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Comparison of Estrogen receptors, Progesterone receptors and HER2-neu immunohistochemistry results in breast cancer with those of Oncotype Dx

Maher A. Sughayer*, Sallam Alhassoon, Haytham M. Sughayer

Department of Pathology and Laboratory Medicine, King Hussein Cancer Center, Amman, Jordan

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ABSTRACT

Oncotype Dx (ODx) recurrence score (RS) is used in early breast cancer to guide the use of adjuvant therapy. In addition to RS the test produces results of reverse transcriptase-polymerase chain reaction (RT-PCR) of Estrogen receptors (ER), Progesterone receptors (PgR) and Human epidermal growth factor receptor 2 (HER2-neu). Our goal was to determine the correlation between immunohistochemistry (IHC) and RT-PCR testing of ER, PgR and HER2-neu and to correlate the results of ODx RS with tumors' grade, age and PgR status.

113 patients with ER+, HER2-neu- breast cancers that underwent ODx testing were analyzed for receptors correlation and concordance rates by the 2 methods.

A total of 104 patients had ER+/PgR+ tumors and 9 patients had ER+/PgR- tumors by IHC, the average RS were 17.5 ± 9.1 and 31.2 ± 8.7 ($P < 0.001$) respectively.

The Spearman correlation coefficient between IHC and ODx results were 0.5 (95% CI 0.34–0.62) for ER and 0.78 (95% CI 0.7–0.84) for PgR.

The concordance rate between IHC and ODx was 98.2% for ER, 89.4%.for PgR and 99.1% for HER2-neu. Most of the discordant cases (9 out of 13) were low positive (1–10%) by IHC and negative by RT-PCR. In addition higher tumor grade was associated with a higher ODx RS.

Our data show that the IHC results were highly concordant with RT-PCR for ER, PgR and Her2-neu. In addition low positive (1–10%) ER/PgR might indicate a real negative status. Our study shows that ER+/PgR- breast cancers are associated with a significantly higher ODx RS.

1. Introduction

Invasive breast cancer biomarkers have been developed to help diagnose, prognosticate, and personalize breast cancer care. Estrogen receptors (ER), progesterone receptors (PgR) and Human epidermal growth factor receptor 2 (HER2-neu) expression are routinely assessed on all newly diagnosed breast cancers as determining these markers status is essential to optimize treatment outcomes in breast cancer patients [1-4].

Estrogen and ER play crucial roles in normal breast development and the development of breast cancer. The PgR is expressed in both normal and malignant cells in the breast and its synthesis is reliant on both estrogen and the ER [4]. About 75% of breast cancers express ER, while more than 50% of ER+ breast cancers also express PgR generally [5,6]. Therefore, among the cluster of ER+ tumors is the ER+/PgR- subgroup, where the PgR negativity is currently acknowledged as a definite clinical biomarker related to a less favorable outcome [7]. Recent studies have revealed that the absence of PgR is an independent prognosticator of poor response to antiestrogen therapy, and is related to higher recurrence rates and shorter survival time [8].

Oncotype DX (ODx) is a quantitative reverse transcription polymerase chain reaction-based assay (RT-PCR) developed by Genomic Health (Redwood City, CA, USA) that has been proven to have additional prognostic and predictive value in early-stage ER positive breast cancers [9-12]. This assay using Formalin fixed paraffin-embedded (FFPE) tumor tissue performed in a central lab showed a significant prognostic role for distant recurrence at 9 years from diagnosis in addition to the potential benefit of chemotherapy in early stage ER+ breast cancer [9,10,12,13].

The ODx recurrence score (RS) is reported on a 0–100 scale, that was originally divided into three risk categories: low (< 18), intermediate (18–30), or high risk (> 30). This has been recently modified into much simpler categories of low (0–25) and high (> 25) in women > 50 years of age. Women ≤50 years of age have different risk stratification: low (< 16), intermediate (16–25) and high (> 25) [10,11].

* Corresponding author at: Department of Pathology, King Hussein Cancer Center, Queen Rania AlAbdullah Str., P.O. Box: 1269, Amman 11941, Jordan.
E-mail address: msughayer@khcc.jo (M.A. Sughayer).

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This multi-gene expression assay has been incorporated into several guidelines including but not limited to the American Society of Clinical Oncology (ASCO) [14], National Comprehensive Cancer Network (NCCN) guidelines [15] and National Institute for health and care excellence (NICE) [16]. In addition to RS the test produces results of RT-PCR of ER, PgR and HER2-neu.

