ORIGINAL RESEARCH

Clinicopathological Features and Survival for Low ER-positive Breast-cancer Patients

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ABSTRACT

Context • Testing patients for estrogen-receptor (ER) expression has become an important factor in the prognosis and prediction of breast cancer. Many studies have shown that endocrine therapy has no benefit for breast-cancer patients with low ER (ER+) expression, in which the proportion of positively stained cells is 1% to 9%.

Objective • The study intended to explore the response to endocrine therapy of ER+ breast-cancer patients and to evaluate the benefits of the clinical use of endocrine therapy for treatment.

Design • The research team designed a retrospective analysis and reviewed the data and survival rates of patients with early breast cancer.

Setting • The study took place at the Hebei Breast Disease Clinic at the Fourth Hospital of Hebei Medical University in Shijiazhuang, China.

Participants • Eligible participants in the study were 862 patients were diagnosed at and admitted to the clinic with early, nonadvanced breast cancer between January and December 2012.

Outcome Measures • Based on ER-expression levels, participants were divided into ER negative (ER-), which indicates no positive staining of cells; ER+; and ER positive (ER++)—high expression in which the proportion of positively stained cells is ≥10%. The clinicopathological characteristics and the survival rates of the three groups were compared.

Results • The clinicopathological features were similar for the ER- and ER+ groups. Compared to participants in the ER++ group, participants in the ER+ group: (1) were in an earlier stage, (2) had larger tumors, (3) were more likely to be positive for human epidermal growth factor receptor-2 (HER-2), (4) had a higher expression rate of Ki-67, (5) had a lower progesterone-receptor (PR) expression rate, (6) were more likely to receive chemotherapy, and (7) were less likely to receive endocrine therapy. Regardless of whether a participant received endocrine therapy or not, the seven-year overall survival (OS) between the ER- group and the ER+ group showed no significant difference, but both were in a worse condition than the ER++ group ($P = .026$).

Conclusions • The current study found that the clinicopathological features of ER+ breast cancers were different from those of ER++ breast cancers and similar to those of ER-negative breast cancers. The benefits of endocrine therapy for ER+ breast-cancer patients weren't obvious. (*Altern Ther Health Med.* [E-pub ahead of print.])

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Endocrine therapy plays an important role in the comprehensive treatment of breast cancer. Some studies had shown that estrogen-receptor (ER)-positive patients could benefit significantly from endocrine therapy, so testing patients for ER expression has become an important factor in the prognosis and prediction of breast cancer.[1-4]

The percentage of positively stained cells in the definition of ER-positive can range between >1% and 20%.[5-7] Until 2010, the guidelines formulated by the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) recommended that the percentage of ER-positive cells detected by immunohistochemistry (IHC) be at least 1% to be defined as ER-positive, with endocrine therapy being recommended in that case [8]. The guidelines also pointed out that for some patients with low ER-positive (ER+) expression, in which the proportion of positively stained cells is 1% to 9%, clinicians can decide whether to apply endocrine therapy based on the pros and cons of that therapy.[9]

Viale et al,[10] in a five-year follow-up study, analyzed results from the BIG 1-98 trial for 3596 patients receiving

only letrozole or tamoxifen as treatments. That study showed that patients with different expression states of ER had different survival rates. That study also indicated that the prognosis for ER-positive patients was better when the 1% cut-off value was used to identify them and that patients who were at least 1% ER-positive had a certain degree of response to endocrine therapy.

Collins et al[11] and Harvey et al[3] reached similar conclusions and recommended that ER-positive patients receive endocrine therapy if they had a score of 3, equivalent to at least 1% ER-positive, or above on the Allred scoring system.[12]

A large number of studies have shown that the majority of tests of ER expression in breast cancer are ER negative (ER-), indicating no positive staining of cells, or are strongly ER positive (ER++), indicating a high expression in which the proportion of positively stained cells is ≥10%. Those studies also found that the proportion of ER+ is very low.[11,13]

Chen et al[14] analyzed the ER expression of 16 606 breast-cancer patients and found that the clinicopathological features of the ER+ group were between the ER- group and the ER++ group, such as in pathological type, tumor size, and histological grade. Comparing the prognosis of patients receiving or not receiving endocrine therapy in the ER+ group, that study found that no statistical differences existed in their survival rates, indicating that the ER+ patients didn't benefit or benefited little from endocrine therapy for patients with ER (1%-9%) breast cancer. Those researchers indicated that patients with ER+ expression showed more characteristics that were similar to those of ER- patients than to those of ER++ patients. In terms of tumor prognostic characteristics, however, such as tumor size and degree of differentiation, ER+ patients fared worse than those with ER++, with the benefits of endocrine therapy to those patients being not as good as those for ER++ patients.

