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Risk assessment tools and adjuvant therapy for breast cancer

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Chapter 2

HIGHER ER LOAD IS NOT ASSOCIATED WITH BETTER OUTCOME IN STAGE 1-3 BREAST CANCER: DESCRIPTIVE OVERVIEW OF QUANTITATIVE HR ANALYSIS IN OPERABLE BREAST CANCER

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ABSTRACT

Purpose

In breast cancer, hormone receptor (HR) status is generally a qualitative measure; positive or negative. Quantitatively measured estrogen and progesterone receptors (ER and PR) are frequently proposed prognostic and predictive markers, some guidelines even provide different treatment options for patients with strong versus weak expression.

Aim

To evaluate quantitative HR load assessed by immunohistochemistry as a prognostic and predictive measure in stage 1-3 breast cancer.

Methods

We reviewed all the available literature on quantitatively measured HRs using immuno-histochemistry.

Results

All included studies (n = 19) comprised a cohort of 30,754 patients. Only 2 out of 17 studies found a clear correlation between higher quantitative ER and better disease outcome. Only one trial examined quantitative ER both as prognostic and predictive marker and found no association between ER% and survival. Ten studies examined quantitative PR load, only two of those found a significant correlation between higher PR load and better disease outcome. Two trials examined quantitative PR both as prognostic and predictive marker, neither found any association between PR% and disease outcome.

Conclusions

There is no clear evidence for using quantitatively assessed ER and PR as prognostic nor predictive marker in patients with stage 1-3 breast cancer. We recommend only using a qualitative HR status in future guidelines and treatment considerations.

INTRODUCTION

Breast cancer is the most common type of cancer amongst women worldwide and the leading cause of cancer specific death for women in Europe.[1] The estrogen receptor (ER) and progesterone receptor (PR) expression are the oldest biomarkers in breast cancer.[2,3]

Different methods exist for determining the expression of hormone receptors (HRs). The tissue can be analyzed using enzyme immunoassays (EIA), in which the amount of HRs is expressed in fmol/mg, defining HR positive as 15 fmol/mg or more.[4,5] More recently however, immunohistochemistry (IHC) has been the preferred method of staining hormone receptors. The number of cells expressing HRs is counted, generating a percentage of positive cells.[6] Different cut-off levels are used to determine whether a tumor is considered HR positive. Usually, a tumor is considered HR positive when more than 10% of the tumor cells express HRs.[7,8]

Furthermore, nuclei can be grouped into categories of negative, weak, moderate and strong nuclear staining to generate a continuous histoscore ranging from 0 to 300, calculated by multiplying the sum of the percentage of weakly stained cells times 1, moderately stained cells times 2, and strongly stained cells times 3.[9] Tumors with a histoscore of 50 or more are usually considered HR positive.

Additionally, the Allred scoring system has been used, which is a semi-quantitative measure that takes into consideration the proportion of positive cells (scored on a scale of 0-5) and staining intensity (scored on a scale of 0-3). The sum of these produces a score between 0 and 8, and tumors with a score of 3 or more are usually considered HR positive.[10]

Another semi-quantitative measure is the ER immunoreactive score (IRS), which also relies on the proportion and intensity. This produces a score between 0 and 12, considering tumors with a score of 2 or higher HR positive.[11]

Already more than 15 years ago, IHC was proposed as the reference method by different boards and peer committees and a dichotomous, qualitative scale of HR expression (i.e. “positive” or “negative”) was unanimously adopted.[12,13] This method remains the gold standard for HR expression evaluation.[14]

Although it is generally claimed that tumors with strong ER and/or PR expression are more sensitive to endocrine therapy (ET), there is no clear definition of weak or strong ER and PR expression. The most recent guidelines as proposed by the St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer in 2017, briefly mention high ER expression as a characteristic of a low risk tumor and vice versa, but fail to provide any definition or cut-off value to determine which tumors are in fact high in ER expression.[14] As there is no consensus on the value of quantitative HR expression analysis, it is not (yet) common practice to report on HR load in the clinical setting.

This systematic review gives an overview of the methods to quantitatively assess HR load, the predictive and prognostic value of determining the HR load, gives recommendations

for clinical practice and discusses future developments for HR analysis and endocrine treatment.

METHODS

Data searches and study selection

In order to obtain all relevant literature, the electronic databases PubMed, Embase and Web of Science were searched in March 2018. This search was updated in August 2018 and in January 2019. The following key words were used for the data search: breast neoplasm, estrogen, progesterone, and hormone receptor, quantitative expression, and endocrine treatment.

