

# Triage of Ovarian Masses

Andreas Obermair

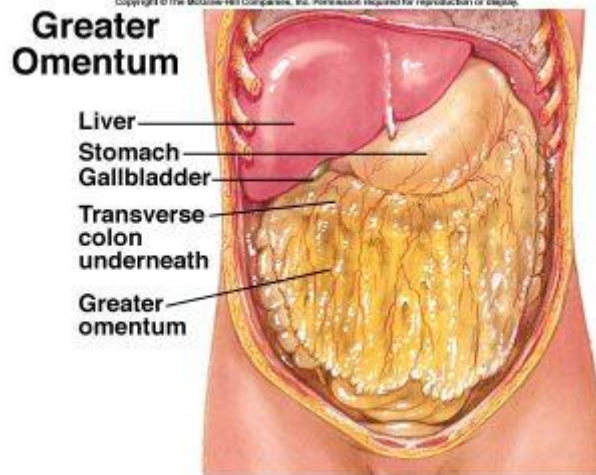
Brisbane

# Why Triage?

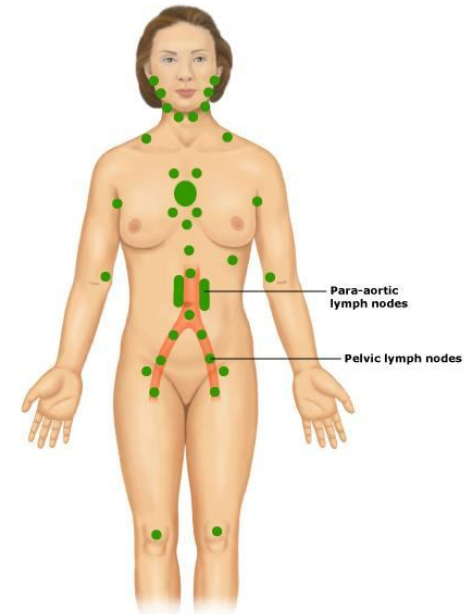
- In ovarian cancer, best outcomes for patients can be achieved when patients are treated in tertiary centres by a multidisciplinary team led by a gynaecological oncologist.
- Suboptimal outcomes are achieved in countries where referral of ovarian cancer patients is problematic.
  - Complication rates are higher (~30%)
  - Survival outcomes are lower (~10%)

