Only Estrogen receptor "positive" is not enough to predict the prognosis of breast cancer

Running head: Revisiting estrogen positive tumors in 8th AJCC staging era

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- One of the most important predictive and prognostic biomarkers in breast cancer
- ER positive tumors are associated with better survival than ER negative tumors

- \geq 1% of cells stained considered positive for ER & PR
- Multiple results always use positive results
 - If biopsy and resection specimens are tested, and one is positive, while the other is negative, then use the positive results to assign the study group

AJCC Level of Evidence: I

Biomarkers incorporated into 8th AJCC staging

• Prognostic Stage (2018.1~)

When TNM is	And	And HER2	And ER	And PR	Then the	When TNM is	And	And HER2	And ER	And PR	Then the	When TNM is	And	And HER2	And ER	And PR	hen the			
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ER positive tumors in 8th AJCC staging

When T/N is	7 th Stage	And Grade is	And HER2 status is	And ER status is	And PR status is	8 th Stage Group is
T0/T1, N1mi	IB	G1-G3	(+/-)	positive	(+)	IA
T0/T1, N1mi	IB	G3	(-)	positive	(-)	IB
T0N1, T1N1, T2N0	IIA	G1-G3	(+/-)	positive	(+)	IB
T2N1, T3N0	IIB	G1-G3	(+)	Positive	(+)	IB
T2N1, T3N0	IIB	G1-2	(+)	positive	(-)	IIA
T0N2, T1N2, T2N2, T3N1, T3N2	IIIA	G1-2	(+/-)	Positive	(+)	IIA

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Multigene panels incorporated into 8th AJCC staging

- Patients with
 - <u>ER</u>/PR-<u>positive</u>, HER2-negative and N(-) tumors
 - Size less than or equal to <u>5 cm (T1-2)</u>
 - Combined with any of the following multigene panels
 - ➢ Oncotype Dx[®]: score less than 11
 - Mammaprint[®]: low-risk score
 - Endopredict[®]: low-risk score
 - > PAM50[®]: ROR score in the low range
 - Breast Cancer Index (BCI): low-risk range

→ "<u>Stage IA</u>"

: same category as T1-2 N0 M0 with ER(+) HER-2 (-)

Heterogeneity of ER positive



Positive

≥ 1% cells Quantify results Endocrine Therapy Expect ~75% ER and 65% PgR

Allred DC Mol .Pathology 2010; 23: S52-59

- We hypothesized that the level of ER expression could affect the prognosis and the risk score of multigene panel.
- We analyzed the prognosis and examined multigene panel based on the levels of ER expression.

Schematic diagram



SMC, Samsung Medical Center; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; ER, estrogen receptor; Progesterone receptor; NG, nuclear grade

- New developed prognostic model for predicting the risk of distant metastasis in patients with HR+/HER2-, pT1-2, pN0-N1 breast cancer
- The patients were categorized as the high risk or low risk group according to a pre-specified <u>cutoff BCT score of 4</u>.



Gong, Gyungyub, et al. Scientific Reports 2017;7:45554.

- Primary breast cancer operated at SMC
- BCT scores were retrospectively obtained from <u>386 patients</u> with <u>pT1-T2, pN0-N1, HR+/HER2-</u> breast cancer.
- BCT scores were classified by the levels of ER expression. (Allred score 0-2/ 3-5/ 6-8)

Statistics

- Categorical variables/ Kruskal-Wallis test or analysis of variance (ANOVA) test
- Categorical variables/ Chi-square or Fisher's exact test
- Kaplan-Meier curves with corresponding results of log-rank tests
 - Disease free survival (DFS), Distant metastasis free survival (DMFS), and Overall Survival (OS)
- Univariate and multivariate analyses for OS
- Cox regression and proportional hazard model to estimate hazard ratio (HR) and 95% confidence interval (CI)
- All tests were two sided, and P < .05 was considered significant
- SAS version 9.4 (SAS Institute, Cary, NC, USA) and R3.4.0

