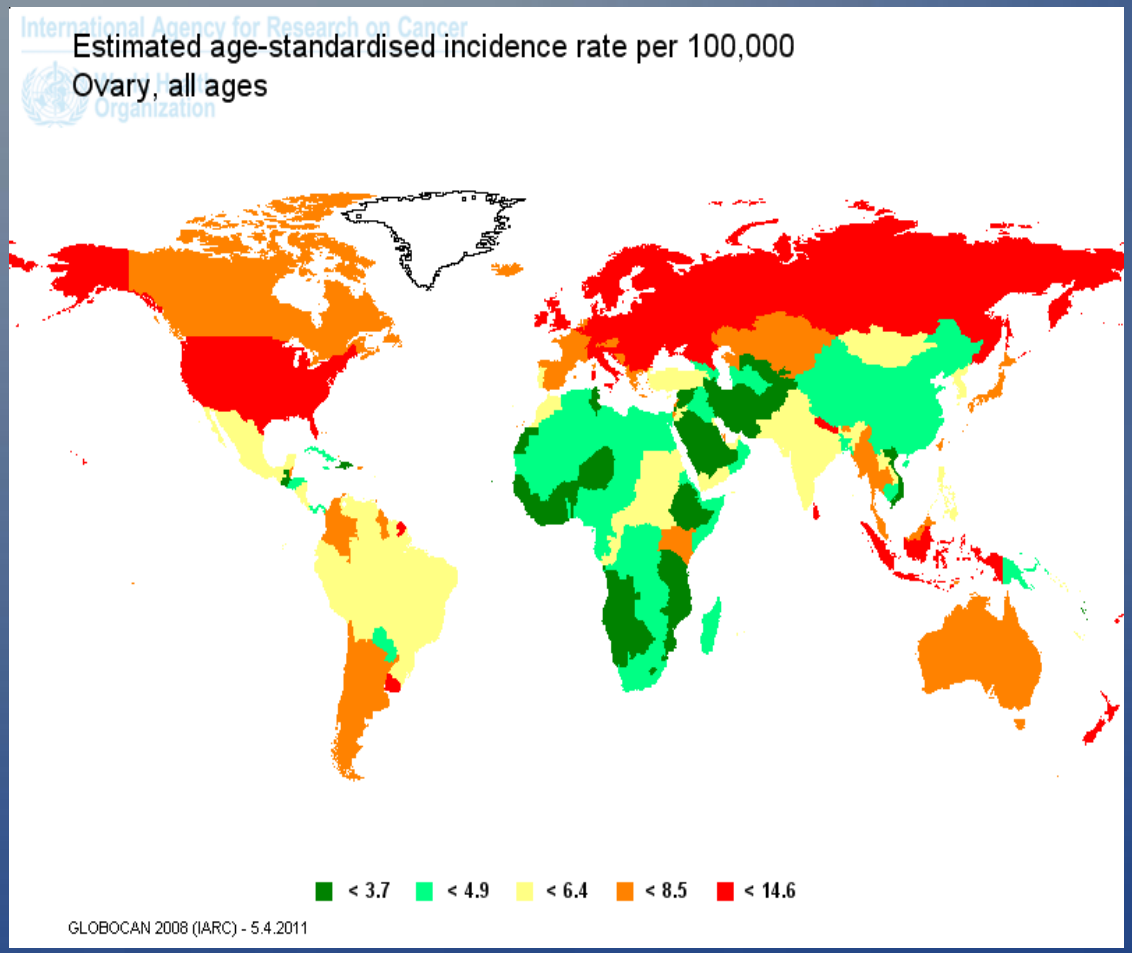
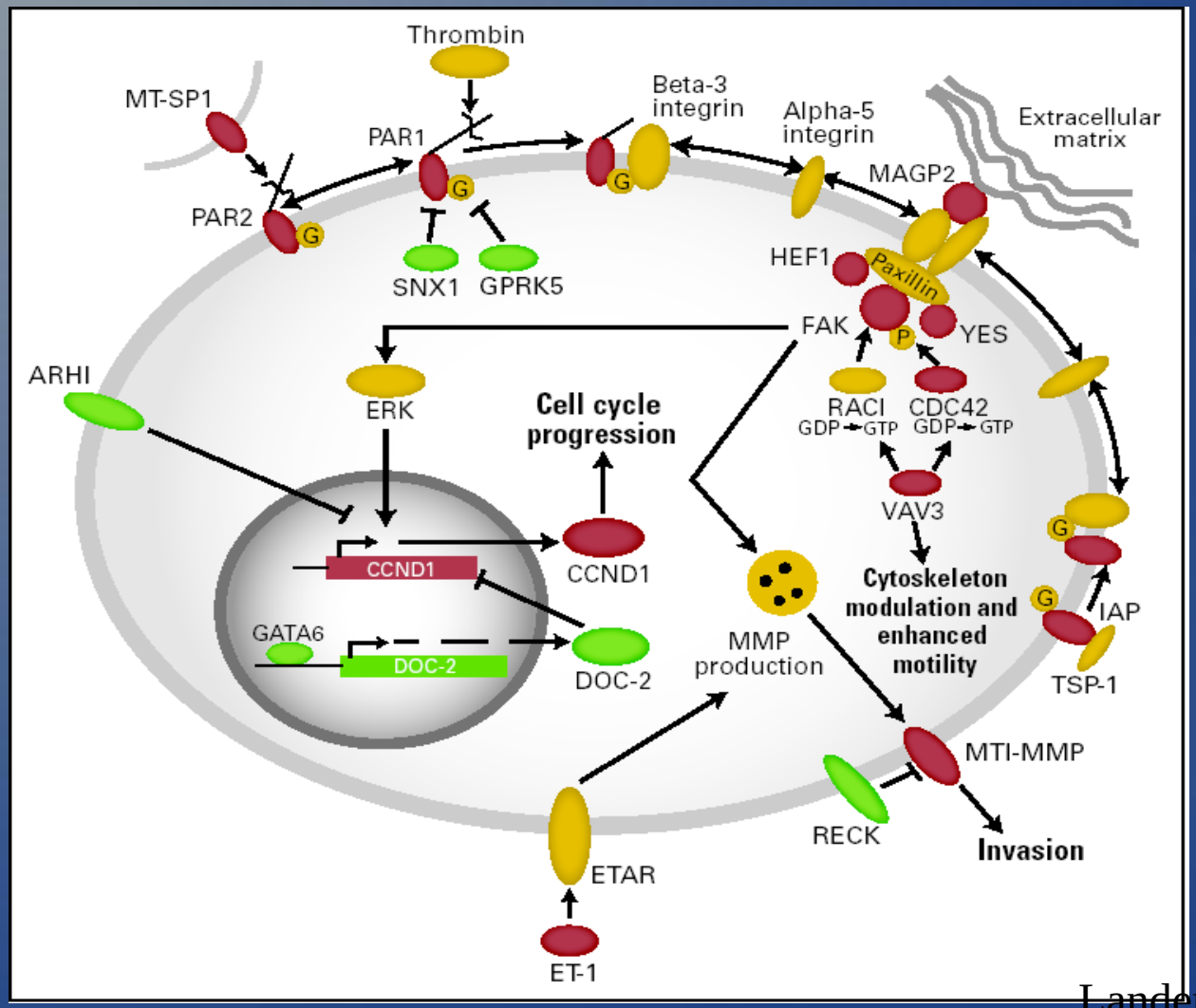
CARCINOMA OVARICO



224.747 nuovi casi/anno
140.163 decessi/anno

Pathway identification by microarray analysis.



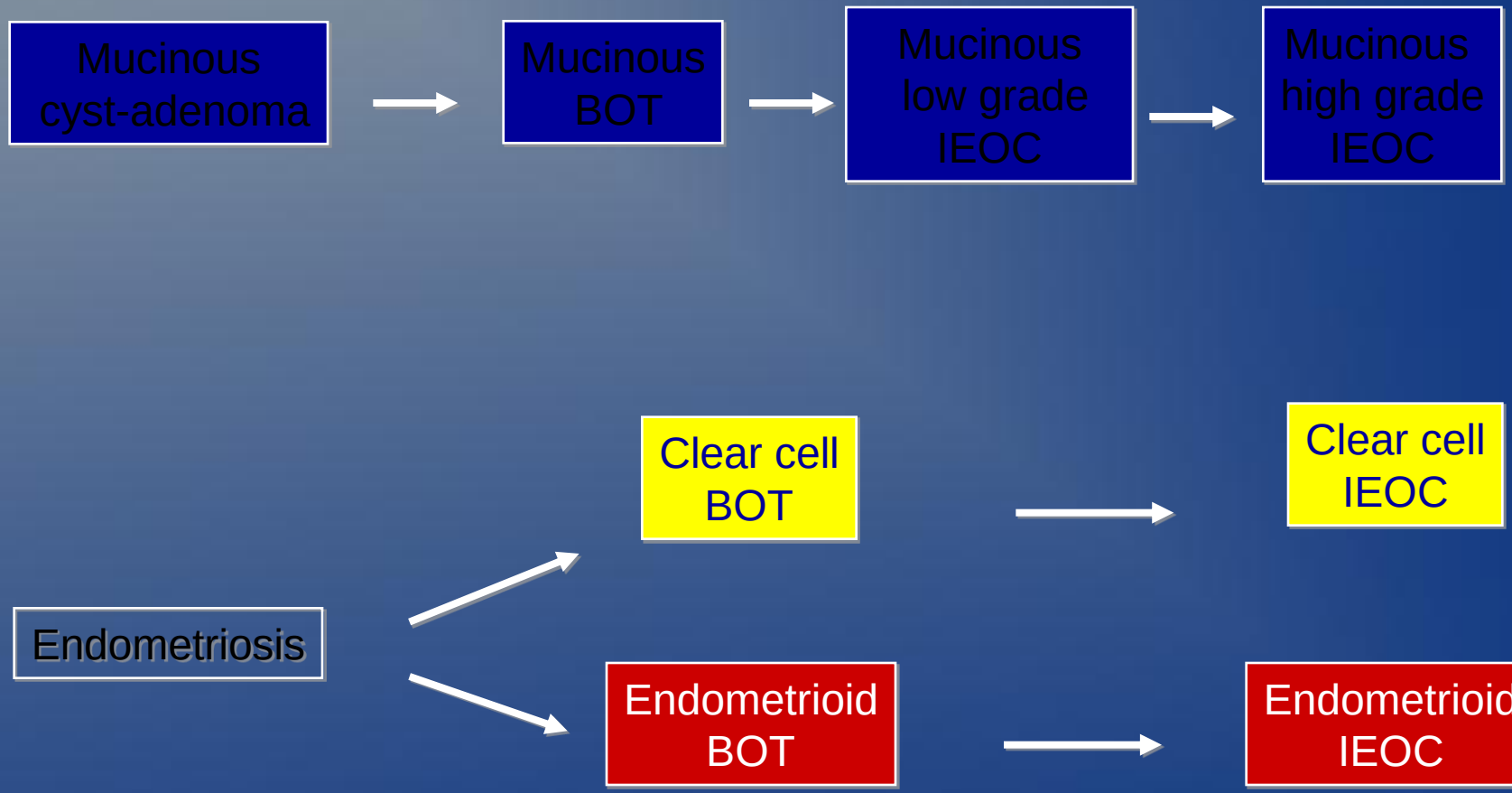
Landen et al. JCO, 2008

Epithelial Ovarian Cancer (Pathogenesis)

