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Breast cancer hormone receptor assay results of core needle biopsy and modified radical mastectomy specimens from the same patients

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Abstract

Background—Hormone receptor expression is the most important biomarker and is the cornerstone in the management of breast cancer, hence, the accuracy of its testing is critical in treatment decisions.

Patients and Methods—One hundred sixty consecutive patients accrued to an adjuvant hormonal therapy clinical trial between March 2003 and May 2008 were studied. Estrogen receptor (ER) and progesterone receptor (PR) protein assays of tissues from MRM specimens were compared to their prior CNB ER and PR immunohistochemical assay results.

Results—The tumors of 146 (91.2%) out of the 160 CNB HR positive patients remained HR positive in MRM specimen assays. Estrogen receptor positivity decreased from 95% in the CNB to 81.9% in MRM specimens and PR positivity from 93.8% to 86.9%. The overall agreement between CNB and MRM specimens was 81.9% for ER and 85.6% for PR. The mean Allred scores were significantly higher in CNB than in MRM specimens – ER: 6.6 (SD 2.02) vs 4.71 (SD 2.62); PR: 6.68 (SD 2.16) vs 5.99 (SD 2.68); $p < 0.001$ and $p = 0.001$ respectively.

Conclusion—Core needle biopsy specimens are associated with identification of more frequent and higher levels of tumoral hormonal receptor proteins than MRM specimens. Delayed fixation of MRM tissues likely accounted for this finding. Optimal selection of patients for hormonal therapies is dependent on tissue management strategies prior to formal hormonal receptor protein testing procedures.

Keywords

breast cancer; hormone receptor assay; core needle biopsy; modified radical mastectomy

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Introduction

Hormone receptor expression remains the most important biomarker in breast cancer and is the cornerstone of optimal individual patient treatment decisions. Because of the remarkable heterogeneous behaviour of this disease, treatment guidelines emphasize tailoring therapy primarily based on the hormone receptor status of the tumor. The United States National Cancer Comprehensive Network (NCCN) Guidelines call for determination of estrogen receptor (ER) and progesterone receptor (PR) content for all primary invasive breast cancer and for adjuvant endocrine treatment for all hormone receptor (HR) positive patients regardless of age, axillary lymph node status and whether adjuvant chemotherapy is also given.¹ Likewise, the 2005 Philippine College of Surgeons' Evidence-based Clinical Practice Guidelines on the Diagnosis and Management of Breast Cancer stress the importance of HR status in selecting the type of adjuvant treatment and at the same time call for rigorous efforts to standardize testing methods.² Across several populations, despite likely differences in tissue management and testing methods, two-thirds of breast cancer tumor are HR positive. When “false negative” HR test results are found, these deprive women of the proven benefits of endocrine therapies and may lead to choosing unwarranted chemotherapy treatments with significant financial costs and toxicities.

While studies in populations of Asian women have been reported to show greater proportions of HR negative breast cancers compared to those found in Western women, more recent investigations, with careful attention to tissue management before formal laboratory testing, and standardization of cut-off levels for assignment of “positive” HR status, have determined these parameters to be similar in these diverse populations.^{3,4,5,6,7} For example in our own report of 1000 patients, the percentage of HR positive tumors in Filipinos was 68.9% after changes in fixation were instituted.⁸ Of particular interest in our earlier work was the observation that HR positivity was 7% higher in core needle biopsy (CNB) than in modified radical mastectomy (MRM) specimens.

To investigate this observation rigorously, in the current study we evaluated ER and PR assay results of specimens obtained from CNB and MRM in a consecutive series of the same patients. Standardized fixation strategies, immunohistochemical (IHC) staining methods, and reading guidelines were implemented.

Patients and methods

Patients

This study included a subset of all patients recruited at the Philippine General Hospital, Manila, Philippines from March 2003 to May 2008 to an ongoing international adjuvant hormonal therapy trial in premenopausal women with operable breast cancer. Included trial participants were patients who had CNB as their initial diagnostic procedure from which tissue hormonal receptor assays were done, and whose paraffin blocks of their subsequent MRM specimens contained residual tumor. All these patients had been found to have HR positive tumors from their CNB specimens. No chemotherapy or hormonal therapy was given prior to their MRM surgeries. This research has been approved by Institutional Review Boards of both sponsoring (Ohio State University) and Filipino institutions.

Excluded were patients who underwent excision or section biopsies instead of CNB for diagnosis. Likewise excluded were cases in which the MRM paraffin blocks contained no residual invasive tumor after sections were taken for cryogenic preservation.