Baseline characteristics

	ER-negative, n (%)	Weakly ER-positive, n (%)	Strongly ER-positive, n (%)) p-value		
	Group I	Group II	Group III	Group I vs II	Group II vs II	
Mean age, ±SD	49.5 ± 9.9	46.5 ± 8.1	48.4 ± 9.0	<.0001	<.0001	
Age				<.0001	0.039	
≤35	114 (8.7)	21 (5.8)	137 (4.2)			
35-55	858 (65.5)	286 (79.2)	2,489 (76.0)			
≥56	338 (25.8)	54 (15.0)	651 (19.9)			
PR status				<.0001	<.0001	
PR negative	1,262 (96.3)	103 (28.5)	182 (5.6)			
PR weakly positive	40 (3.0)	112 (31.0)	486 (14.8)			
PR positive HER-2 status	8 (0.7)	146 (40.4)	2,609 (79.6)	0.913	<.0001	
Amplification	534 (40.8)	146 (40.4)	348 (10.6)			
Not amplification	776 (59.2)	215 (59.6)	2,929 (89.4)			
Ki-67				<.0001	<.0001	
> 20.0 %	197 (15.0)	130 (36.0)	2,013 (61.4)			
≤ 20.0 %	1,113 (85.0)	231 (64.0)	1,264 (38.6)			
Nuclear grade				<.0001	<.0001	
Low	18 (1.4)	30 (8.3)	738 (22.5)			
Intermediate	245 (18.7)	123 (34.1)	1,826 (55.7)			
High	1,047 (79.9)	208 (57.6)	713 (21.8)			
LVI				0.065	0.303	
Yes	386 (29.5)	125 (34.6)	1,047 (32.0)			
No	916 (69.9)	235 (65.1)	2,220 (67.7)			
Pathologic stage				0.721	0.319	
Stage I	526 (40.2)	153 (42.4)	1,519 (46.4)			
Stage II	610 (46.6)	160 (44.3)	1,327 (40.5)			
Stage III	174 (13.3)	48 (13.3)	431 (13.2)			

Treatment characteristics

	ER-negative, n (%)	Weakly ER-positive, n (%)	%) <i>p</i> -v	/alue	
	Group I, n = 1,310 (26.5)	Group II, n = 361 (7.3)	Group III, n = 3,277 (66.2)	Group I vs . II	Group II vs. III
Breast Surgery				0.028	< 0.0001
BCS	876 (66.9)	219 (60.7)	2,358 (72.0)		
TM	434 (33.1)	142 (39.3)	919 (28.0)		
Axillary Surgery				0.011	0.049
SLNB	627 (47.9)	186 (51.5)	1,697 (51.8)		
ALND	611 (46.6)	143 (39.6)	1,393 (42.5)		
No operation	72 (5.5)	32 (8.9)	187 (5.7)		
Anti-hormonal therapy	,			<.0001	<.0001
Yes	11 (0.8)	350 (97.0)	3,240 (98.9)		
No	1201 (91.7)	7 (1.9)	16 (1.3)		
Unknown	98 (7.5)	4 (1.1)	21 (0.6)		
Chemotherapy				<.0001	<.0001
Yes	1,105 (84.4)	284 (78.7)	2,257 (68.9)		
No	197 (15.0)	75 (20.8)	1,013 (30.9)		
Unknown	8 (0.6)	2 (0.6)	7 (0.2)		
Radiotherapy				<.0001	<.0001
Yes	969 (74.0)	249 (69.0)	2,581 (78.8)		
No	331 (25.3)	109 (30.2)	681 (20.8)		
Unknown	10 (0.8)	3 (0.8)	15 (0.5)		

DFS/DMFS and ER expression



OS and ER expression

Median follow-up: 57.8 (12.0-136.4) months



Univariate analysis for OS

	HR for OS (95% CI)	n-value
		P-value
ER expression		<.0001
ER-negative (Group I)	3.588 (2.612, 4.930)	<.0001
Weakly ER-positive (Group II)	2.051 (1.202, 3.500)	<.0001
Strongly ER-positive (Group III) (re	ef)	
Pathologic stage		<.0001
Stage I		
Stage II	2.407 (1.584, 3.658)	<.0001
Stage III	7.012 (4.584, 10.724)	<.0001
Nuclear grade		<.0001
Low		
Intermediate	3.345 (1.438, 7.780)	0.005
High	7.372 (3.244, 16.751)	<.0001
Lymphovascular invasion		
Yes	2.982 (2.207, 4.030)	<.0001
No (ref)		
Ki-67		
≤ 20.0 %	0.333 (0.233, 0.475)	<.0001
> 20.0 % (ref)		
PR expression		
Positive	0.299 (0.221, 0.404)	<.0001
Negative (ref)		
HER-2 status		
Amplification	1.079 (0.753, 1.547)	0.677
Not amplification (ref)		

	Number (%)	Expire ,N (%)	HR (95% CI) ^a	HR (95% CI) ^b	HR (95% CI) ^c
ER expression					
ER-negative	1,310 (26.5)	92 (7.0)	3.617 (2.630, 4.973)	2.943 (2.019, 4.291)	1.868 (1.002, 3.481)
Weakly ER positive	361 (7.3)	17 (4.7)	2.035 (1.192, 3,472)	1.757 (1.015, 3.044)	1.773 (1.002, 3.137)
Strongly ER-positive (ref)	3,277 (66.2)	65 (2.0)			