Molecular evidence

- Serous Borderline — *B-RAF, K-RAS*
- Serous Ca — *p53*, LOH 17q21 (*BRCA1*), 13q12-q14 (*BRCA2, RB1*)
- Mucinous tumors — *K-RAS*
- Endometrioid Ca — Beta-catenin, *PTEN*, PIK3CA, Microsatellite instability
- Clear cell Ca — Microsatellite instability, K-RAS, TGFB RII

Pathogenesis of non serous ovarian cancer



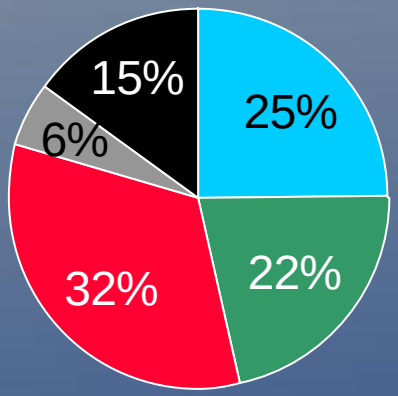
Low grade and high grade Ovarian Serous Tumors are separate diseases

OVARIAN CANCER

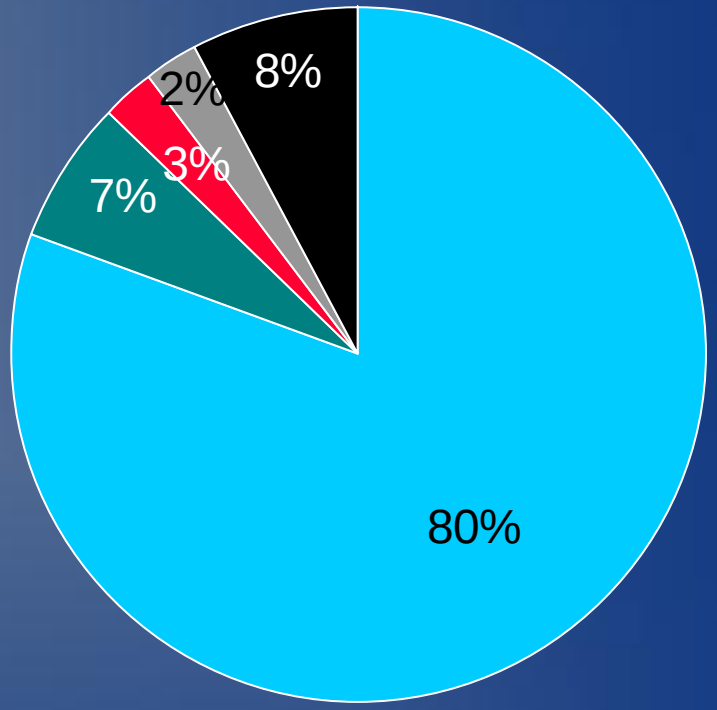
Type1 Adenoma-Carcinoma	Type2 "de novo"
endometrioid clear cell mucinous LG serous	HG serous

Ovarian Histology by Stage

GOG 0157
Stage I-II



GOG 0182
Stage III-IV

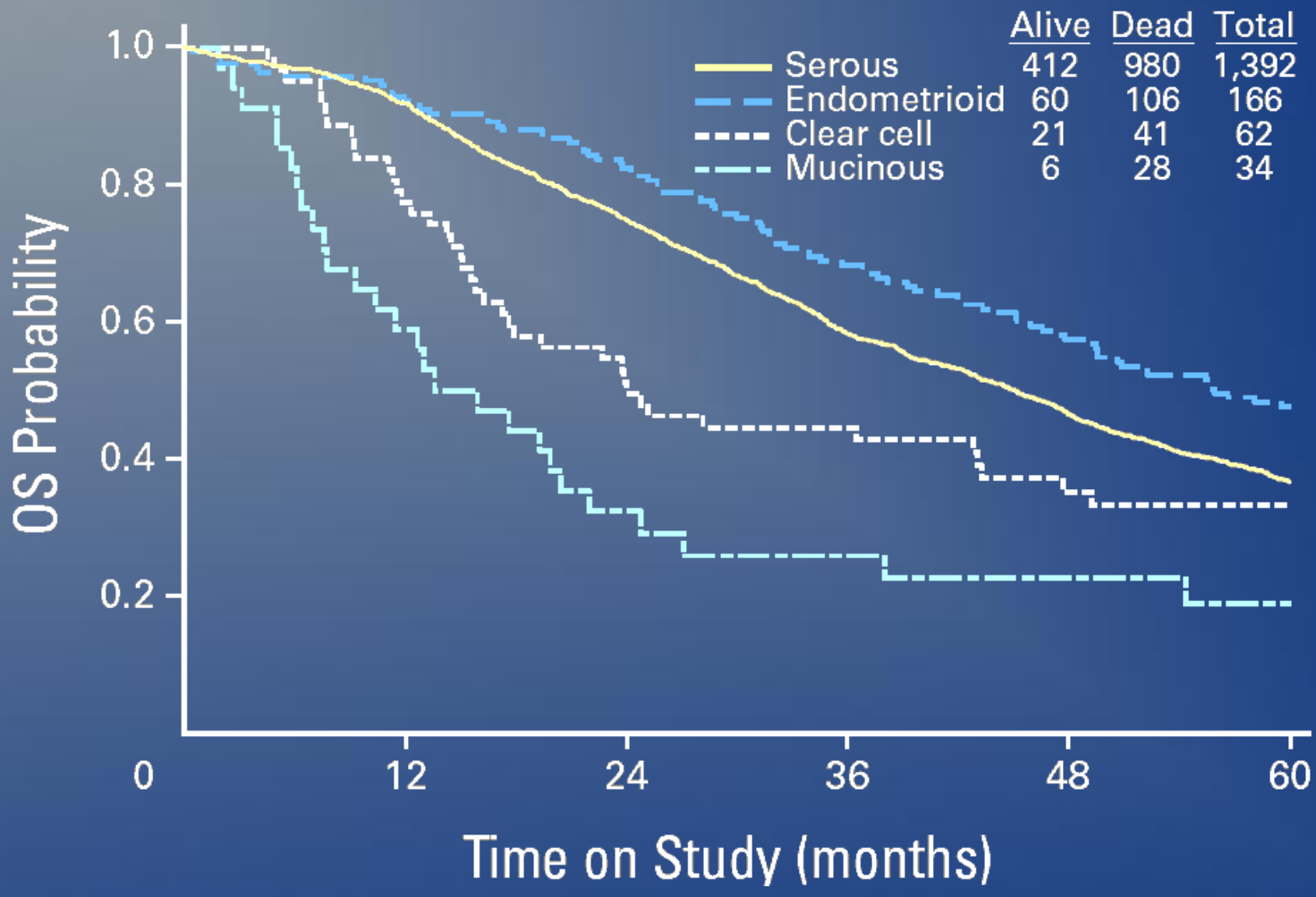


Serous Endometrioid Clear Cell Mucinous Mixed

Bell JG. *Gynecol Oncol* 102:432-9, 2006

Bookman MA, et al. *J Clin Oncol* (10.1200/JCO.2008.19.1684)

GOG Prognostic Analysis: Histology



Winter WE, *J Clin Oncol* 25:3621-3627, 2007

Origin of ovarian cancer

Past

Ovary: Mullerian inclusion cyst.

But…histologically the single layer mesotelium overlying the ovaries bears no resemblance to serous,endometrioid, mucinous, clear cell carcinomas

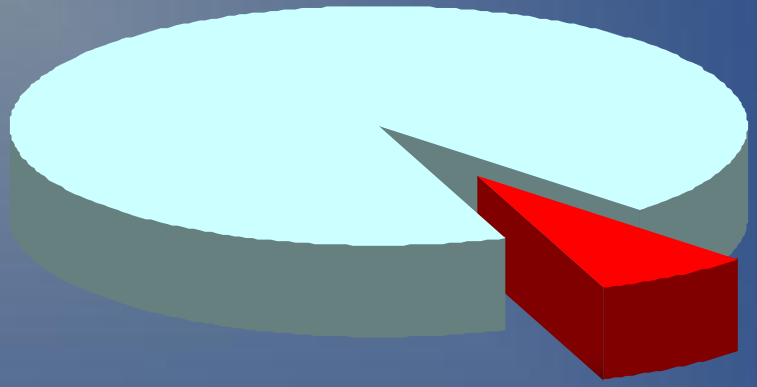
Present

Fallopian tube and endometrium

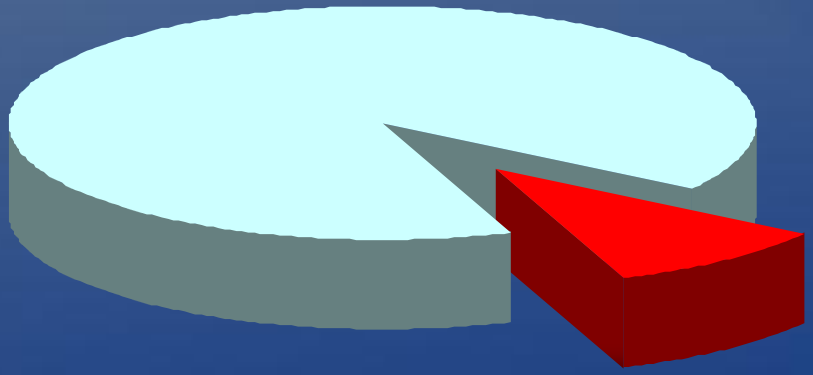
are emerging as important sites of origin of ovarian cancer

