, UK | Tom Bourne | 100 | 0 | 12 | 88 | 83 | 2 (2%) | 2 (2%) | 77 (93%) |
| Florence, Italy | Maria Elisabetta Coccia | 95 | 0 | 31 | 64 | 62 | 7 (11%) | 4 (6%) | 49 (79%) |
| Cairo, Egypt | Mona Aboulghar | 64 | 0 | 21 | 43 | 43 | 14 (33%) | 1 (2%) | 20 (48%) |
| Milan 4, Italy | Chiara Lanzani | 64 | 0 | 21 | 43 | 42 | 12 (28%) | 11 (26%) | 29 (67%) |
| Nottingham, UK | Nandita Deo | 62 | 0 | 40 | 22 | 20 | 3 (15%) | 3 (15%) | 15 (75%) |
| Tampa, USA | Lauri Hochberg | 60 | 0 | 2 | 58 | 58 | 6 (10%) | 0 | 50 (86%) |
| Tienen, Belgium | Thierry Van den Bosch | 60 | 0 | 8 | 52 | 51 | 39 (76%) | 0 | 6 (12%) |
| Beijing, China | Jing Zhang | 60 | 0 | 40 | 20 | 16 | 4 (25%) | 9 (56%) | 11 (69%) |
| Lisbon 2, Portugal | Fatima Alves | 49 | 1 | 30 | 18 | 17 | 2 (12%) | 1 (6%) | 13 (76%) |
| Maurepas, France | Ulrike Metzger | 48 | 0 | 4 | 44 | 42 | 11 (26%) | 3 (7%) | 26 (62%) |
| Cremona, Italy | Paola Pollastri | 47 | 0 | 29 | 18 | 18 | 1 (6%) | 0 | 12 (67%) |
| Aarschot, Belgium | Thierry Van den Bosch | 45 | 1 | 4 | 40 | 40 | 27 (67%) | 1 (2%) | 10 (25%) |
| Paris, France | Perrine Capmas | 28 | 14 | 14 | 0 | 0 | 0 | 0 | 0 |
| Catania, Italy | Maria Concetta Blanco | 28 | 0 | 17 | 11 | 11 | 2 (18%) | 1 (9%) | 6 (54%) |
| Vienna, Austria | Samir Helmy | 16 | 0 | 4 | 12 | 12 | 0 | 0 | 9 (75%) |
| Total | | 8494* | 21 | 3906 | 4567 | 4447 | 597 (13%) | 452 (10%) | 3551 (80%) |

# Details of adnexal tumors

| | |
|---|---|
| Tumour type using IOTA terminology | |
| Unilocular | 1354 (61%) |
| Unilocular-solid | 88 (4%) |
| Multilocular | 574 (26%) |
| Multilocular-solid | 92 (4%) |
| Solid | 125 (6%) |
| Presence of solid components | 305 (14%) |
| Maximum diameter of lesion (mm) | 42 (30-56), 7-216 |
| Bilateral masses | 242 (11%) |
| Ultrasound examiner´s subjective impression | |
| Certainly benign | 1588 (71%) |
| Probably benign | 645 (29%) |
| Ultrasound examiner´s presumed diagnosis | |
| Simple/para-ovarian/salpingeal cyst | 552 (25%) |
| Serous cystadeno(fibr)oma | 470 (21%) |
| Endometrioma | 407 (18%) |
| Teratoma | 249 (11%) |
| Functional cyst | 172 (8%) |
| Fibro(theco)ma | 103 (5%) |
| Hydrosalpinx | 96 (4%) |
| Mucinous cystadeno(fibr)oma | 81 (4%) |
| Abscess / salpingitis / PID | 33 (1%) |
| Inclusion/peritoneal cyst | 24 (1%) |
| Rare benign tumour | 1 (<1%) |
| Not possible | 45 (2%) |