ER, Estrogen receptor; HR, Hazard ratio; CI, confidence interval; ref, reference

a adjusted for Stage

b adjusted for Stage, nuclear grade, lymphovascular invasion, Ki-67

c adjusted for Stage, nuclear grade, lymphovascular invasion, Ki-67, progesterone receptor, HER-2 status

Descriptive characteristics of patients with distant metastases

	ER-negative, n=117 n (%)	Weakly ER-positive, n=21 n (%)	Strongly ER-positive, n=170 n (%)
Metastasis site			
Bone	7 (6.0)	2 (9.5)	56 (32.9)
Lung/Pleura	21 (17.9)	6 (28.6)	34 (20.0)
Liver	6 (5.1)	3 (14.3)	12 (7.1)
Brain	8 (6.8)	1 (4.8)	1 (0.6)
Lymph node	4 (3.4)	0 (0)	7 (4.1)
Other sites or combination	71 (60.7)	9 (42.9)	60 (35.3)
DMFI			
≥ 3 years	32 (27.4)	10 (47.6)	110 (64.7)
< 3 years	85 (70.1)	11 (52.3)	60 (35.3)
Stage			
Stage I	19 (16.2)	6 (28.6)	18 (10.6)
Stage II	59 (50.4)	8 (38.1)	77 (45.2)
Stage III	39 (33.3)	7 (33.3)	75 (44.1)
Ki-67			
< 20%	19 (16.2)	5 (23.8)	62 (36.5)
≥ 20%	98 (84.8)	16 (76.2)	108 (63.5)

DMFI, distant metastasis free interval

BCS score according to ER expression





- Almost ER positive tumors are down-staged in 8th AJCC staging
- Nomogram to predict Oncotype Dx breast cancer recurrence score
- ER positive tumors with 1% 9% by IHC have possible misclassification
- \rightarrow Patients with ER weakly positive breast cancer could be underestimated

Nomogram to predict ODX RS

- <u>27,719</u> Oncotype DX (ODX) Recurrence Score (RS)
 - Female, ER+, HER2-, N0, invasive, 6–50 mm tumor size
 - National Cancer Data Base, USA (2010-2012)
- 12,763 ODX-tested patients in 2013 (external validation)

Points	0 10 20 30 40 50 60 70 80 90	100
Age	90 80 70 60 50 40 30 20	
Tumor Size	5 10 20 30 40 50	
Histologic Grade	2	3
Progesterone Receptor	Positive	Negative
LVI	Yes	
Histologic Type	ILC IDC IDC+ILC IDC+Others	
Total Points	0 20 40 60 80 100 120 140 160 180 200 220 240 2	260 280
Predicted High Score	0.03 0.05 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9	0.997

Amila et al. Breast Cancer Res Treat (2017) 163:51–61

• ER positive tumors with 1% - 9% by IHC may arise from testing artifact (?)

			ESR1 m RNA Expression				
	ER IHC		Positive		negative		
IHC Level(%	%) Nc	. of pts.	No (%)		No (%)		
0	18.	3	16 (8.7)	_	167 (91.3)		
1-9	25		6 (24.0)	[19 (76.0)		
10	6	-	4 (66.7)		4 (66.7)		
>10	25	1	232 (92.4)		19 (7.6)		
IF	łC		Molecular	subtype by	/ PAM 50		
IHC level	No. of	Luminal A	Luminal B	HER-2	Basal	Normal	
(%)	Patients						
0	183	2	1	51	111	18	
1-9	25	0	2 (8.0%)	8 (32.0%)	12 (48.0%)	3	
10	6	2	1	1	1	1	
>10	251	120	61	38	16	16	

Iwamoto et al. J Clin Oncol. 2012;30(7):729-734.

ER expression and prognosis

- 1,700 invasive breast cancer, 2000-2011, Rochester Medical Center
- As the ER expression is lower
 - More unfavorable pathological features such as NG, PR
 - Worse survival in DFS.



Zhang Z et al. Histopathology. 2014;65(4):508-516.

Conclusion

- Weakly ER-positive group
- Worse OS, Higher BCT score and much more high risk group than strongly ER-positive group
- Weakly ER-positive group has significantly higher HR for OS than Strong ER-positive group.
- Only ER "positive" is not enough to predict the prognosis of breast cancer.
- We should not underestimate in patients with Weakly ER-positive.

Limitations

- No central testing for IHC
 - Possibility subjectivity in interpretation
- Grouped by Allred score (Total score=Intensity score+ Proportion score)
 Possibility of misclassification
- Retrospective study, treatment was not assigned in a randomized method
 Possibility of affect to prognosis
- Follow-up duration was 57.8 months
 - Relatively short

Thank you for your attention

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