Determinants of Prognosis in Breast Cancer Patients with Tumor Involvement of the Skin (pT4b)

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Abstract: Determinants of prognosis were studied in patients with breast cancer with histologically proven tumor extension to the skin without clinical evidence of distant metastases (i.e., pT4b N0–3 M0). Data were collected retrospectively on 77 consecutive patients diagnosed in one community teaching hospital over the period from 1980 to 1995. The prognostic factor of tumor size showed a 5-year survival rate for patients with a tumor ≤ 3 cm of 81% compared to 45% for patients with tumors larger than 3 cm (p = 0.002). Achievement of complete remission resulted in a 5-year survival rate of 66%, compared to 27% when complete remission was not achieved (p = 0.005). Another important prognostic factor was the development of local-regional recurrence: the 5-year survival rates for patients with and without local-regional recurrence were 39% and 87%, respectively (p < 0.001). Development of local-regional recurrence was also significantly related to tumor size (p = 0.02). Pathologic tumor size and the achievement of complete remission and local-regional control appear to be the most important prognostic factors for survival in patients with pT4b breast cancer without distant metastases. We conclude that the finding of a pT4b breast cancer does not always imply a dismal prognosis, especially for those patients with a tumor ≤ 3 cm. A favorable prognosis can be expected when treatment is effective in achieving complete remission and in preventing the development of local-regional recurrence.

Key Words: breast neoplasms, prognosis, recurrence, remission induction, skin

The term locally advanced breast cancer encompasses a heterogeneous group of cancers, including T3–4 N0–3 M0 breast cancers, according to the Union Internationale Contre le Cancer (UICC) tumor-node-metastasis (TNM) classification system of malignant tumors (1). Patients with locally advanced breast tumors account for 5–10% of all cases of breast cancer in economically developed countries (2). Common aspects of locally advanced breast cancers include the often large local-regional tumor burden and the poor 5-year survival rate. Systematic evaluations of patients with locally advanced breast cancer and well-conducted randomized trials of therapeutic interventions are still rare. Reported prognostic factors for locally advanced breast cancer are primary tumor size, axillary lymph node status, age at diagnosis, and estrogen receptor (ER) status (3–9).

A specific group of patients with locally advanced breast cancer are those with tumor extension to the skin (i.e., T4b breast cancers). Between 1980 and 1995 we treated 107 breast cancer patients with histologically proven tumor extension to the skin in our community teaching hospital. This treatment did not contain preoperative systemic treatment. Since literature on pT4b breast carcinoma is rare, it was decided to investigate the prognosis and prognostic factors in this subgroup.

METHODS

Patients

Data on all consecutive patients diagnosed at the Sint Joseph Hospital Veldhoven between 1980 and 1995 with a pT4b stage breast cancer were analyzed retrospectively. Patients were identified by the population-based Eindhoven Cancer Registry, which has collected data on new cancer patients since 1955 according to international guidelines (10). According to the TNM classification system, T4b is defined as tumor involvement of the skin,
including edema (peau d’orange), ulceration, or satellite skin nodules confined to the same breast (1). In our series, we only included patients in whom skin involvement was confirmed by histologic examination. During the study period, patients with pT4b breast cancer were considered as incurable, and in the treatment guidelines a multidisciplinary approach was recommended in which preoperative chemotherapy had not yet been included.

During the period from 1980 to 1995, 107 patients were diagnosed with pT4b breast cancer. In 30 patients, distant metastases were already present at the time of diagnosis. After exclusion of these patients, 77 remained available for analysis. Data on diagnosis, stage of disease, and treatment of these patients were retrieved from the Eindhoven Cancer Registry database and patient hospital records, also including pathology reports and correspondence from the regional radiotherapy institute. Radiologic or clinical tumor size was used in case of missing information on pathologic tumor size. For patients with missing information on ER and progesterone receptor (PR) status, review of the tumor slides that had been stored at the Regional Institute of Pathology was performed. Data on clinically relevant concomitant diseases were registered according to a modified version of the list of Charlson et al. (11). This included cardiovascular diseases, respiratory diseases, diabetes mellitus, hypertension requiring medical treatment, renal failure, and obesity.

### Statistical Analysis

Survival analysis was carried out using the life table method to evaluate prognosis after treatment (12). The primary endpoint was overall survival. Survival curves were calculated from the date of diagnosis of the primary tumor. The following variables were analyzed to assess their ability to predict overall survival: age at diagnosis, size of the tumor, pathologic axillary nodal status, histologic tumor type, ER and PR status, the presence of comorbidity, the achievement of local-regional control, and complete remission after treatment. Actuarial survival curves were compared by means of the two-tailed log rank test. Separate analyses were performed after exclusion of the patients without complete remission. Because of the small number of patients, multivariate analyses were not performed.