# Risk of complications in patients with conservatively managed ovarian tumors

*(Froyman et al, Lancet Oncol, 2019)*

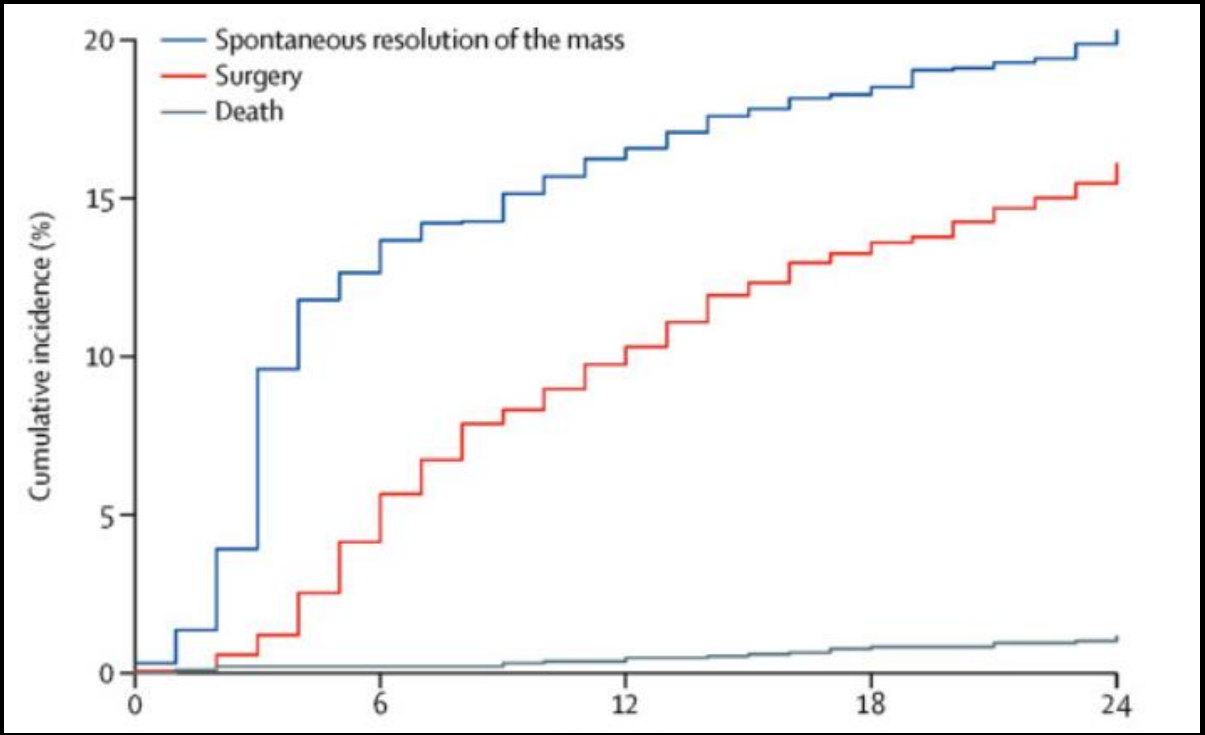
8519 patients recruited in IOTA 5

3144 (37%) selected for conservative management

2587 Pts with follow up at 2 yrs

- incidence of spontaneous resolution 20%
- incidence of any surgical intervention 16%
- incidence of surgical intervention for suspected malignancy: 2%
- Incidence of death for any cause: 1.2%

# Cumulative incidence of spontaneous resolution, surgery, death




Months of follow up

# Results of IOTA 5 @ 2 yrs FU:

- incidence of invasive malignancy 0.4%
  - 0.1% premenopause, 0.7% postmenopause
- incidence of BOT 0.3%
- incidence of torsion 0.4%
  - Increased with size, teratoma had highest incidence @ 2 yrs (1.3%)
- incidence of rupture 0.2%

# How to deal with benign looking adnexal masses?

- Surgical removal of all benign lesions?
  - complication rate 2-15%; medical expenses
  - does not reduce ovarian cancer incidence
- Left unmonitored
  - Some could progress to ovarian cancer
  - Some may be wrongly categorized as benign
- Role of single CA 125 in benign looking cysts
  - Does not improve mathematical models
  - Does not add to an expert sonologist

# Should we remove all persistent adnexal masses?

Prostate, Lung, Colorectal, Ovarian Cancer Screening trial (PLCO Screening trial) (15735 women 55-74 yrs)

