

MITÄ UUTTA KASVAINMERKKIAINEISTA?

Prof. Johanna Mäenpää
Tampereen yliopisto ja Tays,
naistenklinikka
18.4.2013

MERKKIAINEITA GYNEKOLOGISESSA ONKOLOGIASSA

- Epiteliaalinen munasarjasyöpä
- Itusolukasvaimet ja trofoblastisairaudet
- Granuloosasolukasvaimet
- Endometriumkarsinooma
- **Ca-125, HE4, TATI**
- HCG, AFP, LDH
- Inhibiini B, estradioli, **AMH**
- **HE4?**

GRANULOOSASOLUKASVAIN

- Matala-asteisesti maligni: 10-33% uusiutuu
- Uusii myöhään (ad 20 vuoden kuluttua)
- 5% ennen puberteettia
- Tuottaa estrogeenia ->diagnoosi (E2 postmenop. $<0,20$ nmol/l) ja komplikaatiot (10%:lla myös endom. Ca)
- Inhibiini B markkeri (postmenop. <10 ng/l)
- 10-yr OS 90% St I, 0-22% St III

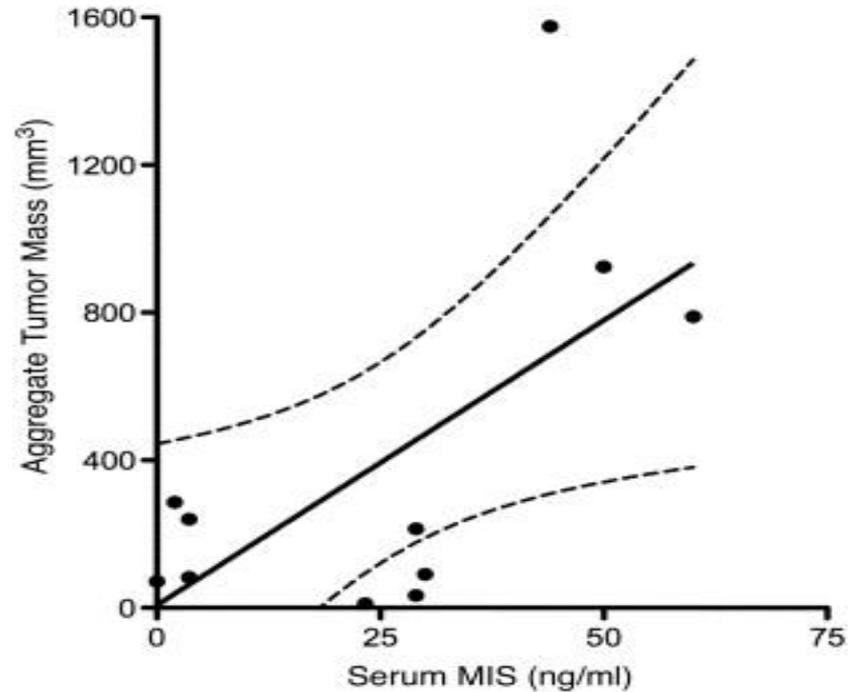


Fig. 1 Serum MIS/AMH measurements correlate with gross aggregate tumor mass. Linear regression analysis shows significant direct correlation between patient serum MIS/AMH levels in ng/ml drawn within 3?days before surgery and gross aggregate tumor mass in ...

Henry L. Chang , Nima Pahlavan , Elkan F. Halpern , David T. MacLaughlin

Serum M?llerian Inhibiting Substance/Anti-M?llerian Hormone levels in patients with adult granulosa cell tumors directly correlate with aggregate tumor mass as determined by pathology or radiology

Gynecologic Oncology Volume 114, Issue 1 2009 57 - 60

<http://dx.doi.org/10.1016/j.ygyno.2009.02.023>

ITUSOLUKASVAINTEN KASVAINMERKKIaineet

Tyyppi	AFP	HCG	LDH
Dysgerminooma	-	<u>±</u>	+
Endodermal sinus tumor	+	-	-
Maligni teratooma	<u>±</u>	-	-
Koriokarsinooma	-	+	-
Embryon. karsinooma	+	+	-
Sekatumori	<u>±</u>	<u>±</u>	?
Polyembryooma	<u>±</u>	<u>±</u>	?

EPITELIAALINEN MUNASARJASYÖPÄ

CA-125: SEKOITTAVIA TEKIJÖITÄ

- Hyvänlaatuiset tilat (raskaus, endometrioosi jne.)
- Endometrium-karsinooma, tuubakarsinooma
- Haimasyöpä, paksusuolen syöpä
- Rintasyöpä
- Keuhkosyöpä
- Ascites mistä tahansa syystä

DIAGNOOSI

Lieviä CA125 –nousuja voi esiintyä
10 – 60 kk ennen diagnoosia (Zurawski
et al. 1988, Bast et al. 2005)

ONGELMIA

- 20 % munasarjasyövistä ei ilmennä CA125:tä (erityisesti musinoottiset)
- FIGO STAGE I:ssä seerumin CA125 on koholla (> 35 kU/L) vain 50 – 60 %:ssa potilaista

TOISTUVAT CA125-MITTAUKSET

- Benignit tilat: stabiili
- Munasarjasyöpä: ↑ tasot ajan kuluessa (Skates et al. 1995 and 2003)
- CA125-II testi: päivittäinen variaatiokoeffisienssi $< 5 \%$

LANTIOTUUMORI: RMI

- Jacobs et al. 1990 originally
- $RMI = U \times M \times \text{serum CA125}$
- U = Ultrasound score (1 – 4)
- M = Menopausal status (1 – 4)
- $RMI > 200$: viittaa maligniteettiin

**Early treatment of relapsed ovarian cancer
based on CA125 level alone
versus
delayed treatment based on conventional
clinical indicators**

**Results of the randomized
MRC OV05 and EORTC 55955 trials**

Gordon Rustin (Mount Vernon Cancer Centre)
and Maria van der Burg

On behalf of all OV05 and 55955 Collaborators

31st May 2009

Objective of Trial



- To investigate the benefit of early chemotherapy for relapsed ovarian cancer, based on a raised CA125 level alone, versus delayed chemotherapy based on conventional clinical indicators

