Fibrotic focus in infiltrating ductal carcinoma of the breast: A significant histopathological prognostic parameter for predicting the long-term survival of the patients

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Summary

The presence of fibrotic foci (FF) in infiltrating ductal carcinoma (IDC) has been shown to be an important histological factor associated with high tumor aggressiveness, or early tumor recurrence or death. However, the clinicopathological significance of FF for predicting the long-term survival of the patients with IDC has not been fully investigated. In order to elucidate this aspect, we divided 140 IDCs with at least 10 years of follow up into tumors with FF and those without. IDC with FF showed significantly higher histologic grade (P = 0.02), higher frequency of tumor necrosis (P = 0.02), higher frequency of cases with more than three positive lymph node metastases (P = 0.04), higher T classification (P = 0.009), and higher pathological stage (P = 0.0002) than those without FF. Relative risk (RR) of tumor recurrence and death was significantly higher in tumors with FF than in those without (RR = 4.5, P < 0.00001 and RR = 5.6, P < 0.00001, respectively). In cases of early stage cancer (stages I, IIA, and IIB), or in those with less than four lymph node metastases, IDCs with FF demonstrated a significantly higher risk than those without. Multivariate adjustments for other pathological factors did not change the RRs significantly. These results indicate that in long-term follow up the presence of FF is a significant prognostic parameter for IDC, and therefore strongly suggest that IDCs must be divided into those with and without FF.

Introduction

It is known that the number of lymph node metastases and tumor stage are the most important clinical factors determining the outcome of breast cancer. Histologically, it has been shown that histologic grade of tumor, tumor size, and the presence of tumor necrosis are also significant prognostic parameters for breast cancer patients [1-9]. In addition, recent developments in immunohistochemistry, DNA ploidy analysis, and molecular genetics have made it possible to predict the outcome of breast cancer more precisely [10-21]. However, in routine practice it is difficult to incorporate these methodologies in all cases. If certain histological parameters accurately predict the outcome of the
patients with breast cancer, they are more practical for routine use.

We have already reported that infiltrating ductal carcinomas (IDC) with fibrotic focus (FF) have higher histologic grade, higher frequency of lymph node metastasis and erbB-2 protein expression, and higher proliferative activity than those without FF [22], and that the former showed significantly shorter disease-free survival period than the latter within three years after the initial operation [23]. However, it has not been studied whether the presence of FF in IDC has a prognostic significance for the long-term survival. Therefore, in this study, we examined whether FF is associated with poor prognosis of IDC in the long-term follow-up.

Materials and methods

Cases

One hundred forty consecutive cases of IDC, which had been treated surgically at the National Cancer Center Hospital between January 1982 and February 1984, were examined. Clinical information was obtained from the patients' medical records. All the patients were Japanese women ranging in age from 21 to 72 yr (average age, 46 yr) and all had solitary lesions. Sixty-two patients were premenopausal and 38 post-menopausal. Menopausal status was unknown in 15 cases. Estrogen receptor (ER) assay was performed on 89 of the 140 tumors by enzyme immunoassay (EIA) method using fresh frozen tissues in the Otsuka Assay Laboratories. ER positivity was observed in 55 tumors and the remaining 34 tumors were negative. Standard radical mastectomy was performed in 123 of the cases, modified radical mastectomy in eight, and extended radical mastectomy in nine. Axillary lymph node dissection was done in 138 cases. None of the patients received radiotherapy or chemotherapy before surgery. After surgery, 93 patients were treated with single-agent chemotherapy using cyclophosphamide (CPA) \((n = 31)\) or vincristine \((n = 1)\), or with combination chemotherapy using two to four agents as follows: 1) CPA + adriamycin (ADM) + mitomycin C (MMC) + 5 fluorouracil (5FU) \((n = 27)\), 2) CPA + MMC + 5FU \((n = 11)\), 3) CPA + I UFT (combination of tegafur and uracil) \((n = 10)\), 4) CPA + 5FU \((n = 8)\), 5) MMC + UFT \((n = 2)\), 6) ADM + CPA \((n = 1)\) or 7) CPA + tamoxifen \((n = 1)\). Chemotherapy was given to patients at advanced stages IIB and IIIB \((n = 24)\), and those with lymph node metastases \((n = 62)\), respectively. Radiotherapy was performed in only one case and antistrogen therapy was performed in three cases. All cases were classified according to the pathological TNM (PTNM) classification [24]. The presence of lymph node metastasis was examined microscopically and divided into three groups according to the number of metastasis-positive lymph nodes, i.e., no metastasis, metastasis in one to three lymph nodes, and metastasis in four or more lymph nodes. When metastases to the ipsilateral axillary lymph nodes were fixed to one another or to other structures, or if metastasis to ipsilateral parasternal mammary lymph nodes was present, the nodal status was classified as pN2 and pN3, respectively.

Histological examination of tumors

Surgically resected tissue specimens were fixed in 20% formalin overnight at room temperature and each entire tumor was cut into slices at intervals of about 0.5 to 0.7 cm. The size and gross appearance of the cancer were recorded, and the tumor was validated by comparison with the tumor size on histologic slides. Multiple histological sections were taken from each tumor in order to measure the maximum tumor diameter and area. The sections were processed routinely and embedded in paraffin. Serial sections of each tumor were cut from the paraffin blocks. One section was stained with hematoxylin and cosin and examined pathologically to confirm the diagnosis and to evaluate histological parameters. All the tumors were classified according to the guidelines of the World Health Organization [25], and their histologic grade was assigned using the classification of Elston [26], which is a modification of the Bloom and Richardson classification [27].