7% OF BREAST AND 10% OF OVARIAN CANCERS ARE HEREDITARY

BREAST CANCER



OVARIAN CANCER



Rischio di carcinoma ovarico:

- 1/70 (1.4%) se familiarità negativa
- 1/20 (5%) se 1 familiare affetta
- 1/14 (7%) se ≥ 2 familiari affette
- 1/2.5 (40%) se sindrome ereditaria

Data supporting the distal fallopian tube as a source of serous carcinoma

- Detection of in situ and early tubal carcinoma in over 70% of malignancies detected in BRCA+ women following risk-reducing S-O
- Detection of Serous Tubal Tntraepitelial Carcinoma (STIC) in 70% of sporadic ovarian and peritoneal high grade serous carcinoma
- Presence of a putative precursor (p53 signatures) in the distal tube that shares characteristics with tubal carcinomas
- Continuity between p53 signatures and early tubal carcinomas, supporting a transition from one to the other

Modified from Kurman R. et al. Am J Surg Pathol ,vol 34, March 2010

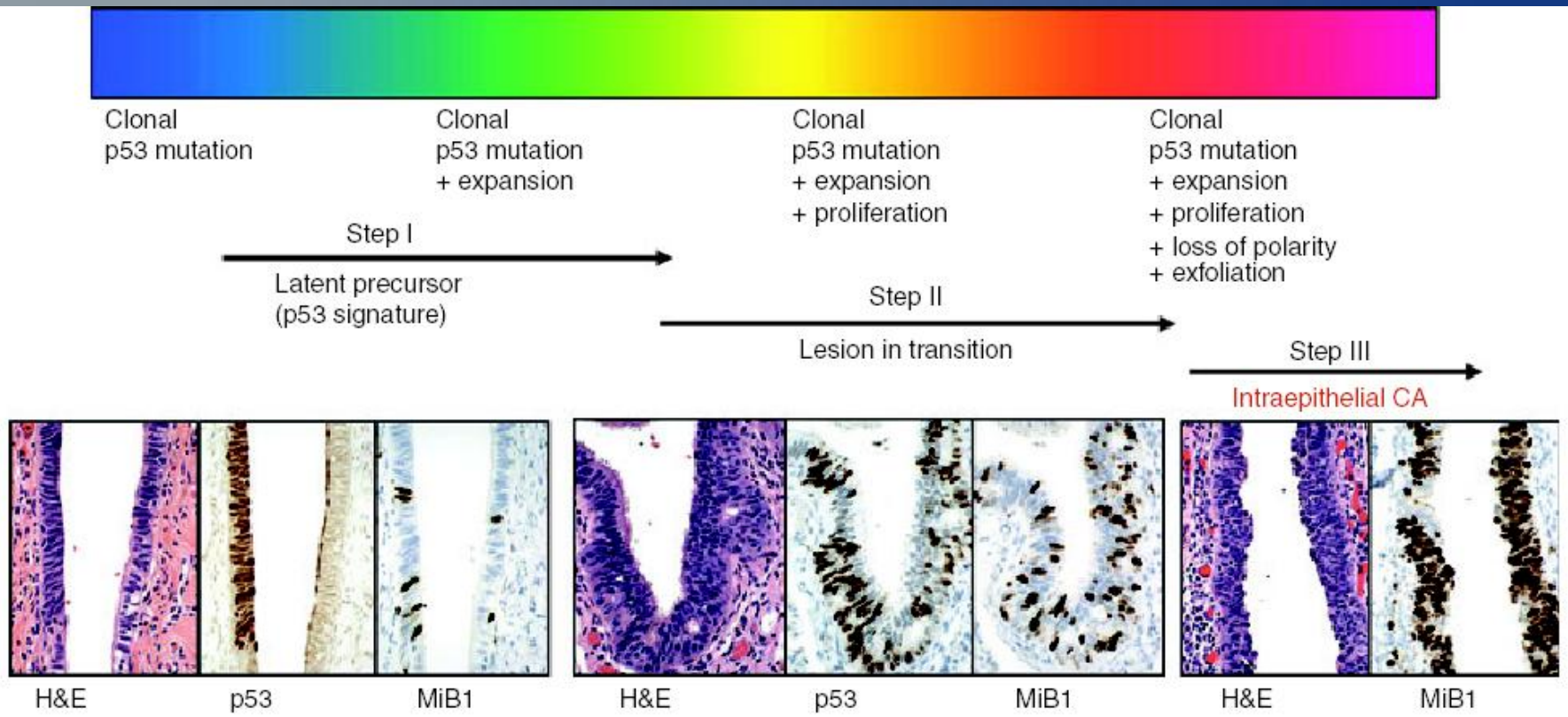
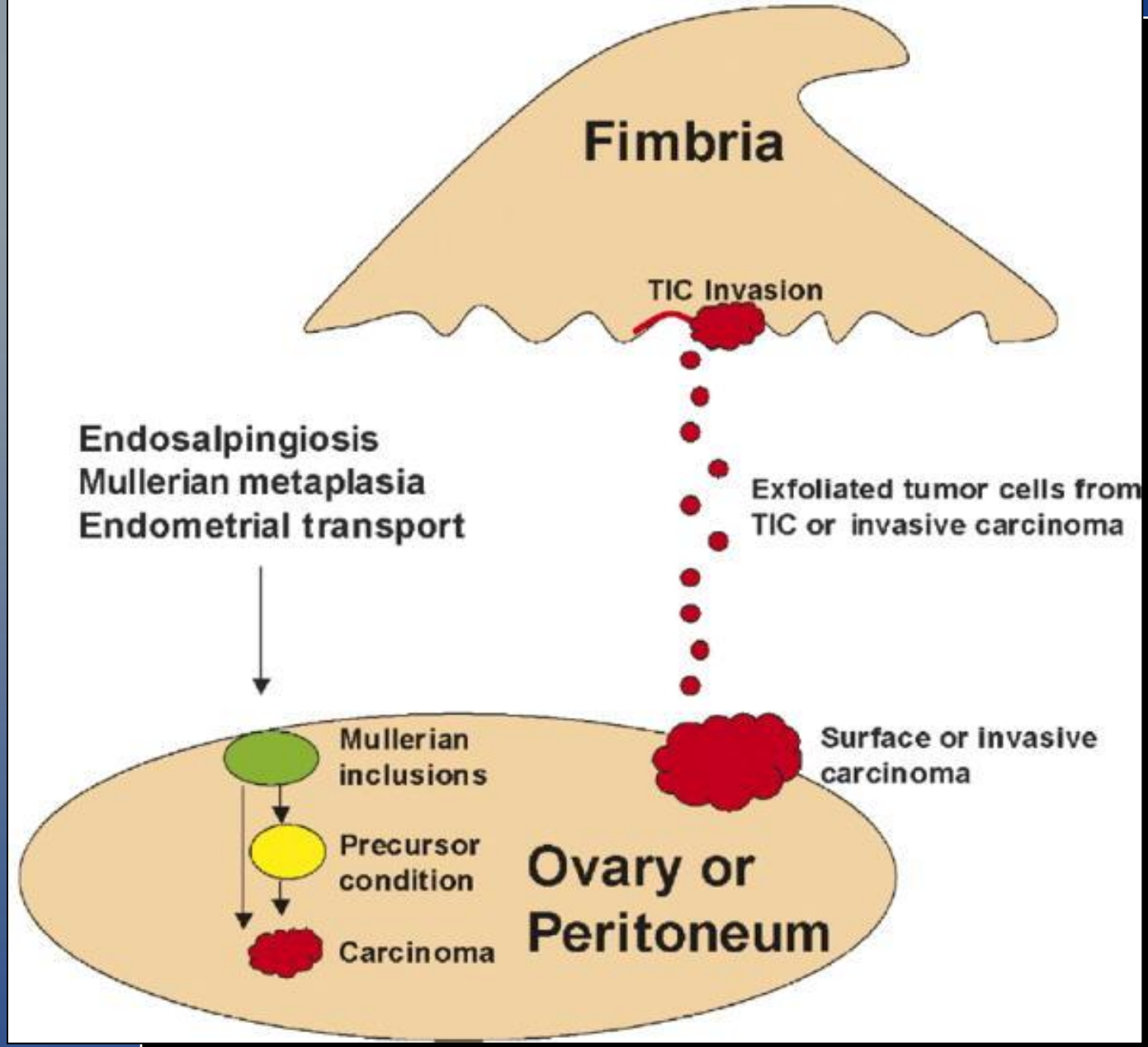
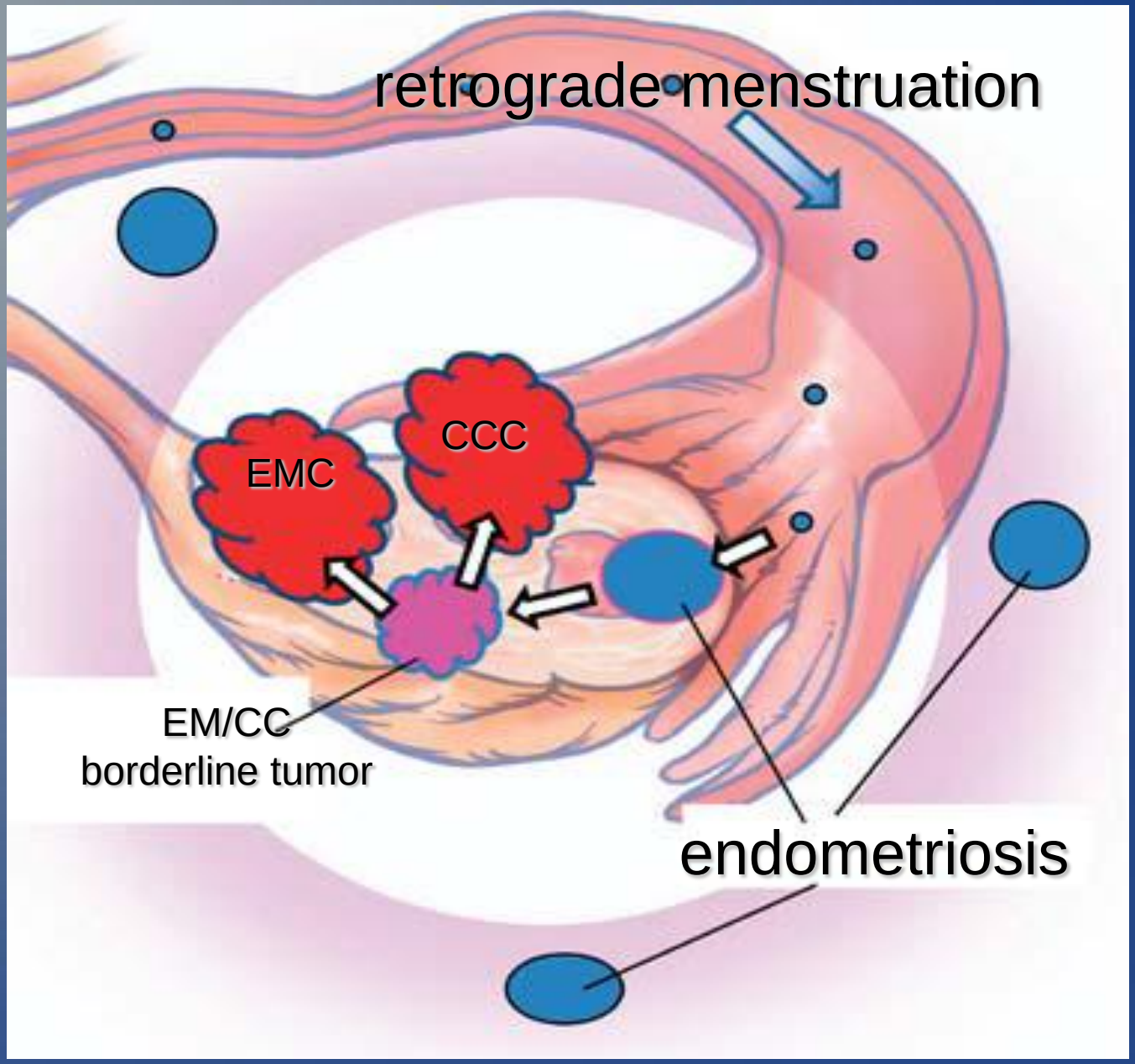


