Impact of Multicentricity on Clinical Outcome in Patients With T1–2, N0–1, M0 Breast Cancer

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Background: The objective was to determine the impact of multicentric breast cancer on recurrence and survival and to evaluate the current tumor, node, metastasis staging system recommendations for multicentricity in the breast.

Methods: This study included 284 nonpregnant patients with T1–2, N0–1, M0 breast cancer, without previous cancer, who were treated by modified radical mastectomy followed by doxorubicin-based adjuvant chemotherapy. Clinical and pathological data were collected retrospectively and survival was calculated from the date of initial diagnosis using the Kaplan-Meier method.

Results: The median follow-up time was 8 years (range, 0.3–24.0), and the median age was 47 years (range, 23–76). The median clinical size of the index tumor was 2.5 cm. In 17% of patients, the clinical nodal status was N1. In 84% of patients, pathology of the index lesion was invasive ductal in situ. Multicentric breast cancer was detected in 60 patients (21%): 30 patients with two lesions, 13 patients with three lesions, and 17 patients with four or more lesions. Locoregional recurrence, contralateral breast cancer, distant metastasis, and survival (disease-specific and disease-free) were similar in both groups of multicentric versus unicentric breast tumors. There was a significant difference between groups in estrogen receptor and axillary lymph node positivity, but these did not contribute significantly to outcome on multivariate analysis.

Conclusions: Multicentricity does not increase the risk of poor outcomes in patients with early-stage breast cancer. This supports the current recommendations of the tumor, node, metastasis staging system that tumor size should be based on the diameter of the largest lesion in patients with multicentric breast cancer.

Key Words: Breast neoplasms—Multicentric—Multiple primary—Local recurrence—Survival.
a correlated clinical, radiographic, and pathologic study of whole-organ breasts. This approach consists of freezing the breast, slicing in serial sections, radiography of the sections, and microscopic analysis of suspicious areas identified on the radiographs.

There are conflicting reports about the influence of multicentricity on patient outcome. At issue is whether the presence of multicentricity is indicative of a more aggressive type of cancer, with a likelihood of increased rates of recurrence and higher mortality. Using whole-organ sectioning, Egan examined outcomes at a median follow-up time of 10 years in 118 patients with primary breast carcinomas, 72 of whom were found to have multicentric tumors. He found that in patients with stage II carcinoma, unincentric tumors had a mortality rate of 27%, compared with a mortality rate of 65% in multicentric tumors. Fowble et al. examined recurrence and survival in 57 patients with MBC treated with modified radical mastectomy compared with 1295 patients with unicentric stage I-II breast cancer treated with conservative surgery and radiation during the same time period. In contrast to the findings of Egan, they found no difference in overall survival, recurrence-free survival, local-regional recurrence, distant metastases, or contralateral breast cancer, at a median follow-up time of 4 years.

In the tumor, node, metastasis (TNM) staging system, as currently defined by the American Joint Committee on Cancer and the Union Internationale Contre le Cancer (AJCC/UICC), only the largest tumor, rather than a combination of all tumors synchronously present in the breast, is used to classify tumor size (T) in cases of multicentric cancer. In addition, multicentricity is not listed as a prognostic parameter for human breast carcinoma in the AJCC/UICC system. It is recommended, however, that multicentric cases be analyzed separately.

The purpose of this study was to examine the impact of MBC on locoregional recurrence, contralateral breast cancer, distant metastasis, and survival in patients with T1-2, N0-1, M0 breast cancer treated with modified radical mastectomy with adjuvant therapy. The findings were used to reevaluate the current recommendations about MBC in the TNM staging system.

PATIENTS AND METHODS

Patient Selection

From 1974 through 1993, 1651 patients were treated at The University of Texas M. D. Anderson Cancer Center on adjuvant chemoendocrine protocols. This study involved a subset of 284 patients with T1-2, N0-1, M0 breast cancer (AJCC/UICC classification). The subset consisted of nonpregnant women, without previous cancer, who have been treated in our institution by modified radical mastectomy followed by adjuvant therapy.

Patients were excluded from this study for the following reasons: outside surgery (n = 869), breast conservation (n = 146), advanced disease (n = 139), multifocality (n = 12), previous breast (n = 4) or other cancer (n = 91), bilateral breast cancer at diagnosis (n = 4), preoperative treatment (n = 14), other reasons (male gender, pregnancy) (n = 19), and information not available or incomplete (n = 69).

Chemotherapy Protocol

After surgery, all patients received adjuvant treatment according to one of four protocols. Before entering the protocol, written informed consent detailing the investigational nature of the protocol was obtained from each patient, according to the policies of our institution. In all of these protocols, drug regimens with the combination of fluorouracil, doxorubicin, and cyclophosphamide (FAC) were evaluated. Treatment dosage and schedules are described in Table 1.

In the first study, all patients received a regimen of FAC. The total accumulated dose of doxorubicin was limited to 300 mg/m²; after the dose was reached, all patients were continued on a maintenance regimen of cyclophosphamide, methotrexate, and 5-fluorouracil. Chemotherapy was continued for 2 years. Nonspecific immunotherapy with Bacillus Calmette-Guérin (BCG) was received by all patients. Most had postoperative radiation therapy.

In the second study, all patients received FAC alone or FAC + BCG, and in the latter part of the study, patients who had not undergone irradiation previously were randomized for postoperative radiation therapy.

In the third study, vincristine and prednisone were added to FAC. The total dose of doxorubicin was 400 mg/m² for each patient. After completion of adjuvant chemotherapy, all patients with estrogen-positive (or unknown) status were randomized to receive either tamoxifen alone or tamoxifen associated with additional chemotherapy with methotrexate and vinblastine for 6 months. All estrogen-receptor-negative patients received additional chemotherapy with methotrexate and vinblastine. The total duration of the therapy was 1 year.

In the fourth study, all patients were treated with escalating doses of doxorubicin (as a continuous infusion over 72 hours) and cyclophosphamide. Estrogen-receptor-positive patients received tamoxifen for 1 year. After chemotherapy, patients who were randomized to immunotherapy received human leukocyte interferon for 1 year.