# Impact of Surgery on Stage 1 ovarian cancer

Survival of staged patients ~ 85% @ 5 years



Nodes ~ 20%  
Omentum ~ 9%

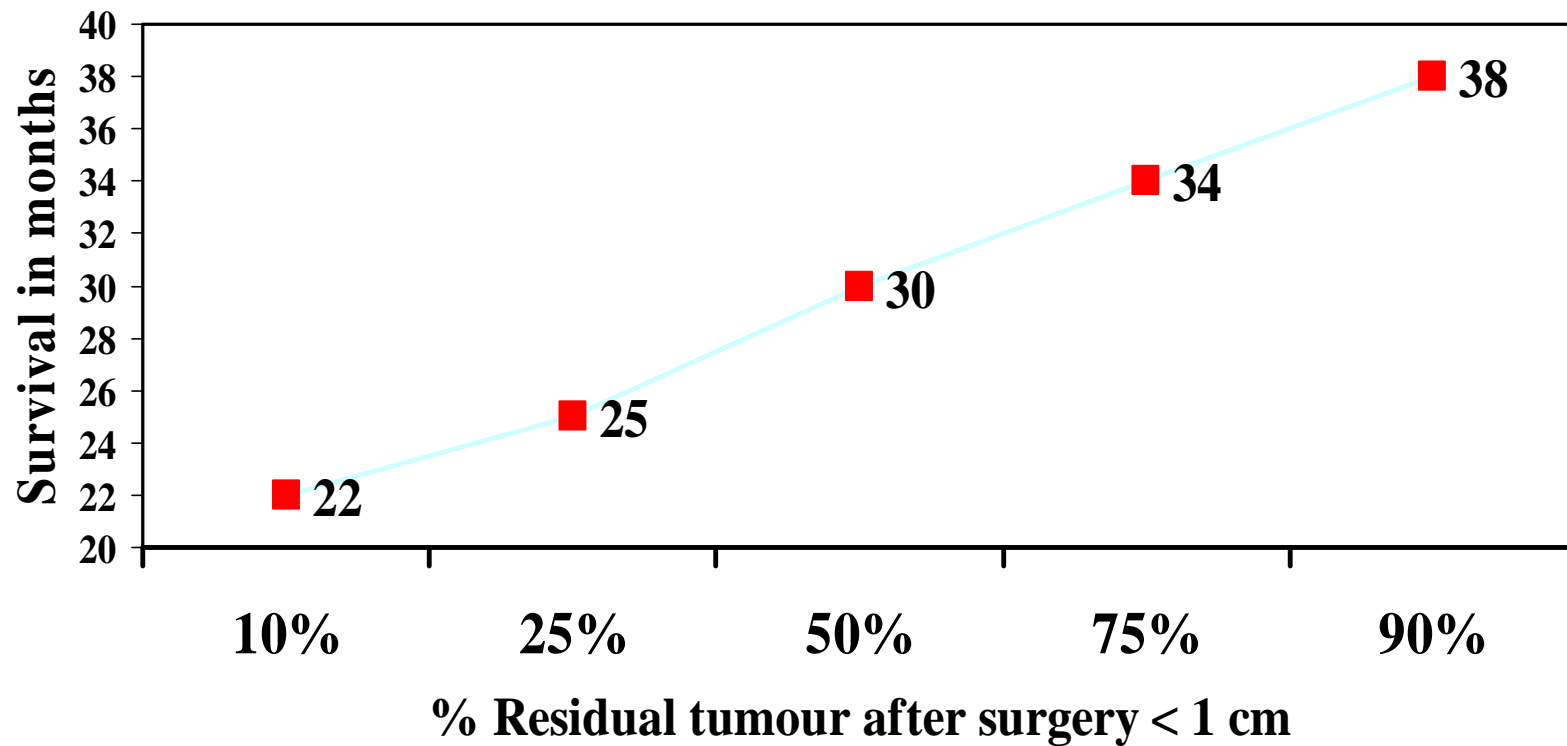


Survival of unstaged patients ~ 70% @ 5 years

**Half of +ve lesions look macroscopically normal!**

# Impact of Surgery on Advanced Stage Ovarian Cancer (St 3C)

Advanced ovarian cancer – chemotherapy identical



Bristow et al.: J Clin Oncol 2002

# Benign vs. malignant ovarian masses

Characteristic	Benign mean (range) (n = 119)	Malignant mean (range) (n = 61)	<i>p</i> <sup>a</sup>
Age (years)	46 (15-82)	57 (19-92)	< .001
CA125 (IU/mL)	76 (15-850)	1637 (15-17,800)	< .001
US <sup>b</sup>			
Ascites	5% (5/109 <sup>c</sup> )	37% (19/52 <sup>c</sup> )	< .001
Metastases	0% (0/109)	13% (7/52)	< .001
Multilocular cysts	49% (53/109)	79% (41/52)	< .001
Solid areas	61% (67/109)	87% (45/52)	.001
Bilateral	15% (16/109)	25% (13/52)	NS
US score: 0, 1, 3	21, 43, 45 (n = 109)	1, 7, 44 (n = 52)	< .001
RMI	219 (0-5130)	5513 (0-83,700)	< .001

Van Trappen P: Int J Gynecol Cancer 2007

# What is CA-125 ?

- Glycoprotein produced from mesothelial cells (peritoneum, pleura, pericard)
- 80% of ovarian cancer CA- 125 positive
- 30% - 50% of patients with stage 1 ovarian cancer present with negative CA 125.

# Limits of CA125

- **Low specificity**
  - Elevated in a large number of benign conditions
- Sensitivity is low in early stage ovarian cancer
  - Half of patients with stage 1 ovarian cancer are CA125 negative
- RMI seeks to overcome these weaknesses
- >Ultrasound (TVUS)
- >Age

# Elevated serum CA 125

## Nongynaecological

Liver disease

Renal disease

Pleural effusion

Pericarditis

Ascites

Colitis & Diverticular disease

Congestive heart failure

Lupus

Postoperative period

Previous radiotherapy

Mesothelioma

Sarcoidosis

Tuberculosis

## Gynaecological cancer

Epithelial Ovarian Cancer (EOC), Fallopian Tube Cancer, Primary Peritoneal cancer