### RESULTS

The median age of the 77 patients at the time of primary diagnosis of breast cancer was 68 years (range 40–93 years). In 28 patients (36%) the size of the tumor was ≤3 cm. Tumor size was missing for one patient. Ductal carcinomas tended to be smaller than lobular or mixed carcinomas: ≤3 cm, 40% versus 18% (p = 0.17). Other tumor characteristics and information on the presence of comorbidity are presented in Table 1.

### Treatment and Achievement of Complete Remission

Surgical treatment consisted of local excision in 10 patients (13%) and mastectomy in 62 patients (81%) (Table 2). Axillary dissection was performed in 55 patients (71%). Five patients underwent only a diagnostic incisional biopsy without any further surgery. Of all patients, 55 (71%) received radiotherapy and 59 (77%) received some form of adjuvant systemic treatment. Patients less than 50 years of age were more likely to undergo breast-conserving surgery (p = 0.02) and to receive chemotherapy (p < 0.0001), whereas patients ≥50 years of age were more likely to receive endocrine treatment (p = 0.005). Patients with tumors ≤3 cm were less likely to receive chemotherapy or endocrine treatment than patients with larger tumors (64% versus 85%; p = 0.03). No significant association was found between comorbidity and the decision for the different types of
surgery, radiotherapy, chemotherapy, or endocrine treatment. Complete remission of disease was obtained in 66 of the 77 patients (86%) (Table 3).

**Follow-up and Prognostic Factors**

The median length of follow-up after treatment was 3.9 years (range 0.3–16.3 years) for the entire group and 5.4 years for the patients who were still alive. Of the 77 patients with pT4b breast cancer, 42 had died (55%). The 5-year survival for the entire group of patients with pT4b breast cancer was 60% (95% confidence interval [CI] 48–72).

The results of univariate analysis of prognostic variables for survival are shown in Table 4. Significant prognostic factors were size of the tumor (p = 0.002), achievement of complete remission (p = 0.005), and development of local-regional recurrence (p < 0.001). The 5-year survival rate for patients with a tumor ≤3 cm was 81% (95% CI 65–97), compared to 45% (95% CI 29–61) for those with a tumor larger than 3 cm (p = 0.002) (Fig. 1). Of the 11 patients without a complete remission, 10 had died. Age at diagnosis, presence of comorbidity, histologic type, pathologic lymph node status, and ER and PR status were not significant prognostic factors (Table 4). However, a prognostic effect of the pathologic lymph node status was present up to 8 years after diagnosis (Fig. 2). A separate analysis, excluding the patients without complete remission, did not substantially alter the results, except for the effect of histologic type. Patients with a lobular or mixed carcinoma had a significantly poorer

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**Table 2. Treatment of 77 Patients with pT4b Breast Cancer without Clinical Evidence of Distant Disease Diagnosed in the Period from 1980 to 1995**

| Characteristic                          | n  | Percent |
|-----------------------------------------|----|---------|
| Primary surgical treatment              |    |         |
| Local excision without axillary dissection | 4  | 5       |
| Local excision and axillary dissection  | 6  | 8       |
| Mastectomy without axillary dissection  | 13 | 17      |
| Mastectomy and axillary dissection      | 49 | 63      |
| Incisional biopsy                       | 5  | 6       |
| Radiotherapy                            |    |         |
| Yes                                     | 55 | 71      |
| No                                      | 22 | 29      |
| Adjuvant systemic treatment             |    |         |
| Chemotherapy                            | 6  | 8       |
| Hormonal therapy                        | 46 | 60      |
| Chemotherapy and hormonal therapy       | 7  | 9       |
| None                                    | 18 | 23      |

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**Table 3. Treatment of 77 Patients with pT4b Breast Cancer and Achievement of Complete Remission**

| Treatment     | n  | Percent | Yes | No |
|---------------|----|---------|-----|----|
| LE + RT       | 6  | 8       | 5   | 1  |
| LEa           | 4  | 5       | 2   | 2  |
| MAS + RT      | 47 | 61      | 46  | 1  |
| MASa          | 15 | 19      | 12  | 3  |
| RT + ST       | 2  | 3       | 1   | 1  |
| ST only       | 2  | 3       | 0   | 2  |
| No treatment  | 1  | 1       | 0   | 1  |
| Total         | 77 | 100     | 66  | 11 |

LE, local excision; MAS, mastectomy; RT, radiotherapy; ST, adjuvant systemic treatment (hormonal therapy or chemotherapy).
aWith or without adjuvant systemic treatment and with or without axillary dissection.