Our goal was to determine the correlation between the results of ER, PgR and HER2-neu determination by traditional immunohistochemical (IHC) assay to those of ODx assay which employs a RT-PCR assays to quantify hormone receptor (HR) status of breast cancer. In addition we wanted to determine the level of concordance in the status of hormone receptors and HER2-neu reported by the two methods.

Our secondary objective was to correlate the results of ODx RS with tumors' grade, age and PgR status.

2. Materials and methods

2.1. Patient population and data collection

A retrospective review analysis was performed at the Department of pathology and laboratory medicine in King Hussein Cancer Center. A total of 113 patients with ER positive, HER2-neu negative invasive early breast cancer who underwent ODx testing between 2013 and 2018 were included in our study. Patients' age, tumor grade and PgR status by IHC were collected from pathology reports. Discordant cases were identified for a second review.

2.2. IHC analysis of the primary tumor

ERs, PgRs and HER-2/neu results were collected from patients' pathology reports as they were originally evaluated by IHC on FFPE tissue according to the ASCO/CAP 2010 ER and PgR reporting Guidelines [17] for ER and PgR and the ASCO–CAP 2013 HER2 Test Guidelines [18]. IHC was performed using clone SP1 (Ventana Medical Systems Inc., Tucson, AZ, USA) for ER, clone 1E2 (Ventana Medical Systems Inc., Tucson, AZ, USA) for PgR and clone 4B5 (Ventana Medical Systems Inc., Tucson, AZ, USA) for HER-2/neu.

2.3. Data collected from Oncotype DX report

The results of RS, ER, PgR and HER2-neu status by RT-PCR were retrieved from the ODx reports.

2.4. Statistical analysis

Descriptive analysis of Patients' information was done. Categorical data, such as Age group, grade and other factors were presented as counts and percentages.

ER, PgR and HER2-neu IHC results were compared to those obtained by the ODx RT-PCR using Spearman correlation coefficient (R) [19].

In addition to the correlation, concordance rates were calculated for ER and PgR to those obtained by ODx RT-PCR.

Wilcoxon rank test was used for the continuous variables grade vs. RS and PgR by IHC vs. RS.

Fisher exact test was used to analyze PgR vs. RS and age.

A significance criterion of $P \leq 0.05$ was used in the analysis. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Descriptive patient characteristics

There were 113 patients included in the study (Table 1), 88 of whom had invasive ductal carcinoma (77.9%), 13 had invasive lobular carcinoma (11.5%), 4 had mixed ductal/lobular carcinoma (3.5%), and 8 had other types (7.1%).

Table 1
Descriptive patients' characteristics.

Parameter	Value	N (%)
Age	Age ≤ 50	53(46.9%)
	Age > 50	60(53.1%)
Grade	1	25(22.1%)
	2	64(56.6%)
	3	24(21.2%)
ER(IHC)	Positive	113 (100%)
ER (ODx)	Negative	2 (1.8%)
	Positive	111(98.2%)
PgR(IHC)	Negative	9 (8.0%)
PgR (ODx)	Positive	104(92.0%)
	Negative	21(18.6%)
	Positive	92(81.4%)
HER2-nue (IHC)	Negative	113 (100%)
HER2-nue (ODx)	Equivocal	1 (0.9%)
	Negative	112 (99.1%)
Subtype	Invasive ductal carcinoma	88 (77.9%)
	Invasive lobular carcinoma	13 (11.5%)
	Mixed ductal/lobular	4 (3.5%)
	Others	8 (7.1%)
Low PgR (IHC)	PgR (0 − 10)	18 (15.9%)
High PgR (IHC)	PgR (11 − 100)	95 (84.1%)

Regarding the PgR status for all patients included in the study; 104 (92.0%) patients had PgR + tumors and 9 (8.0%) patients had PgR- tumors by IHC.

Fifty three patients were 50 years old or less while 60 were above 50 years of age.

Regarding the grade of the tumor; 25 patients (22.1%) had grade 1 tumors, 64 patients (56.6%) had grade 2 tumors and 24 patients (21.2%) had grade 3 tumors.

There were 18 patients with low/negative PgR expression by IHC (0–10% of the cells) and 95 patients with high PgR expression level (11–100% of the cells).

3.2. Concordance and correlation in hormone receptor assessment by IHC and RT-PCR

Looking at PgR status by IHC vs. PgR status by ODx assay: 12 patients (10.6%) were discordant i.e. were PgR+ by IHC but were negative by RT-PCR.

The concordance rate for PgR between the two methods was 89.4%.

However, the concordance rate between IHC and ODx was 98.2% for ER, and 99.1% for HER2-neu.

