Prognostic significance of Serum Vascular Endothelial Growth Factor-C in Early Stage Cervical Cancer

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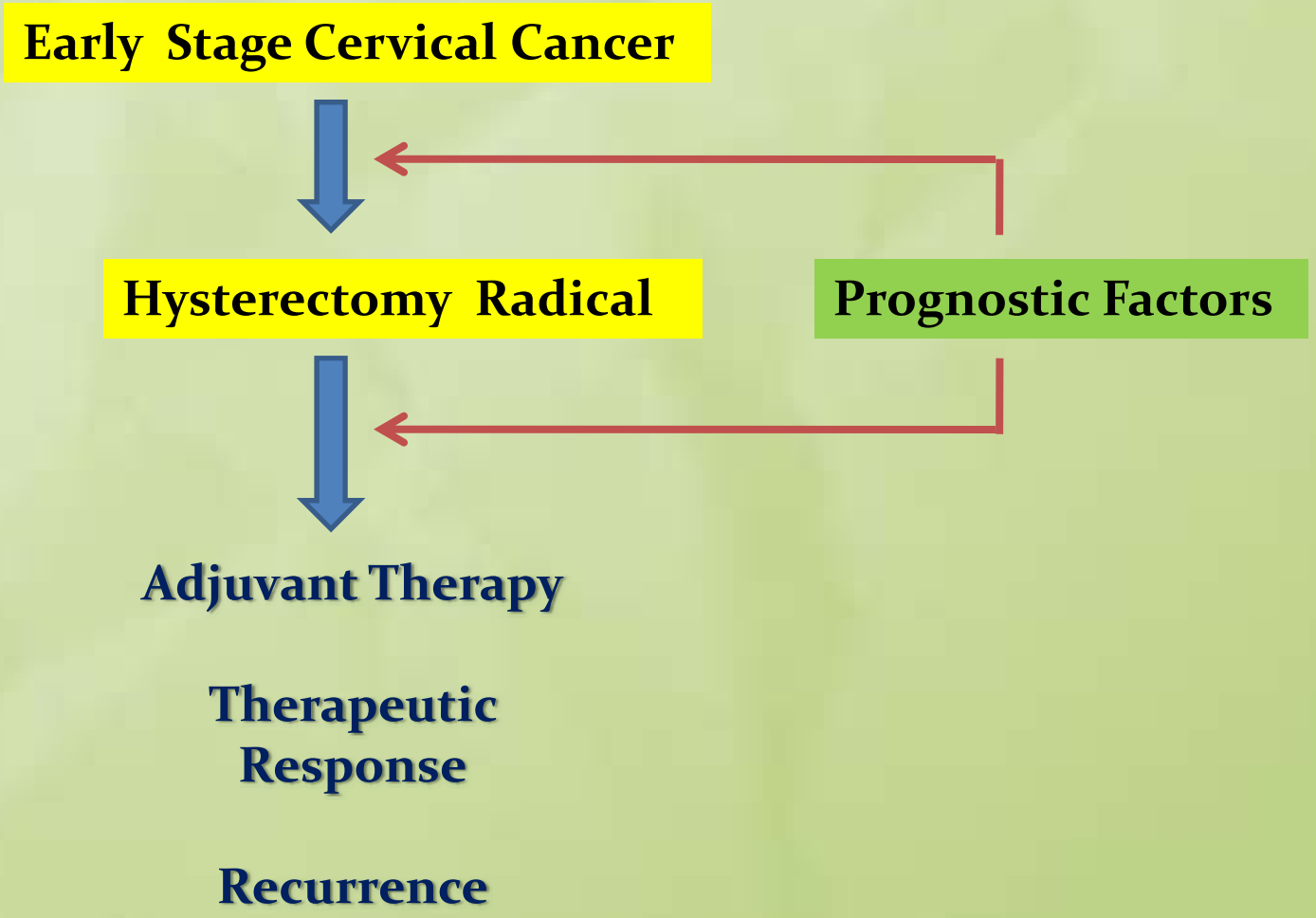
Tokyo - Japan

INTRODUCTION



INTRODUCTION

Prognostic Factors

Clinical –pathological factors

- Stage
- Lesion/Bulky
- Cell type
- Lymphnode met
- Differentiation
- Deep stromal invasion
- Lymph vascular space invasion
- Parametrial invasion

Tumor marker/ Biomolecular marker

- SCC
- MMP, Kapthensin D, Heparanase
  E Kadherin, Katenin,
- Indeks DNA,p53, CD_4,HPV

VEGF → VEGF- C ?

Takeda N, Gyn Scan 2002, Menon U Gyn Onc 2000
Skates JS, Gyn Cancer 2004, Mathus SP, Gyn Onc 2005

Vascular Endothelial Growth Factor (VEGF)

Vascular Endothelial Growth Factor (VEGF)

VEGF = VEGF-A = VPF (Vascular Permeability Factor)

heparin binding glycoprotein

supergene PDGF

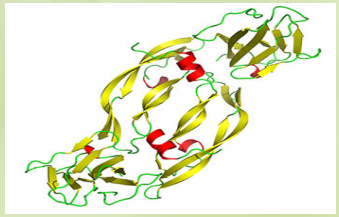
Kromosom 6p12

Family : VEGF A, VEGF B, VEGF C, VEGF D and VEGF E

Jusila L. Phys J.2002, Lymboussaki 1999

Vascular Endothelial Growth Factor (VEGF)

VEGF

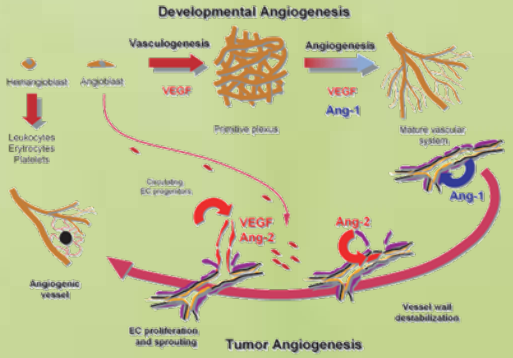


Key Signal

Hipoxic cells

(Oxygen - Hungy Cells)

