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Analysis of the concordance rates between core needle biopsy and surgical excision in patients with breast cancer

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*In memoriam

Summary

Objective: To evaluate whether immunohistochemical marker studies performed on core needle biopsy (CNB) specimens accurately reflect the marker status of the tumor obtained from final surgical specimen. **Methods:** This was a retrospective study that used the database of the Division of Mastology of the Hospital das Clínicas, São Paulo, Brazil. Sixty-nine patients submitted to ultrasound-guided CNB diagnosed with breast cancer were retrospectively analyzed. Immunohistochemistry (IHC) on core biopsy specimens was compared to that of excisional biopsy regarding estrogen receptor (ER), progesterone receptor (PR), human epidermal gowth factor receptor 2 gene (HER2), p53, and Ki67. The analysis of the concordance between CNB and surgical biopsy was performed using the kappa (k) coefficient (95% CI). **Results:** A perfect concordance between the labeling in the surgical specimens and the preoperative biopsies in p53 (k = 1.0; 95% CI: 0.76-1.0) was identified. There was an almost perfect concordance for ER (k = 0.89; 95% CI: 0.65-1.0) and a substantial concordance for PR (k = 0.70; 95% CI: 0.46-0.93). HER2 (k = 0.61; 95% CI: 0.38-0.84) and Ki-67 (k = 0.74; 95% CI: 0.58-0.98) obtained a substantial concordance this analysis. **Conclusion:** The results of this study indicate that the immunohistochemical analysis of ER, PR, Ki-67, and p53 from core biopsy specimens provided results that accurately reflect the marker status of the tumor. The concordance rate of HER2 was less consistent; although it produced substantial concordance, values were very close to moderate concordance.

Keywords: Breast neoplasms; core needle biopsy; hormone receptor; HER2/neu; Ki-67; immunoistochemical.

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Resumo

Análise das taxas de concordância entre a biópsia com agulha grossa e a excisão cirúrgica em pacientes com câncer de mama

Objetivo: Avaliar se a análise dos marcadores imunoistoquímicos obtidos por meio de espécimes de *core biopsy* (CB) refletem com precisão o perfil dos marcadores tumorais obtidos por biópsia cirúrgica excisional (BCE). **Métodos:** Estudo retrospectivo usando dados da Divisão de Mastologia do Hospital das Clínicas de São Paulo. Sessenta e nove pacientes submetidas à CB guiada por ultrassom com diagnóstico de câncer de mama foram analisadas retrospectivamente. O exame imunoistoquímico dos espécimes de CB foram comparados com aquele obtido a partir da BCE em relação ao receptor de estrogênio (RE), receptor de progesterona (RP), *human epidermal gowth factor receptor 2 gene* (HER2), p53 e Ki-67. A análise de concordância entre a CB e a BCE foram realizados usando o coeficiente de kappa (k) (IC 95%). **Resultados:** A concordância perfeita entre a BCE e a CB do p53 (k = 1,0; IC 95%: 0,76-1,0) foi identificada. A concordância foi quase perfeita para o RE (k = 0,89; IC 95%: 0,65-1,0) e concordância substancial foi identificada para o RP (= 0,70; IC 95%: 0,46-0,93). O HER2 (k = 0,61; IC 95%: 0,38-0,84) e Ki-67 (k = 0,74; IC 95%: 0,58-0,98) obtiveram uma concordância substancial nesta análise. **Conclusão:** os resultados deste estudo indicam que a análise imunoistoquímica do RE, RP, Ki-67 e p53 a partir dos espécimes de CB fornecem resultados que refletem com precisão o perfil dos marcadores do tumor. O HER2 foi menos consistente, porque apesar de ter produzido uma concordância substancial, os valores foram muito próximos da concordância moderada.

Unitermos: Neoplasia de mama; biópsia por agulha; receptor hormonal; HER2; Ki-67; HER2.