Yi et al[15] have suggested that patients receiving endocrine therapy should be ER++. Those researchers found that ER+ patients, compared with ER- patients, showed an earlier stage of disease and were less likely to have ductal carcinoma. However, no statistically significant differences existed between the two groups in age; in the likelihood of being positive for human epidermal growth factor receptor-2 (HER-2); in the degree of differentiation, tumor size, and lymph-node-metastasis status; and in other clinicopathological characteristics. Other studies have found that ER+ patients, compared to ER++ patients, were younger, had a larger number of pathological types of ductal carcinoma, had a later stage of disease and a worse degree of differentiation, and were more likely to be HER-2-positive.[14,16]

Ogawa et al[17] also have suggested that patients receiving endocrine therapy should be ER++. Those researchers compared the overall survival (OS) of ER-positive and ER- patients receiving endocrine therapy using various ER-positive cut-off values and found that the difference in OS between the two groups was the most significant when ER-positive was defined to be ≥ 10% cell staining.

Many studies have shown that endocrine therapy for breast-cancer patients with ER+ expression has no benefit.[15-19] Yi et al[15] showed that the five-year OS of the ER+ group was similar to that of the ER- group, and both were worse than that of the ER++ group. Even for patients receiving endocrine therapy, the five-year OS in the ER+ group wasn't as good as that of the ER++ group.

Raghav et al's[18] survival analysis showed that no statistical difference existed in the three-year OS, regardless of the use of endocrine therapy, between the ER+ group and the ER- group and that endocrine therapy had no significant effects on the OS in the ER+ group.

Although the 2010 ASCO/CAP guidelines recommended endocrine therapy for ER+ patients, identifying patients' responses to endocrine therapy is still a difficult problem in the clinic.

Some studies have shown that the application of molecular diagnostic technology can identify and predict the response of patients with ER+ expression to endocrine therapy and can guide clinical decision-making.[20-22] Luminal and basal-like subtypes of cancer can be identified by detecting the mRNA expression of ER-responsive genes. [20-22]

Those studies found that only a small number of participants showed luminal subtypes, suggesting that only a small number of patients can benefit from endocrine therapy.[21,22] In the recent ABC5 meeting, the International Consensus Conference for Advanced Breast Cancer (ABC) indicated that breast cancer that was both HER-2-negative and between 1% and 10% ER-positive should be regarded as triple-negative breast cancer, suggesting that endocrine therapy is of little significance for patients with ER+ expression.

The expression of PR is often related to the expression of ER, and breast cancers with a high expression of PR have a better endocrine reactivity. Luoh et al[23] found a low or no progesterone-receptor (PR) expression in patients with ER- or ER+ breast cancer. Those researchers also found that patients with ER-positive breast cancer could benefit more from endocrine therapy when the PR expression was high, ≥10% PR-positive. Another study suggested that patients with low PR expression and ER+ expression could gain survival benefits through chemotherapy.[24] In that study, all patients with an ER+ expression had a PR-positive rate of lower than 10%, making the findings basically consistent with the results of previous studies. Low or no expression of PR also can indicate poor response to endocrine therapy.

The current study intended to explore the response to endocrine therapy of ER+ breast-cancer patients and to evaluate the benefits of the clinical use of endocrine therapy for treatment.

METHODS

Participants

The research team designed a retrospective analysis and reviewed the data and survival rates of 1025 patients who had been diagnosed with early, nonadvanced breast cancer, including breast cancer in situ, between January and December 2012. The patients were diagnosed at and admitted

to the Hebei Breast Disease Clinic at the Fourth Hospital of Hebei Medical University in Shijiazhuang, China. The patients who did not receive systemic therapy and those who had missing treatment or follow-up data were excluded from the analysis. A total of 862 female patients were included in the final analysis, and these patients were divided into three groups—ER-, ER+, and ER++—according to their ER-expression status.

The study was approved by the medical ethics committee of the Fourth Hospital of Hebei Medical University (2012HB036). The patients consented to participation in the study and signed an informed consent.