Trial Design

Ovarian cancer in complete remission after first-line platinum based chemotherapy and a normal CA125

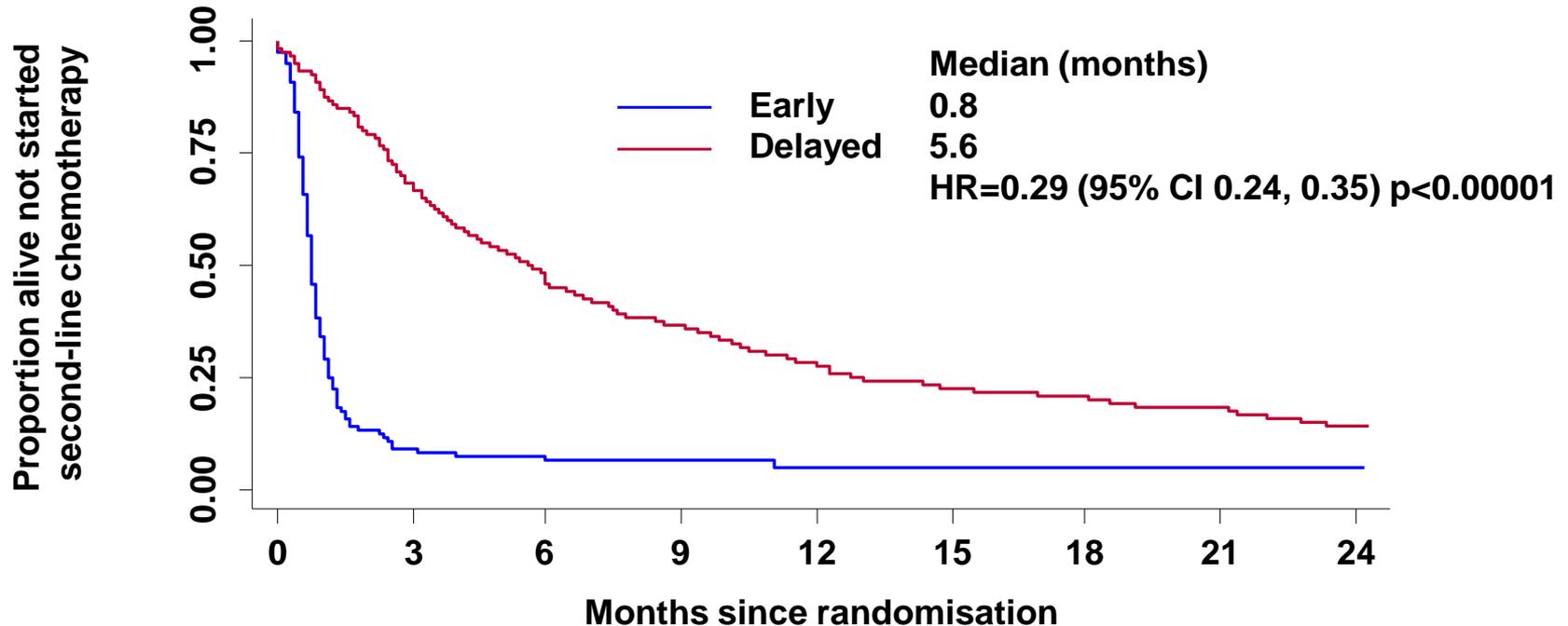
REGISTER
Blinded CA125 measured every 3 months

CA125 > 2 x upper limit of normal
RANDOMISED

Early treatment
Clinician and patient **informed**

Delayed treatment
Clinician **not informed**, treatment delayed until clinically indicated