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**Figure 1.** Overall survival of 76 patients with pT4b pN0–3 M0 breast cancer according to tumor size.

**Figure 2.** Overall survival of 55 patients after surgical treatment of pT4b pN0–3 M0 breast cancer, including axillary lymph node dissection, according to pathologic lymph node status.
survival rate compared to those with ductal carcinoma (p = 0.01).

A local-regional recurrence occurred in 26 of the 66 patients (39%) in whom complete remission was achieved. The 5-year survival rate for these patients was 39% (95% CI 19–59), compared to 87% (95% CI 75–99) for those who did not develop local-regional recurrence (Fig. 3). The risk of local-regional recurrence was associated with the size of the tumor; of the patients with a tumor ≤3 cm, 21% developed local-regional recurrence, while this was 51% for those with a tumor larger than 3 cm (p = 0.02).

**DISCUSSION**

Our study of patients with pT4b tumors without clinical evidence for distant metastases shows that the prognosis

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of this group is not dismal. A direct comparison of our results with other studies remains difficult because of the heterogeneity of these study groups, which include other types of locally advanced breast cancer (i.e., pT3 pN2–3, pT4a, pT4c, or pT4d breast tumors). According to our data, the most important prognostic factor at diagnosis was tumor size. Zucali and Kenda (3) reported tumor size to be a prognostic factor for the entire group of patients with T4 breast cancer, including T4a, T4c, and T4d tumors. In their study, patients with tumors smaller than 3 cm had a 5-year survival of 70%, compared to 35% for those with a tumor larger than 3 cm. In a study of 277 patients with locally advanced breast cancer, Valagussa et al. found that those with a tumor ≤5 cm had a 5-year survival rate of about 65%, compared to 35% for those with a tumor larger than 5 cm; the survival rate was only 17% when positive axillary lymph nodes were present (4,5). In our series, we could confirm that nodal status was of prognostic value, at least during the first 8 years of follow-up. We also found that patients with lobular carcinoma had a poorer survival rate than those with ductal carcinoma. However, this difference only appeared after the exclusion of the patients without complete remission, and might be explained by the somewhat larger size of the lobular carcinomas.

The fact that there were no specific guidelines for the treatment of patients with locally advanced breast cancer in our region during the study period will certainly explain the multitude of treatment modalities and combinations. Of interest is that treatment choice appeared to be much more dependent on age than on the presence of comorbidity. The use of systemic treatment seemed to be in accordance with the guidelines for patients without locally advanced breast cancer, recommending chemotherapy for premenopausal women and hormonal therapy for postmenopausal patients (13). As most of the patients in our study were elderly and postmenopausal, this would explain why endocrine treatment was preferred to chemotherapy.

The main purpose of the treatment of pT4b breast cancers is to prevent the development of local-regional recurrence. The treatment in our series, which did not contain preoperative chemotherapy, was not effective in obtaining local-regional control (i.e., 39% of the patients developed local-regional recurrence after complete remission). In the literature, much better local-regional control rates have been described after preoperative chemotherapy followed by local-regional treatment (surgery and/or radiotherapy) and hormonal treatment for patients with receptor-positive tumors (14–20). But again, direct comparisons are difficult to make because of the heterogeneity of these study groups. For example, Piccart et al. (16) achieved only 23.5% local-regional recurrence 6 years after treatment of patients with locally advanced breast cancer, including preoperative chemotherapy and radiotherapy, followed by surgery and adjuvant endocrine therapy, and Touboul et al. (20) reported a 10-year actuarial local-regional failure rate of 20% when preoperative chemotherapy was followed by radiotherapy alone, 23% when it was followed by wide excision, and 6% when followed by mastectomy. Since we proved the risk of local-regional recurrence is dependent on the size of the primary tumor, preoperative chemotherapy should be seriously considered for pre- and postmenopausal patients with pT4b tumors larger than 3 cm. Although randomized trials have failed to show an improvement in survival after treatment with preoperative chemotherapy, it will improve the resectability and local-regional control of the tumor and might therefore have a positive effect on the quality of life.

We conclude that the finding of a pT4b breast cancer does not always imply a dismal prognosis, especially for those patients with a tumor ≤3 cm. A favorable prognosis can be expected when treatment is effective in achieving complete remission and in preventing the development of local-regional recurrence.

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