Figure 4. The serous carcinogenesis sequence in the fallopian tube consists of a spectrum of changes initiating with *p53* mutations (p53 signatures) and terminating in tubal intraepithelial carcinoma. In some instances, intermediate forms (lesions in transition) can be identified (from Jarboe *et al.*[49]).

E A Jarboe et al , Histopathology 2008



A proposed model for the pathogenesis of pelvic serous carcinoma.
Kindelberger DW, et al. Am J Surg Pathol 2007;31:161-169



Endometrioid and clear cell carcinomas

Lessons

- Ovarian carcinomas comprise a heterogenous group of neoplasms, each with a different genomic make-up, pathogenesis and natural behaviour.

Why treatment should be the same?

- Precursors have been identified for type I tumors:
  - Serous cystadenoma-----SBT---Low grade serous ca.
  - Mucinous cystadenoma---MBT—mucinous carcinoma
  - Endometriosis:----------EBT---endometroid carcinoma

  ---------- CCBT—clear cell carcinoma

US screening makes sense in type 1 tumors, which unfortunately represent only 25% of ovarian cancers and account for only 10% of ovarian cancer deaths !!!!!

Lessons

If the majority of type II tumors originate outside the ovary……

Why utilizing screening approaches designed to detect these tumors while confined to the ovary ? (US and pelvic exam)

They represent 75% of all ovarian carcinomas and 90% of ovarian cancer deaths: type II tumors should be the real target of screening !!!

Lessons

If the majority of type II tumors originate outside the ovary……

Why utilizing screening approaches designed to detect these tumors while confined to the ovary ? (US and pelvic exam)

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Past, Present, and Future

- Etiology and pathogenesis
- Screening and early diagnosis
- Surgical treatment
- Medical treatment

Screening in the general population

Mission impossible!!!

Ovarian screening History

1. Ultrasound as a 1° screen:

   7-20 unnecessary operations for each cancer detected

2. CA 125 as a 1° screen + USS 2° screen:

3 unnecessary operations for each cancer detected

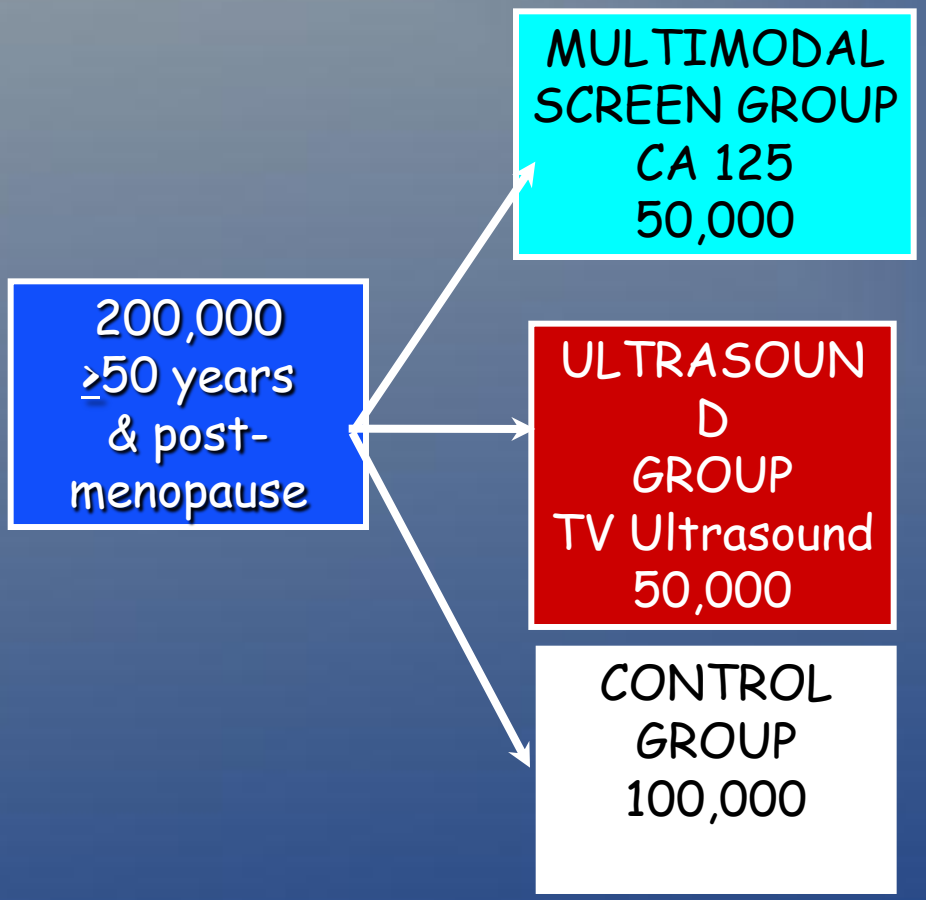
1. Adding the 'Risk of Ovarian Cancer Algorithm':

   2 unnecessary operations for each cancer detected

2. Randomised Controlled Trials

UKCTOCS

UK Collaborative Trial of Ovarian Cancer Screening



OBJECTIVES

Primary:
Ovarian Cancer Mortality

Secondary:
Morbidity
Health Economics
Quality of Life
Acceptability
Compliance

Additional:
Serum Bank

Early detection

Present

- No assay with sufficient sensitivity and specificity to screen for ovarian cancer

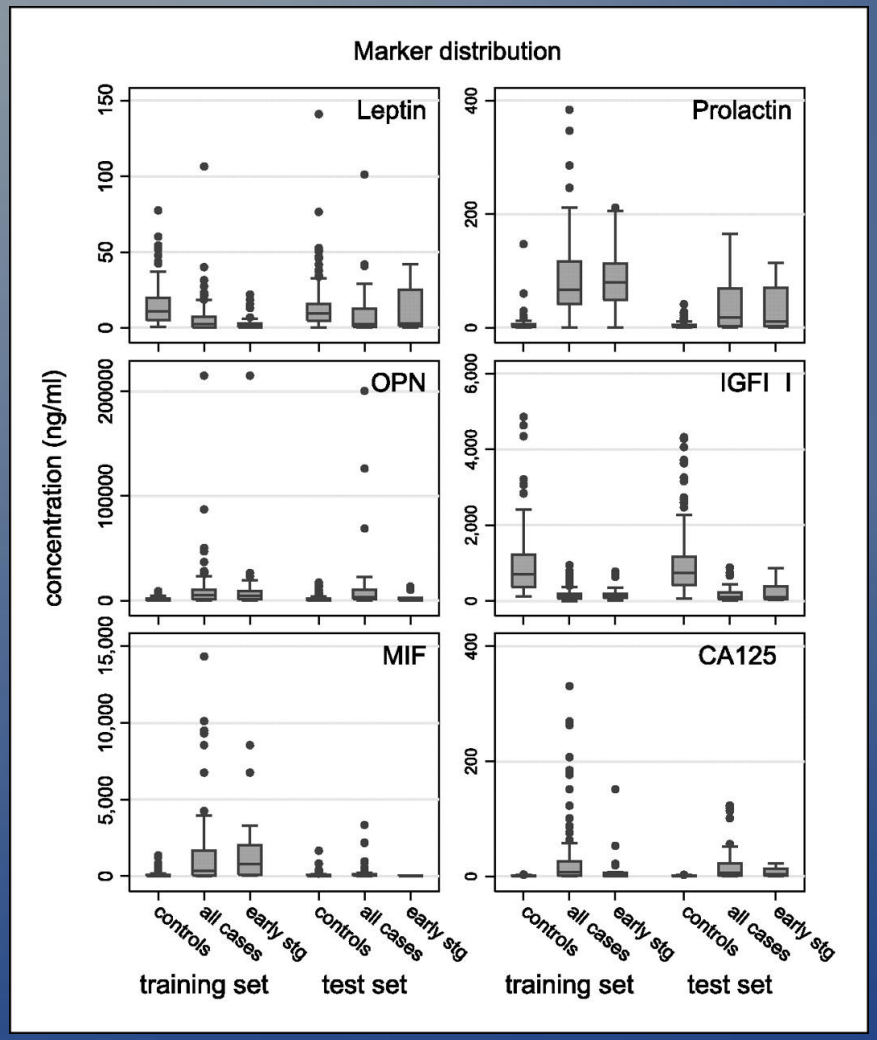
Future

- Identification of high risk groups using genomic technology
- Identification of early ovarian cancer using blood based biomarkers