Procedures

Participants. Participants' clinicopathological characteristics and treatments, such as age, menstrual status, lymph node status, and other molecular markers, were determined by consulting their medical records.

Pathological examination. Molecular markers were obtained: (1) for ERs, from MXB (Fuzhou, Fujian, China); (2) for progesterone receptors (PRs), from MXB; (3) for HER-2s from Roche (Basel, Switzerland, USA), and (4) for Ki-67, from Roche. The receptors were stained by immunohistochemistry (IHC) staining using a Maxvision rugged portable computer (MaxVision, Rugged Portable Computers, LLC, Manhattan, New York, USA) and were read and counted by at least two pathologists jointly.

ERs and PRs were classified as: (1) negative—no positive staining of cells; (2) low expression—the proportion of positively stained cells was 1% to 9%; or (3) high expression—the proportion of positively stained cells was ≥10%. High expression for Ki-67-expressing cells was defined to be greater than 20%.

According to the standard established by ASCO/CAP in 2013,[14] the criterion for HER-2 positive was IHC (3+), and the criterion for HER-2 negative was IHC3 (0, 1+). When the IHC test result was 2+, the expression of HER-2 was considered to be uncertain, and fluorescence in situ hybridization (FISH) detection needed to be performed to clarify the HER-2. In this study, some IHC (2+) that have not been tested by FISH or whose FISH result is unknown are classified as HER-2 negative.

Outcome measures. All participants were followed-up by telephone or outpatient review.

Outcome Measures

In the outpatient review, all participants underwent chest and abdomen and local imaging, including chest-and-abdomen, plain computerized tomography (CT); a chest radiograph; abdominal ultrasound; and breast ultrasound or mammography as well as laboratory tumor-marker examinations at six months or one year after leaving the hospital according to the physical reexamination.

For suspected cases of recurrence and metastasis that showed up in imaging, live tissues were taken for pathological examination. Overall survival (OS) was defined as the time from surgery to death from any cause.

Table 1. Comparison of the Clinical Characteristics of Participants With Expression Levels of ER-, ER+, and ER++ (N = 862)

Clinical Characteristics	ER- n (%) n = 194	ER+ n (%) n = 25	ER++ N (%)	*P* Value
Age				
<50 years	84 (43.3)	13 (52.0)	313 (48.7)	.381
≥50 years	110 (56.7)	12 (48.0)	330 (51.3)	
Menstruation				
Premenopause	86 (44.3)	13 (52.0)	337 (52.4)	.138
Postmenopause	108 (55.7)	12 (48.0)	306 (47.6)	
TNM stages				
Stage 1	51 (26.3)	2 (8.0)[*]	223 (34.7)	.002
Stage 2	96 (49.4)	10 (40.0)	241 (37.5)	
Stage 3	23 (11.9)	8 (32.0)	96 (14.9)	
Unclear	24 (12.4)	5 (20.0)	83 (12.9)	
Lymph Nodes				
Negative	132 (68.0)	11 (44.0)	409 (63.6)	.356
Positive	62 (32.0)	14 (56.0)	234 (36.4)	
Endocrinotherapy				
Yes	8 (4.1)[a]	6 (24.0)[a,b]	512 (79.7)	<.001
No	186 (95.9)	18 (72.0)	53 (8.2)	
Unclear	0 (0)	1 (4.0)	78 (12.1)	
Chemotherapy				
Yes	132 (68.0)[a]	21 (84.0)[a]	342 (53.2)	<.001
No	62 (32.0)	4 (16.0)	301 (46.8)	

[a]$P < .05$, indicating a statistically significant difference between the ER- or the ER+ group and the ER++ group

[b]$P < .05$, indicating a statistically significant difference between the ER+ group and the ER- group

Abbreviations: ER, estrogen receptor; ER-, ER-negative; ER+, low ER-positive; ER++, ER-positive; TMN, tumor/node/metastasis.

Statistical Analysis

Data induction, calculation, and processing were all done using the SPSS 21.0 software (IBM, Armonk, NY, USA). The relationship between different expression states of ER and prognosis was measured using the chi-square test and Kaplan-Meier method. Receipt of endocrinotherapy was used as a stratification factor to analyze the prognosis of patients with different ER statuses. $P < .05$ indicated that a difference was statistically significant.