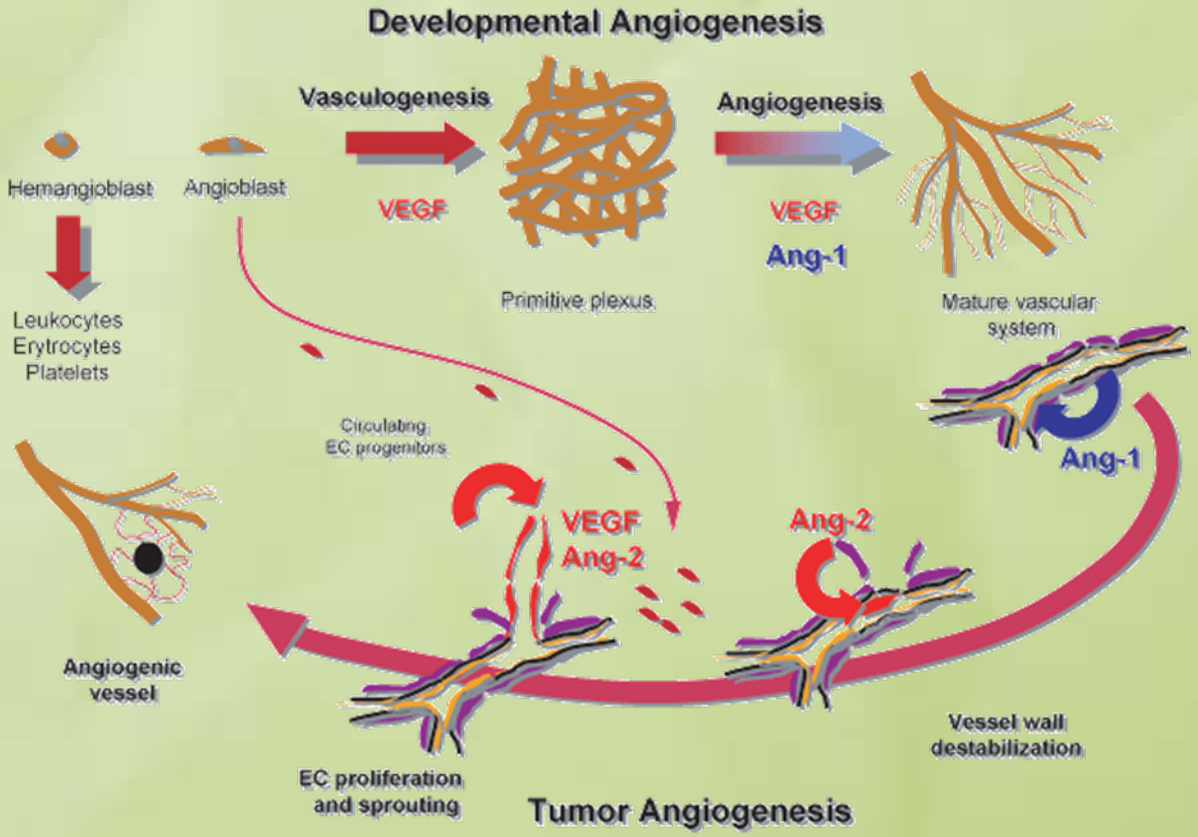
Angiogenesis



Kodama et all, Onc Rep,2005

Pilch H,IJGC, 2001, Ferara N, Nature Medicine, 2003

DEVELOPMENTAL AND TUMOR ANGIOGENESIS



Athina L, 1999

Jusilla L,Physiological Review-2002

Angiogenesis is tightly regulated by balanced expression of many factors

Regulators of angiogenesis