Approaches to identifying novel markers for epithelial ovarian cancer

- Murine Monoclonal Antibodies
  - Mesothelin
- Lipid Analysis-LPA
- Expression Array Analysis
  - HE4
  - Kallikreins
  - Prostasin
  - Osteopontin
  - VEGF
  - IL-8
- Proteomics

Diagnostic markers for Early detection of Ovarian cancer



Boxplot display of biomarker distributions for controls, ovarian cancer cases, and the subset of early stage (I and II) cases, by training and validation set assignment

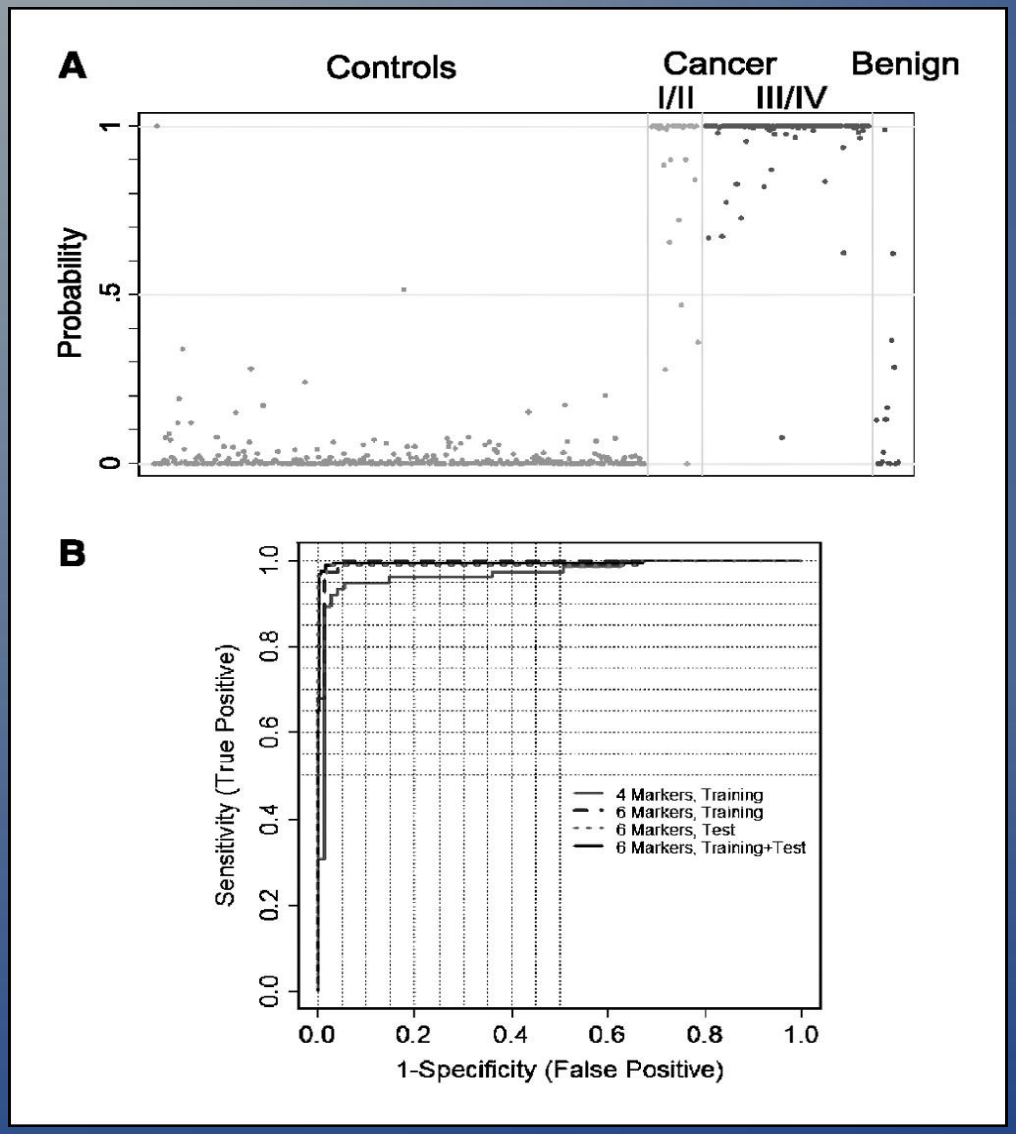
MIF – Prolactin – OPN - CA 125 ↑

Leptin – IGF1 ↓

Visintin I et al. Clin Cancer Res 2008;14:1065-1072

AACR Clinical Cancer Research

Diagnostic markers for Early detection of Ovarian cancer



Sensitivity

Stage I/II:	91,6 %
Stage III/IV:	99,8%
Benign:	88,2%

Sensitivity: 95.3%

Specificity: 99,4%

Accuracy: 98,7%

Visintin I et al. Clin Cancer Res 2008;14:1065-1072

Multiplex assay of early stage ovarian cancer

- The multi-marker panel that provided the highest diagnostic power for both early and late stage disease was comprised of 4 biomarkers:

CA125, HE4, s-EGFR and sVCAM-1

- Sensitivity for pre-clinical disease remains to be determined with PLCO and UKCTOCS specimens

Screening and early diagnosis
Lessons

- ✓ Develop accurate methods for risk assessment with transcend BRCA1/2 (whole genome SNP analysis)
- ✓ Identification of moderately high risk groups should permit cost/effective prevention
- ✓ Improve efficiency of screening with novel biomarkers
- ✓ Pending the results of ongoing clinical trials screening is not recommended

MASSE ANNESSIALI

- Frequente causa di consulto ginecologico:
- Natura benigna: 80%
- Natura maligna: 20%

Età media alla diagnosi: 63 anni

- La corretta caratterizzazione di una massa annessiale è fondamentale per una gestione appropriata e un trattamento ottimale

- **Ecografia transvaginale**: metodica diagnostica di prima scelta
- Valutazione soggettiva (*pattern recognition*) da parte di un ecografista esperto