Two specimens were discordant for ER (1.8%). Upon further examination the ER discordant cases showed that one was just positive above the cutoff with only 1% by IHC and the other one was performed in an outside lab but was not available for central review. (Note: there was a third case that was discordant as it was reported to be negative by ODx and highly positive by IHC with 90% expression level of cells, however, upon request to repeat ODx it turned out to be positive by the latter).

The 12 discordant cases for PgR were mostly low positive by IHC (eight out of twelve were less than 10%) and four cases were 20%, 30%, 40% and 70%.

The single discordant case for HER2-neu was negative by IHC and equivocal by ODx.

The numerical IHC results for ER were moderately correlated with the numerical ODx results with Spearman correlation coefficient of 0.5 (95% confidence interval 0.34 to 0.62) (Fig. 1).

For PgR there was a stronger correlation with Spearman correlation coefficient of 0.78 (95% confidence interval 0.7 to 0.84) (Fig. 2).

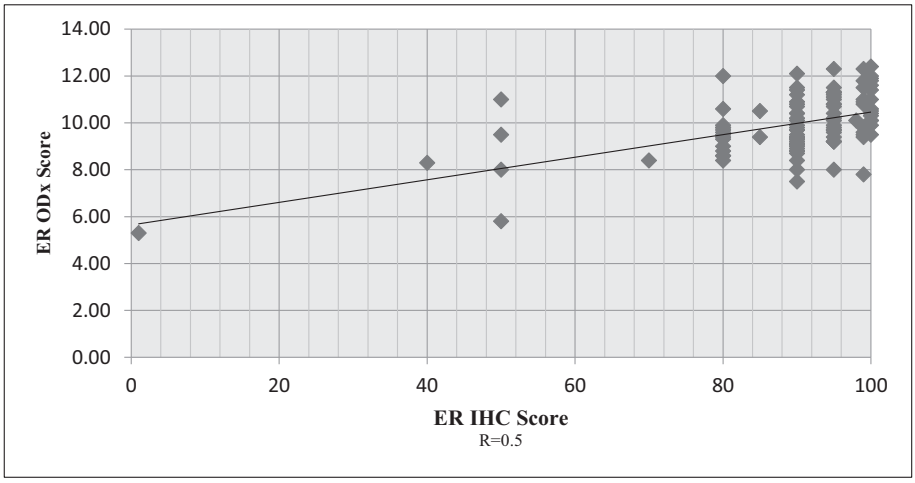

Fig. 1. Correlation between IHC results of ER and RT-PCR results.

3.3. PgR status vs. ODx RS

Univariate analysis (Fisher exact test) showed that PgR- tumor status was associated with significantly higher mean ODx RS when compared with PgR+ tumors [31.2 ± 8.7 (mean ± SD) with median 29] vs. [17.5 ± 9.1 with median 16] (P value < 0.001), thereby predicting a greater 9-year risk of distant recurrence.

Examining the relationship between RS and PgR for patients ≤50 years old, we found that 5 of 6 patients (83.33%) with low/negative PgR by IHC of (0–10%) had high RS (RS ≥ 16 for this age group). While a less proportion; 25 of 47 patients (53.2%) with PgR of (11–100%) had high RS (RS ≥ 16 within the same age group) (Fig. 3-a).

For patients > 50 years old; 9 of 12 patients (75%) with low/negative PgR by IHC of (0–10%) had high RS (RS > 25), while those with PgR by IHC of (11–100%) only 6 of 48 (12.5%) patients had high RS (RS > 25) (P < 0.05) (Fig. 3-b).

3.4. Grade and ODx RS

Higher tumor grade (Fig. 4) was associated with a higher mean ODx RS when compared with intermediate- and low grade tumors [grade 3 RS (mean ± SD) 24.1 ± 11.6 vs. grade 2 RS (mean ± SD) 18.2 ± 8.4] and [grade 3 RS (mean ± SD) 24.1 ± 11.6 vs. grade 1 RS (mean ± SD) 14.2 ± 9].

The median RS for grade 1 was 12.0 (range: 0.0–43.0), for grade 2 was 17.0 (range: 4.0–49.0) and for grade 3 was 21.5 (range: 10.0–61.0) (P value < 0.001).

For grade 3 tumors (58%) of the patients had high RS. The grade and HR status according to the recurrence score category are summarized in Table 2.

4. Discussion

Our study shows that there was a moderate to strong correlation when IHC and RT-PCR for both ER and PgR were compared quantitatively. However when looking at concordance rates between IHC and ODx it was 98.2% for ER and 89.4% for PgR.

The concordance rate for HER2-neu was very high at 99.1%.