Uterine & Cervical (Adeno) Carcinoma

Non-epithelial tumours

## Benign Gynae Conditions

Menstruation, Pregnancy

Adenomyosis, Endometriosis, Fibroids

PID, functional ovarian cysts

## Non-gynae cancers

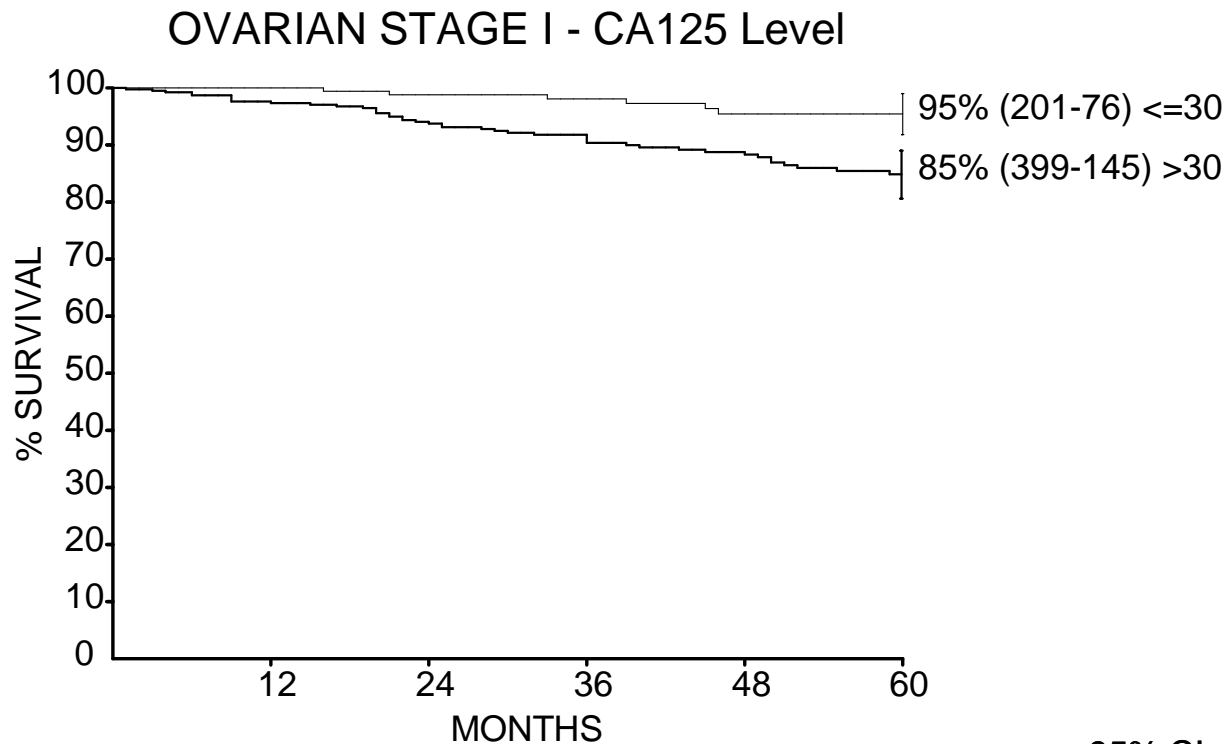
Breast, Colon, Lung, Pancreas



# Limits of CA125

- Low specificity
  - Elevated in a large number of benign conditions
- **Sensitivity is low in early stage ovarian cancer**
  - Half of patients with stage 1 ovarian cancer are CA125 negative
- RMI seeks to overcome these weaknesses
- >Ultrasound (TVUS)
- >Age

# Preoperative serum CA125 in Stage 1 Ovarian Cancer



	0	12	24	36	48	60	95% CI
<=30	201	182	154	130	97	76	[ 92, 99 ]
>30	399	350	306	258	204	145	[ 81, 89 ]

# Limits of CA125

- Low specificity
  - Elevated in a large number of benign conditions
- Sensitivity is low in early stage ovarian cancer
  - Half of patients with stage 1 ovarian cancer are CA125 negative
- RMI seeks to overcome these weaknesses
- >Ultrasound (TVUS)
- >Age

# Risk of Malignancy Index

Criteria	Scoring system
<b>Menopausal status (A)</b> Premenopausal Postmenopausal	1 3
<b>Ultrasound features (B)</b> Multiloculated Solid areas Bilateral Ascites Metastases	No feature = 0 One feature = 1 >1 feature = 3
<b>Serum CA 125 (C)</b>	<b>Absolute level</b>
<b>Risk of Malignancy Index (RMI) = A x B x C</b>	

Simple ovarian cysts: malignancy < 1%;