10 screening centers in the USA (annual TVS):

- 2217 (14%) women had an ovarian cyst
- 1080 underwent surgery
- 163 (15%) experienced a total of 222 major complications (20.6 complications per 100 surgeries)
- Survival rates were similar in screened and non screened women

Buys et al., JAMA 2011

# Conservative management

1. Might be an alternative per asymptomatic benign-looking ovarian cysts
2. But:
    1. No data about natural history of cysts left in situ
    2. Few large studies about follow up exist
    3. Protocols for follow up? For how long? How often?
3. Which is the rate of disappearance?
4. Which real risk of malignancy over time?

# Theoretical benefits of serial ultrasound follow up

- US follow up increase in morphologic complexity has been used as the basis for surgical decisions in the single arm of Kentucky and UKCTOCS trials
  - Half of the masses resolved spontaneously
  - Reduction of surgical complications
- TVS follow up is advantageous because cost effective and low risk
- Provides greater margin of safety than dismissing and extant mass based on presumed benign status

Ormsby, Diagnostics 2017
Cooper, Curr Women's health review, 2009


AZIENDA OSPEDALIERA S. ORSOLA - MALPIGHI
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SEGRETERIA ORGANIZZATIVA
BOLOGNA
Savoia Hotel Regency
25-26 SETTEMBRE 2020

*...Thanks!*

*...grazie!*

# What to do with benign looking masses?

Will be discussed later on

# Practical drawbacks of unnecessary imaging

- Wasted time
- False positive results
- Unnecessary surgery
- Anxiety

Grady, D et al. *Less is more: how less health care can result in better health*. Arch Intern Med, 2010; 170(9):749-750

# Ultrasound follow up of an adnexal mass has the potential to safe lives

*(Ornsby, Pavlik, van Nagell. Am J Obstet Gynecol, 2015)*

- Systematic review of the literature, 169 articles
- GRADE criteria to evaluate quality of evidence

1. Serial TVS leads to improved PPV for ovarian cancer
2. Shift to detection at an earlier stage
3. Malignancy found in stable masses that eventually enlarge and increased in morphologic complexity
4. Reduction of unnecessary benign surgeries

# First International Consensus Report on Adnexal Masses – Management recommendation

*(Blanc et al. J Ultrasound med, 2017)*

- International panel of experts
- Examination state of the science on asymptomatic adnexal masses
- Formulate recommendations for assessment and management

# First International Consensus Report on Adnexal Masses – Management recommendation

*(Glanc et al. J Ultrasound med, 2017)*

Benign masses → serial transvaginal sonographic follow up should be considered

1. Many cysts will resolve
2. Decrease number of operations
3. Evaluation of size & morphology
4. Risk stratification should be based on Pattern Recognition or Risk Prediction Models

# International Consensus Report on Adnexal Masses – Management recommendation

*(Glanc et al. J Ultrasound med, 2017)*

- Color Doppler sonography is recommended
- Spectral Doppler parameters alone do not discriminate
- Simple or unilocular cysts do not need surgery
- Short term follow up may be appropriate for unilocular cysts with 1 or few solid avascular papillary projections
- Caution in diagnosing fibrotechomas (overlap with malignant masses)

# First International Consensus Report on Adnexal Masses – Management recommendation

*(Glanc et al. J Ultrasound med, 2017)*

Indeterminate masses on initial sonograpy → second step evaluation may include:

- referral to an expert sonologist
- Serial ultrasonography (follow up scans are appropriate to monitor those cysts difficult to evaluate)
- Application of established risk prediction models
- Correlation with MRI
- Referral to a Gyne Oncologist

# The problem of ultrasound: subjectivity and technical considerations

1. Subjectivity (operator dependent imaging modality)
2. No definition of *expert sonographer*
3. Small lesions may be missed due to technical factors (motion, obesity, poor acoustic penetration, myomas, position of the ovaries…)
4. Large masses cannot be entirely evaluated
5. Limited inter-observer agreement on presence of solid components/papillae (IOTA), solid component versus collection of septa…

