Prognostic value of nuclear and non-nuclear estrogen receptor expression by IHC with phosphor-integrated dots in hormone receptor-positive early breast cancer

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Background and Objectives

Background

Estrogen receptor α (ERα) is associated to cell proliferation and survival through genomic (nuclear) and non-genomic (non-nuclear) signaling pathway. Endocrine therapy is the most effective therapies for patients with hormone receptor(HR) positive breast cancer. Recent progress shows that both nuclear and non-nuclear crosstalk was considered to contribute to endocrine resistance. Clinically, ERα is predominantly observed using IHC as a nuclear protein while unable to detect nuclear and non-nuclear ERα separately. Our group recently created new fluorescent nanoparticles called phosphor-integrated dots (PIDs). PIDs has extremely brightness so that it could be double stained with hematoxylin and quantitated without influence. In addition, the localization of biomarker protein can be visualized and analyzed on cell as PIDs score by this method.

Objective

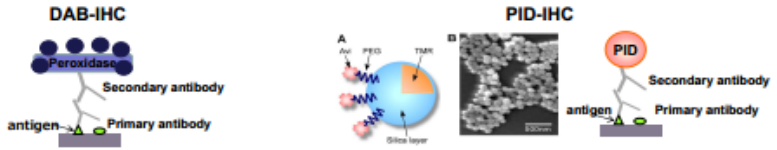
In this study, we aim to evaluate prognostic value of nuclear and non-nuclear estrogen receptor expression by IHC with PIDs in hormone receptor-positive early breast cancer.

Material and Methods

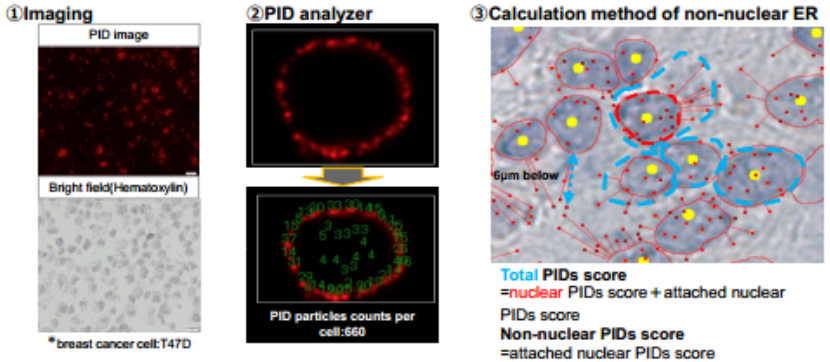
➢ **Patients and samples**

65 HR+/HER2- breast cancer patients from 2001 to 2003 who treated with postoperative endocrine therapy were selected in this study.

➢ **IHC**



➢ **PID analyzer and calculation method of non-nuclear ER**



Total PIDs score
=nuclear PIDs score + attached nuclear PIDs score

Non-nuclear PIDs score
=attached nuclear PIDs score

Results

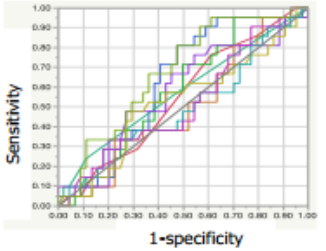
Table 1. Patient characteristics

Characteristics	No.of patients(%)	Characteristics	No.of patients(%)
Age		**Histological grade**	
<55	37 (57)	1	20 (31)
≥55	28 (43)	2	34 (52)
Pathology type		3	11 (17)
Ductal	63(97)	**Adjuvant chemotherapy**	
Lobular	2 (3)	+	19 (29)
Stage		-	46 (71)
Ⅰ	30(46)	**Radiotherapy**	
Ⅱ	29(45)	Post op+	30 (46)
Ⅲ	6 (9)	Post op-	35 (54)
Ki67 status(%)		**Outcome**	
<14	44 (68)	Relapse:≤10 y/>10 y	18 (27)/3 (5)
≥14	21(32)	No recurrence	44 (68)

