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PROGNOSTIC SIGNIFICANCE OF LYMPH NODE STATUS IN STAGE III BREAST CANCER

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Abstract

Case histories of 103 patients with locally advanced (stage III) breast cancer have been reviewed. Ninety of the patients were judged operable. The median follow-up time was 52 months. The 5-year survival rate for the whole group was 54%. The 5-year relapse-free survival rates for the pN0, pN1 and pN2–3 were 91, 50 and 19% respectively and the 5-year survival rates for the groups were 86, 53 and 30% respectively. These results underline the heterogeneity and the very different prognoses for the different subgroups in stage III breast cancer patients. A reevaluation of the staging system is therefore suggested.

Key words: Breast cancer, stage III, axillary nodal status, prognosis.

Breast cancer patients show very great variations concerning clinical manifestations and course of the disease. Adequate staging is of great importance for estimation of prognosis as well as choice of initial therapy (4). It is also important for allocation of patients to different therapeutic trials and for comparison of trial results.

According to the international TNM classification system (24) patients are clinically separated into 4 groups (stages I–IV) with progressively poorer survival. Stage III is defined either as T3–4, N0–1, M0 or T0–4, N2–3, M0 thus encompassing both inoperable and operable tumours and a wide spectrum as regards extent of primary tumour and nodal involvement. It is accordingly a very heterogenous group of patients. This is reflected by the highly variable survival figures reported in the literature (2, 3, 6, 7, 9, 14, 16, 17, 19, 20, 22, 28, 33, 37).

This variability makes it difficult to find a uniform treatment policy. The present retrospective study was undertaken specifically to investigate the prognostic significance of lymph node involvement which may guide the choice of primary therapy.

Material and Methods

A retrospective analysis of the case records of 103 consecutive patients with stage III breast cancer admitted to the Department of Oncology, University Hospital, Lund, Sweden from January 1976 through December 1982 has been performed. The primary investigations included chest x-ray, bone scan, blood chemistry including liver chemistry and if indicated liver scan. The case records were screened for clinical systemic adjuvant therapy, remission rate, relapse-free survival, pattern of local and distal failure as well as survival.

The median age of the patients was 60 years (22–91) and 25 of the patients were less than 50 years of age. The stage of the disease at diagnosis was based on clinical and pathological parameters and was defined using the international TNM classification system. The distribution of the patients according to TNM stage is shown in Table 1. In 8 of the patients the axillary nodal status was judged only clinically by palpation. These were all inoperable and therefore no axillary dissection done. These patients are therefore not included in the relapse-free survival analysis as shown later. The diagnosis of breast carcinoma was histopathologically confirmed in 99 and cytologically in 4 of the cases.

Ninety of the patients were judged operable. Of these 86 were operated with modified radical mastectomy including axillary dissection. In the remaining 4 simple mastectomy was performed. Of the operable patients 82 received postoperative irradiation, 4 were irradiated preoperatively and 4 received no irradiation. The postoperative radiation therapy was delivered to the chest wall, internal

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Table 1

Distribution of patients by T and N classification

	pN0	pN1	pN2	pN3	pNX	Total
T1			1	1		2
T2			3	5		8
T3	21	33	7	1		62
T4	2	13	7	1	8	31
Total	23	46	18	8	8	103

mammary, supraclavicular and axillary lymph nodes with doses of 45–48 Gy in 20 fractions given in 2 series (12 plus 8) with an interval of 3 weeks between the series. In 24 of the 26 cases with nodal stage pN2–3 boost therapy of 10 Gy were delivered to the axilla and supra- and infraclavicular lymph node regions. The 10 patients judged inoperable received radiation therapy as the primary treatment. This was delivered with kilovoltage and megavoltage equipment to the breast and regional lymph node regions in doses ranging from 37 Gy to 64 Gy in 3.5 to 6.5 weeks.

Forty-five patients received some form of systemic adjuvant therapy. One patient was treated with oestrogen for one year, 4 patients received cytotoxic combination chemotherapy. Three patients had surgical oophorectomy, 41 received tamoxifen in doses of 30–40 mg daily, the majority for one year or until relapse.

The method of Kaplan & Meier was used to calculate and plot disease-free survival and survival curves and the statistical difference between the curves was calculated by the Lee-Desu method.

In the operable cases disease-free interval was defined as the time lapse in months from the operation and in the inoperable cases from the date of complete disappearance of all visible and palpable disease. Survival was defined as the time in months from the diagnosis to the date of death. Patients were considered free of recurrence only if they were free of both local and distant relapse. All the patients have been followed to September 1987 or until death. No patient has been lost to follow-up. The median follow-up time was 52 months.