Time from randomisation to second-line chemotherapy

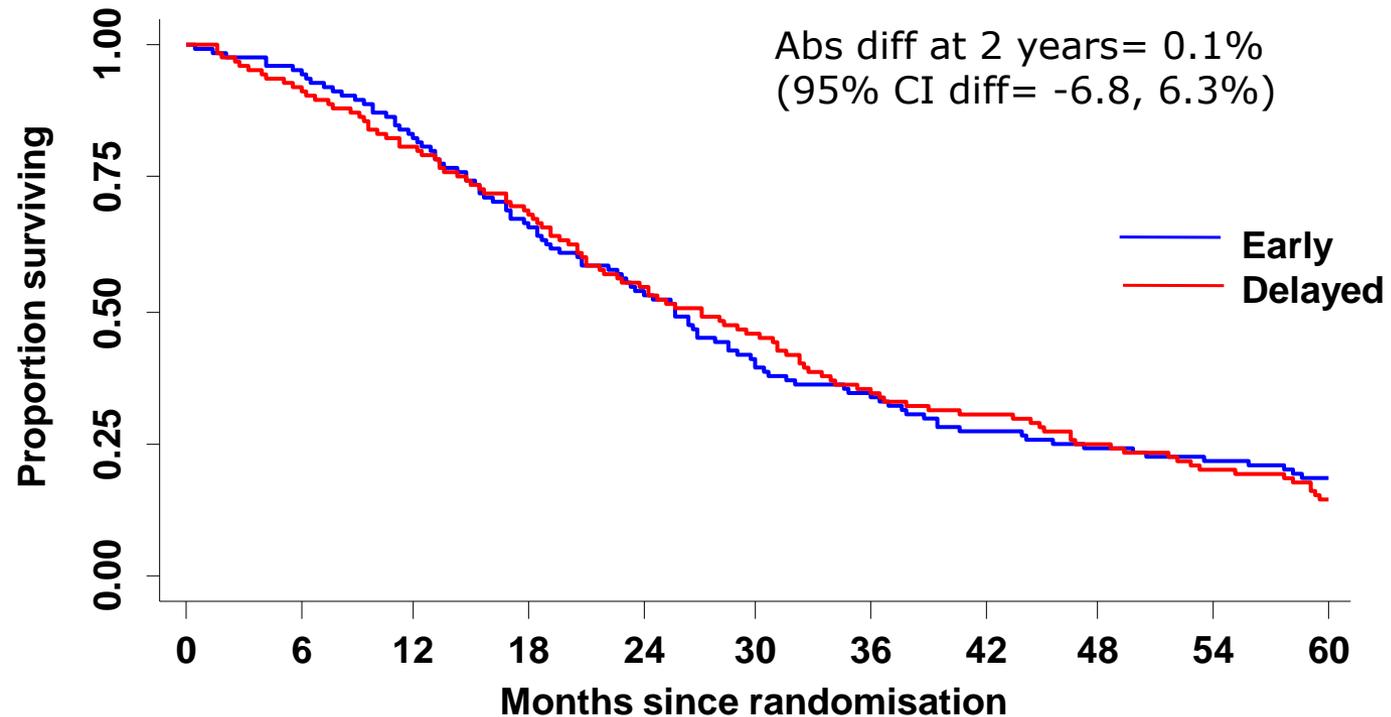


Number at risk

	0	3	6	9	12	15	18	21	24
Early	265	23	16	14	11	11	10	10	9
Delayed	264	177	116	91	69	56	49	42	33

Overall Survival

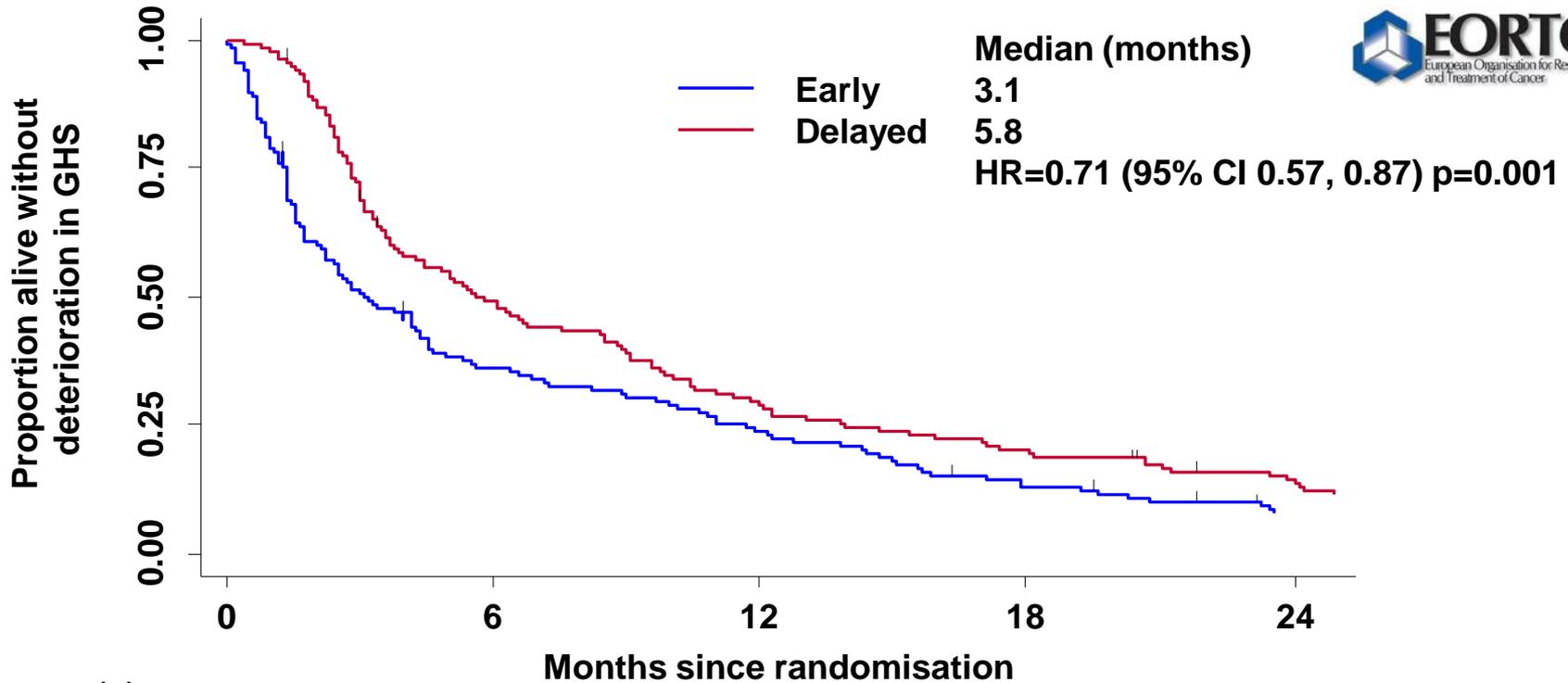
HR=1.00 (95%CI 0.82-1.22) p=0.98



Number at risk

Early	265	247	211	165	131	94	72	51	38	31	22
Delayed	264	236	203	167	129	103	69	53	38	31	19

Time from randomisation to first deterioration in Global Health Score (or death)



Number at risk

	0	6	12	18	24
Early	190	68	44	23	12
Delayed	194	93	55	38	25

HE4 (WFDC2)*

- Alunperin löydetty epididymiksestä (Kirchhoff ym. 1991)
- Merkitys: proteiini-proteiini interaktiot, immuunipuolustus, solujen kasvu ja erilaistuminen, miehen fertiliteetti?? (Li ym. 2009)
- Erytisesti seroosissa munasarjasyövässä
- Soveltuu mahdollisesti myös korpuskarsinoomaan
- Käyttäytyy naisilla iän mukaan päinvastoin kuin Ca-125

ENDOMETRIOOSI, CA-125 JA HE4 (Huhtinen K ym. Br J Ca 2009)

- **s-Ca-125**
- Koholla SEKÄ munasarjasyövässä ETTÄ endometrioosissa
- Ei koholla kohtusyövässä
- **s-HE4**
- Ovario-ca: 1125 pM
- Korpus-ca: 99,2 pM
- Endometrioosi: 46 pM
- Terveet: 41 pM

