

# Urokinase- type Plasminogen Activator(uPA), Plasminogen Activator Inhibitor- 1(PAI- 1) nm23

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=Abstract=

Expression of Urokinase- type Plasminogen Activator (uPA),  
Plasminogen Activator Inhibitor- 1 (PAI- 1) and nm23 protein,  
as Prognostic Factors in Epithelial Ovarian Cancer

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The prognosis of ovarian cancer remains poor, and there is a need to identify patients who are less likely to respond to treatment, in the hope that the identification of these patients with a poorer prognosis may allow the administration of more intensive or different treatment. But, most clinical and pathological factors were considered to lack satisfactory predictive power.

Recently, essential role of protease in tumor cell invasion and metastasis have been elucidated in tumor biology. Urokinase-type plasminogen activator (uPA) and its inhibitor, plasminogen activator inhibitor-1 (PAI-1), play a key role in tumor-associated proteolysis. Thus, the presence of both uPA and PAI-1 modulates the invasive and metastatic phenotype of cancer cells. Genetically, nm23 protein from chromosome 17q may act independently as a metastasis suppressor.

The purpose of this study was to determine the relative predictive power of some of those prognostic variables such as uPA, PAI-1 and nm23 protein in a selected group of patients of ovarian cancer.

Immunohistochemical staining was used to determine the overexpression of uPA, PAI-1 and nm23 protein. Specimens were rated positive and negative. Then, scored '1' in case of positive for uPA, PAI-1, and negative for nm23, and '0' in case of negative for uPA, PAI-1, and positive for nm23, respectively. The sum of scores were divided into three groups ( , , and



1. 1985 1 1994 12 가 , 80

Age	46.4(20 79)	Stage	37
Histo-type	Serous		1
	Mucinous		32
	Endometriod		10
	Undifferentiated	Residual tumor	
	MMMT	None	43
	Clear cell	< 2 cm	20
	Unclassified	2 cm	17
Grade	1		26
	2		21
	3		21
	4		12
Second-look laparotomy(n=36)			
	Negative		22
	Positive		14
	Microscopic		8
	Gross		6
Recurrence	6/22(27%)		
Death	26		
Mean follow-up(months)	57.1		

- 153 -

Urokinase-type Plasminogen Activator(uPA), Plasminogen Activator Inhibitor-1(PAI-1) nm23

Barbara, CA. USA) 20

Buffer saline  
Meyer's hematoxylin

1)

0.5 μm L-lysine (2)

xylene 10 2 7†

2) Rehydration and Blocking

100% ethanol 95%, 75%, 50%

25% 5 pH 7.4 Buffer

Saline 5

3) peroxidase

3% H<sub>2</sub>O<sub>2</sub> 1:4

7† 20

endogenous peroxidase

5 , PBS(Phosphate Buffer Saline) 5

4)

Antisera 10%

(normal goat serum)

30

5)

2

Urokinase-type plasminogen activator, Plasminogen activator inhibitor Nm23 protein (monoclonal antibody)

Fig. 1. Positive uPA immunostaining of serous cystadenocarcinoma(×114).

urokinase-type plasminogen activator(uPA) #3689 American Diagnostica Inc., Greenwich, Conn.(Human Urokinase Murine Mo Ab against β-chain(33 kD) fragment, affinity purified)

plasminogen activator inhibitor-1 # 3785 American Diagnostica Inc., Greenwich, Conn.(Murine Mo Ab against PAI-1)

nm23 NCL-nm23, Novocastra Lab.(Mouse Mo Ab against nm23/ NDPK-1 protein)

PBS 5 Link Antibody

5

6)

Buffer saline 5

Streptavidin-biotin(LSAB kit; DAKO, Santa

Fig. 2. Positive PAI-1 immunostaining of mucinous cystadenocarcinoma(×114).

(3) (Scoring)

uPA, PAI-1 nm23

7†

uPA, PAI-1

(- , +) 0 , (+

Fig. 3. Positive PAI-1 immunostaining of endometrioid adenocarcinoma (×114).

Fig. 4. nm23 protein was diffusely stained in endometrioid adenocarcinoma cells (×114).