According to PRISMA guidelines for systematic reviews, two of the authors (IN and AFG) individually and independently screened the articles for predefined inclusion criteria.[15] These were stated as follows:

- The article was published in English in a peer reviewed journal;
- The article was a primary report of original data;
- The study concerned women diagnosed with stage 1 to 3 adenocarcinoma of the breast;
- The tumor's ER and/or PR expression was analyzed using IHC (the international gold standard);
- ER and/or PR expression was reported quantitatively (continuous) or semi-quantitatively (minimum of 3 groups);
- Within the subset of HR positive cases, the (semi-)quantitative measure of ER and/or PR was analyzed in association to the primary clinical endpoint.

Only studies that the reviewers reached a consensus on were included. If needed, a third reviewer was consulted. Due to the retrospective nature of most included studies, it was elected not to perform a formal risk of bias assessment. Each study was awarded a level of evidence according to the Oxford Centre of Evidence Based Medicine.[16]

Data extraction

All data from the included studies were analyzed and data regarding the following items were extracted: number of participating patients, method to determine HR expression, method of HR expression quantification, type and timing (adjuvant *versus* neoadjuvant) of systemic treatment, primary clinical endpoint and follow-up time, and association primary clinical endpoint to quantified HR expression. Due to the heterogeneity of the included studies, data was not pooled, and no meta-analyses were performed.

RESULTS

Characteristics of the included studies

In total, 777 unique articles were identified. After matching these to the inclusion criteria, 19 articles were included. The most common ground to exclude studies was not reporting ER and/or PR expression quantitatively (n=273) (**figure 1**). Combined, all included studies comprised a cohort of 30,754 patients.

Quantitative assessment of HR expression

Of the 19 included studies, six studies performed HR staining on whole-section slides of the tumor tissue, whereas nine studies first created TMAs, where several cores are taken of the tissue blocks. HR staining is then performed on these cores instead of on whole-section slides. In four studies, it was not specified how the staining was performed.

In five studies, a continuous quantitative measure (percentage or histoscore) was used to determine HR load, in four studies patients were divided in groups of negative, low and high expression and in nine studies patients were divided in four or more groups according to HR expression. In one study both a continuous and a semi-quantitative measure was used.

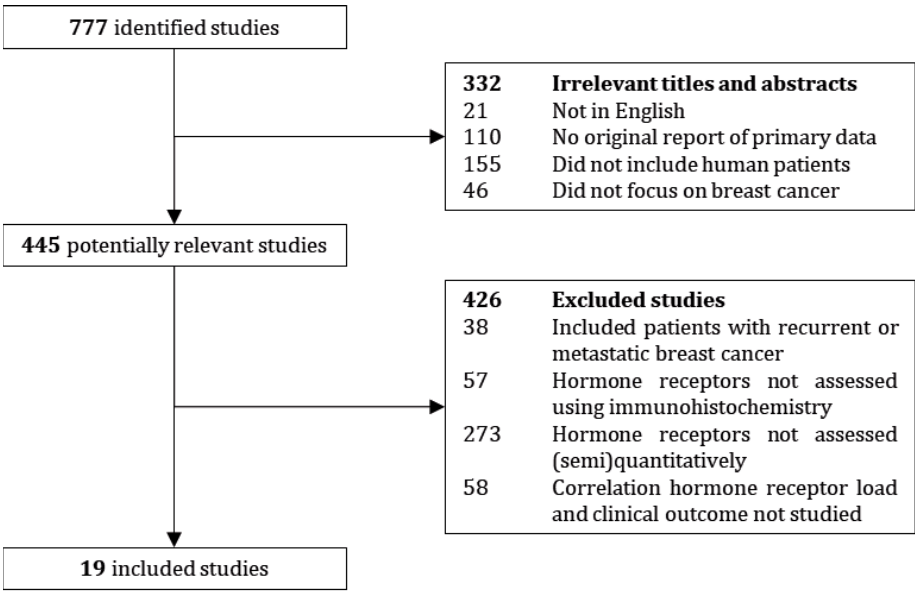

Figure 1: CONSORT diagram to account for excluded studies.