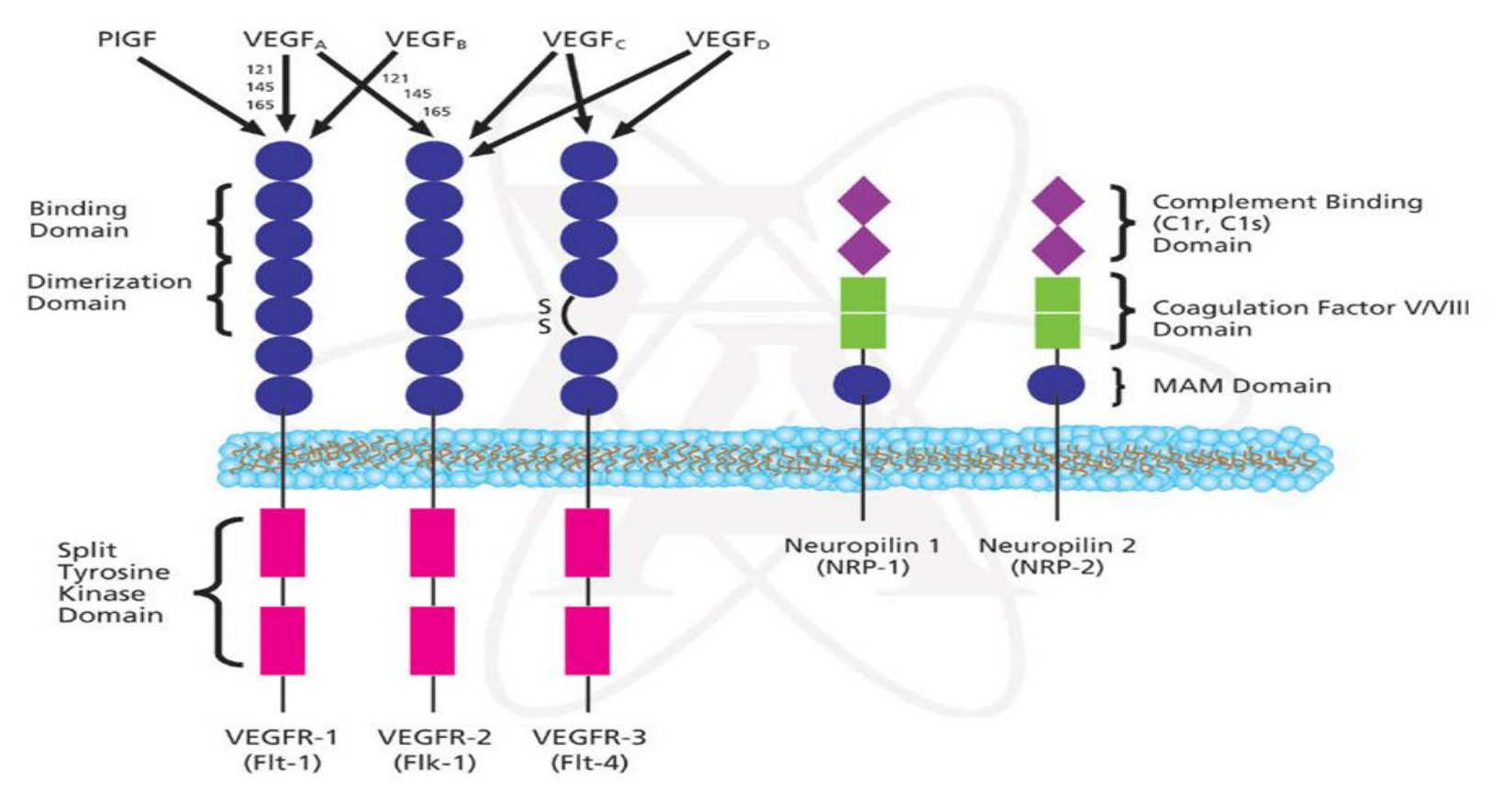
Promoters

- VEGF
- aFGF
- bFGF
- TGF-a, b
- EGF
- TNF-a
- Angiogenin
- IL-8
- Ang-1, 2

Inhibitors

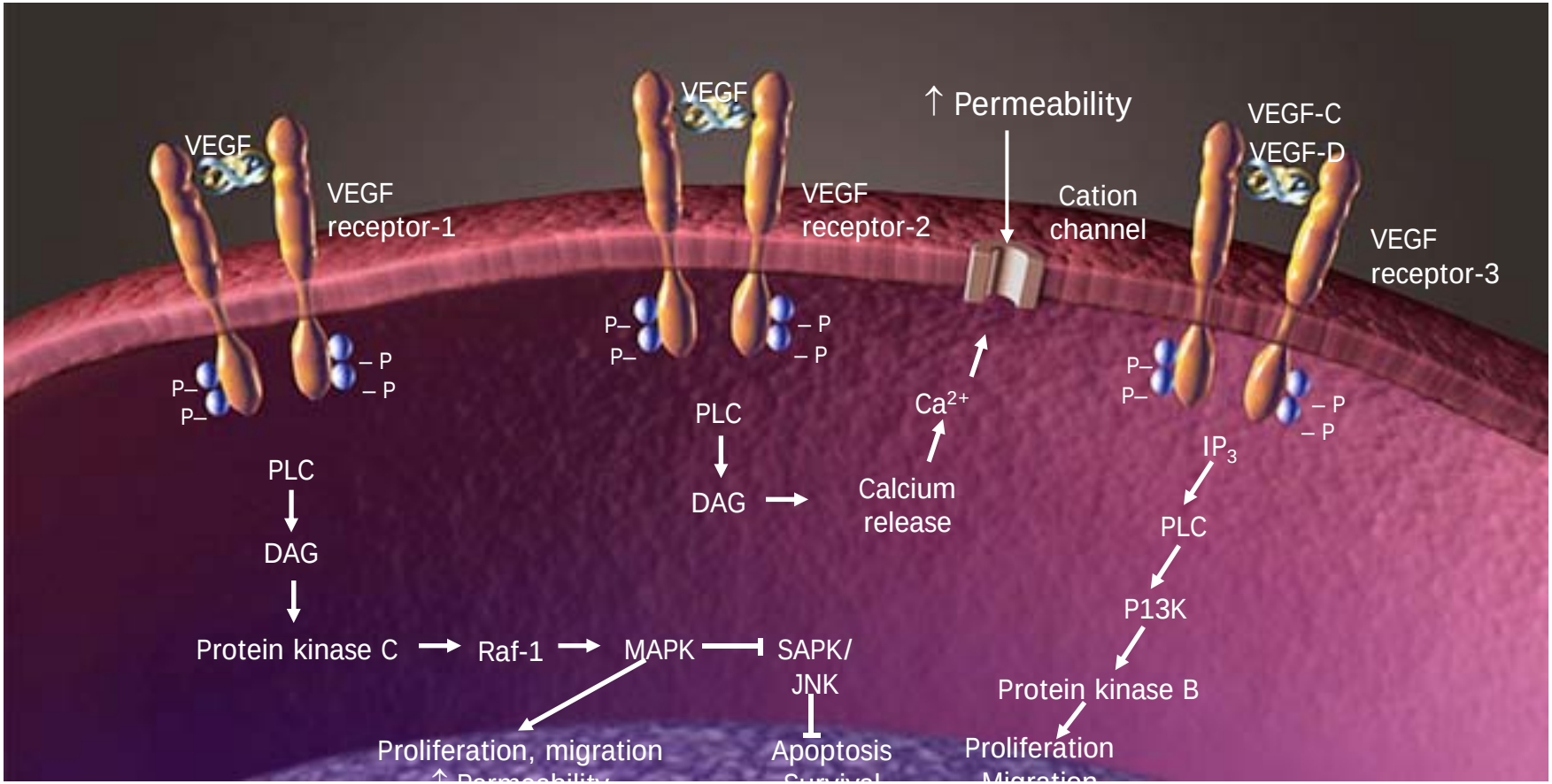
- Thrombospondin (TSP)
- Angiostatin
- Endostatin
- Vasostatin
- Prolactin
- Growth hormone
- Canstatin
- Tumstatin
- Interferon-a (IFN-a)