+, + + +) 1  
nm23 (-, +) 1  
(+, +, + + +) 0  
가  
가 0  
가 1 2, 가 3  
가 uPA(+), PAI-1(-), nm23(+)  
1  
(4)  
(5)  
Student-t-test Fisher exact chi test  
SAS

1. UPA, PAI-1, nm23  
80 uPA 36%(29/80)  
, PAI-1 35%(28/80), nm23  
43%(34/80) (Table 2).

Table 2. Overexpression of uPA, PAI-1, and nm23 in Epithelial Ovarian Cancer(n=80)

uPA		
uPA( - )	51	64%
uPA( + )	29	36%
PAI-1		
PAI-1( - )	52	65%
PAI-1( + )	28	35%
nm23		
PAI( - )	34	43%
PAI( + )	46	57%

2. uPA  
uPA  
(univariate analysis) uPA

, ,  
,  
, 5  
(Table 3).

Table 3. Overexpression uPA and Clinical Parameters

Parameters	uPA( - ) (n=51)	uPA( + ) (n=29)	p-value
Age	44	49	NS
Stage	and	AND	p=0.2468
Predominant			
Histologic type	Mucinous	Serous	p=0.2816
Grade	1 and 2	3 and 4	p=0.0053
Residual tumor	< 2 cm	> 2 cm	p=0.2460
CA 125	-	+	NS
LN metastasis	-	+	p=0.7388
Clinical response	CR	P	p=0.5481
Second look findings	-	+	p=0.4672
Recurrence	-	+	p=0.3089
Median survival(M)	38	30	p=0.1423
5-year survival	69%	50%	p=0.1319

### 3. PAI-1

#### PAI-1

PAI-1 가 ,

가 가 , 5

nm23

(Table 5).

#### PAI-1

, 5  
(Table 4).

Table 4. Overexpression PAI-1 and Clinical Parameters

Parameters	PAI-1( - ) (n=52)	PAI-1( + ) (n=28)	p-value
Age	43	52	NS
Stage	and	AND	p=0.0001
Predominant			
Histologic type	Mucinous	Serous	p=0.0013
Grade	1 and 2	3 and 4	p=0.1526
Residual tumor	< 2 cm	> 2 cm	p=0.0480
CA 125	-	+	NS
LN metastasis	-	+	p=0.0933
Clinical response	CR	P	p=0.1155
Second look findings	-	+	p=0.7956
Recurrence	-	+	NS
Median survival(M)	38	30	p=0.0746
5-year survival	69%	47%	p=0.0779

### 4. nm23

#### nm23

nm23

Table 5. Overexpression nm23 and Clinical Parameters

Parameters	nm23( + ) (n=46)	nm23( - ) (n=34)	p-value
Age	48.3	49.9	NS
Stage	and	AND	p=0.0068
Predominant			
Histologic type	Mucinous	Serous	NS
Grade	1 and 2	3 and 4	p=0.0110
Residual tumor	< 2 cm	> 2 cm	NS
CA 125	-	+	NS
LN metastasis	-	+	p=0.0642
Clinical response	CR	P	p=0.6205
Second look findings	-	+	NS
Recurrence	-	+	NS
Median survival(M)	37.6	32.7	NS
5-year survival	72%	58%	p=0.2266

5. uPA, PAI- 1 nm23 (

1)

80 24 ,

49 , 7 .

2)

(Table 6)

Table 6. Scoring System and Clinico- pathological Parameters

	0(n=24)	1 2(n=49)	3(n=7)	p value
Age(Mean: years)	42	47.5	57.2	p=NS
Stage and	16(67)	22(45)	0(0)	p=0.0051
and	8(33)	27(55)	7(100)	
Histologic type				p=0.0388
Serous	10(42)	25(51)	5(100)	
Mucinous	13(54)	13(27)	0(0)	
Endometrioid	0	5	1	
Others	1	6	1	
Grade 1 and 2	20(83)	27(55)	0(0)	p=0.0001
3 and 4	4(17)	22(45)	7(100)	
Residual tumor				p=0.3990
< 2 cm	22(92)	37(76)	4(47)	
2 cm	2(8)	12(24)	3(53)	

( ): %

(1) 42 , 47.5 ,  
57.2 가 .

(2) (0 )  
16 (67%), 8 (33%)  
(3 ) 7 (100%) .  
가 ( , ) 가  
( , ) ,  
가 (p=0.0051).