RESULTS

Participants

Among the 862 participants, 194 (22.5%) were ER-, 25 (2.9%) were ER+, and 643 (74.6%) were ER++ (Table 1). Participants' median age was 50 years, with a range from 22 to 83 years (data not shown). No statistically significant differences existed in age, menstruation, or lymph-node metastasis among the three groups.

The percentage of participants with stage 1 cancer in the ER+ group was significantly lower than that of the ER++

Table 2. Comparison of the Pathogenic Characteristics of Participants With Expression Levels of ER$^-$, ER$^+$, or ER^{++} (N = 862)

Clinical Characteristics	ER- n (%) n = 194	ER+ n (%) n = 25	ER++ n (%) n = 643	*P* Value
Diameter of Tumor (cm)				
≤2	79 (40.7)[a]	4 (16.0)[a]	320 (49.8)	.005
>2 and ≤5	90 (46.4)	13 (52.0)	236 (36.7)	
>5	4 (2.1)	1 (4.0)	13 (2.0)	
Unclear	21 (10.8)	7 (28.0)	74 (11.5)	
Pathologic Types				
DCIS/IDC	163 (84.0)	19 (76.0)	499 (77.6)	.147
Others	31 (16.0)	6 (24.0)	144 (22.4)	
Ki-67 Levels				
High	181 (93.3)[a]	23 (92.0)[a]	460 (71.5)	<.001
Low	13 (6.7)	2 (8.0)	183 (28.5)	
HER-2				
Negative	121 (62.4)[a]	9 (36.0)[a,b]	551 (85.7)	<.001
Positive	73 (37.6)	16 (64.0)	92 (14.3)	
PR				
Negative	182 (93.8)	13 (52.0)[b]	66 (10.3)	<.001
1%-9%	8 (4.1)	12 (48.0)	45 (7.0)	
≥10%	4 (2.1)[a]	0 (0)[a]	532 (82.7)	

[a]$P < .05$, indicating a statistically significant difference between the ER- or the ER+ group and the ER++ group
[b]$P < .05$, indicating a statistically significant difference between the ER+ group and the ER- group

Abbreviations: ER, estrogen receptor; ER$^-$, ER-negative; ER$^+$, low ER-positive; ER^{++}, ER-positive; DCIS, ductal carcinoma in situ; IDC, infiltrating ductal carcinoma; HER-2, human epidermal growth factor receptor 2; PR, progesterone receptor.

Table 3. Comparison of the Survival of Patients With ER$^-$, ER$^+$, ER^{++} (N = 862)

Survival	ER- n (%) n = 194	ER+ n (%) n = 25	ER++ n (%) n = 643	*P* Value
Overall Survival				
Death	26 (13.4)[a]	4 (16.0)[a]	51 (7.9)	0.029
Survival	168 (86.6)[a]	21 (84.0)[a]	592 (92.1)	
Survival With Endocrinotherapy				
Death	1 (12.5)	1 (16.7)	21 (4.1)	0.172
Survival	7 (87.5)	5 (83.3)	491 (95.9)	
Survival Without Endocrinotherapy				
Death	25 (13.4)	3 (16.7)	7 (13.2)	0.926
Survival	161 (86.6)	15 (83.3)	46 (86.8)	

[a]$P < .05$, indicating a statistically significant difference between the ER- or the ER+ group and the ER++ group

Abbreviations: ER, estrogen receptor; ER$^-$, ER-negative; ER$^+$, low ER-positive; ER^{++}, ER-positive.

group. The percentage of participants with stage 3 cancer in the ER+ group was higher than that in the ER++ group.

The percentage of participants receiving chemotherapy was not statistically different between the ER- and ER+ groups, but the percentage of participants in both the ER- group and the ER+ group who received it was significantly higher than that in the ER++ group ($P < .001$).

The percentage of participants receiving endocrinotherapy was the highest in ER++ group, followed by ER+ group, with the lowest being the ER- group. The percentage of participants receiving endocrinotherapy in both the ER- and the ER+ group was significantly lower than that in the ER++ group, but the percentage in the ER+ group was significantly higher than that in the ER- group.

Pathogenic Characteristics

No significant difference existed in the tumor diameter between the ER- and the ER+ groups, while the tumor diameter of participants in the ER++ group was significantly smaller than those of the ER- and ER+ groups ($P = .005$). The pathological types for most participants were ductal carcinoma, including ductal carcinoma in situ (DCIS), or infiltrating ductal carcinoma (IDC). The percentage of pathological DCIS or IDC tumors in the ER- and ER+ groups was slightly higher than that in the ER++ group, with no statistical significance.