Moore RG et al. Gynecol Oncol 2008;108:402-8

Table 6
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*

- Premenopausal: predictive index (PI):
- $-12.0 + 2.38 * \text{LN}[\text{HE4}] + 0.0626 * \text{LN}[\text{CA 125}]$
- Postmenopausal: predictive index (PI)
- $-8.09 + 1.04 * \text{LN}[\text{HE4}] + 0.732 * \text{LN}[\text{CA 125}]$
- → Risk of Ovarian Malignancy score:
- ROMA score (%) = $\exp(\text{PI}) / [1 + \exp(\text{PI})] * 100$

ROMA

- Prospektiivinen, sokkoutettu tutkimus
- 472 naista, joilla lantiotuumori ja suunniteltiin leikkausta
- 255 pre- ja 217 postmenopausaalista
- 383 benigniä tautia ja 89 syöpää
- Syöpäinsidenssi 15 % (ovarioca:n 10 %)

ROMA JA MUNASARJASYÖPÄ

- PREMENOPAUSI
 - Sens. 100%
 - Spesif. 74,2%
 - NPV 100%
- POSTMENOPAUSI
 - Sens. 92,3 %
 - Spesif. 76,0 %

ROMA JA KAIKKI SYÖVÄT (MYÖS RAJALAATUISET)

- PREMENOPAUSI
 - Sens. 81,3 %
 - Spesif. 74,2 %
 - NPV 98,3 %
 - PPV 17,8 %
- POSTMENOPAUSI
 - Sens. 90,2 %
 - Spesif. 76,0 %
 - NPV 95,8 %
 - PPV 56,1 %

TABLE 1

Statistical characteristics of HE4 levels (pM) for benign disease

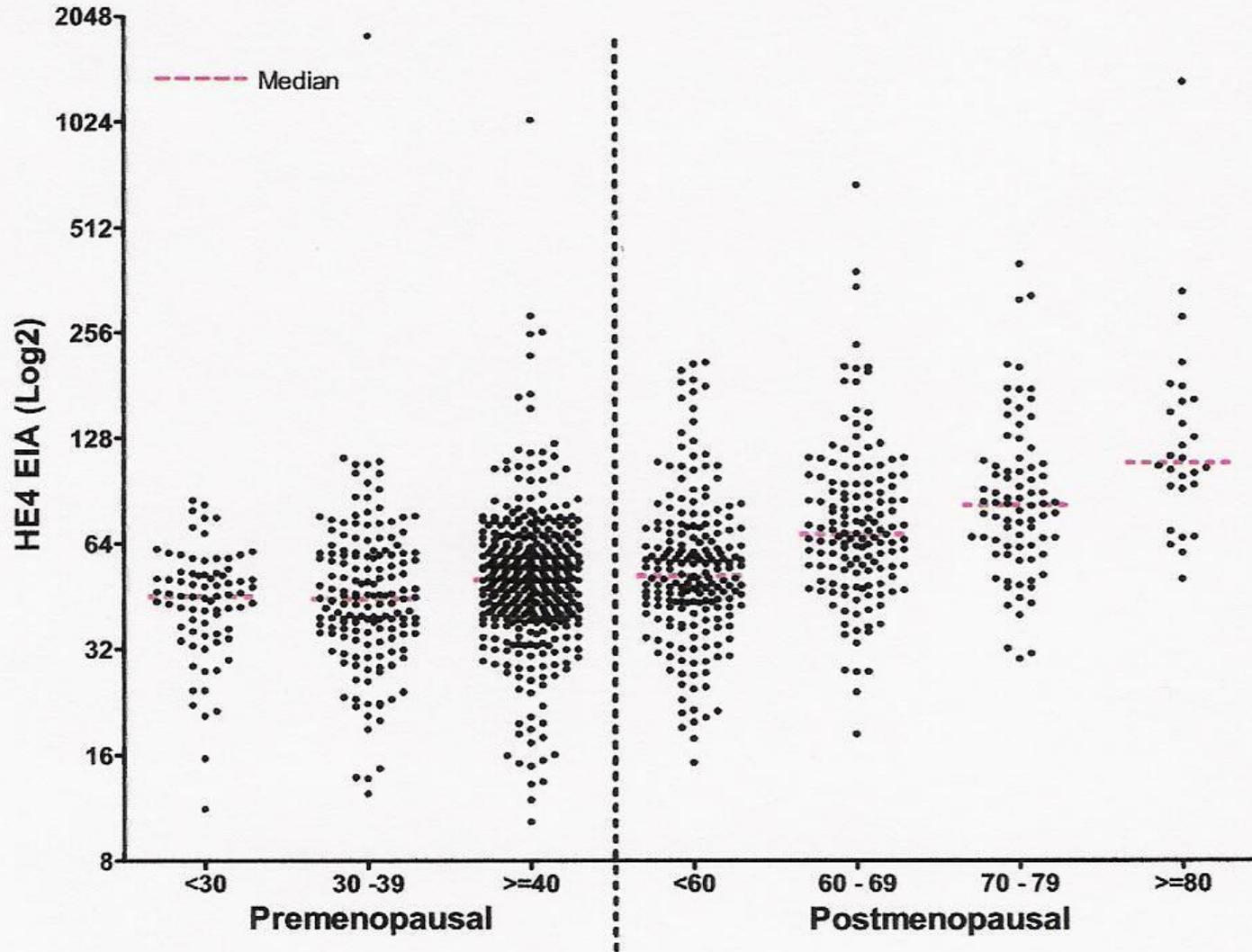
Age group (n = 1042)	Premenopausal			Postmenopausal			
	>30 y	30–39 y	≥40 y	<60 y	60–69 y	70–79 y	≥80 y
n	76	155	362	197	145	79	28
Mean	45.9	60.0	58.2	61.4	86.4	98.8	171.6
SD	14.9	142.1	59.9	35.5	71.5	64.4	238.0
Median	45.5	44.9	50.9	52.2	68.5	83.0	109.5
Range	11.2–84.9	12.4–1799	10.3–1037	15.2–210.3	18.3–678.6	29.9–403.2	50.8–1339

HE4, human epididymis protein 4.