Reference	Study design	N	Pathologic methodology
Bartlett, 2011 [17]	Randomized trial	4325	Staining on TMA. Continuous histoscore (1-300).
Campbell, 2016 [18]	Cohort	503	Staining on TMA. Allred scoring system (negative *vs* low *vs* high).
Chae, 2011 [19]	Cohort	171	Staining on whole-section slides. Allred scoring system (negative *vs* low *vs* high).
Chapman, 2013 [20]	Randomized trial	345	Staining on TMA. Continuous score (0-100%).
Dowsett, 2008 [21]	Randomized trial	1856	Staining on TMA. Continuous histoscore (1-300).
Esslimani-Sahla, 2004 [22]	Case-control	50	Staining on whole-section slides. Continuous score (1-100%).
Harigopal, 2010 [23]	Randomized trial	1715	Staining on TMA. Continuous score (0-100%) and quartiles.
Hill, 2017 [24]	Case-control	1098	Staining on TMA. Visual score groups (1-59 *vs* 60-89 *vs* 90 *vs* 91-96 *vs* ≥97%).
Liu, 2010 [25]	Cohort	4046	Staining on TMA. Visual score groups (<1 *vs* 1-25 *vs* 26-75 *vs* ≥76%).
Ma, 2013 [26]	Case-control	1206	Staining on whole-section slides. Visual score groups (<1 *vs* 1-39 *vs* 40-59 *vs* 60-79 *vs* ≥80%).
Mazouni, 2010 [27]	Cohort	797	Staining method NS. Visual score groups (negative *vs* weak *vs* moderate *vs* high).
Morgan, 2011 [28]	Cohort	563	Staining on whole-section slides. Histoscore groups (1-50 *vs* 51-100 *vs* 101-200 *vs* ≥201).
Nordenskjöld, 2016 [29]	Randomized trial	449	Staining on TMA. Visual score groups (<1 *vs* 1-9 *vs* 10-24 *vs* 25-49 *vs* 50-74 *vs* 75-89 *vs* ≥90%).
Prabhu, 2014 [30]	Cohort	231	Staining on whole-section slides. Visual score groups (<1 *vs* 1-10 *vs* ≥11%).
Prat, 2013 [31]	Cohort	701	Staining method NS. Continuous histoscore (1-300).
Regierer, 2011 [11]	Cohort	3971	Staining method NS. IRS groups (negative *vs* weak *vs* moderate *vs* high).
Ryu, 2018 [32]	Cohort	4948	Staining method NS. Allred scoring system (negative *vs* low *vs* high).
Turbin, 2008 [33]	Cohort	3484	Staining on TMA. Visual score groups (<1 *vs* 1-24 *vs* 25-75 *vs* ≥76%).
Zhang, 2014 [34]	Cohort	295	Staining on whole-section slides. Visual score groups (<1 *vs* 1-10 *vs* 11-50 *vs* 51-70 *vs* ≥71%).

Table 1: Overview of methods used by the included articles.

Systemic treatment	Median FU, endpoint	ER load studied	PR load studied
ET: Tamoxifen followed by exemestane (n=2164) *vs* exemestane (n=2161). Chemotherapy: n=NS.	5 years Disease-free survival	Yes	Yes
ET: Tamoxifen (n=368) *vs* none (n=135). Chemotherapy: n=208.	5.7 years Disease-free survival	Yes	Yes
ET: Tamoxifen *vs* AI *vs* tamoxifen with GnRH-analogue *vs* tamoxifen followed by AI (n=NS). Chemotherapy: n=114.	4.3 years Disease-free survival	Yes	Yes
ET: Tamoxifen *vs* none (all n=NS). Chemotherapy: n=NS.	9.7 years Disease-free survival	Yes	Yes
ET: Tamoxifen (n=906) *vs* anastrozole (n=950). Chemotherapy: n=167.	5.7 years Disease-free survival	Yes	Yes
ET: Tamoxifen (n=50). Chemotherapy: n=0.	5 years Recurrence rate	Yes	Yes
ET: Tamoxifen *vs* none (all n=NS). Chemotherapy: n=1715.	7.2 years Disease-free survival	Yes	Yes
ET: n=NS. Chemotherapy: n=NS.	7.8 years Overall survival	Yes	No
ET: Tamoxifen (n=1,606) *vs* other (n=12) *vs* none (n=2,428). Chemotherapy: n=1,045.	10 years Breast cancer-specific survival	No	Yes
ET: n=NS. Chemotherapy: n=NS.	10 years Breast cancer-specific survival	Yes	No
ET: n=NS. Chemotherapy: n=NS.	6.3 years Overall survival	Yes	No
ET: Tamoxifen (n=563). Chemotherapy: n=0.	10 years Overall survival	Yes	No
ET: Tamoxifen (n=233) *vs* none (n=216). Chemotherapy: n=0.	18 years Recurrence rate	No	Yes
ET: Any (n=143) *vs* none (n=88). Chemotherapy: n=204.	2.4 years Disease-free survival	Yes	No
ET: Tamoxifen (n=701). Chemotherapy: n=0.	12.5 years Recurrence rate	Yes	Yes
ET: Any (n=2463) *vs* none (n=1508). Chemotherapy: n=1844.	5 years Recurrence-free survival	Yes	No
ET: Any (n=2463) *vs* none (n=1224). Data on ET missing: n=123. Chemotherapy: n=3646.	4.8 years Overall survival	Yes	No
ET: Tamoxifen (n=1385) *vs* none (n=2099). Chemotherapy: n=920.	12.5 years Breast cancer-specific survival	Yes	No
ET: Any (n=224) *vs* none (n=71). Chemotherapy: n=173.	5 years Overall survival	Yes	No