No significant differences existed in Ki-67 expression between the ER- and ER+ groups, but both were significantly higher than that in the ER++ group ($P < .001$). The percentage of HER-2-positive participants was highest in the ER+ group, followed by the ER- group, and both were significantly higher than that of the ER++ group ($P < .001$).

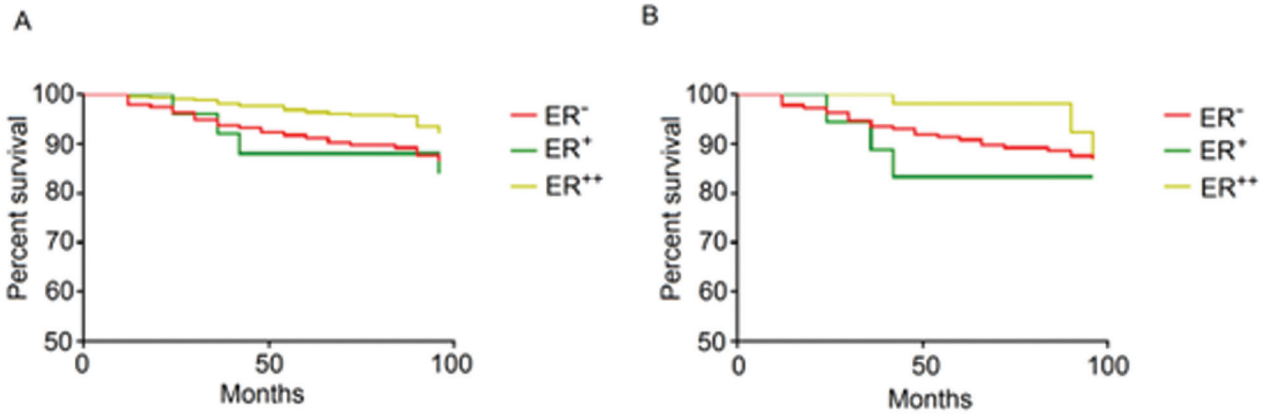
The percentage of participants with a PR expression ≥10% in the ER++ group was significantly higher than those in the ER- and ER++ groups ($P < .001$). In ER- group, almost all the participants showed a PR that was negative. The percentage of participants with a negative PR expression was significantly lower in the ER+ group than in the ER- group.

Mortality

The median follow-up time was 7.4 years. The mortality rates for the ER- and ER+ groups were similar and were significantly higher than that of the ER++ group, with $P = .029$ (Table 3). The seven-year overall survival (OS) rates of the ER- , ER+, and ER++ groups were 86.6%, 84.0%, and 92.1%, respectively. The seven-year OS rates of the ER- and ER+ groups were worse than that of ER++ group, with $P < .05$ (Figure 1A).

For the participants receiving endocrinotherapy in each group, the mortality rates for the ER- and ER+ groups were similar, but those were higher than that of ER++ group, without being statistically significant. No significant differences existed between the ER- and ER+ groups in mortality rates for participants who hadn't received endocrinotherapy. No significant differences existed in the seven-year OS rates between the ER- and ER+ groups (Figure 1B).

Figure 1. Survival Rates for Participants With Different Expression Levels of the Estrogen Receptor (ER). Figure 1A shows the survival rates among participants with ER-negative (ER-), low ER-positive (ER+), and ER-positive (ER++), and Figure 1B shows the rate among patients with ER-, ER+, and ER++who didn't receive endocrine therapy.



DISCUSSION

In the current study, the clinicopathological characteristics of patients with ER+ breast cancer were different from those of patients with ER++ breast cancer but similar to that of patients with ER- breast cancer. The percentage of participants with a pathological type of duct carcinoma at a histologic grade 3 and with a high expression of Ki-67 (>14%) in the ER- group was higher than that of the ER+ group. Yi et al[15] also found that ER+ patients showed a lower incidence of ductal carcinoma compared to ER- patients, but other studies have found that ER+ patients had a larger number of pathological types of ductal carcinoma than ER++ patients.[14,16]

The current study showed that the percentage of patients who were HER-2 positive in the ER+ group was larger than that in the ER- group. Other major clinicopathological features of the ER+ group were similar to those of the ER- group, including age, lymph node metastasis status, and Ki-67 expression. Compared with the ER++ group, participants in the ER+ group showed a later disease stage, higher expression of Ki-67 and HER-2, and larger tumor diameter, which would indicate a worse prognosis.