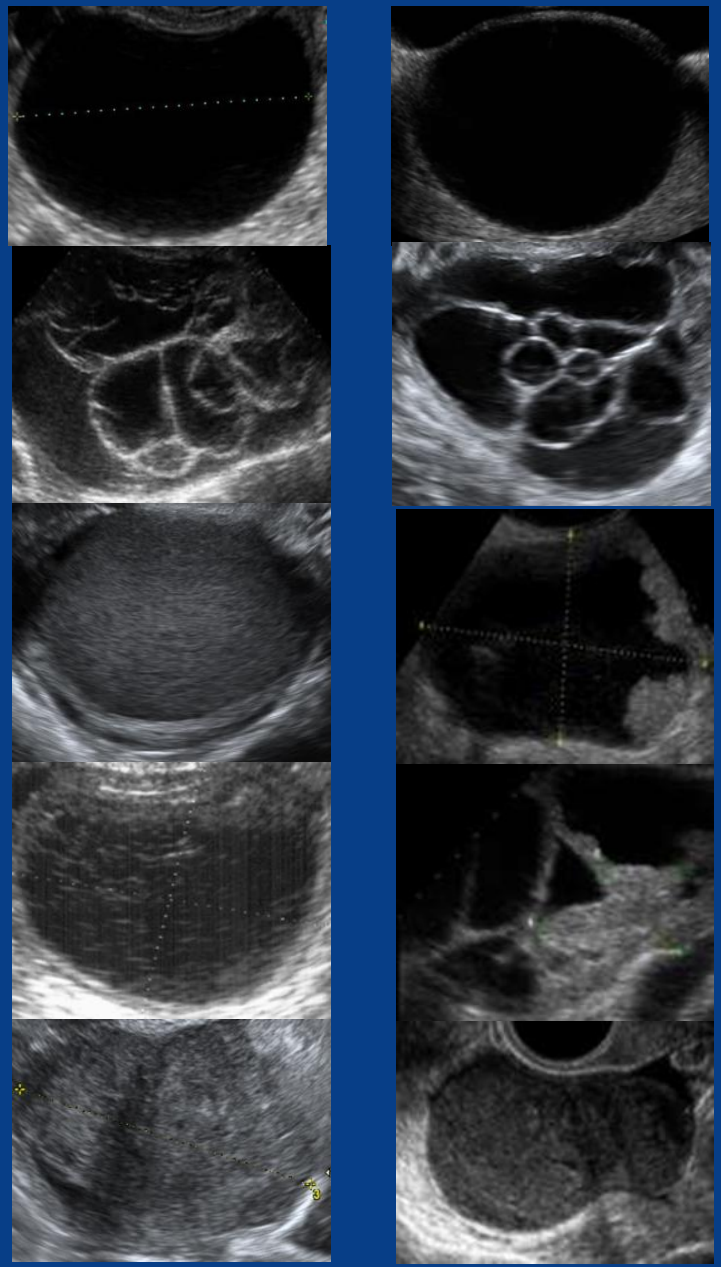
Sensibilità: 88-96%

Specificità: 90-96%

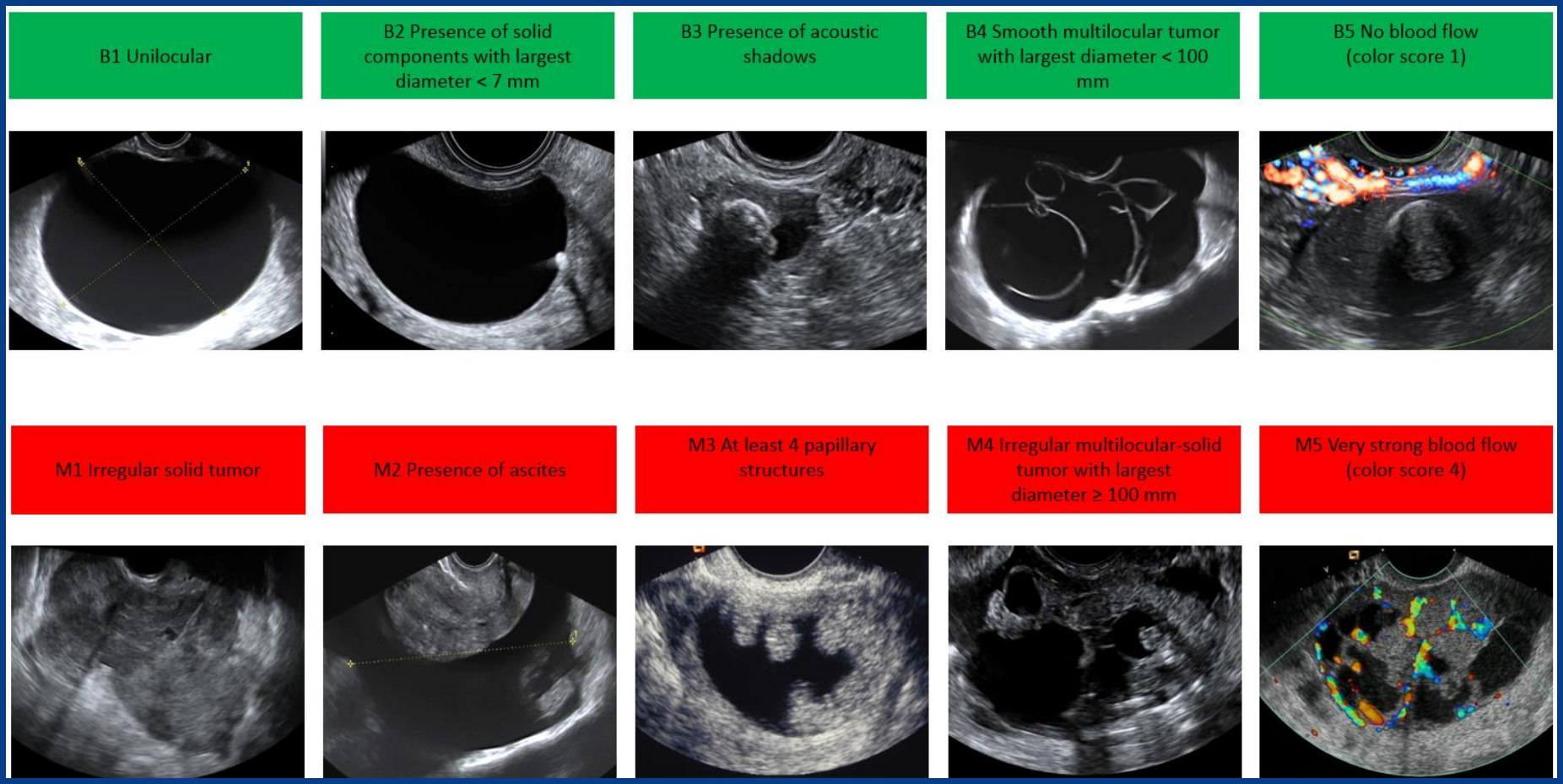
CARATTERISTICHE ECOGRAFICHE

Classificazione IOTA
(*International Ovarian Tumor Analysis*):

- Contenuto cistico
- Papille e/o componenti solide
- Regolarità dei contorni esterni
- Regolarità della parete interna
- Setti
- Classificazione morfologica
- Vascolarizzazione: *color score* 1-4
- Reperti aggiuntivi: cono d'ombra, ascite…



IOTA *Simple Rules*



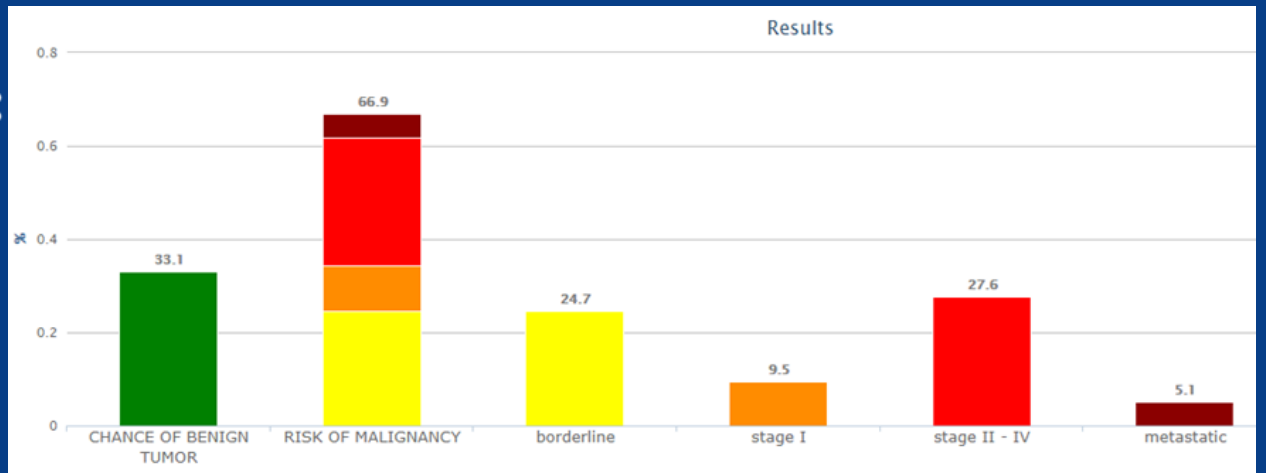
Queste 10 semplici regole sono applicabili al 75% di tutti i tumori ovarici, con sensibilità del 90% e specificità del 93%.

PREDIZIONE DEL RISCHIO DI MALIGNITÀ

- ***Risk of Malignancy Index* (RMI)** – Jacobs et al.
  - Sensibilità 85%, specificità 97%

- **Modelli di regressione logistica: LR1** (12 variabili) e **LR2** (6 variabili).

- **Modello ADNEX:**
  - 3 dati clinici, 6 dati ecografici
  - Distinzione in 5 sottoclassi



	Patient Specific Risk	Relative Risk	Baseline Risk
CHANCE OF BENIGN TUMOR	33.1 %	0.5	68.2%
RISK OF MALIGNANCY	66.9 %	2.1	31.8 %
->Risk borderline	24.7 %	3.9	6.3 %
->Risk stage I ovarian cancer	9.5 %	1.3	7.5 %
->Risk stage II-IV ovarian cancer	27.6 %	2	14.1 %
->Risk metastatic cancer to the adnexa	5.1 %	1.3	4.0 %

Sassone Morphological Score

Score	Wall	Septa	Wall Thickness	Echogenicity
1	Smooth	None	≤3 mm	Anechogenous
2	Papillae ≤ 3 mm	≤ 3 mm	> 3 mm	Hypoechogenous
3	Papillae > 3 mm	> 3 mm	Solid, Not Evaluable	Mixed, Mainly Hypoechogenous
4	Solid, Not Evaluable			Mixed
5				Hyperechogenous solid

SCOPO DELLA TESI

Raccogliere dati anamnestici, clinici ed ecografici di pazienti affette da cisti ovariche sottoposte a chirurgia, al fine di predirne il rischio di malignità attraverso la costruzione di un nomogramma.

Dati relativi a **1053 pazienti** sono stati raccolti all'interno di tre centri di ginecologia oncologica di riferimento: Ospedale San Gerardo (476), Istituto Nazionale dei Tumori (173), Istituto Europeo di Oncologia (404).

- Età media: 51,7 anni.
- Valori di CA125 preoperatori: 1018 casi. Valore medio: 431.6 U/ml.
- Diagnosi di malignità: 458 (43%) casi.

Per ogni paziente inclusa nello studio sono stati eseguiti:

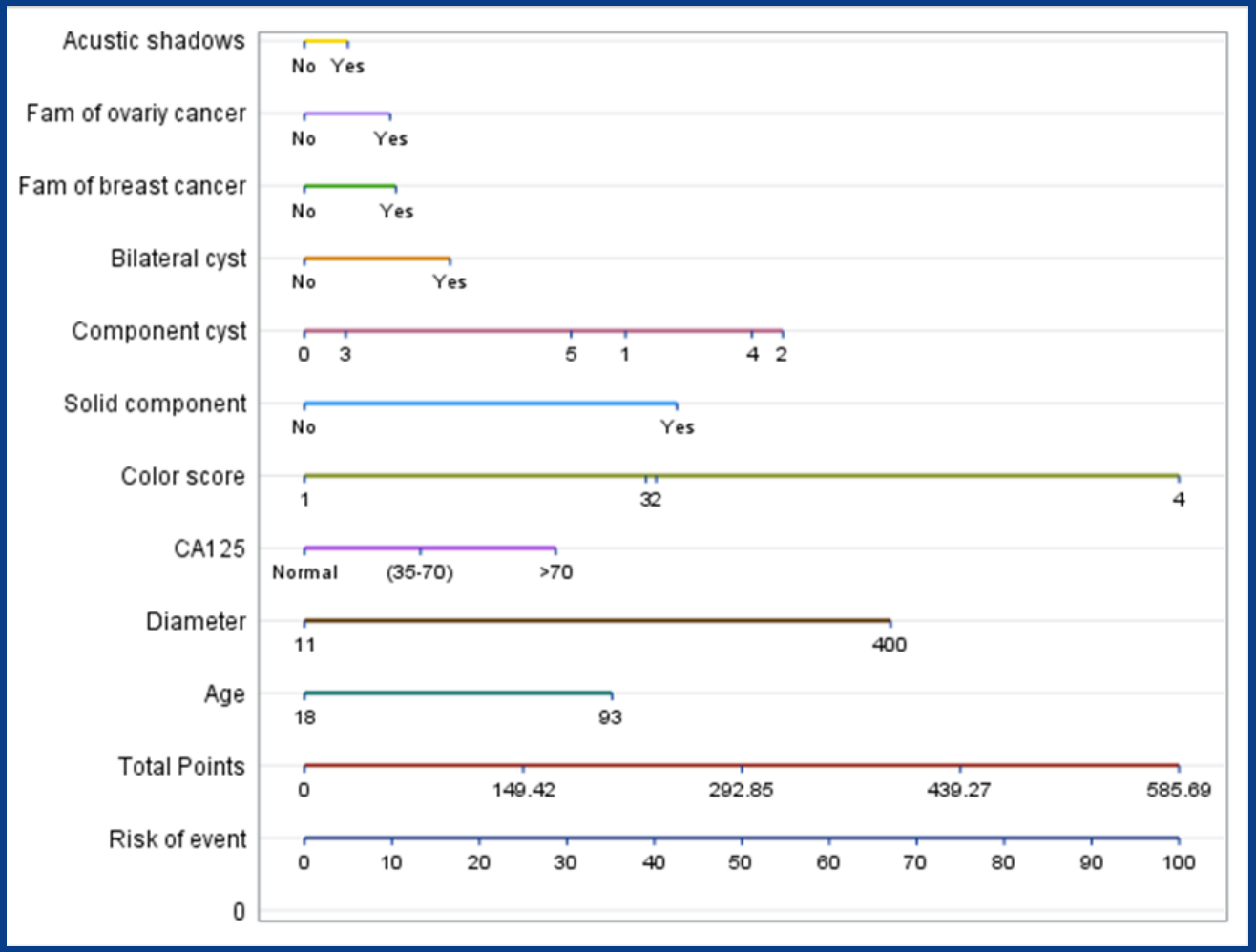
- Raccolta anamnestica
- Visita ginecologica
- Ecografia transvaginale
- Stadiazione preoperatoria
- Trattamento chirurgico
- Esame istologico definitivo

