[P3-05-08] Discordance in hormone receptor (HR) assessment by IHC and RT-PCR in an estrogen receptor (ER) low-positive group (1-10% positive cells): Does accurate assessment of HR status require dual testing?

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Background: Accurate determination of hormone receptor (ER/PR) and HER2 status is critical for making treatment (Tx) decisions in early stage breast cancer (EBC) patients (pts). ASCO/CAP guidelines categorize pts with >1% ER/PR staining as 'positive' for HR expression. A formal interaction between quantitative ER expression by RT-PCR and tamoxifen response was demonstrated in NSABP B-14 (Kim C, JCO, 2011). Prognosis and Tx decisions depend on the status of ER expression and pts with ER(-) disease have a worse prognosis. A comparative study to evaluate ASCO/CAP cutoffs for ER protein expression and prospectively validated ER mRNA expression by RT-PCR was undertaken in consecutive EBC pts with either negative or low-positive ER by IHC from a single institution.
Methods: Consecutive EBC pts with IHC defined ER(-) (<1% positive cells) or ER low-positive (1-10% positive cells; by ASCO/CAP guidelines) were identified at New York University School of Medicine. ER, PR and HER2 protein assessment used standard IHC methods (SP1, 1E2, 4B5, Ventana). ER, PR and HER2 mRNA assessment used the Onco*type* DX® 21-gene assay, reference-normalized expression measurements ranged from 0 to 15, where each 1-unit increase reflects about a two-fold increase in RNA. The validated thresholds for positivity for the three markers were used: ER, 6.5, PR, 5.5 and HER2, 11.5. Descriptive statistics were calculated for baseline characteristics, and two-way classification tables were produced for ER by IHC versus RT-PCR.
Results: Of 140 IHC evaluable samples, 106 (76%) were ER(-), 34 (24%) were ER low-positive, 116 (83%) PR(-), and 24 (17%) PR+. Pts included showed: 69.3% $\geq$50 yrs; 83.6% had poor differentiation; 31.2% had $\geq$1 positive nodes; 34.3% were $\geq$ 2.0cm. 37 pts (26.4%) were HER2+ by IHC or FISH. The cross classification of ER status by RT-PCR versus IHC is in the Table. For IHC ER(-) cases there was a 93.3% percent negative agreement (PNA) between IHC and RT-PCR. For IHC ER low-positive cases the percent positive agreement (PPA) was 38.2% between IHC and RT-PCR. ER expression (C_T units) ranged from 2.8 to 8.3 for IHC negative cases and 3.4 to 9.2 for IHC low-positive cases.
Conclusions: The status of ER, PR and HER2 is critical for Tx decision making in pts with EBC. In this cohort of ER(-) or low-positive expressing EBC cases there was high agreement between IHC and RT-PCR for negative ER expression (93% PNA); however, only 40% of ER- low-positive (1-10%) cases by IHC were positive by RT-PCR. While many of the discordant cases were near the RT-PCR cutpoint of 6.5, about 10% of the discordances were either strongly ER+ or strongly ER(-) by RT-PCR suggesting misclassification by central IHC. Thus, in many IHC ER- low-positive cases there may be little or no benefit from the addition of hormonal therapy. Accurate assessment of ER is critically important to ensure the best Tx and these findings indicate that dual testing of low-positive ER by IHC merits consideration and additional study.

ER Status	IHC		
RT-PCR	Negative	Low-positive	Total
Negative	99 (93.3%)	21 (61.7%)	120 (85.7%)
Positive	7 (6.6%)	13 (38.2%)	20 (14.3%)
Total	106 (100%)	34 (100%)	140 (100%)

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Poster Session 3: Prognosis and Response Prediction: Biomarkers – Methods (5:00 PM-7:00 PM)