Table 1 continued

Systemic treatment of included patients

Of all included patients, 5,812 were treated with tamoxifen, 3,111 were treated with an aromatase inhibitor (AI), 2,164 were treated with a combination of tamoxifen and an AI, 6,614 were treated with unspecified ET and 7,769 patients did not receive any ET. For 5,284 patients, it was not specified whether they received ET or not (**figure 2**). Additionally, 10,036 patients were treated with chemotherapy. For 7,788 patients, it was not specified whether they received chemotherapy or not, 12,930 patients did not receive chemotherapy. Treatment with anti-HER2 medication was explicitly stated for only three patients.[30] **Table 1** provides detailed information on all included studies.

Overall association ER load and clinical outcome

In 17 of the 19 included studies, the ER load was analyzed, in a total of 26,259 patients with stage 1-3 breast cancer patients (**table 2**).[11,17-24,26-28,30-34] In 11 studies, HR negative patients were also included, all reported associations between the ER load and the primary outcome measure regard the subset of HR positive cases only. Disease-free survival (DFS) was used as primary outcome measure in seven studies, overall survival (OS) was used in five studies, recurrence in three studies and breast cancer specific mortality in two studies.

When studying ER load as a continuous measure (either using percentage or histoscore, n=6), a higher ER load was found statistically significantly associated with better clinical outcome in two studies, marginally significantly associated in one study, and three studies did not find a significant association between higher ER load and better clinical outcome.

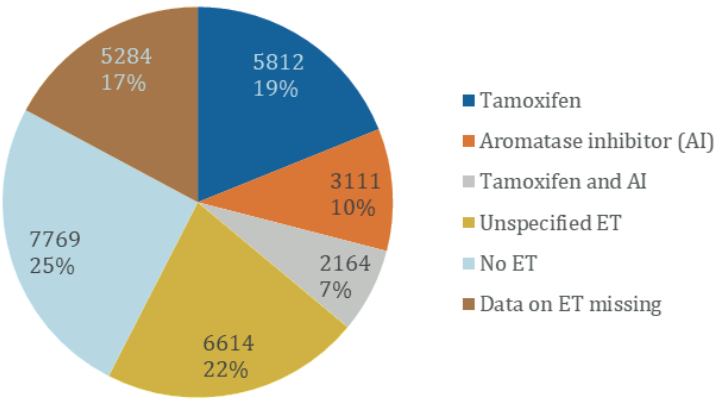

Figure 2: Distribution of types of endocrine therapy (ET) over patients.

When dividing patients in three groups, i.e. ER-negative, low ER and high ER expression (n=4), three studies did not find a significantly longer DFS for patients in the high ER expression group than patients in the low ER expression group, one study only found a marginally significant association between longer OS and higher ER expression.

When dividing patients in four or more groups based on ER expression (n=8), seven studies did not find a significantly better clinical outcome for patients with a higher ER expression and one study only found a marginally significant association between better clinical outcome and higher ER expression. These results are summarized in **table 2**.