RISULTATI RAGGIUNTI

Variabili predittive di malignità:

- Valori di CA 125
- Bilateralità delle formazioni annessiali
- Diametro massimo della lesione
- Contenuto cistico
- Componente solida
- *Color score* al Doppler

NOMOGRAMMA



	Nomogramma point
Età (18-93)	35.16
Diametro (11-400)	67.01
CA125 (35-70)	13.27
CA125 (>70)	28.75
Color score 2	40.23
Color score 3	39.06
Color score 4	100
Componente solida	42.58
Low level	36.70
Emorragico	54.69
Ground glass	4.73
Misto	51.17
NV/solido	30.49
Bilateralità	16.65
Anam fam k mam	10.46
Anam fam k ov	9.79
Acoustic shadows	4.96

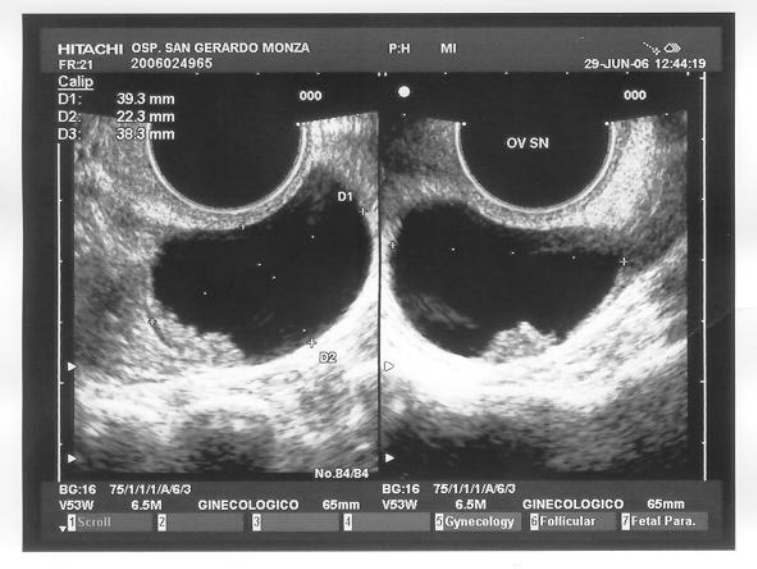
CONCLUSIONI

- La valutazione soggettiva (*pattern recognition*) da parte di un ecografista esperto rimane, ad oggi, lo strumento più accurato nella diagnosi differenziale tra masse ovariche benigne e maligne.

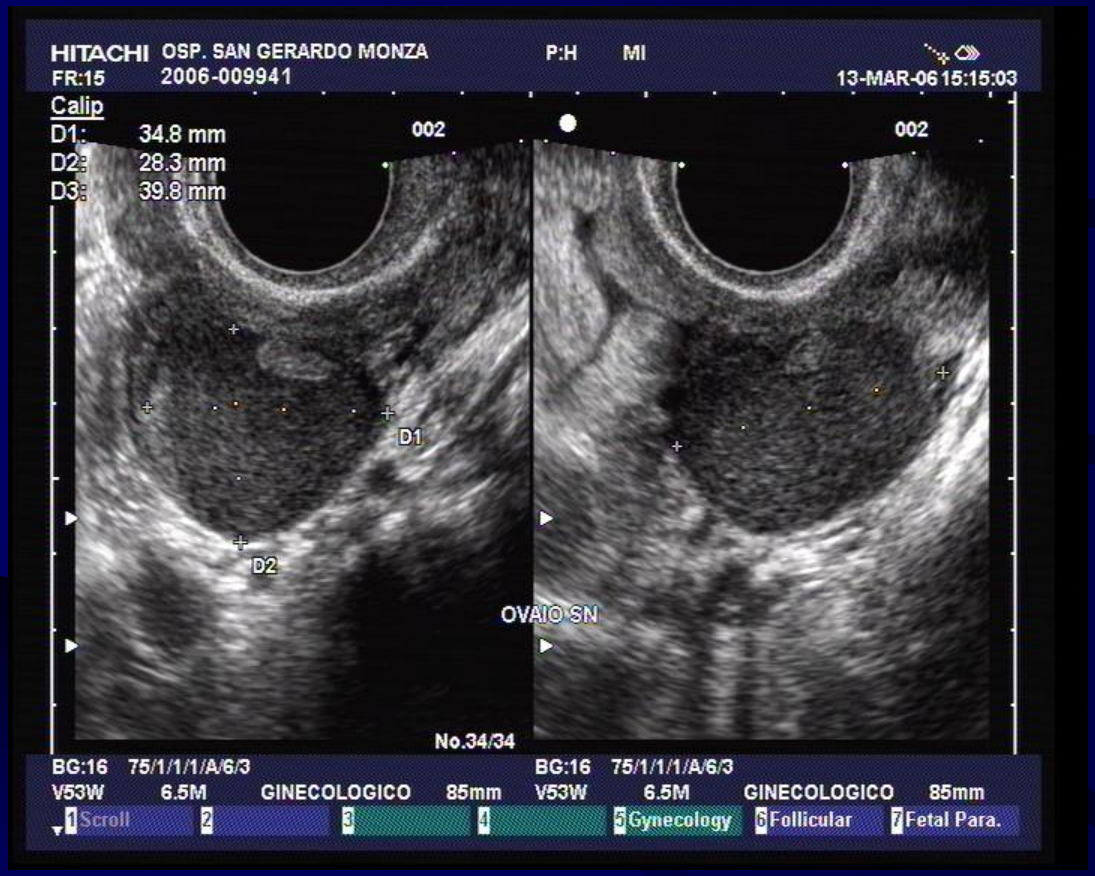
- La possibilità di integrare la valutazione morfologica con una predizione del rischio di malignità si conferma essere un approccio valido per il futuro della diagnosi ecografica della patologia ovarica.

- Se i risultati del nostro studio venissero confermati si andrebbe a delineare uno strumento efficace attraverso cui integrare ed ottimizzare la valutazione ecografica delle masse annessiali.