Results

The survival for the whole group of 103 patients is shown in Fig. 1. The median survival was 81 months and the 5-year survival 54%. There was a relatively constant mortality rate during the observation period. Ninety-three of the 103 patients had an initial complete remission (CR) after primary therapy. Of the remaining 10 patients who never had CR 8 have died in generalized disease and 2 are living with the disease. Of the 93 CR patients 40 have relapsed. Five have had local recurrences, one in supraclavicular nodes and 34 at distant sites. The median time to the development of recurrences was 21 months. In 14 of the 40 patients the recurrences developed within one year and 31 within 2 years after primary therapy.

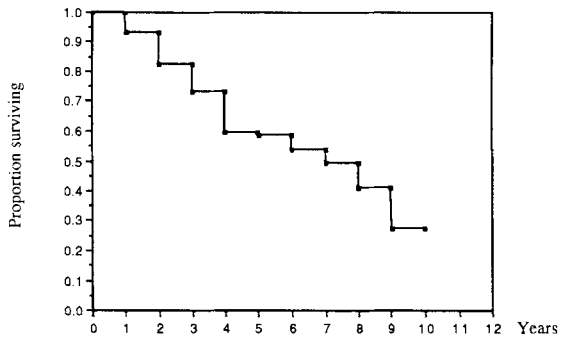

Fig. 1. Survival of the whole series (103 patients).

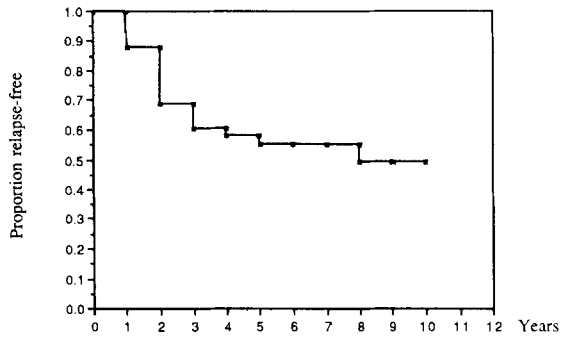

Fig. 2. Relapse-free survival.

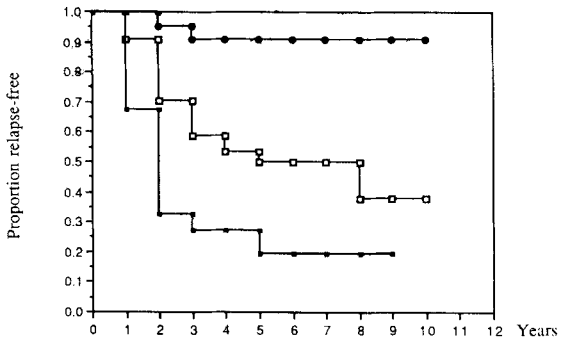

Fig. 3. Proportion relapse-free according to lymph node status, pN0 (●—●), pN1 (□—□), pN2–3 (■—■).

The relapse-free survival (RFS) for the 93 CR patients is shown in Fig. 2. The relapse-free survival at 5 years was 55%. There was a fairly constant recurrence rate during the observation period. The fact that the 5-year survival was almost the same as the 5-year relapse-free survival is explained by the fact that in the survival analysis the 10 patients not having initial complete remission after primary therapy are included.

Fig. 3 illustrates RFS of the patients having initial complete remission according to nodal status. The 5-year RFS for the node negative patients was 91%, for the pN1

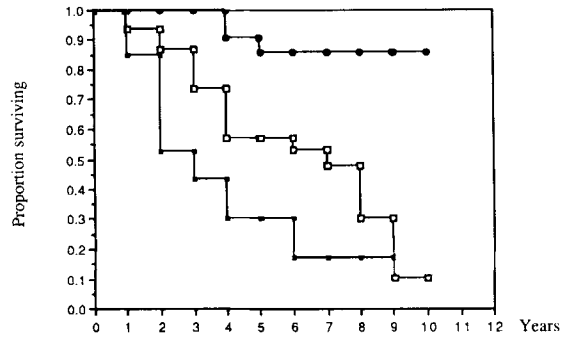

Fig. 4. Survival according to lymph node status, pN0 (●—●), pN1 (□—□), pN2–3 (■—■).

Table 2

Percentage relapsed or dead according to lymph node status

	Relapsed	Dead
pN0	11	13
pN1	51	52
pN2–3	69	73

patients 50% and for the pN2–3 patients 19%. There is a statistically significant difference between the groups. The p-value between pN0 and pN1 is 0.002, between pN0 and pN2–3 <0.0001 and between pN1 and pN2–3 0.004.

As shown in Table 2, 11% of the node negative patients have relapsed whereas 51% of the pN1 and 69% of the pN2–3 respectively have relapsed.

Fig. 4 illustrates the survivals according to nodal status. The 5-year survival rate for the pN0 patients was 86%, for the pN1 53% and for the pN2–3 patients only 30%. The p-value between pN0 and pN1 was 0.0035, between pN0 and pN2–3 <0.0001 and between pN1 and pN2–3 0.01.