Moore. Comparison of serum HE4 and CA125 levels in benign gynecologic disease. *Am J Obstet Gynecol* 2012.

FIGURE 1

Scatterplot of serum HE4 levels by age group



HE4, human epididymis protein 4.

Moore. Comparison of serum HE4 and CA125 levels in benign gynecologic disease. *Am J Obstet Gynecol* 2012.

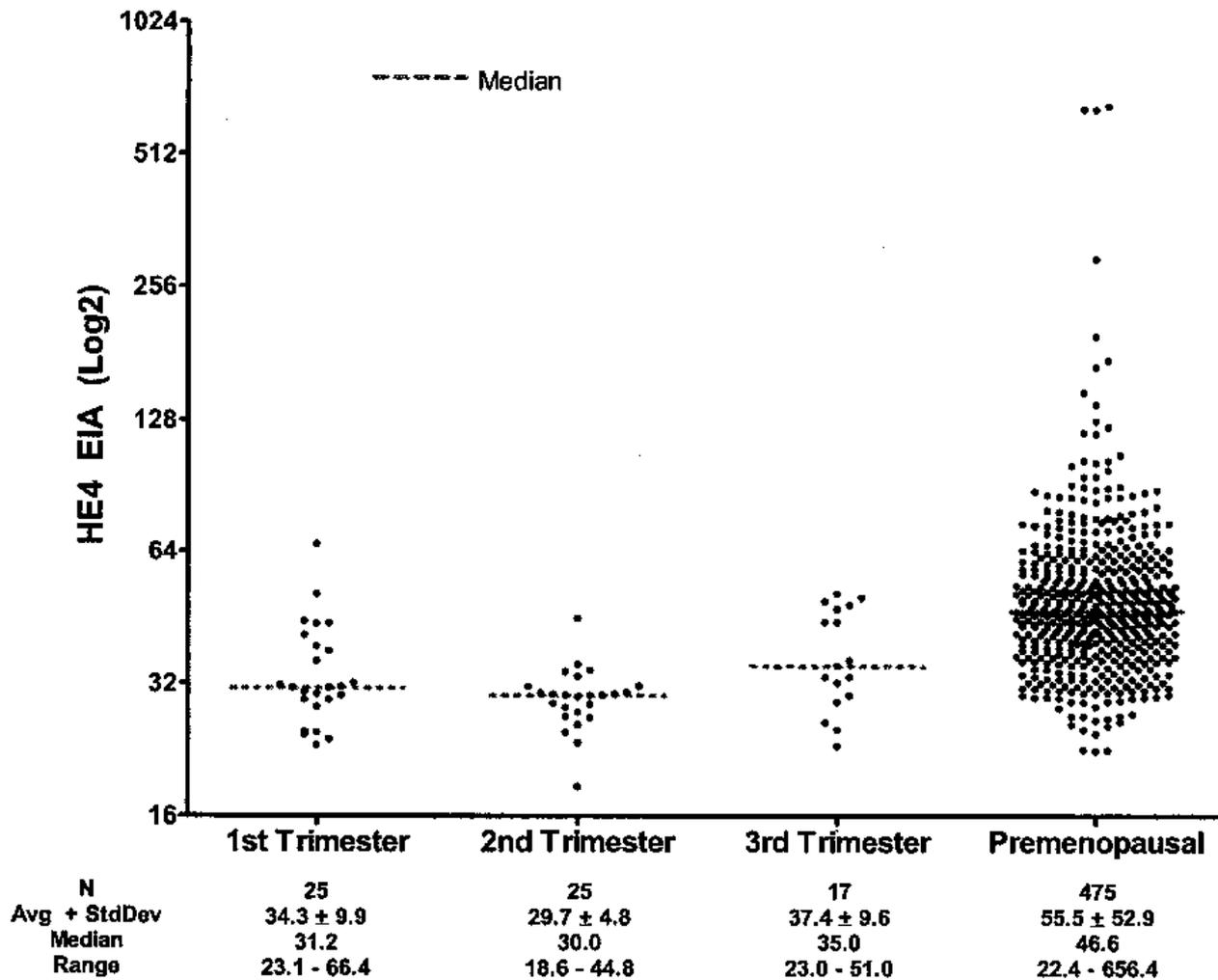
BENIGNIT GYNEKOLOGISET TAUDIT, HE4 JA CA125

n=1042
43/57%

(Moore ym. AJOG 2012)

Tauti	HE4 ↑	Ca-125 ↑	p
Endo- metrioosi	3 %	67 %	<0.0001
Seröösit tuumorit	8 %	20 %	=0.0002
Myomat	8 %	26 %	=0.0083
Dermoidit	1 %	21 %	=0.0004
PID	10 %	37 %	=0.014

FIGURE 3
Scatterplot of pregnant women by trimester
and all premenopausal women



AVG, average; HE4, human epididymis protein 4; EIA, immunosorbent assay; StdDev, standard deviation.