In the current study, due to the small number of ER+ patients, descriptive analysis showed that endocrine therapy didn't improve the prognosis of those patients, and the prognosis of the ER- and ER+ patients receiving endocrine therapy was similar, which was significantly worse than that of the ER++ patients receiving it. This finding agrees with other studies showing that that endocrine therapy for breast-cancer patients with ER+ expression has no benefit.[15-19]

The 2010 ASCO/CAP guidelines recommend that the pros and cons of endocrine therapy should be fully considered for patients with ER+ expression in breast cancer.[9] Compared with chemotherapy and radiotherapy, endocrine therapy is safer, but drugs in endocrine therapy also have side effects, such as night sweats and hot flashes, gynecological diseases, sexual dysfunction, osteopenia, and osteoporosis. In short, the benefits of endocrine therapy for ER+ breast-cancer patients is limited. Also long-term endocrine therapy also increases the economic burden for patients. Considering its disadvantages, endocrine therapy for patients with ER+ expression should be cautious.

The current study had some limitations. First, retrospective analysis lacks randomness, and telephone follow-up can cause some information to be missing. Due to the long period involved in the current study, some patients lost contact with the clinic. Second, the number of patients with ER+ expression that were enrolled was small, and only six participants received endocrine therapy. Finally, based on the drug supply and medical policies at the time, no separate classification analysis was performed on HER-2-positive patients.

CONCLUSIONS

In the current study, the clinicopathological features of ER+ breast cancers were different from those of ER++ breast cancers and similar to those of ER- breast cancers. The benefits of endocrine therapy for ER+ breast-cancer patients weren't obvious.

AUTHORS' DISCLOSURE STATEMENT

No financial or nonfinancial benefits have been received by or will be received from any party related directly or indirectly to the subject of the study.

REFERENCES

1. Schiff R, Osborne CK, Fuqua SAW. *Clinical aspects of estrogen and progesterone receptors*. Dis Breast; 2010:408-430.
2. Bartlett JM, Brookes CL, Robson T, et al. Estrogen receptor and progesterone receptor as predictive biomarkers of response to endocrine therapy: a prospectively powered pathology study in the Tamoxifen and Exemestane Adjuvant Multinational trial. *J Clin Oncol*. 2011;29(12):1531-1538. doi:10.1200/JCO.2010.30.3677
3. Harvey JM, Clark GM, Osborne CK, Allred DC. Estrogen receptor status by immunohistochemistry is superior to the ligand-binding assay for predicting response to adjuvant endocrine therapy in breast cancer. *J Clin Oncol*. 1999;17(5):1474-1481. doi:10.1200/JCO.1999.17.5.1474
4. Pertschuk LP, Kim DS, Nayer K, et al. Immunocytochemical estrogen and progestin receptor assays in breast cancer with monoclonal antibodies. Histopathologic, demographic, and biochemical correlations and relationship to endocrine response and survival. *Cancer*. 1990;66(8):1663-1670. doi:10.1002/1097-0142(19901015)66:8<1663::AID-CNCR2820660802>3.0.CO;2-C