Specimen source and processing

Core needle biopsies were done in premenopausal patients presenting with a palpable breast mass suspicious for cancer. A minimum of 3 passes of a gauge 14 Bard Magnum reusable core biopsy system were done to assure adequate sampling for morphologic evaluation and IHC staining. Specimens were immediately placed in 10% neutral buffered formalin for fixation of minimum of 6 hours and maximum of 30 hours prior to tissue processing.

Patients underwent bilateral oophorectomy immediately followed by MRM on their assigned dates. The surgical technique for MRM was uniform and involved en bloc mastectomy followed by axillary dissection using electrocautery. Each MRM specimen was brought to the Pathology Department within 15 minutes after removal from the patient and 1–2 grams of tissue samples from the tumor and surrounding breast were obtained for cryogenic preservation. The rest of the MRM specimen was breadloafed with about 1–2 cm thickness, placed in a container with 10% neutral buffered formalin with a 1:2 to 1:3 ratio of tissue:fixative and fixed for a minimum of 24 hours and a maximum of 54 hours. The fixed specimen was then sectioned and representative samples from different areas of the tumor were processed into paraffin blocks and stored at room temperature. At dates from 3 months to 5 years later the paraffin blocks were retrieved in batches and sections were created for IHC staining.

Immunohistochemical staining

Core needle biopsies and MRM specimens were stained manually by a dedicated laboratory technician using the same protocol except for the first 109 patients recruited in the study when their CNB specimens were stained using the labelled streptavidin-biotin (LSAB, Dako) instead of the Envision+ (Dako) visualization system. Paraffin blocks to be used for IHC were selected by the pathologists by reviewing the hematoxylin-eosin slides and choosing the sections that contained well preserved, non-necrotic tumor and preferably also normal breast tissue epithelium. These blocks were cut and then stained for IHC the following day. Heat induced antigen retrieval was achieved using a microwave oven for 20 minutes with Tris/EDTA buffer pH 9. Clone 1D5 (Dako, Code N1575) anti-estrogen antibody and clone PgR 636 (Dako, Code N1630) anti-progesterone antibody were used at their prediluted, ready to use concentration.

Three types of controls were employed - strong external control, weak external control and internal positive control (normal breast epithelium) to evaluate the adequacy and reproducibility of each IHC procedure.

Interpretation

All slides were read by one of three study pathologists (J.M.C.J., F.G.L., A.M.F.) who for the mastectomy specimens were blinded on the previous CNB results. The percentage of nuclei stained and the staining intensity were evaluated and scored using the Allred Scoring System.⁹ Staining of at least 1% of tumor cells was considered positive and corresponded to an Allred score of 3–8 while a score of 0 or 2 was negative. If either ER or PR was positive then the patient was deemed hormone receptor (HR) positive.

Statistical Analysis

Data were encoded and processed in Microsoft Excel ver. 2003. OpenEpi ver. 2.2 (Dean AG, Sullivan KM, Soe MM. OpenEpi: Open Source Epidemiologic Statistics for Public Health, Version 2.2. www.OpenEpi.com, updated 2007/11/18, accessed 2009/02/04.) was used for statistical analysis. Data were described using proportions for positivity (or negativity rates) and means and standard deviations for continuous variables. The Chi-square or Fisher's exact tests, whichever was more appropriate, were used to test for

significant differences in positivity rates, while the paired t-tests were utilized to determine significant differences between means. The 95% confidence intervals for positivity rates were determined using the Mid-P Exact limits formula. Agreements between the two assays were tested using Cohen's kappa. All tests were two-tailed and considered significant with p values less than 0.05.

Results

During the period covered, a total of 241 premenopausal patients had been recruited into the parent study on adjuvant hormonal therapy for breast cancer. Of these, 160 patients had appropriate CNB and mastectomy specimens available for the current investigation. In this study, the median pathologic tumor size was 5.0 cm (1.0 cm – 13.0 cm) with the following distribution: T1 = 7 (4.4%); T2 = 72 (45%); T3 = 56 (35%) and T4 = 25 (15.6%) based on the TNM classification system.¹⁰

All 160 samples of CNB were HR (either ER and/or PR) positive. One hundred forty six out of 160 (91.2%; 95% CI 86.1 – 94.9) MRM specimens were HR positive (Table 1). Estrogen receptor was positive in 152 (95%) cases of CNB specimens while 131 (81.9%) were ER positive in MRM specimens. This observed difference in positivity rates of 13.1% was highly significant ($p < 0.001$). Similarly, PR receptor positivity was significantly higher in CNB than in MRM specimens, 93.8% (150/160) versus 86.9% (139/160) ($p = 0.035$), respectively.