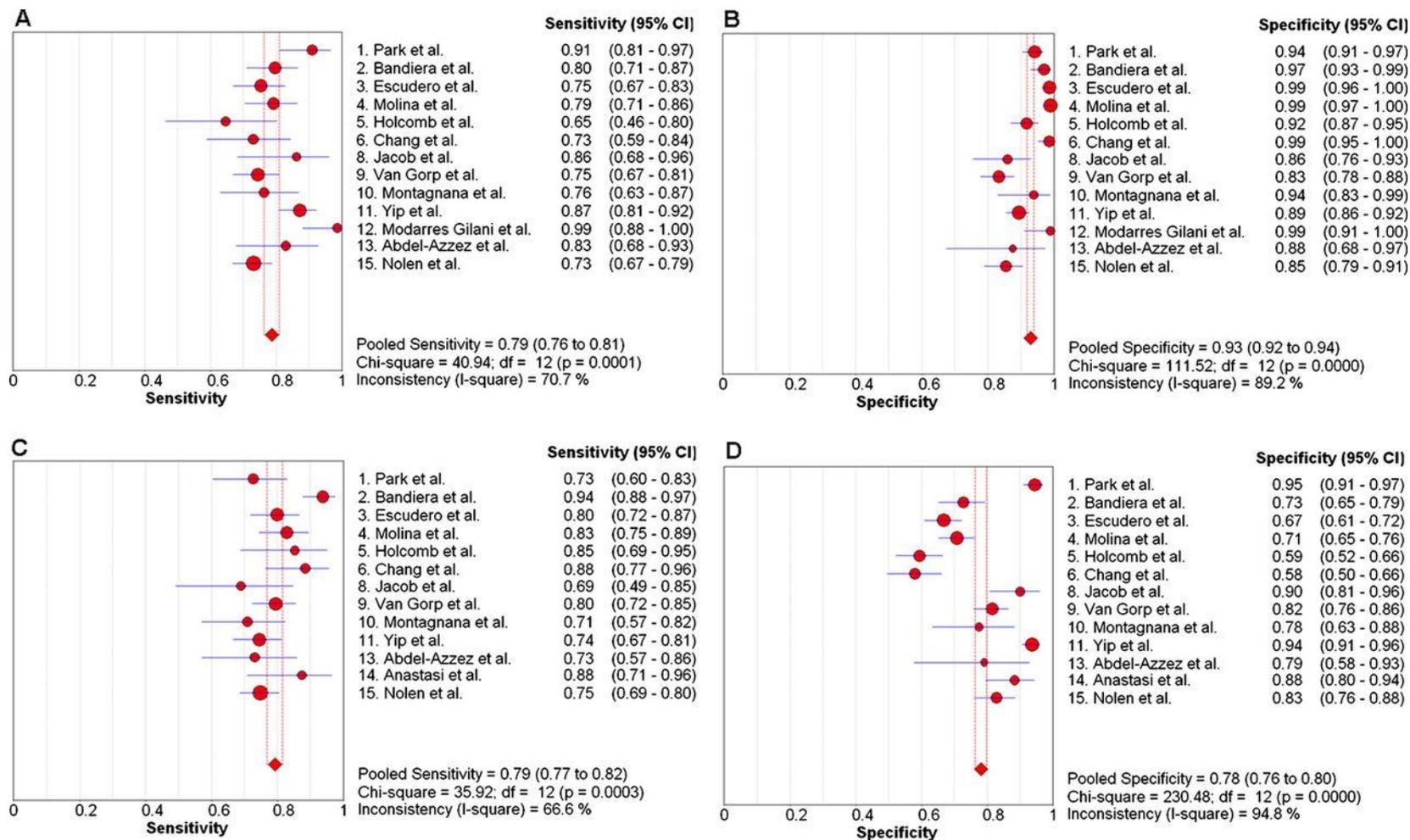
Moore. Serum HE4 levels in healthy women. Am J Obstet Gynecol 2012.

i
t
r
l
c
l
f
e
z
r
l
v
c
c
c
c
l
r
i
c
l
c
t
c
e
s
r
t

HE4:N NORMAALIARVOT (pmol/l)

- **Moore ym. 2012**
- Premenopause <89
- Postmenopause <128
- **Fimlab**
- Premenopause <70
- Postmenopause <140
- Obs: Sydämen vajaatoiminnassa voi olla ad 500!

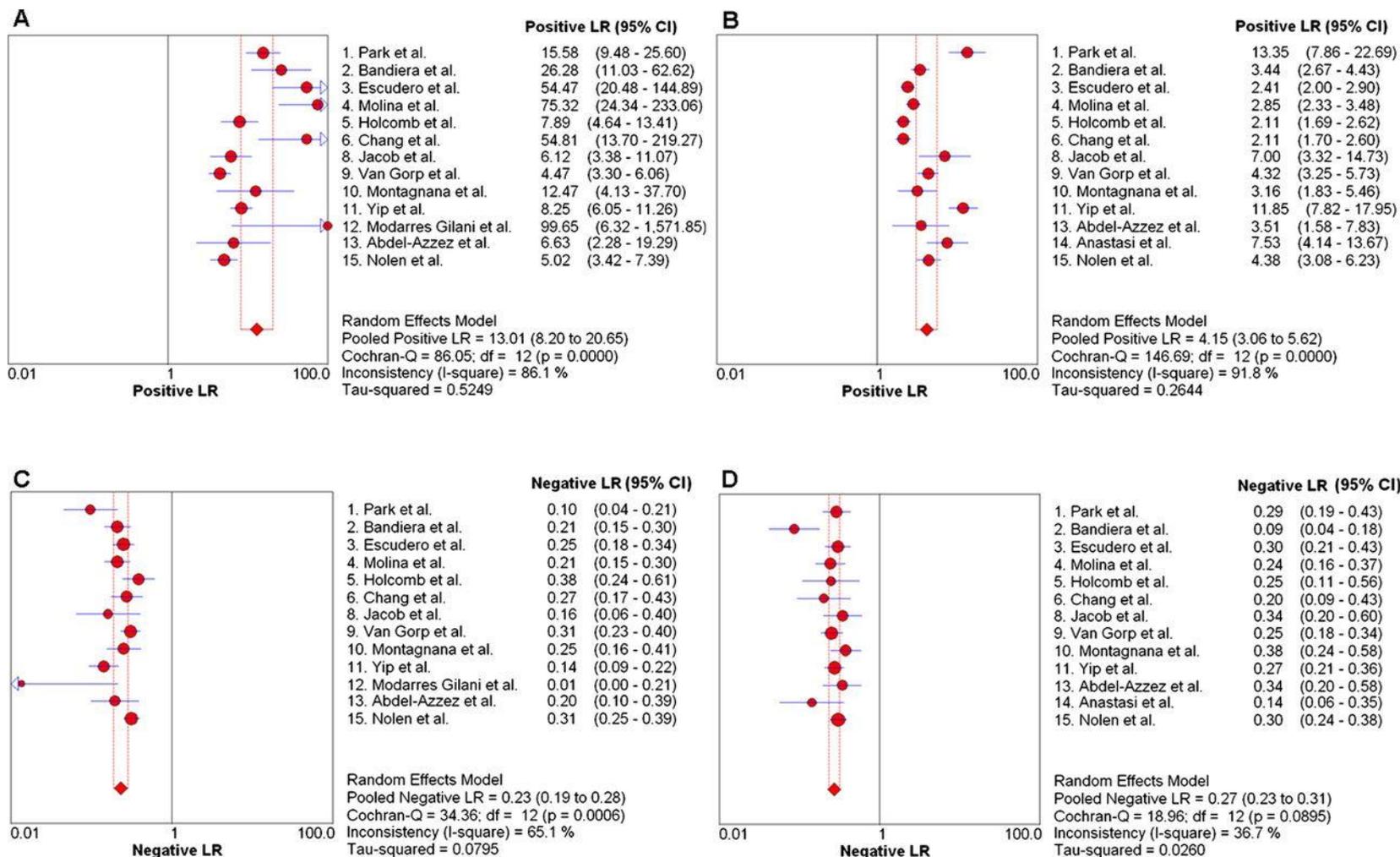
Sensitivity and specificity plots of human epididymis protein 4 (HE4) (A and B, respectively) and carbohydrate antigen 125 (CA-125) (C and D, respectively) determination in the diagnosis of ovarian cancer.