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INTRODUCTION

Breast cancer is a molecularly heterogeneous disease. Markers such as estrogen receptor (ER), progesterone receptor (PR), and human epidermal gowth factor receptor 2 gene (HER2) are used for prognostic evaluation and to stratify patients for appropriate target therapies. Core needle biopsy (CNB) specimens provides adequately sized samples permitting a histological diagnosis, allowing, for example, the differentiation between *in situ* and invasive carcinoma[1,2]. CNB samples can also be utilized in immunohistochemical (IHC) assays of hormone receptor and other prognostic tumor markers[3-14]. The ER, PR, HER2, and Ki-67 status of these samples provide valuable prognostic information and predict tumor response to neoadjuvant and adjuvant chemotherapy[7,15].

Estrogen and progesterone hormone receptor status tests are typically performed on all invasive breast cancers[10]. Patients who have ER-positive and PR-positive tumors tend to have a better prognosis for disease-free survival and overall survival than those with ER-negative or PR-negative tumors. They are also much more likely to respond to endocrine therapy. HER2 overexpression is associated with certain clinical outcomes, such as higher risk of recurrence and mortality, relative resistance to endocrine therapy, and apparent lesser benefit from certain chemotherapeutic regimens[16]. Ki-67 is a cancer antigen that is found in growing, dividing cells, but is absent in the resting phase of cell growth. This characteristic makes Ki-67 a good tumor marker. The researchers agreed that high levels of Ki-67 indicate an aggressive tumor and predict a poor prognosis[16].

In some breast cancer patients, especially those treated with preoperative chemotherapy or neoadjuvant endocrine therapy, the CNB specimen may be the only pretreatment tissue sample available for assays of prognostic and predictive markers[17]. In theory, cytotoxic chemotherapy may result in sufficient tumor regression to alter histological, hormonal, and proliferative markers[7,16]. Tumor ablation may completely modify the status of prognostic markers, and IHC analysis of ER, PR, HER2 expression, and Ki-67 index may be analogous to molecular analysis by microarray[18,19].

The diagnoses obtained from the pathologic examination of CNB and surgically excised specimens have been shown to be similar, with a sensitivity for non-palpable tumors controlled radiologically of 90% to 95% for the detection of breast cancer[20]. CNB specimens accurately sample a very small target without false-positive diagnosis[20,21].

Several previous studies have shown that, in general, the histologic features of carcinomas in core biopsy specimens accurately reflect those seen in subsequently excised tumors[6,20]. In one study, the nuclear grade and combined grade of the CNB samples agreed to the respective grade of the corresponding excised specimens in approximately 75% of patients[22]. In contrast, there have been few studies assessing the correlation between ER, PR, p53, HER2 staining, and Ki-67 index in preoperative CNB and final surgical specimens.

METHODS

This is a retrospective cross-sectional study that included CNB samples obtained before surgery and excised breast tumor specimens from 69 patients with breast cancer, not selected consecutively, in the Department of Mastology of the Hospital das Clínicas in São Paulo. Data were collected between May through October 2011. Tumor size was not used as a factor in selection of cases. The study protocol was approved by the ethics in research committee of the institution. None of the patients had received chemotherapy, radiotherapy, or hormone therapy between CNB and surgical excision. CNB samples were obtained under real time ultrasound guidance, using a linear transducer with a frequency of at least 7.5 MHz. The tissue samples were obtained using an automated biopsy gun with a 14-gauge needle (Bard Magnum – C.R. Bard, Covington, Ga) while monitoring the needle's passage within the lesion to assure adequate sampling.

Paraffin sections of the core biopsy specimens and corresponding resected tumors were incubated with antibodies to ER (clone 1D5, DAKO), PR receptor (clone PgR 636, DAKO), HER2 (polyclonal, DAKO), p53 (clone DO-7, DAKO), and Ki-67 (clone MIB1, Immunotech). Blots were developed using the streptavidin-biotin-peroxidase method for HER2 or the avidin-streptavidin-biotin peroxidase method for the other antibodies. Staining was estimated semiquantitatively, based on staining intensity and on the percentage of positive cells. ER and PR staining were considered positive when > 10% of the tumor cells showed distinct nuclear staining. For HER2, immunohistochemical staining scores of 0 and +1 were considered negative and scores of +3 were considered positive; scores of +2 were considered inconclusive, and these samples were excluded from analysis. The Ki-67 index measured the percentage of invasive cancer cell nuclei that were positive, with cut-offs for analysis of < 10%, 10-25%, 25-50%, and > 50%.