# The problem of ultrasound: subjectivity and technical considerations

1. Pseudofindings due to inflammation, abscess, infection
2. Uncertainty cannot be eliminated
3. → Reasons for serial ultrasound imaging approach
4. Repeated TVS monitoring does not negatively impact psycosocial well-being *

* Barret et al. Psycosocial morbidity associated with ovarian cancer screening. BJOG, 2014

# Risk of malignant ovarian cancer based on US findings in a large unselected population

*(Smith-Bindman, JAMA, 2019)*

"the best way to minimize the harms of unnecessary surveillance in incidental benign lesions is to avoid surveillance"

Simple cysts:

- highly prevalent
- Lack of association with ovarian cancer
- No elevated risk compared to women with normal ovaries

→ Should be considered normal and frequent finding and IGNORED

# How often to monitor? For how long?

1. Serial sonography is a beneficial strategy, but there are limited prospective data to support an exact interval and duration (Glanc et al., J Ultrasound med, 2017)
2. Low-risk adnexal masses can undergo an initial 3-month follow-up, with those that remain stable or decreasing in size being examined every 12 months for 5 years (van Nagell et al., Obstet Gynecol, 2016)

# Disclaimer

1. "As research continues, the recommendations regarding management of adnexal cysts may vary"
2. Stay tuned with scientific research and evidence
3. Always consider the patient, not *only* the cyst
4. Reassuring the patient will positively impact on well-being

# Ovarian cancer: statistics

- Common genital tract malignancy in developed countries:
  - 1-2% life-time risk
  - 66700 women will develop OC each year
  - 41900 will die from the disease
  - Peak during menopause
- Most lethal malignancy:
  - Overall 45% 5-years survival

# The fact

- Usually late presentation
  - 70% advanced stage → 10% 5 yrs survival
  - 30% early stage → survival up to 95%
- Over 90% are sporadic

EFFECTIVENESS OF SCREENING?

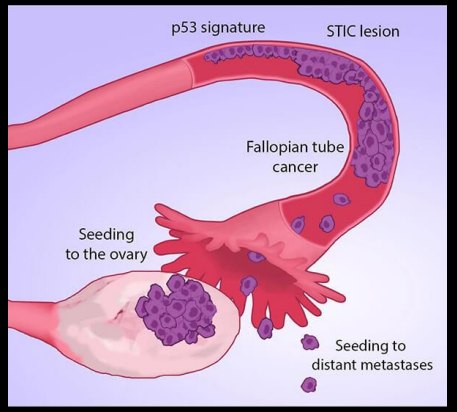
# Origin and pathogenesis of OC

Traditional view: various serous tumors arise *de novo* from single layer epithelium (mesothelium) of the ovary

- Metaplastic changes occur following proliferation/repair of ovulation defect

Precursor *in situ*: "Serous intraepithelial tubal carcinoma" (STIC)

- Fimbriated end of Fallopian tube
- Mullerian (not mesothelial) origin



# Types of OC: pathogenesis and molecular alterations

Type I: slow-growing cancers (25% of OC, 10% deaths). Stepwise progression

- Low-grade serous, low-grade endometrioid
- Clear-cell, mucinous and Brenner carcinomas, BOT

Type II: more aggressive OC (75% of OC, 90% deaths). Arise de novo

- High grade serous and endometrioid
- Undifferentiated tumors, carcinosarcomas

P53 mutation in over 80% cases

# Imaging of Type 1 and 2 OC

Currently no data to differentiate the subtypes of ovarian cancers by means of ultrasound imaging

Cysts with lesser degrees of complexity may harbor micro foci of ovarian cancer → a wide spectrum of abnormal morphology should be considered at TVS

# Screening for OC: the fact

- On the basis of available data on screening trials, screening for ovarian cancer cannot be recommended in asymptomatic women
- A huge amount of adnexal masses/ovarian cysts are diagnosed on a daily basis as a result of:
  - Pelvic symptoms (pain/bloating/bleeding…)
  - Incidental finding at US, MRI, CT performed for other indications
  - diffusion of US machines (bed-side sonography)