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Original article

Proportion of estrogen or progesterone receptor expressing cells in breast cancers and response to endocrine therapy

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ABSTRACT

Immunohistochemical determination of ER/PR status has been the gold standard in clinical practice of breast cancer for decades. A cut-off of '1%' is commonly used; however, this is not supported by strict evidence. How the proportion of ER/PR-positive cells influences the response to endocrine therapy has been scarcely reported, either. To address these issues, 486 and 663 invasive breast cancer cases treated with or without adjuvant tamoxifen respectively (median follow-up period, 12.8 years) were enrolled, and effect of tamoxifen treatment was compared among ER/PR-positive or -negative groups immunohistochemically determined using various cut-offs. Tamoxifen significantly improved 5 years disease-free survival in ER/PR-positive, but not in ER/PR-negative, cases even using immunohistochemical >0% cut-off. Cases with ≥67% ER/PR expressing cells responded to tamoxifen by far the best. Patients having tumors without any ER/PR-positive cells should be excluded from endocrine therapy, whereas this therapy should be strongly recommended for those with ≥67% ER/PR-positive cells.

Introduction

Estrogens play important roles in the pathogenesis and development of most breast cancers, and estrogen receptor (ER) expression is a marker of estrogen responsiveness of tumors [1,2]. The gene encoding for progesterone receptor (PR) has been reported to be estrogen dependent and PR expression has been hypothesized to serve as an indication of an intact estrogen-ER signaling pathway [3,4]. ER/PR status is important as a prognostic and predictive biomarker, and evaluation of ER/PR status has been part of the routine assessment for the management of breast cancer for decades [5,6]. Endocrine therapy is given to patients with ER-positive and/or PR-positive tumors for whom substantial benefit is expected. Formerly, biochemical assays such as ligand-binding assays (LBAs) or enzyme immunoassays (EIAs) using fresh tumor tissue were routinely performed to determine ER/PR status [7,8]. Cut-off values were determined considering the results of prospective trial study estimating the predictive value of ER/PR for endocrine therapy. For the last two decades, ER/PR status has been immunohistochemically examined using formalin-fixed and paraffin-embedded materials. This method is much more convenient than biochemical assays and has enabled not only the assessment for small amount of cancer cells but also retrospective ER/PR examination of archival materials from breast cancer patients with abundant clinicopathological information including clinical outcome. Cut-off values for ER/PR immunohistochemistry (IHC) were initially determined by the comparison with the cut-off of biochemical assays, and 10% had been conventionally used as cut-off for ER/PR IHC [9]. Harvey et al. examined the disease-free survival (DFS) curves for all possible Allred scores for ER within different treatment groups [10]. Marked difference of DFS was observed between Allred score 2 and 3 among patients receiving any adjuvant endocrine therapy, and Allred score ≥ 3 (mostly ≥ 1% positive tumor cells) was

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suggested as cut-off for IHC. Mohsin et al. did the same analyses for PR and also suggested ≥3 for PR IHC cut-off [11]. In those studies, ER/PR status determined by Allred score ≥ 3 was not an independent predictor of DFS in patients group without endocrine therapy. Although Allred score ≥3 was first suggested by the data on only patients treated with adjuvant endocrine therapy, and the study was performed in unconventional manner (samples were prepared from frozen tissue concentrated by centrifugation) [10], usefulness of this cut-off has been validated in studies based on conventionally prepared samples [6,11]. Most of these studies, however, included only patients uniformly treated with tamoxifen with the assumption that patients who fared less well did not respond to it. There are few large studies directly addressing the predictive effect of ER/PR for benefit from endocrine therapy compared with no therapy; however, it is recommended that ER/PR assays be considered positive if there are at least 1% positive tumor nuclei in the sample in American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) Guideline [6]. '1%' cut-off is not supported by strict evidence, but is recommended and widely followed with the expectation to enable more patients to be treated with less toxic endocrine therapy [6]. The definition of '1%', however, is different among institutions/studies. In some, ASCO/CAP recommendation is strictly followed, and cancers with 0–<1% staining cells are considered ER/PR-negative. In others, to the contrary, '1%' means that at least one tumor cell exhibits nuclear staining. St. Gallen consensus 2009 adopted 'any ER staining', which means the presence of any detectable ER, to determine ER positivity [12]; however, St. Gallen consensus 2011 has referenced ASCO/CAP recommendation for ER/PR evaluation [13]. It remains to be determined whether >0% cut-off (any detectable ER/PR) and 1% cut-off result in different positivity rate or clinical impact. Cut-off value for ER/PR evaluation has been lowered to increase the chance for breast cancer patients to be treated with less toxic endocrine therapy; however, there are several side-effects which cannot be easily ignored. Although it has been recommended to consider the balance of risk/benefit from endocrine therapy; there are only a few large studies investigating how the proportion of ER/PR expressing cells in breast cancers influences the effect of endocrine therapy. We conducted a large systematic study using conventionally prepared samples which included both patients groups with tamoxifen monotherapy and without any adjuvant therapy, and compared the predictive value of ER/PR status determined by several cut-offs for endocrine therapy.