(3) 가  
가  
가 ,  
가  
(p=0.038).

(4) 가 1 2,  
가 3 4  
(0 ) 1 2가  
20 (83%), 3 4가 4 (17%) ,  
7 (100%) 3, 4  
 , 가 (3 )  
 , 가 (0 )  
가 (p=0.0001).

(5) 2 cm  
, 2 cm  
2 (8%), 12 (24%), 3 (53%)  
(p=0.3990).

3) CA-125  
CA-125가 35 U/ml  
, 71%,  
79%, 86%  
 . CA-125  
173.1, 209, 289.3 가

(Table 7).

4) 80  
43 15  
35% .  
12.5%(2/12), 32%(10/27),  
75%(3/4) , 가

(p=0.0632)

(Table 8).

Table 7. Scoring System and Serum CA 125 Antigen

	0(n=21)	1 2(n=47)	3(n=7)
CA 125			
35 U/ml	15(71%)	37(79%)	6(86%)
<35 U/ml	6(29%)	12(21%)	1(14%)
Median(U/ml)	173.1	209.0	289.3
p=0.7183			

Table 8. Scoring System and Retroper

	0(n=12)	1 2(n=27)	3(n=4)
LN metastasis			
LN( + )	2(25%)	10(32%)	3(75%)
LN( - )	10	17	1
Total LN( + ): 15/43=35%			
p=0.0632			

5) 가  
67%(16/24), 71%(35/49),  
29%(2/7) 가  
, 5 (21%),  
10 (21%), 3 (43%) 가  
가 가 (p=0.0532)

(Table 9).

Table 9. Scoring System and Clinical Response

Response	0(n=24)	1 2(n=49)	3(n=7)
CR	16(67%)	35(71%)	2(29%)
PR	2(8%)	9(0%)	0(0%)
No change	1(4%)	4(8%)	2(29%)
PD	5(21%)	10(21%)	3(43%)
p=0.0532			

6) 80  
36 .  
50%(5/10), 67%(16/24), 50%  
(1/2)  
가 . 27%(6/22)





가 ,  
(neo-vascularization) ,  
가 ,  
uPA (uPA-R) (domain) 30)  
18 32  
(amino-terminal fragment; ATF) ,  
(Growth Factor-like domain; GFD)  
ATF -chain ,  
uPA-R ATF GFD 가 uPA  
pro-uPA  
uPA-R 23)  
uPA가  
1994 Kuhn  
24) uPA가 (p=0.03),  
(p=0.004) ,  
3, 4  
(p=0.059)  
(p=0.7388) ,  
(p=0.2460)  
(p=0.0053).  
가  
2528)  
uPA  
uPA  
uPA  
10 , uPA 가 가  
가 ,  
(multivariate analysis) uPA가  
가 . Duffy 25)  
PAI-1 , Kuhn 24)  
(p=0.0480)  
(p=0.1526) 가 .  
가 가  
가 .7) 가  
가 pro-coagulant initiating pathway  
uPA initiated pathway  
Gastl 29) 가 가  
가

가 ,  
(neo-vascularization) ,  
가 ,  
가 가 30)  
IL-6 . IL-6가 ,  
가 가  
가  
17  
(17q) (tumor suppressor gene)가  
nm23 31) 17  
(early onset  
breast cancer) 가 (fa-  
miliar breast and ovarian cancer syndrome) 32)  
17q12-q23  
337 17q allele  
,34)  
가  
,35) nm23 가  
3436)  
nm23 가  
nm23 human ery-  
throcyte nucleoside disphosphate (NDP) kinase  
nm23 nm23-  
H1 nm23-H2  
NDP kinase A B subunit 3637) NDP  
kinase  
(microtubule assembly), (signal  
transduction), (transcription regulation),  
(cellular adhesion)  
.3740)  
Alessandra 39) nm23-H1 allele  
가  
, nm23-H1  
가 ,  
.39)  
nm23 가  
(p=0.0068), (p=0.0642)



nm23 1

(0 ), (1-2 ), (3 )

, 가

(p=0.0051), (p=0.038), (p=0)

5. 가 (p=0.0632), (p=0.0532)

6.

7. 5 70%, 65%, 14% 가 5 가 (p=0.0096).

uPA, PAI-1, nm23

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