# Sensitivity & Specificity – A Trade Off

**Table 3.** Sensitivity and specificity of the different cutoff values for the RMI

RMI	Sensitivity, %	Specificity, %
25	98	42
50	92	59
75	88	67
100	84	70
125	80	75
150	78	80
175	78	81
200	76	82
225	76	84
250	73	85
300	72	86
500	68	91
1000	54	96

24% of true cancers missed

18% of false positive = benign

# Limitations of the RMI model

## Inaccurate

- Developed for “classical” serous ovarian cancer
  - 85% of all advanced ovarian cancers
- Fails stage 1 ovarian cancer in 30% - 50%
- Not designed to detect Borderline Tumours
- Unsuitable for mucinous tumours
  - Not even frozen section histology is reliable!
- Unsuitable for non-epithelial tumours
  - Sexcord stromal tumours or Germcell tumours
- Not objective (US component)

# Use of Multiple Biomarkers

- 233 patients operated on for adnexal mass
  - 67 invasive cancers (71% serous; 19% stage 1)
  - 166 benign (endometriosis, cystadenoma, fibroids)
  - 82 patients premenopausal
- Markers tested: CA125, SMRP, HE4, CA72-4, activin, inhibin, osteopontin, EGFR, Her2
- Sensitivity and Specificity of all markers alone and in all possible combinations

# Sensitivity of various markers (at specificity of 95%)

- CA125 – 43.3%; SMRP – 53.7%; HE4 – 72.9%
- All other markers: sensitivities less than CA125
- Combination of CA125 and HE4 had the greatest sensitivity of 76.4% (gain of 33% to CA125) [most effective dual combination]
- CA125 + HE4 + CA72-4 yielded 78.8%
- Inclusion of any other markers yielded nil.



# HE4 in premenopausal women

Comparison of premenopausal and postmenopausal benign groups to cancer

Marker combination	Pre-menopausal benign ( <i>n</i> =82) vs. all cancers ( <i>n</i> =67)		Post-menopausal benign ( <i>n</i> =84) vs. all cancers ( <i>n</i> =67)	
	ROC-AUC (95% CI)	<i>p</i> -value for comparison of ROC-AUC to CA125	ROC-AUC (95% CI)	<i>p</i> -value for comparison of ROC-AUC to CA125
CA125	80.6% (73.4–87.7)	–	86.5% (80.6–92.4)	–
HE4	92.9% (88.7–97.0)	0.0004	88.7% (83.0–94.4)	0.5220
CA125+HE4	93.1% (89.0–97.2)	<0.0001	90.7% (85.4–96.0)	0.1173

# Risk of Ovarian Malignancy Algorithm (ROMA)

- Uses CA125 and HE4

Premenopausal: Predictive index (PI)

$$= -12.0 + 2.38 * \text{LN}(\text{HE4}) \\ + 0.0626 * \text{LN}(\text{CA125})$$

Postmenopausal: PI =

$$- 8.09 + 1.04 * \text{LN}(\text{HE4}) \\ + 0.732 * \text{LN}(\text{CA125})$$

Moore et al., AJOG, 2010

- 457 pts w pelvic masses
- 123 Epithelial Ov Ca
- 22 LMPs
- 312 benign
- Review of imaging (needed for RMI) 78% consensus among 3 assessors

# Comparison of RMI and ROMA

Group	n		Sensitivity		
	Benign	Cancer	ROMA	RMI	Pretest <i>P</i> value
Benign vs EOC and LMP	312 (68%)	145 (32%)	89.0%	80.7%	.0113
Benign vs stage I-IV EOC	312 (72%)	123 (28%)	94.3%	84.6%	.0029
Benign vs stage I-II EOC	312 (90%)	34 (10%)	85.3%	64.7%	.0000
Benign vs stage III-IV EOC	312 (78%)	86 (22%)	98.8%	93.0%	.0350
Benign vs stages I-IIIB and IIIC (omentum- and LN+)	312 (88%)	44 (12%)	88.6%	68.2%	.0037

# Recommendations

- Age: Is the RMI model applicable?
  - Consider: AFP, Androstendione, Inhibin, HCG, LDH
- Mucinous tumours don't follow the RMI estimate
- Women in reproductive years: History of endometriosis? [HE4 not elevated in endometriosis]
- Simple and septated cysts are < 1% malignant.
- How concerning are the ultrasound patterns?
  - A negative CA125 is no guarantee for a benign mass

Incidental finding of malignancy: Biopsy only will help quick recovery, intra-operative tumour markers.

Thanks for your interest

[www.Obermair.info](http://www.Obermair.info)