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Original contribution

A histomorphologic predictive model for axillary lymph node metastasis in preoperative breast cancer core needle biopsy according to intrinsic subtypes☆,☆☆

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Summary The aim of this study is construction of a pathologic nomogram that can predict axillary lymph node metastasis (LNM) for each intrinsic subtype of breast cancer with regard to histologic characteristics in breast core needle biopsy (CNB) for use in routine practice. A total of 534 CNBs with invasive ductal carcinoma classified into 5 intrinsic subtypes were enrolled. Eighteen clinicopathological characteristics and 8 molecular markers used in CNB were evaluated for construction of the best predictive model of LNM. In addition to conventional parameters including tumor multiplicity ($P < .001$), tumor size ($P < .001$), high histologic grade ($P = .035$), and lymphatic invasion ($P = .017$), micropapillary structure ($P < .001$), the presence of small cell–like crush artifact ($P = .001$), and overexpression of HER2 ($P = .090$) and p53 ($P = .087$) were proven to be independent predictive factors for LNM. A combination of 8 statistically independent parameters yielded the strongest predictive performance with an area under the curve of 0.760 for LNM. A combination of 6 independent variables, including tumor number, tumor size, histologic grade, lymphatic invasion, micropapillary structure, and small cell–like crush artifact produced the best predictive performance for LNM in luminal A intrinsic subtype (area under the curve, 0.791). Thus, adding these combinations of clinical and morphologic parameters in preoperative CNB is expected to enhance the accuracy of prediction of LNM in breast cancer, which might serve as another valuable tool in determining optimal surgical strategies for breast cancer patients.

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1. Introduction

The presence of axillary lymph node metastasis (LNM) is crucial in predicting clinical outcomes in breast cancer [1,2]. Although axillary lymph node dissection in patients with nodal metastasis is a standard procedure, it carries the risk of complications such as pain, loss of sensation, swelling, infection, impaired shoulder mobility, and lymphedema [3]. Although sentinel lymph node biopsy serves an optimal choice to selectively determine further axillary lymph node dissection, it has been reported to have a 5% false-negative rate in node-positive patients in breast cancer [4]. This false-negative rate increased when only 1 sentinel lymph node was removed, thereby arousing debates as to how many lymph nodes should be removed [5]. Therefore, if there were certain ancillary methods to predict LNM, it might be helpful in reducing the false-negative rate as well as aid in making more accurate surgical decisions. Several predictive models for LNM have been introduced, many of which are being widely accepted for planning optimal surgical intervention in breast cancer patients [6,7]. Nevertheless, a predictive model or a pathologic nomogram for preoperative biopsy specimens incorporating characteristic histomorphologic parameters has not yet been evaluated thus far.

Core needle biopsy (CNB) is an economic, valuable, and easily accessible preoperative diagnostic procedure used in daily practice. Although recent advances in diagnostic tools include molecular/genetic methods such as the next-generation sequencing, their application in daily diagnostic processes is extremely limited due to high costs.

In this study, we examined the utility of preoperative CNB not only as a diagnostic tool but also as a predictor of LNM in breast cancer patients. In addition to the distinct morphologic characteristics of micropapillary structures and retraction tissue artifact, which are already known morphologic parameters related with LNM [8], we also adopted the small cell–like crush artifact observed in biopsy samples and constructed a model with the best predictive performance for LNM with a combination of these morphologic and other clinicopathological parameters found significant in breast cancer.

2. Materials and methods

2.1. Case selection

Cases to be included in the study were selected from the pathologic archives of Seoul National University Hospital: we identified 5810 cases with CNB specimens over a 3-year period (January 2010 to December 2012). Among those patients, 534 cases fulfilling the following criteria were enrolled: (1) those who received axillary lymph node dissection (510 cases, 95.5% underwent sentinel lymph node biopsy) in subsequent surgical excision allowing evaluation of cancer metastasis; (2) those with the final diagnosis of invasive ductal carcinoma; (3) CNB samples with at least 4 well-preserved cores; and (4) cases that had been grouped into intrinsic subtypes with immunostains. Patients who received neoadjuvant chemotherapy after undergoing CNB were excluded for precise evaluation of LNM. All the cases in the study underwent surgical excision. Thus, although we were able to guess each cancer to be either a solitary nodule or having multiple nodules through imaging studies before surgery, their solitary/multiplicity status was confirmed and changed according to the postoperative pathologic evaluations.

Biopsy was performed using either an 11- or 14-gauge automated needle–assisted or with an 8- or 10-gauge vacuum–assisted device. All specimens fixed in 10% buffered formalin were paraffin embedded and hematoxylin and eosin (H&E) stained. To improve the accuracy of the results, 2 pathologists (S. H. Y. and H. S. R.) who were blinded to the clinical details of the patients reviewed histomorphologic findings. The patients' clinicopathological information was obtained from the patient database. This study was approved by the Institutional Review Board of Seoul National University Hospital.

2.2. Histomorphologic evaluations

The following histologic factors were evaluated: micropapillary structure, retraction tissue artifact, small cell–like crush artifact of tumor cells, cribriform architecture, solid sheet growth showing syncytial arrangements of tumor cells with no tubule formation, spindling or multinucleated giant cells, presence of extracellular mucin, intratumoral calcification, tumor necrosis, loose myxoid fibrous stroma found in early phases of fibroadenoma, lymphatic invasion, neural invasion, and ductal carcinoma in situ (DCIS) component. Histologic grading was categorized into 1 to 3 based on Nottingham combined histologic grading system described by Elston and Ellis [9].

Micropapillary structure was defined as a nest of tumor cells forming discrete tubular or solid structures floating in the middle of an empty space (detached from the stroma) with or without immunohistochemical positivity for epithelial membrane antigen [10,11] (Fig. 1A and D). The presence of micropapillary structure was defined when more than 50% of the structure was identified in the entire core.

Retraction tissue artifact was defined as the narrow cleft between the tumor glands and the surrounding stroma [12,13] (Fig. 1B and E). A tumor was considered to have a retraction tissue artifact when such histomorphologic finding occupied greater than or equal to 30% of the entire core biopsied.

Small cell–like crush artifact was defined as infiltrative tumor cells with small-sized hyperchromatic nuclei and scanty cytoplasm resulting in a high nuclear/cytoplasmic ratio and crush artifact [14]. The tumor cells were distributed as either infiltrative cells showing streaming pattern or conglomerated clusters without tubule formation accompanied by severe crush artifact (Fig. 1C and F). Such small