The concordance or discordance between core biopsy and surgical biopsy specimens was analyzed by determining the kappa coefficient (95% CI) using the kappa (k) test of concordance. Concordances of 0.21-0.40, 0.40-0.60, 0.60-0.80, 0.80-1.00, and 1.00 were defined as fair, moderate, substantial, almost perfect, and perfect, respectively[23].

RESULTS

Sixty-nine patients with a breast CNB diagnosed as carcinoma followed by surgical excision of the tumor were assessed. An average of five core samples per lesion (range: 3–8) was obtained, with each specimen consisting of core tissues suitable for standard histologic analysis. Mean patient age was 52 years (range: 30-76 years), and tumor size ranged from 10 to 80 mm. Of the 69 patients, 42 (60.8%) were diagnosed with invasive ductal carcinoma, eight (11.7%) with invasive ductal carcinoma and ductal carcinoma *in situ* (DCIS), 17 (24.7%) with invasive lobular carcinoma, one (1.4%) with intra-cystic papillary carcinoma, and one (1.4%) with primary squamous cell carcinoma of the breast.

The histologic types determined on core biopsy correlated with the types determined on surgical biopsy. When the concordance between the CNB and surgical biopsy specimens for ER, PR, Ki-67, p53, and HER2 was assayed, concordance was observed in specimens from 66 (95%), 60 (87%), 57 (82%), 69 (100%), and 54 (78%) patients, respectively. Using kappa statistics, the concordance between the preoperative biopsy and surgical specimens was perfect (k = 1.0) for p53, almost perfect for ER (k = 0.89), and substantial for Ki-67 index (k = 0.74), PR (k = 0.70), and HER2 (k = 0.61) (Table 1).

Discussion

Breast cancer is a heterogeneous disease, and gene expression studies have identified molecularly distinct subtypes with prognostic implications across multiple treatment settings. The IHC evaluation of ER, PR, Ki-67 index, and HER2 has been considered accurate in identifying molecular subtypes of breast cancer[19]. Four subtypes (luminal A, luminal B, HER2, and triple negative) have been found useful in defining different prognostic subgroups with different responses to adjuvant treatment[18,19]. Luminal A tumors are those with hormone-receptor-positive (either estrogen and/or progesterone-positive) and are HER2-negative; luminal B tumors are hormone-receptor-positive (either estrogen and/or progesterone-positive) and are HER2-positive; HER2 over-expressing tumors are hormone-receptor-negative and are HER2-positive; and triple-negative tumors are hormone-receptor-negative and are HER2-negative[18,19]. The use of neoadjuvant chemotherapy for locally advanced tumors has increased the importance of a correct preoperative evaluation of the proliferative activity and immunohistochemical markers of the tumor[7]. Pilot studies have shown that neoadjuvant treatment with trastuzumab combined with chemotherapy induces marked clinical and pathologic responses in patients with tumors overexpressing HER2[24]. In these patients, CNB samples are assayed to diagnose patients before the start of chemotherapy or monoclonal antibody treatment, since treatment may alter the tumor expression of biologic markers, such as ER, PR, Ki-67, p53, and HER2[25].

The concordance rates for CNB and surgically excised specimens have been found to range from 81.3% to 100% for ER, from 42% to 89% for PR, from 86% to 100% for p53, and from 86.9% to 100% for HER2[3-14]. In agreement with previous findings[8,21], concordances between CNB and surgical samples were observed for all of tumor markers. At least three core samples were needed for the reliable assessment of HER2 after adding chromogenic *in situ* hybridization (CISH), and more than three core samples were needed for PR, possibly due to tissue heterogeneity[8]. ER sensitivity was found to be lower (95%) even in multiple core samples, suggesting that when CNB samples are negative for ER, the surgical samples should be further assayed[8]. Interestingly, when CNB and surgical samples were discordant, the core biopsy samples consistently showed enhanced receptor stain intensity compared with the surgical specimens[26].