Our results are similar to other published literature [20-24] (Table 3).

These results indicate persistent high level of concordance for ER and HER2-neu but less so for PgR (around 90%) which is understandable in view of the pre-defined requirements for cases to be ER positive HER2-neu negative by IHC to be submitted for ODx testing.

Most of our discordant cases in the PgR IHC were actually borderline-low positive (i.e. between 1 and 10%). This underscores the recent observations that low positive hormone receptors (1–10%) cases behave more like a real negative case especially in the case of ER. The RTPCR results being negative in these cases support this notion.

Our data show that ER+/PgR- breast cancers are associated with a significantly higher ODx RS than those with ER+/PgR+ (31.2 vs 17.5)

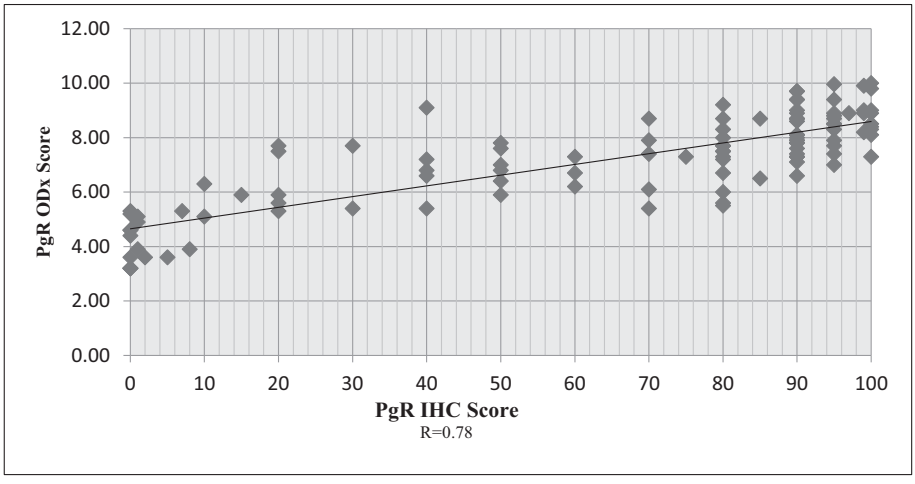

Fig. 2. Correlation between IHC results of PgR and RT-PCR results.

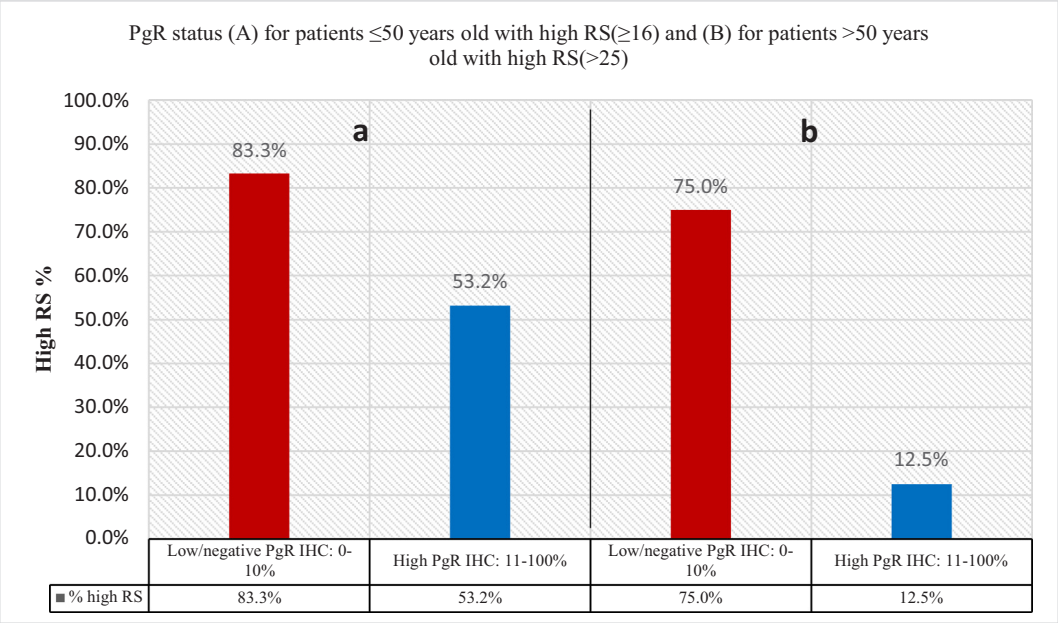

Fig. 3. PgR status (a) for patients ≤50 years old with high RS(≥16) and (b) for patients > 50 years old with high RS(> 25).

which assumes a higher risk of recurrence similar to the previously reported study by Chaudhary et al. which showed that PgR- tumor status was associated with significantly higher Oncotype DX scores when compared with PgR+ tumors (24.7 vs 17.3) and only 5.3% of patients with ER+/PgR + tumors had a high ODx RS [8]. Another study by Hanna et al. showed that 13.6% of cases were PgR negative and 59.2% of which had high RS [21]. The adverse effect of negative/low PgR expression on prognosis of early ER+, Her2- breast cancer has previously been reported. Several studies have clearly demonstrated this effect for a PgR of < 20% [25,26].