VEGF Receptors



Clauss, Tromb Hemost 2000

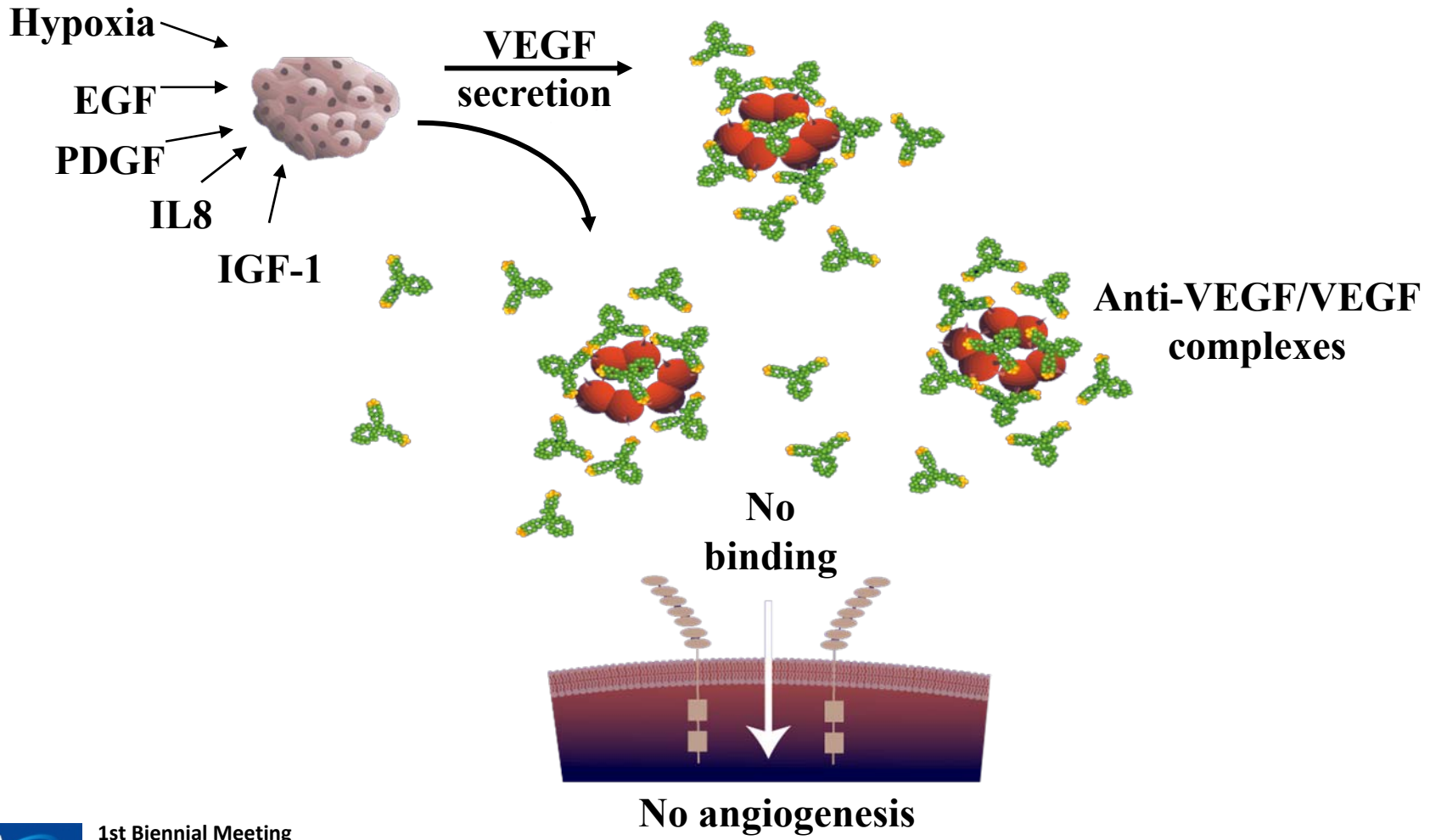
VEGF signal transduction and its effects



VEGF binding to VEGF receptor-2 activates a signalling cascade resulting in cellular effects

Shibuya M. Cell Struct Funct 2001

VEGF is a key target for anticancer therapy

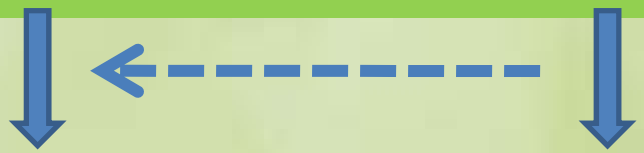


Vascular Endothelial Growth Factor-C (VEGF-C)

Vascular Endothelial Growth Factor - C (VEGF-C)