Using ER load as a prognostic and/or predictive marker

There was only one randomized trial that compared patients with and without ET, which could be used to analyze the prognostic and predictive properties of the quantitative ER load without the risk of bias due to treatment indication. This study by Chapman et. al. (n=345) used a continuous quantitative measure, stained on TMAs and found no significant correlation between higher ER percentages and longer DFS in the overall study population (p=0.24).[20] They did not find any association between higher ER load and longer DFS in the subgroup that was randomized to receive no adjuvant ET and thus conclude that the quantitative ER load cannot be used as a prognostic marker. They also did not find any association between higher ER load and longer DFS in the subgroup of patients that was treated with adjuvant ET and therefore conclude that quantitative ER load is not an adequate predictive marker for sensitivity to ET, either.

Reference	Level of Evidence [16] Study design	N	Endpoint	Median FU (years)	Significant association
Bartlett, 2011 [17]	2b, randomized trial	4325	DFS	5	Yes
Esslimani-Sahla, 2004 [22]	3b, case-control	50	Recurrence	5	Yes
Dowsett, 2008 [21]	1b, randomized trial	1856	DFS	5.7	Marginally
Ma, 2013 [26]	3b, case-control	1206	BCSS	10	Marginally
Ryu, 2018 [32]	3b, cohort	4948	OS	4.8	Marginally
Campbell, 2016 [18]	2b, cohort	503	DFS	5.7	No
Chae, 2011 [19]	2c, cohort	171	DFS	4.3	No
Chapman, 2013 [20]	1b, randomized trial	345	DFS	9.7	No
Harigopal, 2010 [23]	2b, randomized trial	1715	DFS	7.2	No
Hill, 2017 [24]	3b, case-control	1098	OS	7.8	No
Mazouni, 2010 [27]	1b, cohort	797	OS	6.3	No
Morgan, 2011 [28]	3b, cohort	563	OS	10	No
Prahbu, 2014 [30]	2b, cohort	231	DFS	2.4	No
Prat, 2013 [31]	4, cohort	701	DRFS	12.5	No
Regierer, 2011 [11]	2b, cohort	3971	RFS	5	No
Turbin, 2008 [33]	2b, cohort	3484	BCSS	12.5	No
Zhang, 2014 [34]	3b, cohort	295	OS	5	No

Table 2: Overview of results of the included articles studying estrogen receptor (ER) load in 26,259 patients. In case of statistically significant associations, a higher ER load is associated with better clinical outcome.

Overall association PR load and clinical outcome

Of the 19 included studies, ten studies analyzed PR load in 14,161 early breast cancer patients (**table 3**).[17-23,25,29,31] In six studies, HR negative patients were also included, all reported associations between the PR load and the primary outcome measure regard the subset of HR positive cases only. DFS was used as primary outcome measure in six studies, three studies used recurrence as primary outcome and one study used breast cancer specific mortality.

When studying PR load as a continuous measure (n=6), a higher PR load was found to be significantly associated with better clinical outcome in two studies, a higher PR load was found marginally significantly associated with better clinical outcome in one study, and three studies did not find any association between PR load and clinical outcome.

When dividing patients in PR-negative, low PR and high PR expression groups (n=2), DFS was not significantly longer in the high PR expression group than in the low PR expression group. When dividing patients in four or more groups based on their PR expression (n=3), clinical outcome was not significantly better for a higher PR load. These results are summarized in **table 3**.

Using PR load as a prognostic and/or predictive marker

There were two randomized trials comparing patients with and without ET, which could be used to analyze the prognostic and predictive properties of the quantitative PR load without risk of bias.[20,29] Both studies randomized patients between tamoxifen or no adjuvant ET and used TMAs to stain the PR.

The study by Chapman et. al. (n=345) used a continuous quantitative measure and found no association between continuous higher PR percentage and longer DFS in the overall randomized study population (p=0.04; uncorrected for multiple testing). They did not find any association between higher PR load and longer DFS in the subgroup that received no adjuvant ET. They also did not find any association between higher PR load and longer DFS in the subgroup of patients that was treated with adjuvant ET.[20]

The study by Nordenskjöld et. al. (n=449) divided patients in seven groups based on the number of positive PR staining cells and did not find an association between the PR percentage groups and the occurrence of disease recurrences in the overall study population. They found no association between higher PR load and less disease recurrences within the subgroup of patients that did and did not receive ET, either.[29]

Thus, both studies concluded that quantitative PR load is not an adequate tool to determine the prognosis of early breast cancer patients, nor to predict sensitivity to ET.