Table 2 showed that the overall agreement between CNB and MRM specimens was 81.9% (95% CI 75.2 – 87.1) for ER and 85.6% (95% CI: 79.4 – 90.2) for PR. The Kappa test yielded 15.0% (95% CI: 2.7 – 27.2; $p = 0.016$) for ER and 18.9% (95% CI 4.6 – 33.3; $p = 0.009$) for PR indicating that the agreement between the two tests for both receptors was negligible beyond chance expectation. Discordant cases tended to be CNB positive and MRM negative: 25 out of 29 cases for ER and 17 of 23 for PR. Only 4 (2.5%) CNB ER negative cases were MRM ER positive, while 6 (3.8%) CNB PR negatives cases were positive in MRM specimens.

The cross-tabulation of CNB and MRM ER Allred scores are shown in Table 3 and PR Allred scores in Table 4. The Allred scores of CNB specimens tended to be higher than their mastectomy counterparts. The mean ER Allred score for CNB and MRM specimens were 6.6 (SD 2.02) and 4.71 (SD 2.62) respectively, with a significant mean paired difference of 1.89 (SD 2.87, $p < 0.001$). The mean PR Allred scores were 6.68 (SD 2.16) for CNB and 5.99 (SD 2.68) for MRM, and the mean paired difference of 0.69 (SD 2.53) was also significant ($p = 0.001$).

Associations of HR, ER and PR positivity rates with the year of surgery, duration of storage of paraffin blocks prior to IHC and tumor size were examined and no significant differences were seen.

Discussion

Multiple factors have been described to influence findings of estrogen and progesterone hormonal receptors in breast tumors.^{11,12,13,14} While the current study has several strengths which support confidence in concluding that CNB hormonal receptor testing is more likely to identify patients whose treatment can be most accurately guided, it is important to note the possible weaknesses. The case series reported here was assembled over a five-year period, during which time unrecognised or documented critical changes in operative, tissue procurement, tissue management, and all aspects of the IHC laboratory procedures, may have occurred. This long time period results in a situation where the MRM specimen for HR

studies were down in paraffin blocks stored for variable periods as compared to CNB specimens which were stained right after morphological evaluation showed the presence of invasive cancer. Restaining of the CNB and their respective MRM specimens in same batches would have controlled laboratory variables in the conduct of IHC itself but this was not done because of limited resources. Furthermore, standardization of breadloafing of MRM specimens and the ratio of the volume of the MRM tissue with the fixative were difficult to impose in this clinical setting. The MRM specimens were immersed in 10% neutral buffered formalin in the ratio of 1:2 to 1:3 only because of limited resources. Since the Pathology Department was closed on Sundays, operation done on Fridays had the specimens immersed in formalin for an additional 24 hours, unlike for CNB specimens where performance of biopsy at the clinic was limited to Mondays through Thursdays only, therefore the duration of fixation was easier standardized.

This is a single institutional case series in premenopausal Filipino women. The major finding is that of the 160 studied patients, 14 (8.8%) would have been deprived of endocrine treatment if we relied on their mastectomy specimens for HR testing. This finding supports previous claims by other authors that CNB is a more reliable source. Mann and colleagues found that the cores were positive for ER, PR and HR but the surgical specimens were negative in 13%, 11% and 9% respectively.¹⁵ In another study of screen detected, non-palpable breast masses, the false negative rates for surgical specimens compared to CNB were 14% for ER and 15% for PR.¹⁶ Core specimens had homogenous and higher proportions of stained cells while excised specimens were noted to have a less profound staining at the center compared to the edges of the tumor. This study already involved small tumors which subsequently underwent excision, and the authors surmised that false negative rates might be higher for larger tumors because of poorer fixation. In sum, our findings are consistent with those of other authors studying other populations.

