

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 growth 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; immunohistochemical.

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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 growth 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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Submitted on: 05/27/2012
Approved on: 06/08/2012

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Conflict of interest: None.

INTRODUCTION

Breast cancer is a molecularly heterogeneous disease. Markers such as estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth 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 markers³⁻¹⁴. 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 cancers¹⁰. 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 regimens¹⁶. 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 prognosis¹⁶.

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 markers¹⁷. 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 cancer²⁰. 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 patients²². 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, respectively²³.

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

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