VEGF – C : disulphide bonded homodimer

31 kDa and 21 kDa

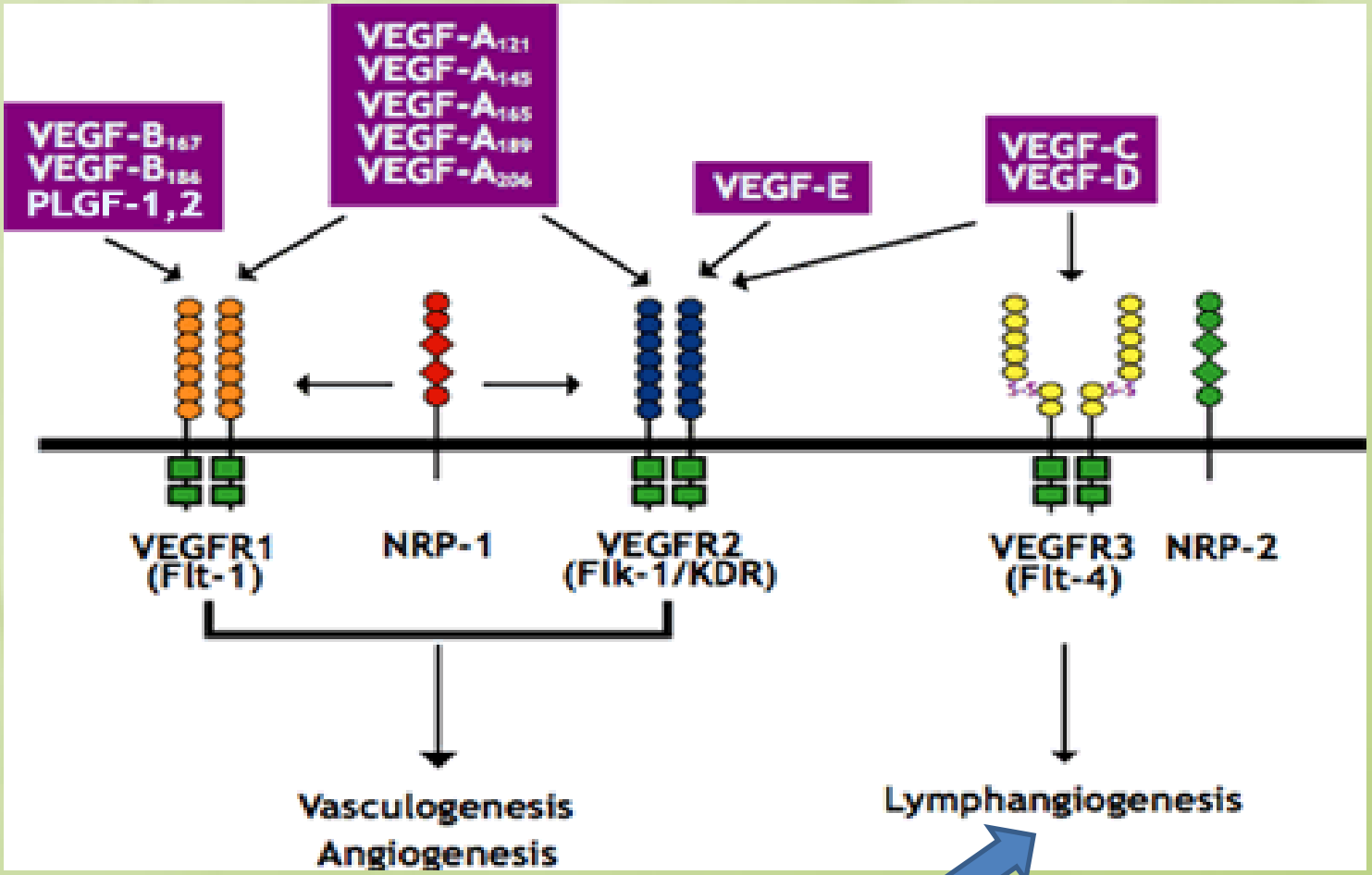


VEGFR2 **VEGFR3**

VEGF- C → **Sel ENDOTEL :**

- Proliferation
- Differentiation
- Migration
- Survival
- Permeability

Vascular Endothelial Growth Factor - C (VEGF- C) Signaling



Clauss, Tromb Hemost 2000

Vascular Endothelial Growth Factor-C (VEGF-C)

VEGF-C ⇒ lymphangiogenesis

⇒ new lymphatics formation

VEGF-C mRNA : significantly higher in tumours exhibiting :

deep stromal invasion
pelvic lymph node metastasis
lymph-vascular space involvement

Multivariate analysis revealed VEGF-C mRNA expression to be the sole independent factor influencing pelvic lymph node metastasis

Hashimoto, BJC 2001

Vascular Endothelial Growth Factor - C (VEGF-C)

Subjects demonstrating VEGF-C mRNA expression displayed significantly poorer prognoses than those lacking VEGF-C mRNA expression (*P* = 0.049).

Ekspresion mRNA VEGF- C : 130 X

These findings provide evidence supporting the involvement of VEGF-C expression in the promotion of lymph node metastasis in cervical cancer.

Hashimoto ,BJC 2001
Van Trapen, BJC 2002

Vascular Endothelial Growth Factor - C (VEGF-C)

Mitsushasi,2005

Serum VEGF-C level ⟺ **FIGO Staging**

Mathur SP,2005

Serum VEGF-C level :

Advanced Stage Cervical Cancer

Metastasis

Mitsushasi,Cancer,2005
Mathur SP, Gyn Onc 2005

Vascular Endothelial Growth Factor - C (VEGF-C)