An IHC study of 56 patients reported concordance rates of 100% for HER2 and p53[6]. In two other studies, HER2 showed relatively higher concordance rates between core and resected samples when assayed by fluorescence *in situ* hybridization (FISH) in relation to IHC[4,14]. Similar to the present findings, the concordance rates were 95% for ER, 89% for PR and 86% for p53[14]. A study using FISH in 336 patients showed a concordance rate of 98.8% for HER2[12]. In another study, involving 353 patients, the concordance rates of ER and PR by IHC were 81.3% and 92.9%, respectively, and the concordance rate of HER2 by FISH was 89.3%[13]. A similar study in 100 patients reported IHC concordance rates of 95.8% for ER and 90.3% for PR, and a FISH concordance rate of 86.9% for HER2[10].

The concordance rate found in the present study was higher for ER than for PR, perhaps due to the relatively homogeneous distribution of ER throughout these tumors. The heterogeneity of ER expression in tumor cell populations may have implications for analytic cell selection and for prognosis in patients with ER-positive carcinomas[3].

Table 1 – Values of the concordance coefficient kappa for the analyzed immunohistochemical markers

Immunohistochemical marker	Concordance (kappa)*	95% CI	p
Estrogen receptor	0.89	(0.65-1.0)	< 0.001
Progesterone receptor	0.70	(0.46-0.93)	< 0.001
HER2	0.61	(0.38-0.84)	< 0.001
Ki-67	0.74	(0.58-0.89)	< 0.001
p53	1.0	(0.76-1.0)	< 0.001

*0.21-0.40 = fair; 0.41-0.60 = moderate; 0.61-0.80 = substantial; 0.81-1.00 = almost perfect; and 1.0 = perfect concordance.

The HER2 results of this study were less consistent. The relative discordance may be due to differences in methodology, because HER2 expression was analyzed by IHC, whereas other studies have analyzed HER2 expression by FISH. FISH assays of HER2 overexpression have been shown to be more sensitive than IHC assays[27].

The present results indicate that the dichotomously scored markers ER and PR can be accurately evaluated in core biopsy specimens. Previous studies have reported that, if core biopsy specimens are ER negative, surgical specimens should be analyzed. The HER2 status of a core biopsy specimen may be more reliable if assayed by FISH or CISH rather than by IHC.

Few studies have assayed differences in Ki-67 index between CNB and excisional biopsy specimens. In one study, the expression of ER, PR, HER2, p53 and Ki-67 correlated in core biopsy and surgically resected tumor samples from 25 patients receiving neoadjuvant chemotherapy, with no significant differences in expression patterns from a group of 30 patients who did not receive neoadjuvant chemotherapy[15]. An analysis of ER and PR status and Ki-67 score in CNB specimens before and after treatment with letrozole in 63 postmenopausal women with breast cancer showed that letrozole treatment decreases the expression of Ki-67 and PR[28].

This study has several potential limitations. First, it was retrospective in design, and therapy or lack of therapy was not determined on a randomized basis. Any discordance between CNB and surgically resected specimens may be due to various factors, including tumor sampling, technical preparation of the immunohistochemical stain, fixation time, or inter-observer variability. Another possible limitation was that HER2 status was analyzed by IHC, not by FISH or CISH, which are considered the standard methods for assessing HER2 status. In addition, patients with IHC HER2 +2 were excluded because of the lack of FISH or CISH results, which may have caused some selection bias. The discordance may also have been related to tumor size diversity of the selected patients, as well as the number of samples obtained by CNB.

Conclusions

These results indicate that immunohistochemical assays of ER, PR, and p53 in CNB samples accurately reflect the marker status of the tumor. The concordances for HER2 status were less consistent, suggesting that FISH or CISH assays of core biopsy specimens may be more specific in predicting prognosis and selecting treatment. The Ki-67 index results should be interpreted with caution to distinguish the luminal A and B breast cancer subtypes.

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Filomena Marino Carvalho MD, PhD.

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