As shown in Table 2, 13% of the node negative patients have died, of the pN1 52% have died compared to 73% of the pN2–3 patients.

Discussion

It is generally accepted that the extent of disease in terms of tumour size and involvement of regional lymph nodes is associated with diminished relapse-free survival and survival. Besides, increasing tumour size is correlated with increasing incidence of nodal involvement and thus shorter relapse-free interval and consequently poorer survival (13, 14, 30, 31, 34).

However, in node negative patients, neither recurrence rate nor survival are correlated with the size of the primary tumour and these patients have markedly improved prognosis compared to patients with nodal involvement (2, 14, 21, 30, 34).

Currently the presence of documented involvement of the homolateral local-regional lymph nodes remain the single most important prognostic factor for patients with breast cancer (13).

Fisher et al. found in an analysis of more then 2000 operable breast cancer patients that survival of patients with big tumours (>6 cm) and negative axillary nodes was not markedly different (85 vs. 75%) from that observed for patients with the same nodal status and the smallest tumours (<2 cm) (14).

The fact that a tumour in the breast has reached a size of 5 cm or more without regional lymph node involvement suggests that the ability of the tumour to metastasize is relatively limited and that the prognosis is better than might be expected. According to a hypothesis of Henderson & Canellos there are at least 2 different populations of breast cancer patients—one in which the tumour grows large before metastasizing to regional or distant sites and another in which the tumour gives metastases before growing extensively (21).

The results of this retrospective review are in agreement with those of other authors regarding the heterogeneity and the highly different prognoses for different subgroups of stage III breast cancer patients (5, 16, 19, 22, 27, 28). The most striking finding of the present study was the great difference between nodal groups pN0, pN1 and pN2–3 with respect to relapse-free survival and survival. The results show that the relapse-free survival for node negative stage III patients is similar to stage I and stage II (14, 21, 26, 34). Similarly the 5-year survival rate figures are at least comparable to those of stage II (14, 17, 21, 31, 34).

These results are similar to those reported by Garcia-Vilanova et al. who in a retrospective review of 380 patients with breast cancer showed higher survival rates for node negative stage III patients than for stage II (17). Similarly Fracchia et al. found in a retrospective analysis of 1307 patients with stage II a 10-year disease-free survival for node negative patients 74% and 43% respectively. Furthermore, the survival of stage II node negative was so similar to stage I and stage III that the authors conclude that most patients with pT1–3, pN0 should be placed in a new stage I category (16). The same authors in a detailed analysis of 484 patients with stage III breast cancer reported that of 58 node negative patients 82% were alive at 5 years and 75% at 10 years (15).

Conversely the present study indicates that patients in nodal stage pN2–3 carry an extremely poor prognosis as only 17% of these were alive 5 years after primary therapy, survival rates approaching these of metastatic stage IV breast cancer (21).

These figures indicate shortcomings of the TNM classification system and it is suggested that in order to obtain prognostically homogenous groups, histologically node negative stage III, II and I should be placed in a new stage I category. Conversely patients with nodal stage pN2–3 should be placed in a non-generalized stage IV group.

However, further analysis on a larger group of patients is needed to substantiate the validity of this suggestion.

The relatively low risk of recurrence and the high survival rate of the node negative patients furthermore indicate that the majority of these can be cured by local methods why adjuvant systemic therapy for these patients is questionable.

On the other hand the node positive patients in stage III and in particular pN2–3 must be considered a high-risk group as these patients have a high recurrence rate and short survival and therefore systemic adjuvant therapy for these patients could be indicated. The relatively low incidence of local failures in the present study indicates that aggressive local therapy is of great value with respect to local and regional control of the disease.

Bedwinek et al. treated 147 patients with irradiation alone (n=54) or with a combination of irradiation and mastectomy (n=93) and found a significantly lower local and regional failure rate in the combination therapy group (5). The incidence of distant metastases was however essentially the same in both groups.

Likewise Zucali et al. showed that the median survival for patients treated with radiotherapy followed by surgery was 3.9 years compared to 2.1 years for those given irradiation alone (37). The influence of each modality on the recurrence rate and survival is however controversial and results can be misleading because of patient selection bias.

Despite optimal local control, however, a substantial portion of the node positive patients develop distant metastases and ultimately succumb in generalized disease after relatively short time. Consequently, the majority of these patients probably harbor micrometastases at the time of primary treatment. This has led many investigators to combine chemotherapy with surgery and/or irradiation as the initial treatment and enhanced recurrence-free interval and longer survival have been reported (1, 3, 6, 8, 11, 19, 22, 27, 29, 32, 36).

However, there are as yet no long-term data indicating that systemic adjuvant therapy may result in increased long-term survival or cure rate. The appropriate role of combined modality approach and their optimal sequencing need further evaluation by prospective randomized studies in which the patients are stratified for factors known to affect prognosis such as tumour size, nodal status and possibly estrogen and progesteron receptor status.

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