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Original contribution

p53 expression in tumor-stromal fibroblasts is closely associated with the nodal metastasis and outcome of patients with invasive ductal carcinoma who received neoadjuvant therapy☆

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Summary The purpose of this study was to determine whether p53 immunoreactivity in tumor-stromal fibroblasts assessed by the Allred scoring system in biopsy specimens obtained before neoadjuvant therapy and assessed in surgical specimens obtained after neoadjuvant therapy is significantly associated with nodal metastasis by invasive ductal carcinoma and with the outcome of 318 patients with invasive ductal carcinoma who received neoadjuvant therapy, according to UICC pathologic TNM stage, in multivariate analyses with well-known clinicopathologic factors. The Allred scores for p53 in tumor-stromal fibroblasts in the surgical specimens were significantly associated with the presence of nodal metastasis. The Allred scores for p53 in the tumor-stromal fibroblasts of biopsy and surgical specimens were a very important outcome predictive factor for patients who received neoadjuvant therapy, independent of UICC pathologic TNM status, but the outcome predictive power of the Allred scores for p53 in tumor-stromal fibroblasts assessed in the surgical specimens was superior to that of the Allred scores for p53 in tumor-stromal fibroblasts in the biopsy specimens. The results indicated a close association between p53 protein expression in tumor-stromal fibroblasts, especially in surgical

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specimens, and both the presence of nodal metastasis and the outcome of invasive ductal carcinoma patients who received neoadjuvant therapy.

1. Introduction

It has recently been reported that the gene expression profile and protein expression profile of the tumor stroma play a very important role in tumor progression in carcinoma [1-3] and that the interaction between tumor cells and stromal cells also plays a very important role in tumor progression by carcinoma [4,5]. We have already reported that the proliferative activity of tumor-stromal fibroblasts plays a very important role in nodal metastasis and distant organ metastasis by invasive ductal carcinoma (IDC) of the breast [6,7]. Recently, a high frequency of p53 mutations in tumor cells and the surrounding stroma has also been reported [8], and p53 mutations in breast cancer stromal cells have been reported to be closely associated with nodal metastasis [9]. These findings strongly suggest a significant role of the tumor stroma in tumor progression by IDC, and the p53 status of tumor-stromal fibroblasts may play a very important role in tumor progression by IDC.

The purpose of the present study was to determine whether p53 protein expression in tumor-stromal fibroblasts assessed in biopsy specimens obtained before neoadjuvant therapy and surgical specimens obtained after neoadjuvant therapy is significantly associated with the presence of nodal metastasis by IDC, and significantly associated with the outcome of IDC patients who received neoadjuvant therapy, according to the UICC (International Union Against Cancer) pathologic TNM (pTNM) stage. The results indicated that p53 protein expressions in tumor-stromal fibroblasts in both the biopsy specimens and the surgical specimens were closely associated with the presence of nodal metastasis and the outcome of IDC patients who received neoadjuvant therapy.

2. Materials and methods

2.1. Cases

The subjects of this study were 318 consecutive patients with IDC of the breast and who received neoadjuvant therapy before surgery at the National Cancer Center Hospital between January 2000 and December 2005. The IDCs were diagnosed preoperatively by needle biopsy, aspiration cytology, mammography, or ultrasonography. Clinical information was obtained from the patients' medical records after complete histologic examination of all IDCs. All patients were Japanese women, and they ranged in age from 26 to 75 years (median, 54 years). All had a solitary lesion; 127 patients were premenopausal and 191 were postmenopausal. Partial mastectomy had been performed in 152 and modified radical mastectomy in 166. Level I and level II axillary lymph node dissection had been performed in all patients, and level III axillary lymph node dissection had been performed in some of patients with IDC.

Of the 318 patients, 37 (12%) achieved a pathologic complete response (34, no residual tumor; 3, only residual ductal carcinoma in situ; they have no nodal metastasis) to neoadjuvant therapy.

The neoadjuvant therapy consisted of chemotherapy in 235 patients, endocrine therapy in 43 patients, and chemoendocrine therapy in 3 patients; and 214 of 281 patients received adjuvant therapy, which consisted of chemotherapy in 47 patients, endocrine therapy in 116 patients, and chemoendocrine therapy in 51 patients. The chemotherapy regimens used were anthracycline-based with or without taxane and non–anthracycline-based, and the endocrine therapy regimens consisted of tamoxifen with or without a gonadotropin-releasing-hormone agonist, tamoxifen with or without an aromatase inhibitor, an aromatase inhibitor alone, or a gonadotropin-releasing-hormone agonist alone. There were no cases of inflammatory breast cancer in this series. All tumors were classified according to the UICC pTNM classification.

For the pathologic examination, biopsy specimens obtained before neoadjuvant therapy and surgically resected specimens obtained after neoadjuvant therapy were fixed in 10% formalin and subsequently examined. The size and gross appearance of the surgically resected tumor specimens were recorded as the residual invasive tumor size. The tumor size of the surgically resected specimens was confirmed by comparison with the tumor size on histologic slides; if more than one invasive focus was present, the size of the largest invasive focus was recorded as the residual invasive tumor size in this study.

2.2. Histologic examination

Serial sections of the biopsy specimens obtained before neoadjuvant chemotherapy and of the tumor area in the surgically resected specimens obtained after neoadjuvant therapy were cut from paraffin-wax blocks. One section of each biopsy specimen and surgical specimen was stained with hematoxylin and eosin and examined histologically to confirm the diagnosis, and another section was subjected to immunohistochemistry. The following 9 histologic features of the primary invasive tumors were evaluated in the biopsy specimens obtained before neoadjuvant therapy and the surgical specimens obtained after neoadjuvant therapy: (1) residual tumor size (no residual tumor or residual ductal