Reference	Level of Evidence [16] Study design	N	Endpoint	Median FU (years)	Significant association
Bartlett, 2011 [17]	2b, randomized trial	4325	DFS	5	Yes
Dowsett, 2008 [21]	1b, randomized trial	1856	DFS	5.7	Yes
Prat, 2013 [31]	4, cohort	701	DRFS	12.5	Marginally
Campbell, 2016 [18]	2b, cohort	503	DFS	5.7	No
Chae, 2011 [19]	2c, cohort	171	DFS	4.3	No
Chapman, 2013 [20]	1b, randomized trial	345	DFS	9.7	No
Esslimani-Sahla, 2004 [22]	3b, case-control	50	Recurrence	5	No
Harigopal, 2010 [23]	2b, randomized trial	1715	DFS	7.2	No
Liu, 2010 [25]	2b, cohort	4046	BCSS	10	No
Nordenskjöld, 2016 [29]	2b, randomized trial	449	Recurrence	18	No

Table 3: Overview of results of the included articles studying progesterone receptor (PR) load in 14,161 patients. In case of statistically significant associations, a higher ER load is associated with better clinical outcome.

Interaction between ER and PR

Of the eight studies that examined both the ER and PR load, only two studied the interaction between ER and PR load. The study by Campbell et. al. found a statistically significant interaction between the quantitative ER and PR load, and only found a significant association between higher PR load and better outcome in those patients that also had a higher ER load.[18] The study by Harigopal et. al. found a moderate interaction between continuous quantitative ER and PR percentage (Pearson $r = 0.43$, $p<0.001$).[23]

This suggests that the quantitative PR load is not independently associated with outcome, but only in relation to the quantitative ER load.

DISCUSSION

Many efforts have been made to identify biomarkers or profiles in breast cancer patients capable of predicting sensitivity to endocrine treatment and the risk of recurrence after treatment is discontinued.[35,36] One of these methods is the quantitative assessment of ER and PR expression, i.e. the ER and PR load, instead of merely assigning tumors an ER and PR positive or negative status.[37]

This review concludes that in patients with an ER-positive tumor (defined as ER >10%), a higher ER load as assessed by IHC is not correlated to better outcome, and no evidence could be found for using quantitative ER load as a prognostic marker. In other words, patients with a higher ER load (e.g. 100%) do not inherently have a better prognosis than patients with a lower ER load (e.g. 20%). Furthermore, no evidence could be found for using quantitative ER load as a predictive marker, i.e. patients with a higher ER load do not have more benefit of ET than patients with a lower ER load.

This review also concludes that in patients with an HR-positive tumor, higher PR load does not seem to be correlated to better outcome. Based on the included studies, quantitative PR load is not a suitable prognostic marker; patients with a higher PR load do not inherently have a better prognosis than patients with a lower PR load, nor is it suitable as a predictive marker. Furthermore, PR load seems to be interacted with ER load and is therefore not recognized as an independent predictor.

One of the included studies, by Esslimani-Sahla, found an unusually high number of recurrences and only found an association between recurrence and ER load when examining ERβ, not when examining ERα.[22] As this is the only study that specifically examines ERβ, it is somewhat of an outlier, and its results should be interpreted with caution.

In this analysis, only studies that examined the HR expression using IHC were included. This method is the gold standard for determining HR status and other methods, such as EIA or mRNA expression profiles are not routinely used in clinical practice. Specifically, we have not focused on articles studying EIA to determine HR status, as this method is outdated and is not routinely used in the current clinical practice. This also ensures that the included studies create a homogenous cohort. Even still, different methods were used

to stain the HRs, such as staining on whole-section slides or on TMAs, though this did not seem to influence the outcome. Studies staining on TMAs were not less likely to find a correlation between HR load and outcome than studies staining on whole-section slides.

Studies also differed in their way of quantitatively measuring HR load; some studies used a continuous percentage or histoscore, some studies used groups of HR-negative, low HR expression and high HR expression and some divided patients in four or more groups based on Allred score or percentage. This does have an influence on the outcome. Studies were more likely to find a positive association between HR load and outcome if a continuous score was used. However, using a continuous quantitative measure to assess HR expression is questioned by several articles. Interobserver variability is high, and samples get assigned different HR percentages depending on the pathologist and the lab it was reviewed in.[38] Most importantly, staining breast cancer tissue using IHC does not allow for precise enough measurement of HR load to generate a continuous score and can only quantify into negative, weak positive and strong positive.[7,39,40] The problem with this approach is defining "weak" and "strong". A lack of generally accepted definition results in pathologists and papers choosing their own definition, making it difficult to compare multiple studies. Furthermore, and as mentioned previously, the St. Gallen Consensus makes a distinction between high and low ER expression but fails to provide any definition or cut-off value to determine which tumors are in fact high in ER expression.[14] The St. Gallen Consensus does not mention high and low PR expression at all.