Before considering the possible explanations for these findings further, it is important to ask whether these findings really have clinical importance. If the patients in whom the discordant findings occur may not truly benefit from more accurate testing, then our report is of but technical interest. The results in Table 3 offer compelling evidence, combined with other findings that in fact these discordant findings do matter. Of 29 cases in whom the MRM specimens showed no evidence at all of ER receptor positivity, 25 had CNB Allred scores of 4–8; half of these positive Allred scores were 7 and 8 (Table 3—first line). In the Harvey et al study correlating Allred ER scores with outcomes from adjuvant hormonal therapy, the cut-off for benefit was clear with scores of 3 or more and patients with tumors showing scores of 7 and 8 enjoyed even greater benefits.⁹ Thus among our patients 15% (25/160) of women would have been denied benefits of hormonal therapy based on their mastectomy ER test results; 7% (with scores of 7 and 8) would have been denied major benefit. For these women the limited toxicities and practical achievability of the combined hormonal therapy they received make this study finding very relevant clinically. In only 5% (8/160) of women in this study who are ER negative PR positive on CNB is endocrine therapy may not be useful since PR positivity may only be artifactual but further pathologic review is necessary. Of these 8 cases, only 3 were ERPR negative on MRM specimens, 4 became ERPR positive and 1 remained ER negative PR positive on their MRM specimens.

Thus the possible explanations for our findings are important to identify. Fixation is a major component of consistent and standardized HR IHC assay procedures. The standard fixative for most surgical specimens is 10% neutral buffered formalin, the pH of which should be checked regularly and maintained at 7.2 to 7.4. Formalin permeates tissue at 1 mm per hour but fixes tissue more slowly, and although it permeates small tissues faster, the fixation time is similar; complete cross-linking takes 24 hours at room temperature or 18 hours at 37°C.¹⁷

The Ad-Hoc Committee on Immunohistochemistry Standardization recommends a minimum of 8 hours of formalin fixation.¹⁸

With respect to pre-analytic tissue management, CNB specimens are easier to handle than MRM specimens. A mastectomy specimen should be sliced or “breadloafed” to about 0.5 to 1 cm thickness for better formalin penetration. It also requires a large volume of buffered formalin for adequate fixation because the recommended volume ratio of tissue/fixative is 1:20.¹⁹ This requirement is likely not met in many low and middle income countries with limited resources for laboratory services.

Delay in fixation has been shown to affect IHC staining because of the thermolabile nature of ER and PR proteins. Delay in fixation of mastectomy specimens is prevalent in many hospitals due to lack of manpower and other logistical problems in operating rooms. An important finding of the present study is that while immediate placement of specimens in formalin was ensured by the staff, the results still demonstrated absent staining in the MRM specimens in 16.4% ER positive and 11.3% PR positive CNB specimens. The loss of staining in MRM specimens was not limited to CNB with low expression levels as 22/25 (88%) and 11/17 (64.7%) had Allred scores of 5–8 for ER and PR respectively. It was also shown that CNB specimens tended to have higher Allred scores compared to their mastectomy equivalents. Warm ischemia due to devascularization and electrocautery-induced thermal injury had been shown to affect hormone receptor determinations with MRM specimens in older studies using fresh frozen tissue and assayed using dextran-coated charcoal technique.^{20,21} With the usual conduct of MRM – creation of skin flaps, mobilization of the breast from the pectoralis muscle followed by en bloc axillary dissection - the breast and tumor has already been devascularized for some time before the specimen is processed and placed in formalin. Thus a likely significant delay in fixation must occur in usual operative practice. In a study by Day et al on the influence of mastectomy technique on ER concentration, they noted that out of the 10 patients who were ER positive pre-mastectomy, 5 became ER negative postmastectomy if the conduct of the operation was breast mobilization followed by axillary dissection. In contrast, all 10 patients with ER positive pre-mastectomy specimens remained positive after the operation if the axillary dissection preceded the breast mobilization.²²

The findings of this study support the recommendation that CNB ought to be the initial procedure of choice for breast masses suspicious for cancer. Hormone receptor studies should be done on the CNB specimens because adequate fixation is more easily achieved and warm ischemia of the tumor is avoided. Nevertheless, a repeat HR testing on the surgical specimen is warranted if there is any doubt in the adequacy of collection and processing of the CNB specimens, particularly if the CNB assay was HR negative.

More work is needed to attain optimal results for IHC assay of hormone receptors in breast cancer because standardization requires control of several variables - fixation, staining method with appropriate choice of heat induced antigen retrieval and antibodies, scoring and interpretation. The staining method should be optimized and results validated through internal and external quality assessment. Laboratory personnel should develop expertise in IHC. However, all these improvements in the laboratory may be insignificant if fixation of specimens is compromised, as the antigen lost during inadequate fixation will never be recovered even by the most sensitive assay.