Table 2. Clinicopathological data

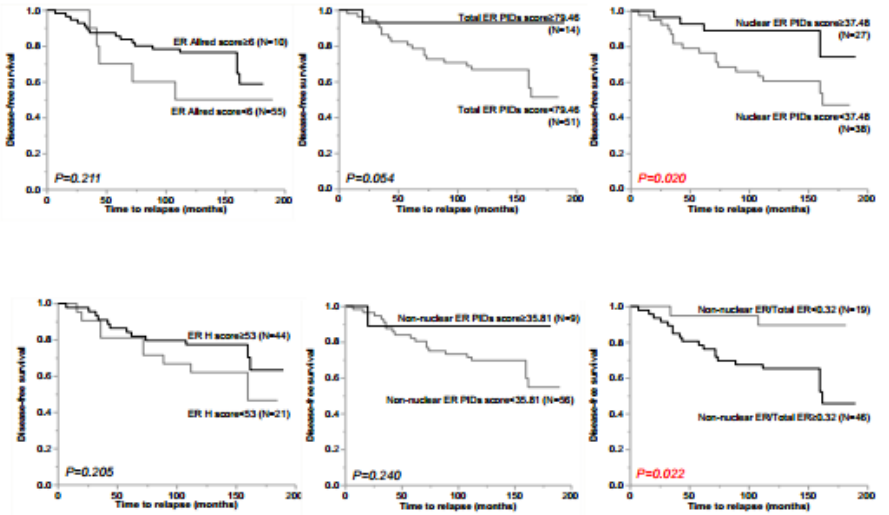
Characteristics	Patient No.(%) with No recurrence (n=44)	Relapse (n=21)	P value(Pearson)
ER status (A score)			
<6	6 (10)	5 (8)	
≥6	38 (58)	16 (25)	0.306
PR status (A score)			
<6	27 (42)	16 (25)	
≥6	17 (26)	5 (8)	0.237
Ki67 status(%)			
<14	12(19)	13 (20)	
≥14	32(49)	8(12)	0.377
ER H score			
<53	12 (19)	9 (13)	
≥53	32 (49)	12 (19)	0.209
PR H score			
<76	24 (37)	16 (25)	
≥76	20 (31)	5 (8)	0.094
PR PIDs score			
<18	34 (52)	14 (22)	
≥18	10 (15)	7 (11)	0.363
Total ER PIDs score			
<79.46	31 (48)	20 (31)	
≥79.46	13 (20)	1(2)	0.023
Nuclear ER PIDs score			
<37.48	21 (32)	17 (26)	
≥37.48	23 (35)	4 (6)	0.011
Non-nuclear-ER PIDs score			
<35.81	36 (55)	20 (31)	
≥35.81	8 (12)	1 (2)	0.143
Non-nuclear ER/total ER			
<0.32	17 (26)	2 (3)	
≥0.32	27 (42)	19 (29)	0.016

Fig 1: Decision of cut off value by receiver-operating characteristic analysis



Biomarker	Cut off	AUC
Total PR	18.15	0.50
Nuclear PR	0.75	0.52
PR TS	5	0.54
Total ER	79.46	0.58
Nuclear ER	37.46	0.62
Non-nuclear ER	35.81	0.49
ER TS	5	0.57
PR H score	76	0.57
ER H score	56	0.52
Non-nuclear ER/Total ER	0.32	0.67

Fig 2: Kaplan-Meier curves for Disease-free survival analysis



Discussion

- We developed a new method to detect expression level of nuclear-ER by PIDs-IHC.
- Our results demonstrate that nuclear-ER PIDs score obtain a higher prognostic value than that of total-ERα PIDs score and H score detected by DAB-IHC.
- Proportion of non-nuclear ER of total ER may play a role of prognostic factor in HR positive breast cancer.