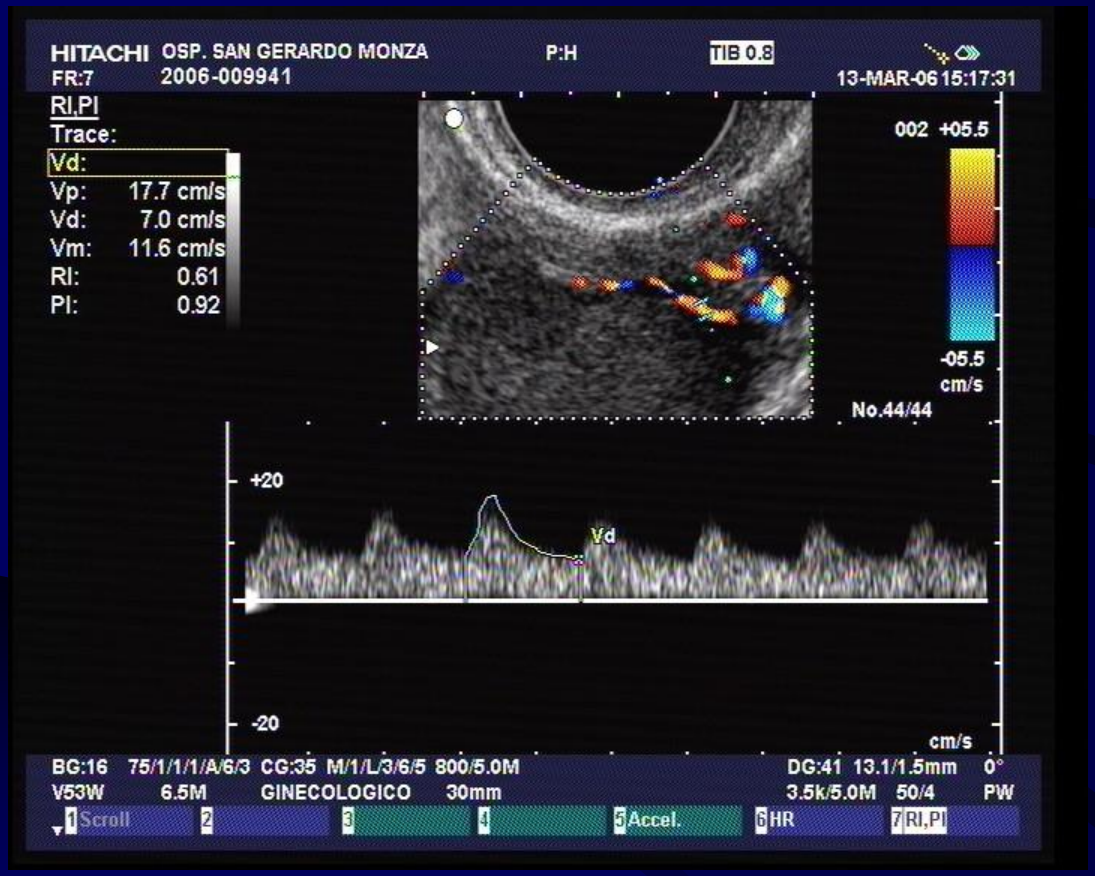
Cistoadenoma sieroso



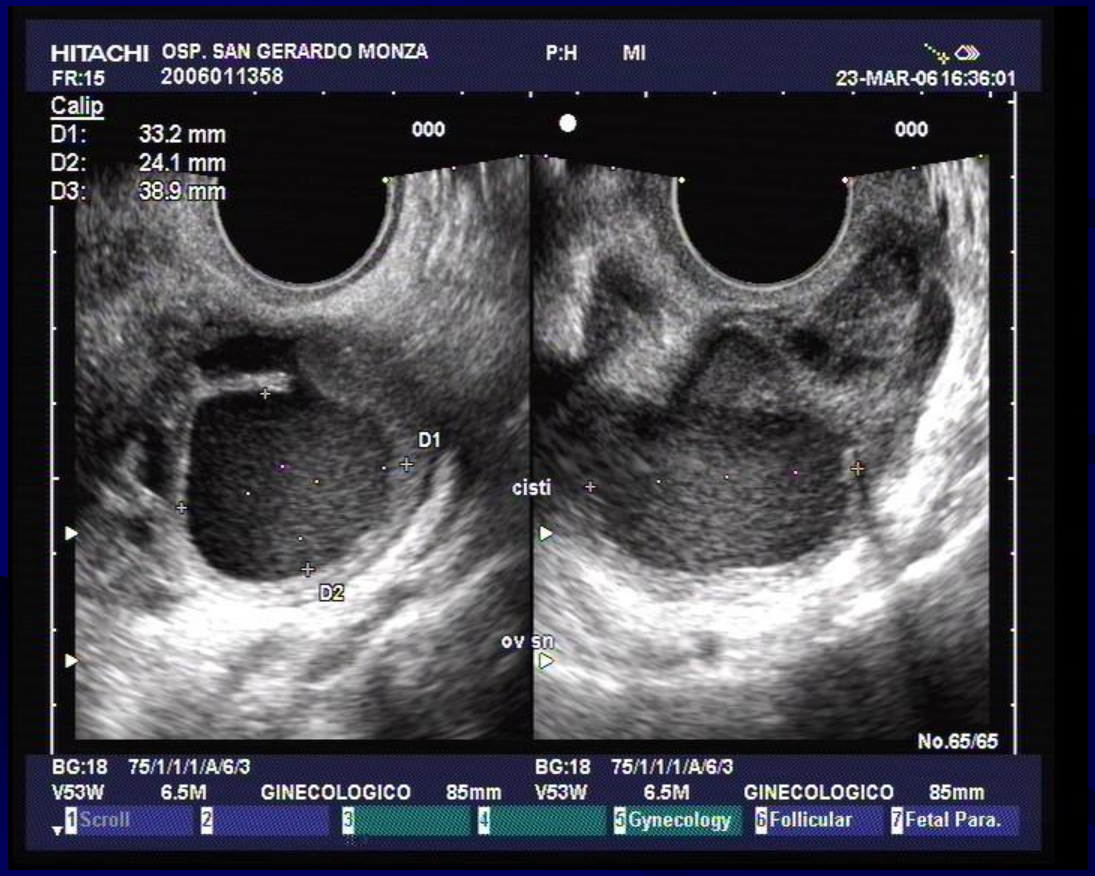
Endometrioma



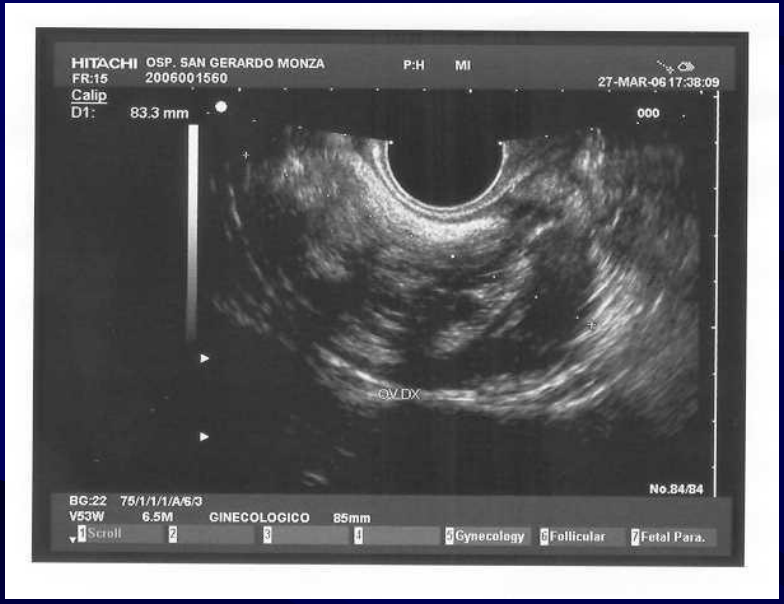
Endometrioma



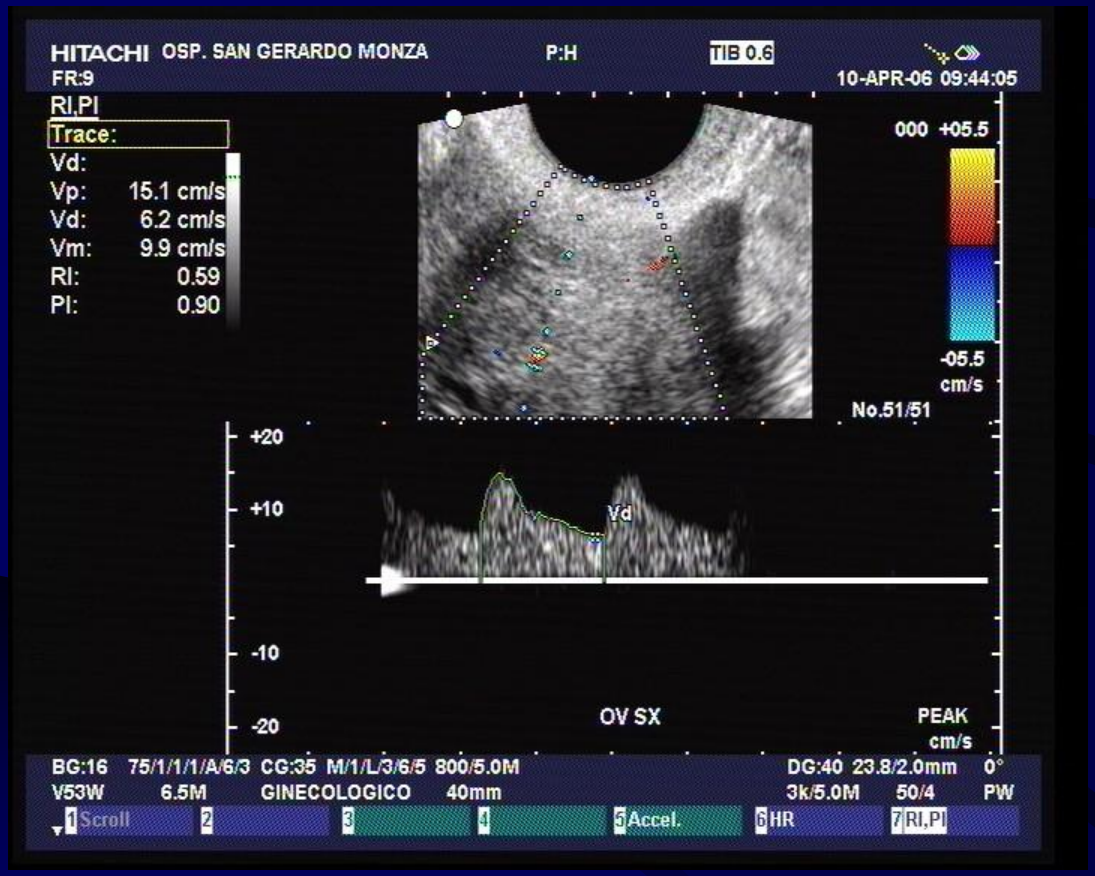
Endometrioma



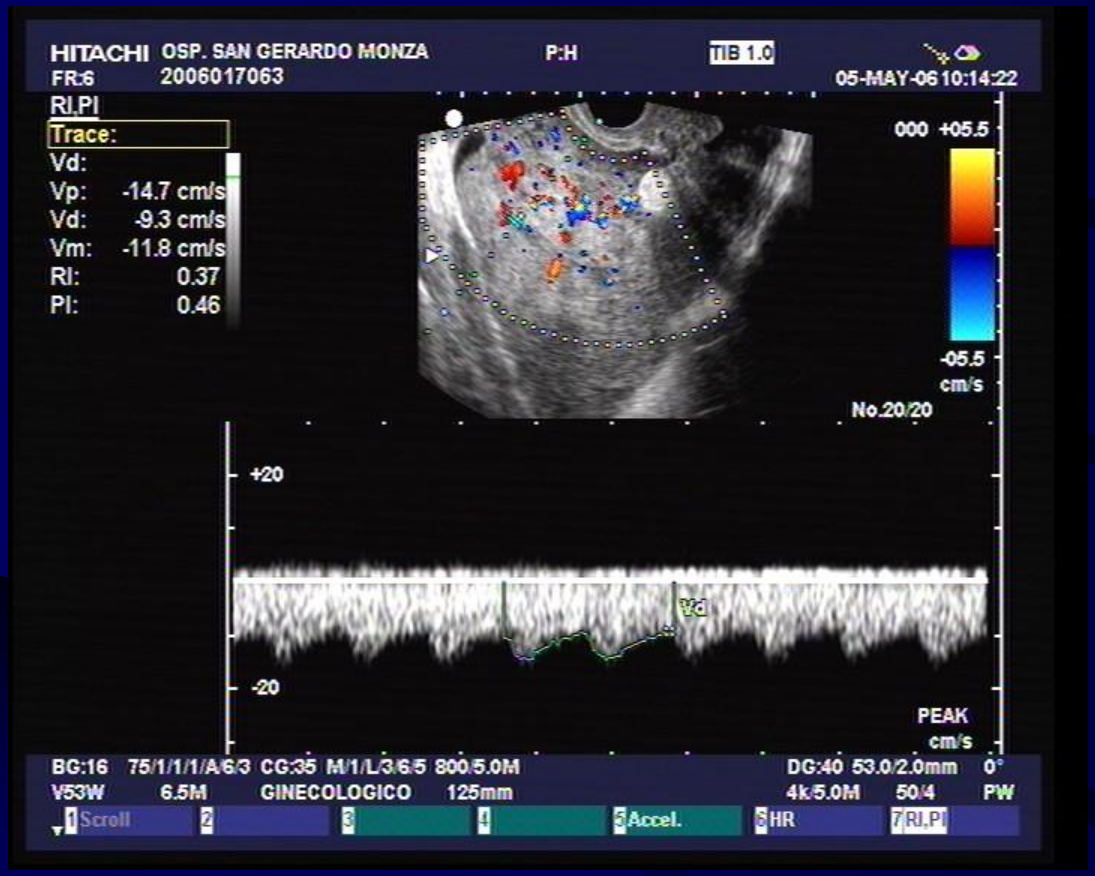
Cisti dermoide



Fibrotecoma



Ca. metastatico (stomaco)



Tumore del seno endodermico