Ferraro S et al. J Clin Pathol 2013;66:273-281



Likelihood ratio plots of human epididymis protein 4 (HE4) (A and C) and carbohydrate antigen 125 (CA-125) (B and D) determination in the diagnosis of ovarian cancer.



Ferraro S et al. J Clin Pathol 2013;66:273-281



EPITELIAALINEN MUNASARJASYÖPÄ: MILLOIN CA-125 JA/TAI HE4?

		Ca-125	HE4
Diagnoosi	Premenop.	Kyllä	Kyllä
	Postmenop.	Kyllä	Ei
Sytostaattihoidon tehon seuranta		Kyllä	Ei vielä
Jälkiseuranta		Ei rutiinisti	Ei

HE4 JA ENDOMETRIUM- KARSINOOMA

Ca125 AND HE4 IN POSTMENOPAUSAL WOMEN

Tumor marker	Controls (n=156) Median (range)	St I Endometrial cancer (n=122) Median (range)	P-value
CA125 (U/ml)	11.2 (3.3-73.6)	14.5 (3.0-432.9)	0.0001
HE4 (pM)	35.4 (18.0- 127.8)	60.5 (1.1-1022.1)	<0.0001

SENSITIVITY OF CA125 AND HE4 IN CONTROLS VS. ST I CANCER

Marker combination	Specificity 90%	Specificity 95%	Specificity 98%
CA125	30.0%	20.8%	12.9%
HE4	48.4%	37.9%	29.3%
CA125+HE4	51.6%	41.7%	34.4%

Preoperative serum concentration of HE4 and CA125 in patients with endometrial carcinoma

S.K. Saarelainen, N. Peltonen, T. Lehtimäki, A.
Perheentupa, M. Vuento, J.U. Mäenpää

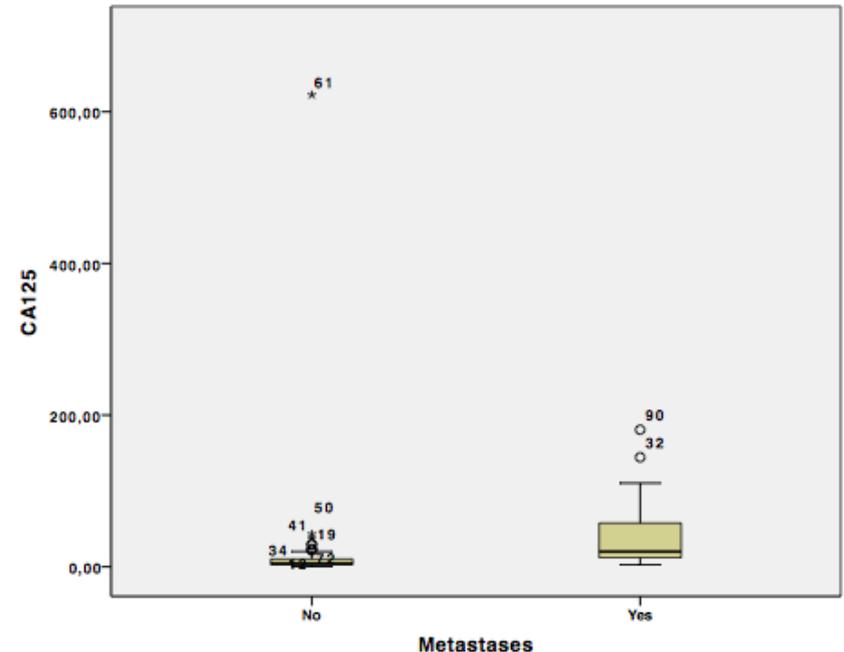
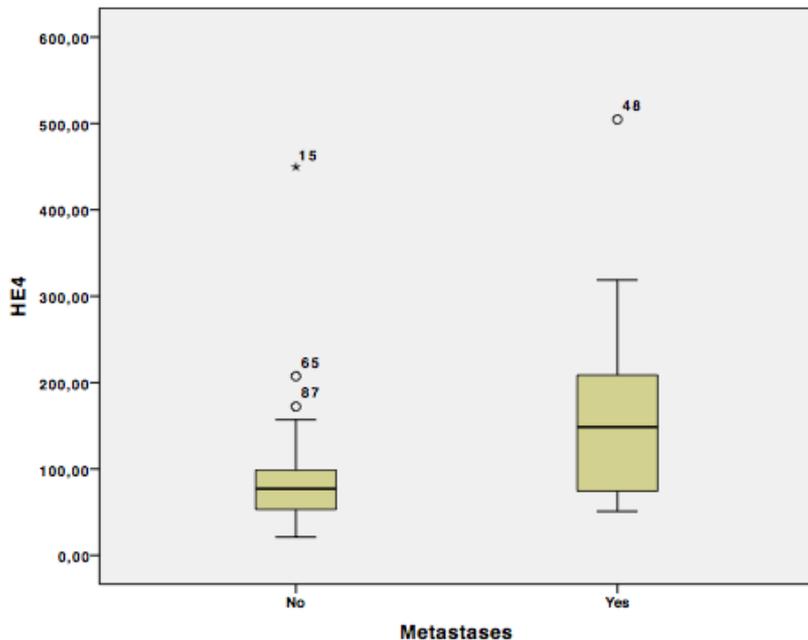
Tampere University Hospital, Turku University
Hospital, Finland