Our results showed that if PgR is low (0–10%) for patients > 50 years old or for patients ≤50 years old there is a high chance (75%) and (83.33%) respectively that RS is high for each of the respective age group.

For patients with strong positive PgR (10–100%) there's a lower chance that the RS is high (12.5%) for patients > 50 years old and a moderate chance (53.2%) for patients ≤50 years old. These findings were similar to Chaudhary et al. and Salih et al. [8,27].

With regards to tumor grade there's a moderate chance for grade 3 tumors (58%) to have high RS (Fig. 4) similar to previous studies where

Table 2
Tumor characteristics according to Recurrence score.

Characteristics	RS (0–25)	RS > 25
ER Positive (IHC)	90 (79.6%)	23 (20.4%)
PgR Positive (IHC)	88 (77.9%)	16 (14.2%)
Grade I	23 (20.4%)	2 (1.8%)
Grade II	54 (47.8%)	10 (8.8%)
Grade III	13 (11.5%)	11 (9.7%)

Chaudhary et al. showed that grade 3 RS mean vs. grade 1 RS mean was (23.3 vs. 16.2 P < 0.0001) [8], Hanna et al. showed that grade 3 carcinomas had intermediate to high RS [21], Bomeisl et al. showed that (70%) of the high RS tumors were grade 3 tumors [28], Lathrop et al. showed that tumor grade correlated significantly with RS [29], and Thibodeau et al. showed that 100% of patients in the high-risk RS group had Grade 3 tumors [30].

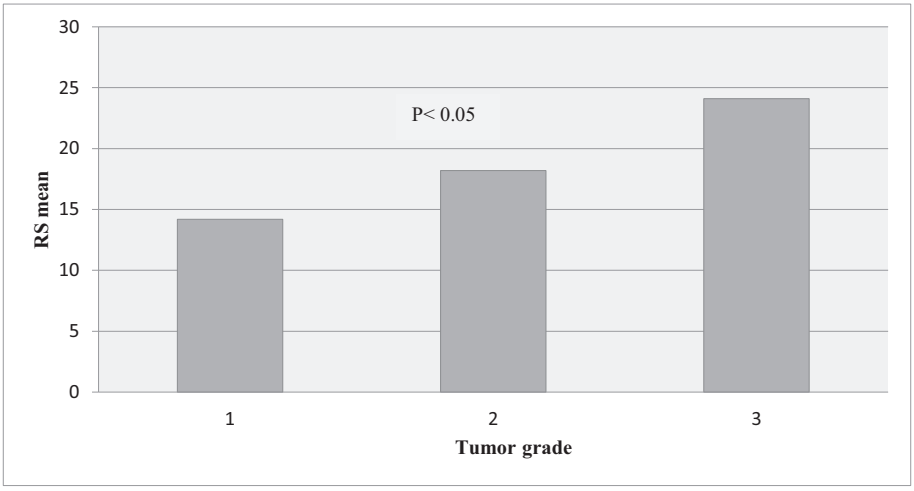

Fig. 4. Tumor grade and RS relationship.

Table 3
Concordance rates between IHC and ODx for ER, PgR and HER2-neu in published literature.

Published literature	ER	PgR	HER2-neu
Current study	98.2%	89.4%	99.1%
Chang et al. [20]	96.7%	90.0%	100%
Hanna et al. [21]	99.8%	91.4%	NA
Neely et al. [22]	98.9%	90%	NA
Park et al. [23]	98.9%	95.1%	99.2%
O'Connor et al. [24]	100%	94%	NA

5. Conclusion

In conclusion our study showed a good correlation between Hormone receptor and Her2-neu by the 2 methods and highlighted the fact that PgR negative or low positive status is associated with high RS therefore, suggesting the possibility of avoiding the testing in such cases. In addition low positive HR between 1 and 10% might indeed be real negative.

Compliance with ethical standards

All ethical approvals obtained (informed consent is waived).

Conflict of interest

The authors declare no conflict of interest.

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