Conclusion

We have demonstrated that CNB specimens assayed for hormonal receptors show significantly higher levels of positive receptors and higher Allred scores than specimens

from subsequent MRM tissues in the same patients. The specific differences are great enough as to be clinically relevant to women with breast cancers. These results are challenging for clinicians working in low and middle income countries, in particular, because of the increased cost implications of approaching all patients with palpable masses with core biopsies and ensuring prompt and standardized fixation of tissue specimens in buffered formalin.

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Table 1

Distribution of hormone receptor, estrogen receptor and progesterone receptor positivity in core needle biopsy and modified radical mastectomy specimens from 160 patients with breast cancer (PGH, 2003–2008).

	CNB+	MRM+	p
HR (ER&/orPR)	160 (100%)	146 (91.2%)	
ER	152 (95.0%)	131 (81.9%)	<0.001
PR	150 (93.8%)	139 (86.9%)	0.035

HR = hormone receptor; ER = estrogen receptor; PR = progesterone receptor; CNB = core needle biopsy; MRM = modified radical mastectomy; PGH = Philippine General Hospital

Table 2

Hormone receptor, estrogen receptor and progesterone receptor agreement and disagreement between core needle biopsy and modified radical mastectomy specimens from 160 patients with breast cancer (PGH, 2003–2008).

	Agreement			Disagreement			p
	CNB+ & MRM+	CNB- & MRM-	Total	CNB+ & MRM-	CNB- & MRM+	Total	
HR (ER&/orPR)	146 (93.1%)	0		14 (8.8%)	0		
ER	127 (79.4%)	4 (2.5%)	131 (81.9%)	25 (15.6%)	4 (2.5%)	29 (18.1%)	0.016
PR	133 (83.1%)	4 (2.5%)	137 (85.6%)	17 (10.6%)	6 (3.8%)	23 (14.4%)	0.009

HR = hormone receptor; ER = estrogen receptor; PR = progesterone receptor; CNB = core needle biopsy; MRM = modified radical mastectomy; PGH = Philippine General Hospital

Table 3

Comparison of estrogen receptor Allred scores between core needle biopsy and modified radical mastectomy specimens from 160 patients with breast cancer (PGH, 2003–2008).

MRM ER Allred Score	CNB ER Allred Score								Total
	0	2	3	4	5	6	7	8	
0	4	0	0	3	4	6	6	6	29
2	0	0	0	0	0	0	0	0	0
3	0	0	0	3	2	0	3	5	13
4	1	0	0	1	1	2	4	8	17
5	0	0	1	1	4	2	4	13	25
6	1	0	0	1	0	4	9	14	29
7	0	0	2	0	0	2	5	19	28
8	2	0	1	0	0	3	2	11	19
Total	8	0	4	9	11	19	33	76	160

Note: Allred score is the sum of the proportion score and the intensity score. Proportion score is the percentage of positive-staining tumor cells (0 = none; 1 = <1/100; 2 = 1/100 to 1/10; 3 = 1/10 to 1/3; 4 = 1/3 to 2/3; 5 >2/3). The intensity score represents the average intensity of positive tumor cells (0 = none; 1 = weak; 2 = intermediate; 3 = strong).⁹

ER = estrogen receptor; CNB = core needle biopsy; MRM = modified radical mastectomy; PGH = Philippine General Hospital

Comparison of progesterone receptor Allred scores between core needle biopsy and modified radical mastectomy specimens from 160 patients with breast cancer (PGH, 2003–2008).

Table 4

MRM PR Allred Score	CNB PR Allred Score								Total
	0	2	3	4	5	6	7	8	
0	4	0	3	3	2	2	2	5	21
2	0	0	0	0	0	0	0	0	0
3	1	0	0	0	1	0	0	2	4
4	1	0	0	0	2	3	2	2	10
5	0	0	2	0	1	1	1	4	9
6	3	0	1	0	0	3	4	10	21
7	1	0	0	0	2	2	6	14	25
8	0	0	0	0	3	4	11	52	70
Total	10	0	6	3	11	15	26	89	160

Note: Allred score is the sum of the proportion score and the intensity score. Proportion score is the percentage of positive-staining tumor cells (0 = none; 1 = <1/100; 2 = 1/100 to 1/10; 3 = 1/10 to 1/3; 4 = 1/3 to 2/3; 5 >2/3). The intensity score represents the average intensity of positive tumor cells (0 = none; 1 = weak; 2 = intermediate; 3 = strong).⁹

PR = progesterone receptor; CNB = core needle biopsy; MRM = modified radical mastectomy; PGH = Philippine General Hospital