Methods

- Preoperative sera were collected from 98 consecutive patients diagnosed with endometrial carcinoma
- All patients were scheduled for a hysterectomy, bilateral salpingo-oophorectomy and pelvic (+/- para-aortic) lymphadenectomy
- Serum concentrations of HE4 and CA125 were assessed by ELISA and correlated with the final histopathological report

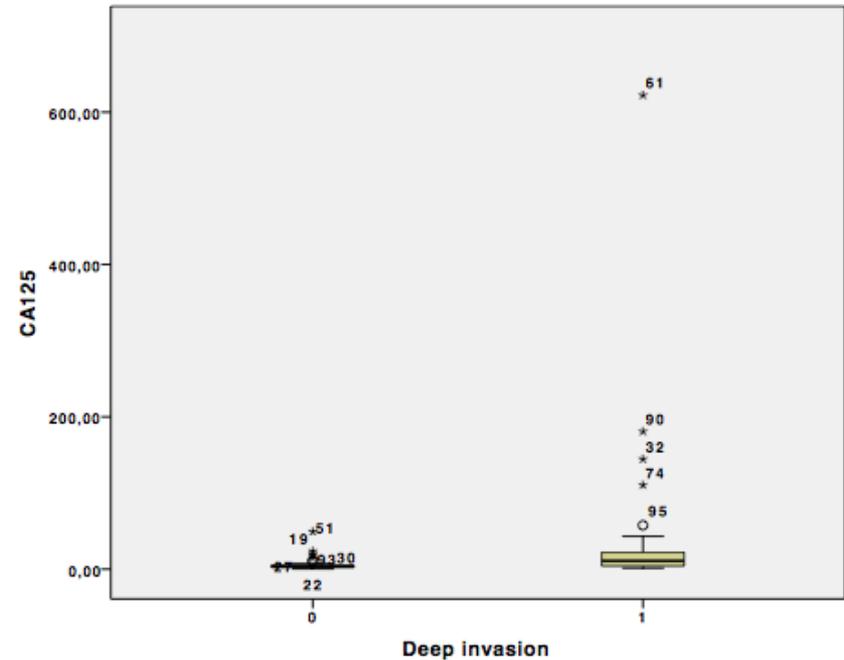
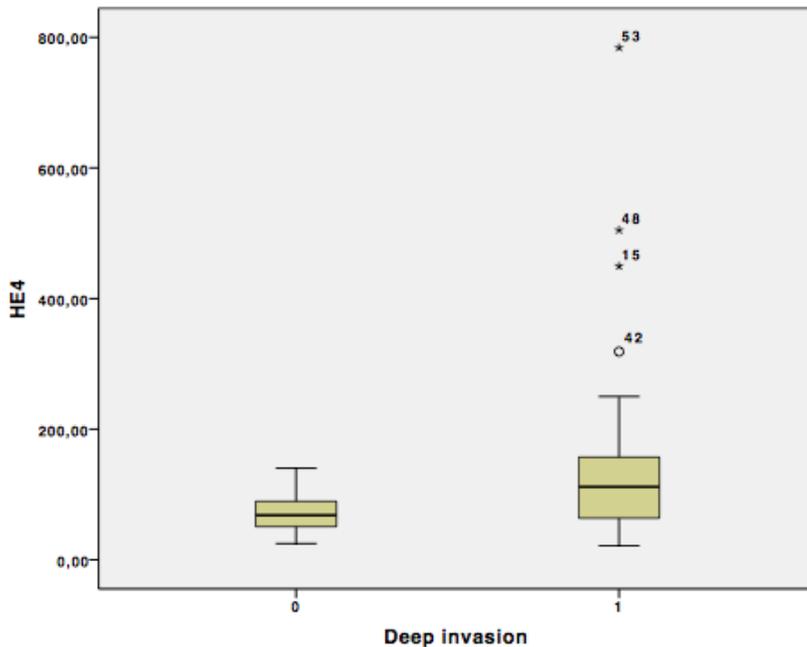
Results

- The serum concentrations of HE4 and CA125 were higher in the metastatic group than in the group with a local disease ($P=0.001$ and $P<0.001$, respectively)



Results

- The serum concentrations of HE4 and CA125 were higher in the group with deep ($\geq 50\%$) myometrial invasion ($P < 0.001$ and $P < 0.001$, respectively)



Multivariate analysis

- HE4 was the only predictor for a metastatic disease (OR, 1.012; 95% CI 1.003-1.021; P=0.007)
- HE4 and grade were associated with the presence of deep invasion (OR, 1.023; 95% CI, 1.009-1.037; P=0.001 and OR, 1.776; 95% CI, 1.011-3.121; P=0.046, respectively)

Conclusion

- Preoperative HE4 may be superior to CA125 in predicting a metastatic disease in endometrial carcinoma

Conclusion

- Serum concentrations with respect to metastatic disease
 - HE4: 148.6 pM (50.9-504.7 pM) vs. 77.2 pM (21.3-449.6 pM)
 - CA125: 20.0 U/mL (2.6-180.7 U/mL) vs. 4.3 U/mL (0.4-622.2 U/mL)
- CA125 levels are below the threshold (35 U/ml)

LOPUKSI

- Ca-125 ja HCG edelleen parhaat
- HE4 kannattaa tutkia ainakin epäselvissä tapauksissa premenopauksissa
- Inhibiini B:n ja E2:n rinnalle GCT:ssä tulee ehkä AMH
- HE4:ssä on potentiaalia endometriumkarsinooman merkkiaineeksi

KIITOS!