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Original article

# Discordance in pathology report after central pathology review: Implications for breast cancer adjuvant treatment

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ABSTRACT

*Aim:* Pathological predictive factors are the most important markers when selecting early breast cancer adjuvant therapy. In randomized clinical trials the variability in pathology report after central pathology review is noteworthy. We evaluated the discordance rate (DR) and inter-rater agreement between local and central histopathological report and the clinical implication on treatment decision.

*Methods:* A retrospective analysis was conducted in a series of consecutive early breast cancer tumors diagnosed by local pathologists and subsequently reviewed at the Pathology Division of European Institute of Oncology. The inter-rater agreement (k) between local and central pathology was calculated for Ki-67, grading, hormone receptors (ER/PgR) and HER2/neu. The Bland–Altman plots were derived to determine discrepancies in Ki-67, ER and PgR. DR was calculated for ER/PgR and HER2.

*Results:* From 2007 to 2013, 187 pathology specimens from 10 Cancer Centers were reviewed. Substantial agreement was observed for ER (k0.612; 95% CI, 0538–0.686), PgR (k0.659; 95% CI, 0580–0.737), Ki-67 (k0.609; 95% CI, 0.534–0.684) and grading (k0.669; 95% CI, 0.569–0.769). Moderate agreement was found for HER2 (k0.546; 95% CI, 0444–0.649). DR was 9.5% (negativity to positivity) and 31.7% (positivity to negativity) for HER2 and 26.2% (negativity to positivity) and 12.5% (positivity to negativity) for ER/PgR. According to changes in Her2 and ER/PgR status, 23 (12.2%) and 33 (17.6%) systemic prescription were respectively modified.

*Conclusions:* In our retrospective analysis, central pathological review has a significant impact in the decision-making process in early breast cancer, as shown in clinical trials. Further studies are warranted to confirm these provocative results.



## Introduction

The introduction of adjuvant systemic treatment into early breast cancer management has led to an improvement in overall breast cancer survival. Estrogen receptor (ER), progesterone receptor (PgR) and human epidermal growth factor receptor-2 (HER2) are strong predictors of efficacy of adjuvant therapy in early breast cancer. The magnitude of the impact of endocrine therapy, chemotherapy and targeted therapy is mainly based on hormonal receptor status (HR) and HER2 status in addition to proliferative markers and on tumor grade [1]. Accurate assessment of pathological parameters is mandatory in the-decision making process of systemic therapy in breast cancer patients.

The American Society of Clinical Oncology (ASCO)-College of American Pathologists (CAP) recommended guidelines for both HER2 and ER and PgR immunohistochemical testing, thus producing an algorithm that relies on accurate and reproducible assays [2,3].

In large clinical trials, central pathology review is usually mandatory. In the Breast International Group (BIG) 1-98 trial, central review changed the assessment of HR status in a substantial

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proportion of patients [4]. Of 6100 women classified ER positive in local assessment, central review found 66 ER negative (1.1%) and 54 low ER (0,9%). The discordance was more marked for PgR. In the ALTTO trial for HER2 positive disease, HER2 and ER were centrally reviewed by the Mayo Clinic in Rochester and the European Institute of Oncology in Milan (IEO). Among locally HER2 positive tumors, 5.8% and 14.5% were centrally negative for the Mayo and the IEO respectively. Among locally ER positive tumors, 16.2% and 4.2% were found negative at the Mayo and the IEO central review respectively [5]. For other pathological parameters, such as Ki67 and grading, the rate of discordance rate appears more marked [6].

Despite the multiple data of discordance rate after central review in breast cancer, the potential clinical impact outside clinical trials remains limited. Previous studies of inter-institutional pathology consultations for breast cancer reported a 4–29% discordance rate, however, information on specific discordant parameters is limited [7,8].

The present study reports the results of the central pathology review of ER, PgR, HER2 status, Ki67 and grading of early breast cancer and the implications for the selection of adjuvant systemic therapies.

## Materials and methods

We conducted a retrospective review of 210 consecutive invasive breast cancer specimens referred to our Institution from 2007 to 2013. Specimens were sent for central pathological review to the European Institute of Oncology (IEO) in Milan. One hundred eighty seven samples were selected for this analysis.

Local HER2, ER, PgR, Ki67 and grading refer to the initial testing performed on the tumor tissue samples. Central HER2, ER, PgR, Ki67 and grading refer to the results from the IEO review.

The invasive component was confirmed in all specimens. Two tumors were excluded from the analysis due to the presence of advanced disease, 13 because only the primary core biopsy was available, and 8 because only hormonal receptor review was performed. The medical records of patients who had discordant diagnoses were reviewed in order to evaluate changes in the management plan.