Cheng WF,1999

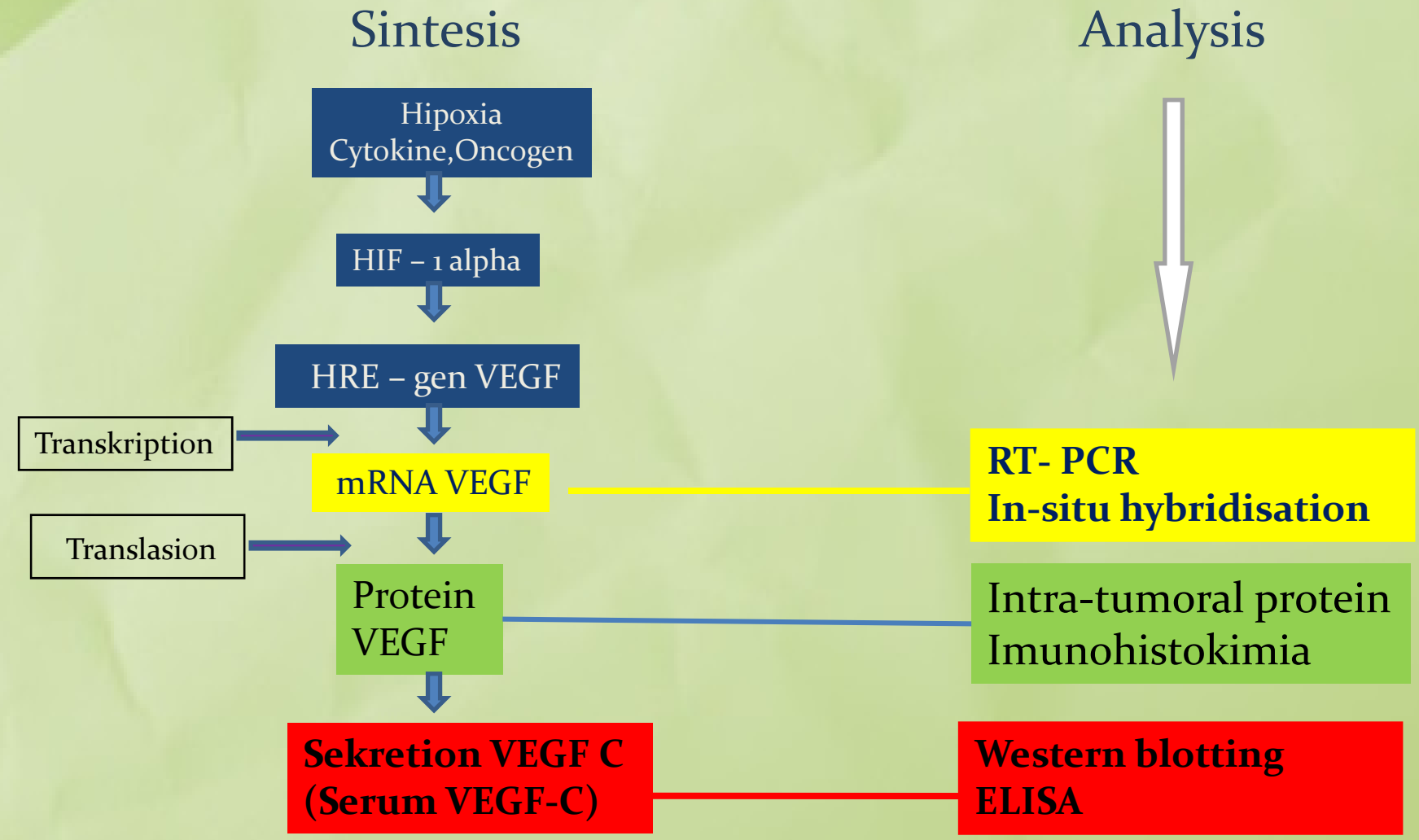
Intratumoral protein VEGF :

- **Biopsi**
- **VEGF** : lymphnode metastasis

tumor progressivness
metastatic ability

Cheng WF, Obs&Gyn,1999

Vascular Endothelial Growth Factor (VEGF)



Matsumra K, Blood 2003, Ferara,1997,
J usilla L,Physiological Review-2002

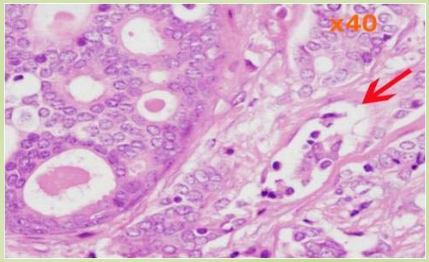
THE RESEARCH

Prognostic significance of Serum VEGF-C and LVSI in Early Stage Cervical Cancer

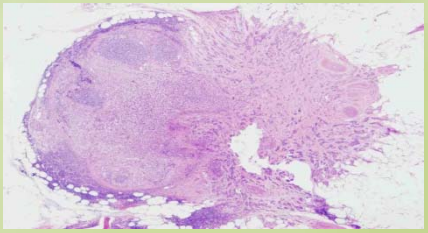
1st Biennial Meeting
of Asian Society of Gynecologic Oncology
(ASGO) Tokyo - Japan

Research Question

CaCx IB – IIA



Lymph Vascular Space Invasion



Lymph node Metastases

Is there any correlation : Serum VEGF-C level with Lymph Vascular Space Invasion and Lymphnode Metastases ?

Research Design

Case control Study

January – October 2007

Total : 69 cases

Independent Variable :

Serum VEGF-C level

LVSI

Clinical dan Histopatological Factors

Dependent Variable :

Lymphnode metastases.

Serum VEGF-C level assay :