5. Layfield LJ, Gupta D, Mooney EE. Assessment of tissue estrogen and progesterone receptor levels: A survey of current practice, techniques, and quantitation methods. *Breast J*. 2000;6(3):189-196. doi:10.1046/j.1524-4741.2000.99097.x
6. Putti TC, Pinder SE, Elston CW, Lee AHS, Ellis IO. Breast pathology practice: most common problems in a consultation service. *Histopathology*. 2005;47(5):445-457. doi:10.1111/j.1365-2559.2005.02246.x
7. Dowsett M, Cuzick J, Wale C, Howell T, Houghton J, Baum M. Retrospective analysis of time to recurrence in the ATAC trial according to hormone receptor status: an hypothesis-generating study. *J Clin Oncol*. 2005;23(30):7512-7517. doi:10.1200/JCO.2005.01.4829
8. Hammond. American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for Immunohistochemical Testing of Estrogen and Progesterone Receptors in Breast Cancer (vol 134, pg 907, 2010). *Arch Pathol Lab Med*. 2010;134:1101.
9. Wolff AC, Hammond ME, Schwartz JN, et al; American Society of Clinical Oncology/College of American Pathologists. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. *Arch Pathol Lab Med*. 2007;131(1):18-43. doi:10.5858/2007-131-18-ASOCCO
10. Viale G, Regan MM, Maiorano E, et al. Prognostic and predictive value of centrally reviewed expression of estrogen and progesterone receptors in a randomized trial comparing letrozole and tamoxifen adjuvant therapy for postmenopausal early breast cancer: BIG 1-98. *J Clin Oncol*. 2007;25(25):3846-3852. doi:10.1200/JCO.2007.11.9453
11. Collins LC, Botero ML, Schnitt SJ. Bimodal frequency distribution of estrogen receptor immunohistochemical staining results in breast cancer: an analysis of 825 cases. *Am J Clin Pathol*. 2005;123(1):16-20. doi:10.1309/HCF035N9WK40ETJ0
12. Allred DC, Harvey JM, Berardo M, Clark GM. Prognostic and predictive factors in breast cancer by immunohistochemical analysis. *Mod Pathol*. 1998;11(2):155-168.
13. Nadji M, Gomez-Fernandez C, Ganjei-Azar P, Morales AR. Immunohistochemistry of estrogen and progesterone receptors reconsidered: experience with 5,993 breast cancers. *Am J Clin Pathol*. 2005;123(1):21-27. doi:10.1309/4WV79N2GHJ3X1841
14. Chen T, Zhang N, Moran MS, Su P, Haffty BG, Yang Q. Borderline ER-positive primary breast cancer gains no significant survival benefit from endocrine therapy: A systematic review and meta-analysis. *Clin Breast Cancer*. 2018;18(1):1-8. doi:10.1016/j.clbc.2017.06.005
15. Yi M, Huo L, Koenig KB, et al. Which threshold for ER positivity? a retrospective study based on 9639 patients. *Ann Oncol*. 2014;25(5):1004-1011. doi:10.1093/annonc/mdu053
16. Benefield HC, Allott EH, Reeder-Hayes KE, et al. Borderline estrogen receptor–positive breast cancers in black and white women. *J Natl Cancer Inst*. 2020;112(7):728-736. doi:10.1093/jnci/djz206
17. Ogawa Y, Moriya T, Kato Y, et al. Immunohistochemical assessment for estrogen receptor and progesterone receptor status in breast cancer: analysis for a cut-off point as the predictor for endocrine therapy. *Breast Cancer*. 2004;11(3):267-275. doi:10.1007/BF02984548
18. Raghav KPS, Hernandez-Aya LF, Lei X, et al. Impact of low estrogen/progesterone receptor expression on survival outcomes in breast cancers previously classified as triple negative breast cancers. *Cancer*. 2012;118(6):1498-1506. doi:10.1002/cncr.26431
19. Balduzzi A, Bagnardi V, Rotmensz N, et al. Survival outcomes in breast cancer patients with low estrogen/progesterone receptor expression. *Clin Breast Cancer*. 2014;14(4):258-264. doi:10.1016/j.clbc.2013.10.019
20. Krijgsman O, Roepman P, Zwart W, et al. A diagnostic gene profile for molecular subtyping of breast cancer associated with treatment response. *Breast Cancer Res Treat*. 2012;133(1):37-47. doi:10.1007/s10549-011-1683-z
21. Iwamoto T, Booser D, Valero V, et al. Estrogen receptor (ER) mRNA and ER-related gene expression in breast cancers that are 1% to 10% ER-positive by immunohistochemistry. *J Clin Oncol*. 2012;30(7):729-734. doi:10.1200/JCO.2011.36.2574
22. Chia SK, Bramwell VH, Tu D, et al. A 50-gene intrinsic subtype classifier for prognosis and prediction of benefit from adjuvant tamoxifen. *Clin Cancer Res*. 2012;18(16):4465-4472. doi:10.1158/1078-0432.CCR-12-0286
23. Luoh SW, Ramsey B, Park B, Keenan E. Quantitative progesterone receptor expression and efficacy of anti-estrogen therapy in breast cancer. *Breast J*. 2014;20(1):46-52. doi:10.1111/tbj.12200
24. Creighton CJ, Kent Osborne C, van de Vijver MJ, et al. Molecular profiles of progesterone receptor loss in human breast tumors. *Breast Cancer Res Treat*. 2009;114(2):287-299. doi:10.1007/s10549-008-0017-2