The study was approved by the Local Ethical Committee.

## Pathology

All the pathology reviews were performed at the IEO (Milan). The same assay and methodology were applied to each sample. The central laboratory run the analysis on the same paraffin block used in local laboratories.

IHC and FISH for HER2 were performed using the HercepTest® kit (Dako, Glostrup, Denmark) and PathVysion HER2 DNA probe kit/HER2/centromere 17 probe mixture (Abbott Molecular, Des Plaines, IL). HER2 positivity was defined according to the FDA scoring system, (intense circumferential membrane staining in >10% of tumor cells by IHC or HER2 gene copy number/CEP17 signals $\geq$ 2 by FISH).

IHC for ER and PgR was tested centrally using the DAKO ER/PR PharmDX kit, and defined positive if $\geq$ 1% immunostained tumor cells [1].

## Statistical analysis

Licenced MedCalc (v. 11.0) was used to analyze the inter-rater variability between the local pathological diagnosis and the central review, according to the Kappa (k) index. The index was interpreted according to the following values: <0.20 (bad); 0.21–0.40 (poor); 0.41–0.60 (moderate); 0.61–0.80 (good); and 0.81–1.00 (excellent) [9]. The significance level (p) was taken as 0.05.

In order to visually test and weigh differences between local and central pathology, the Bland–Altman plots were determined for Ki-67, ER and PgR [10]. Results obtained by central pathology review (retesting) were compared with local tested results and the discordance rate (DR) and inter-rater agreement were calculated. Tumors with one or more target parameters that were unknown or missed (ER, PgR, HER2, Ki67, histologic type, grading, Ki67) were excluded. Correlation analysis between local and central pathology was also conducted l for ER, PgR, and Ki67, according to parametric (Pearson's r, with 95% confidence intervals, CI) and non-parametric (Spearman's Rho and Kendall's Tau) coefficients; a regression equation was calculated according to the regression analysis (parametric $R^2$) [11]. DR was defined as the positive-to-negative or negative-to-positive changes according to ER/PgR status or according to HER2 status. Any main changes in treatment decision from initial purpose to final prescription were also considered: addition or subtraction of endocrine therapy and/or of anti HER-2 therapy. These main changes were calculated as percentage.

## Results

A total of 210 specimens of invasive breast cancer from ten Cancer Centers were reviewed. 23 specimens were excluded from the analysis: two because of the presence of metastatic disease at diagnosis, 13 for whom only biopsy samples were available, 8 because they were re-tested only for hormonal receptors. Median age of patients was 52 years (28–76), 100 (53.4%) patients were postmenopausal (Table 1.)

Local analysis revealed 145 tumors as ER- and/or PgR-positive (77.5%) and 41 tumors as HER2-positive (21.9%). At central review 136 (72.7%) and 42 (22.4%) tumors were ER- and/or PgR-positive and HER2-positive respectively.

Substantial agreement was observed for ER (Kappa = 0.612; 95% CI, 0538–0.686), PgR (Kappa = 0.659; 95% CI, 0580–0.737), Ki67 (Kappa = 0.609; 95% CI, 0.534–0.684) and grading (Kappa = 0.669; 95% CI, 0.569–0.769). Moderate agreement was found for HER2 (Kappa = 0.546; 95% CI, 0444–0.649) (Table 2). The analysis confirmed the dispersions of values according to ER, PgR and Ki67 (Figs. 2–3). The Bland–Altman plot did confirm the absence of major differences or discrepancies between the two assays for ER, PgR and Ki67 (Figs. 1–3). Supplementary Fig. S1 shows the correlation between the two pathologic determinations for the same variables. With regard to HER2 distribution, detailed descriptors are reported in Supplementary Fig. A2.

**Table 1**
Patients and tumors features at diagnosis.

| | n (%) |
|---|---|
| Age (median) (y) | 52 (28–76) |
| Pre/postmenopausal | 87/100 |
| pT1 | 62 (33%) |
| pT2 | 56 (30%) |
| pT3 | 30 (16%) |
| pT4 | 39 (20.8%) |
| pN1 | 102 (54.5%) |
| pN2 | 65 (34.7%) |
| pN3 | 20 (10.7%) |
| Histology | |
| Ductal | 158 (84.4%) |
| Lobular | 17 (9%) |
| Others | 12 (6.4%) |
| ER and/or PgR pos | 145 (77.5) |
| ER and PgR neg | 42 (22.5) |
| HER2 positive | 41 (21.9) |
| Triple negative | 25 (13.3%) |

*HER2 positive*: staining 3+. *ER and/or PgR positive*: staining $\geq$ 1%.