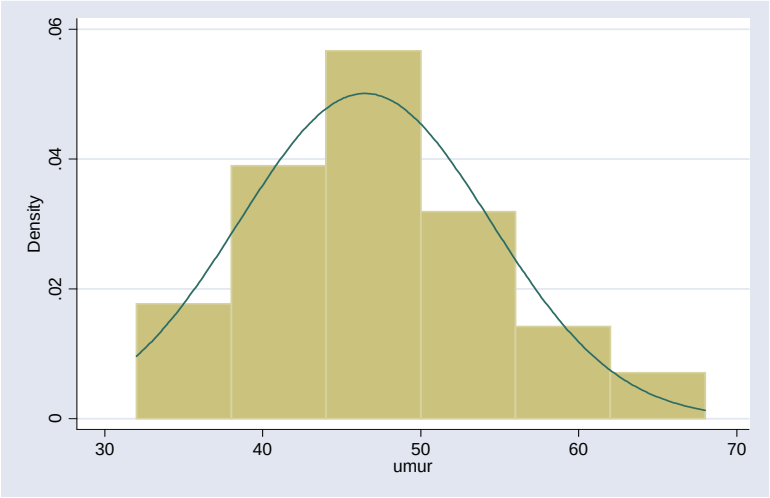
5 cc blood

Serum

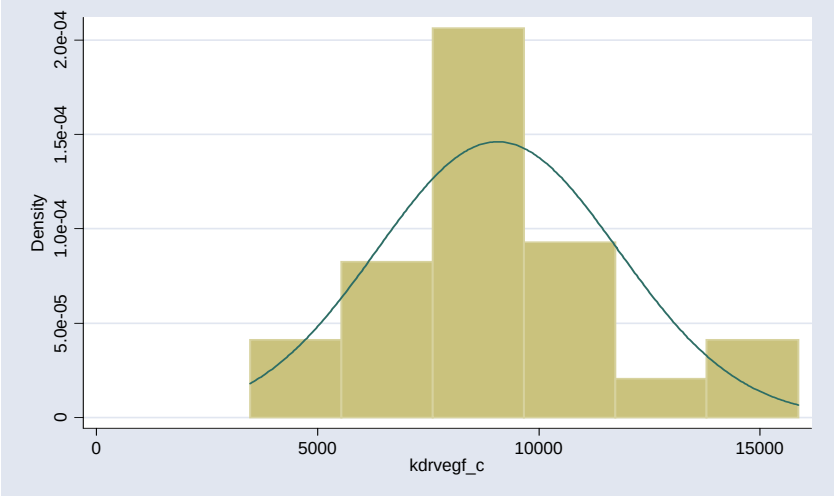
Serum VEGF-C level by ELISA

Study Results

Chi2 dan Shapiro-Wilk NormalityTest : Normal Distribution Data



Histogram of age distribution



Histogram Serum VEGF-C level

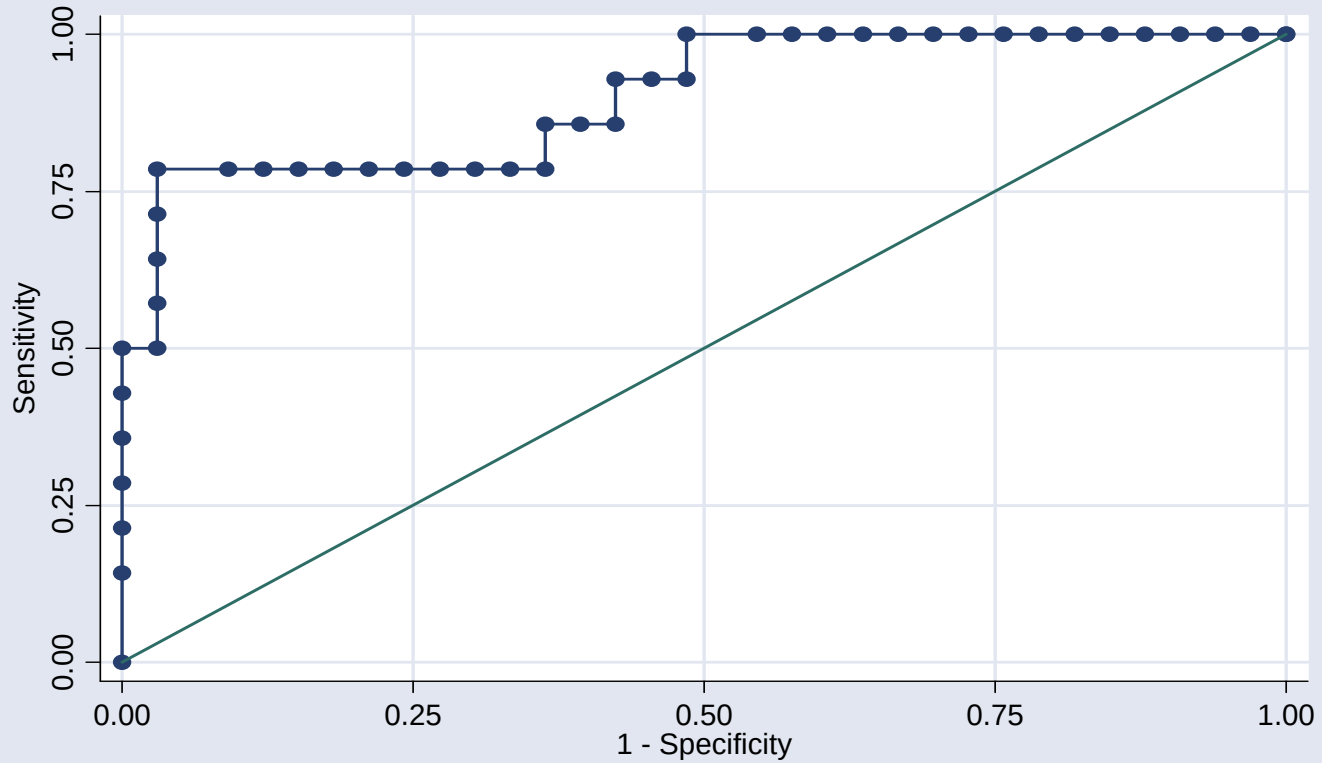
Study Results

Clinical characteristic

Clinical Characteristic	Lymphnode Meta				OR	(95% CI)	P value
	Negatif		Positif				
	n	%	n	%			
Stage							
IB ≤ 4 (IB1)	15	4 5,45	2	14,29	1		
IB > 4 (IB2)	3	9,09	5	35,71	12,5	(1,60;97,64)	0,016
IIA ≤ 4	13	39,39	4	28,57	2,30	(0,36;14,71)	0,376
IIA > 4	4	6,06	3	21,43	11,25	(1,10;114,36)	0,041
Test for trend (Chi2,Pvalue)	9,23	0,026					
Primary Lesion							
≤ 40 mm	30	90,91	7	50,00	1		
> 40 mm	3	9,09	7	50,00	10	(2,05;48,69)	0,004