Based on the results of this review, we propose using both ER and PR expression only as a qualitative measure; defining tumors with less than 1-10% of cells expressing this receptor as negative, and tumors with more than 1-10% of cells expressing the receptor as positive.[30,41] Using a continuous quantitative measure does not seem feasible without centralized, unambiguous and clear pathological measurement. The implications for the daily clinical practice of pathologists are that more detailed information on the HR status beyond "positive" or "negative" should no longer be provided, to prevent oncologists subconsciously or instinctively making different treatment decisions based on this information. Since there is no evidence for different treatment strategies, providing extra information is both unnecessary and undesirable.

Simultaneously, one can speculate whether there is any added value of measuring the PR status at all. It is generally accepted that there is no such thing as an ER negative/PR positive tumor.[42,43] Since the quantitative PR load is correlated to the quantitative ER load and PR load is inversely correlated to the histological grade of the tumor, the question arises whether PR status provides any additional prognostic information, when ER status, grade and potentially a proliferation factor such as ki-67 is known.[18,23] Likewise, when examining guidelines on adjuvant treatment, they do not propose different treatment strategies for tumors that are ER positive/PR positive compared to tumors that are ER positive/PR negative.[8,14] Therefore, if the PR status is unlikely to change the course of treatment, it could be considered wasteful and excessive to continue measuring it.[44,45] It might be worthwhile to focus future research on the independent contribution of PR status using multivariable models.

Gene expression profiling can be used to identify two inherently different entities within breast cancer, known as luminal-A and luminal-B. These are intrinsic molecular subtypes that reflect a different tumor biology and disease prognosis. Unfortunately, neither subtype is predictive for a better response to ET.[31,46-50] Moreover, the gene expression profiles used to differentiate between these subtypes are expensive and not universally available and the added value for daily clinical practice, in particular for which subgroup of patients, is still debated.[35] For these reasons, researchers have tried to approach the distinction between these molecular subtypes using IHC, which resulted in subtypes called luminal-A-like and luminal-B-like.[31] When defining IHC-based luminal-A-like tumors as HR positive, HER2 negative and ki-67 below 14%, approximately 81% to 85% of luminal-A tumors were correctly identified as luminal-A-like. However, approximately 35% to 52% of luminal-B tumors were incorrectly identified as luminal-A-like. When expanding the definition of luminal-A-like to HR positive, HER2 negative, ki-67 below 14% and PR above 20%, the specificity improves somewhat but not enough to accurately discriminate between the two subtypes.[31,48,50]

With these considerations, and the lack of prognostic and predictive value of IHC assessed quantitative ER and PR load as shown in this review, the distinction between IHC-based luminal-A-like and luminal-B-like tumors should not be used to tailor treatment decisions for women with HR positive stage 1-3 breast cancer.

Future perspectives

All in all, identifying the early breast cancer patients that could benefit most from ET remains a challenge, as more than half of all patients with an ER positive breast cancer will not respond to ET.[51] Considering the frequent and often severe side effects of ET, an improved upfront selection of likely responders may lower the treatment burden. Since quantitative measurement of HR does not seem an appropriate instrument for identifying these patients, the oncologic community is searching for much needed other means to predict response to ET. One potential method to identify patients is to measure the activity of the ER-pathway to distinguish in which patients the estrogen receptor is not only expressed, but also active and thus a suitable target for ET.[52] The use of predictive biomarkers in the neoadjuvant ET setting will be clearer after results of ongoing trials become available. Potentially, response to neoadjuvant therapy can be measured at a per patient level using postoperative pathology, bypassing the need for predictive markers altogether.

CONCLUSION

There is no clear evidence for using quantitative ER and PR load assessed by immunohistochemistry as a prognostic measure nor as a predictive marker for response to ET in patients with stage 1-3 breast cancer. Immunohistochemistry is the gold standard for measuring HR status but should only be used to distinguish HR negative and HR positive tumors. Gene expression profiles have prognostic value for women with ER positive disease, early response evaluation to neoadjuvant therapy holds promise in the prediction of long-term response to endocrine therapy.

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