Materials and methods

Subjects

Among 5763 Japanese patients with primary invasive breast cancer who underwent curative surgery with lymph node dissection at the Cancer Institute Hospital between 1982 and 1993, consecutive patients with adjuvant tamoxifen monotherapy (no patient was treated with aromatase inhibitors in this era at our institute) or without any adjuvant therapy were selected. After eliminating non-infiltrating carcinoma, carcinoma with micro-invasion, Stage IV tumors, males, bilateral carcinomas, and no residual carcinoma after biopsy, 486 patients with adjuvant

Table 1
Comparison of the clinicopathological characteristics of the cases according to ER immunohistochemical staining levels.

	ER IHC subgroups												Total		
	0%		0%<, <1%		1%≤, <10%		10%≤, <33%		33%≤, <67%		67%≤		*P*-value	No.	%
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%			
Menopause															
Pre	109	49	27	66	39	55	59	66	61	57	187	35	<0.0001*	482	45
Post	114	51	14	34	32	45	31	34	46	43	351	65		588	55
Tumor size															
≤20 mm	91	37	14	31	20	27	40	41	41	36	291	51	<0.0001*	497	43
>20 mm	153	63	31	69	53	73	58	59	74	64	283	49		652	57
Nodal status															
−	192	79	32	71	50	68	63	64	70	61	365	64	0.0009*	772	67
+	52	21	13	29	23	32	35	36	45	39	209	36		377	33
Histological type															
IDC-NOS	224	92	43	96	62	85	84	86	106	92	520	91	0.0080*	1039	90
ILC	4	2	1	2	7	10	7	7	3	3	25	4		47	4
Muc	5	2	1	2	2	3	5	5	4	3	25	4		42	4
Others	11	5	0	0	2	3	2	2	2	2	4	1		21	2
Grade															
I	22	9	7	16	23	32	33	34	50	44	254	44	<0.0001*	389	34
II + III	222	91	38	84	49	68	64	66	64	56	320	56		757	66
PR															
0%	208	86	34	76	0	0	11	11	25	22	77	13	<0.0001*	355	31
0%<, <1%	10	4	5	11	0	0	12	12	9	8	57	10		93	8
1%≤, <10%	8	3	1	2	73	100	15	15	12	10	84	15		193	17
10%≤, <33%	8	3	0	0	0	0	20	20	20	17	83	14		131	11
33%≤, <67%	3	1	3	7	0	0	21	21	14	12	111	19		152	13
67%≤	6	2	2	4	0	0	19	19	35	30	162	28		224	20
HER2															
−	187	77	33	78	59	81	88	91	104	90	556	97	<0.0001*	1027	90
+	57	23	12	22	14	19	9	9	11	10	16	3		119	10
Tamoxifen															
−	181	74	35	78	57	78	63	64	67	58	260	45	<0.0001*	663	58
+	63	26	10	22	16	22	35	36	48	42	314	55		486	42
Total	244	100	45	100	73	100	98	100	115	100	574	100		1149	100

ER, estrogen receptor; IHC, immunohistochemical; IDC-NOS, invasive ductal carcinoma, not otherwise specified; ILC, invasive lobular carcinoma; Muc, mucinous carcinoma; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; −, negative; +, positive.
* Significant, $P < 0.05$.