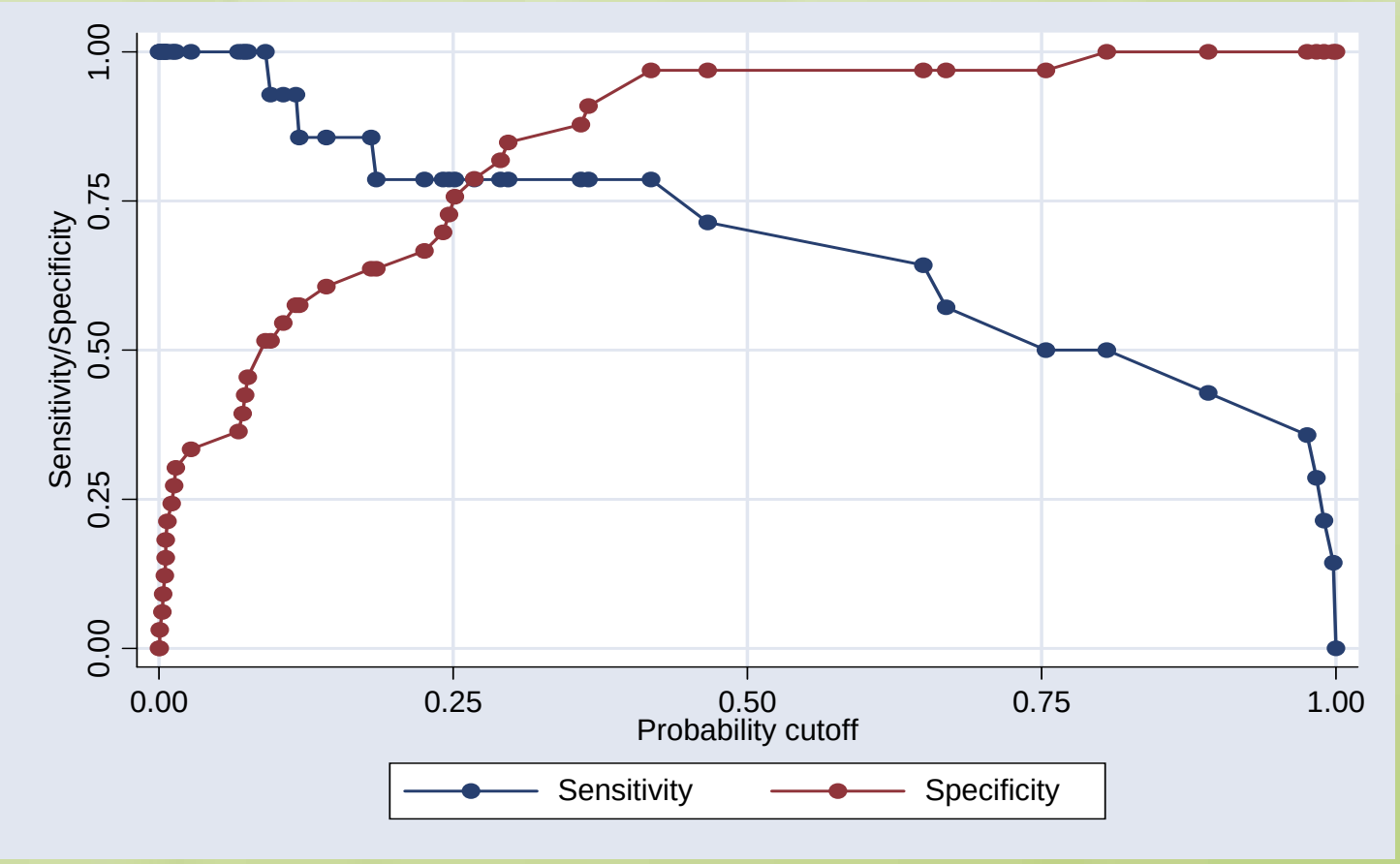
Study Results

ROC Analysis Serum VEGF-C level



Study Results

Cut-off point sensitifitydan spesificty of SerumVEGF-C



Study Results

Serum VEGF- C :

Cut-off point : 10.066 pg/ml

(78,57% sensitivity and 96,97% specificity)

Ca Colorectal : 533 pg/ml
Ca Paru (NSLC): 1850 pg/ ml

Van Trapen, 2002

Study Results

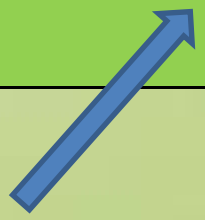
Lymphvascular Space Invasion and Serum VEGF-C

Serum VEGF-C Level	Limph-vask Spc Invs				OR	(95% CI)	P Value
	Negatif		Positif				
	n	%	n	%			
Kadar VEGF-C							
≤ 10.066,90	20	55,56	1	9,09	1		
> 10.066,90	16	44,44	10	90,91	12,5	(1,44;108,18)	0,022

Study Results

Lymphnode Metastases >< Serum VEGF-C level

Serum VEGF-C level	Lymphnode Metastases				OR	(95% CI)	P value
	Negatif		Positif				
	n	%	n	%			
VEGF-C level							
≤ 10.066,90	32	96,97	4	28,57	1		
> 10.066,90	1	3,03	10	71,43	80	(7,99;800,71)	0,000
Test for trend (Chi2,Pvalue)	25,65	0,00					



Study Results

Lymph node metastasis patient with serum VEGF-C level >10.066 pg/ml I increase by OR 80, 95% CI 7,99;800,71 and p=0,000.

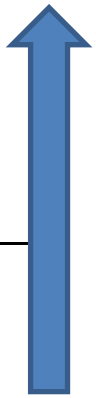
Lymph node metastasis patient with lymph vascular space invasion increase by OR 20, 95% CI 2,32;171,77 and p=0,006.

Lymph vascular space invasion increase by OR 12,5, 95 % CI 1,44;108,18 and p=0,022 in patient with VEGF-C Level > 10.066 pg/ml.

Study Results

Multivariate Analysis

Variable	Koef	SE	(95% CI RI)	z	P value
SerumVEGF-C	0,00095	0,00034	0,00027;0,0016	27,5	0,006
Primary Lesion	1,59	1,26	0,87 ; 4,06	1,26	0,206
LVSI	3,56	2,23	-0,81 ; 7,94	1,6	0,111
Konstanta	-13,39	4,66	-22,43;-4,16	-2,85	0,004



Study Results

Multivariate analysis :

Serum VEGF-C can be use as independent prognostic factor on lymph-node metastasis.

Other Study Results :

Serum VEGF-C Level ⇩

On Cervical Cancer after received
NEOADJUVANT CHEMOTHERAPY

Should be use as marker
to evaluate respon therapy ?

Conclusion

Serum VEGF-C is potential bio-marker
as prognostic factor to lymph node metastasis
in early stage cervical cancer.

Thank You

1st Biennial Meeting of Asian Society of Gynecologic Oncology
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