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RISK FACTORS IN STAGE III BREAST CARCINOMA

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Abstract

Five-year follow-up data of 100 patients with Stage III breast cancer treated by primary irradiation from 1977 to 1981 are presented. The 5-year overall survival rate for the entire group was 38 per cent with a median survival time of 33 months. The data were analysed to determine factors associated with prognosis. Patients with shorter premedical history and premenopausal status had a modest survival advantage. Response to radiation therapy, primary tumor status, regional lymph node condition, postirradiation histologic findings in axillary lymph nodes proved to have a prognostic value. Disease which was not controlled by radiotherapy also tended to be resistant to chemotherapy and the 5-year survival in this group was zero. Risk factors have to be taken into consideration for the combined modality treatment for stage III breast cancer. However, further studies are needed to define the indication and appropriate sequence of systemic treatment in this stage of the disease.

Key words: Breast neoplasms; stage III carcinoma, therapeutic radiology, prognostic factors.

Stage III carcinoma (14) of the breast T3 or T4, N2 or N3–M0 is locally advanced and carries a poor prognosis. Because of the high incidence of local or regional recurrences after surgical treatment (4), radiation therapy has come to play a major role in this stage of the disease. Despite the reasonable level of local control achieved by irradiation and surgery, the five-year survival rate is low (1, 3, 8, 10, 15). The survival is determined by occult distant metastases present at the time of diagnosis (16).

In this presentation some parameters have been examined to evaluate their effect on the survival in stage III carcinoma of the breast. These include premedical history, menstrual status, degree of response to irradiation, pretreatment condition of regional lymph nodes, status of the primary tumor and histologic finding of axillary lymph nodes after radiation therapy and surgery.

Material and Methods

From March 1, 1977 to December 31, 1980, 109 consecutive women with stage III carcinoma of the breast were treated by primary radiation therapy at our outpatient clinic. Patients with inflammatory carcinoma (T4d) were included in the study as long as radiotherapy was not limited by technical factors. All patients had been examined with radiography of the chest and skeleton and bone scintigraphy to exclude overt disseminated disease. In spite of this 9 patients developed metastatic disease during the period of radiation therapy. Since their treatment was altered, these 9 women were excluded from the analysis. Table 1 shows the T and N distribution of all 100 patients suitable for analysis. The mean age of the women was 55.8 years (range 32 to 79 years); 25 were premenopausal and 75 postmenopausal.

Prior to irradiation no limited, excisional or incisional surgery was done. The pretreatment diagnosis was based on triple test: physical examination, bilateral mammography and fine-needle aspiration cytology. The patients were treated with orthovoltage equipment (200 kV, 2 mm Cu HVL). Tangential, upper and inferior breast fields were employed to irradiate the primary tumor, while axillary, supraclavicular and internal mammary lymph nodes were irradiated through direct anterior portals (5 fractions a week, in 10 to 14 weeks). Additional irradiation was given to residual masses through reduced fields. The doses were recorded as tumor doses, the total doses being 50 to 60 Gy to the primary tumor and 40 to 50 Gy to the regional lymph nodes. Response to radiation therapy was assessed on the basis of UICC recommendation (5). Patients with objective response were encouraged to undergo surgery (mastectomy and axillary dissection). Some of

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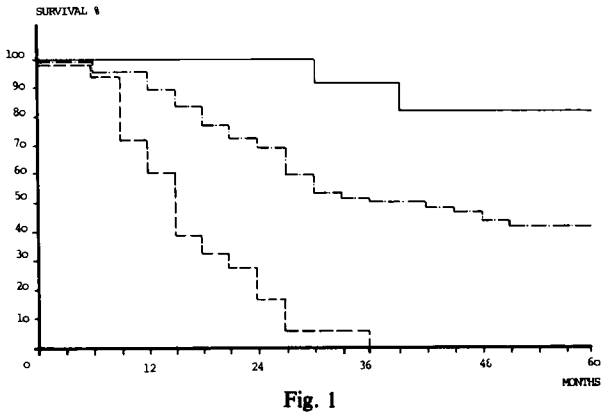

Fig. 1

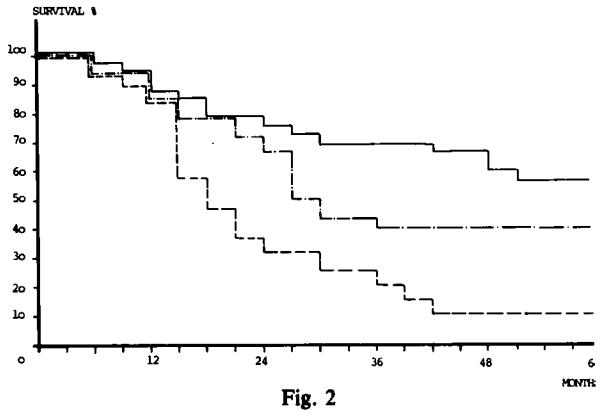

Fig. 2

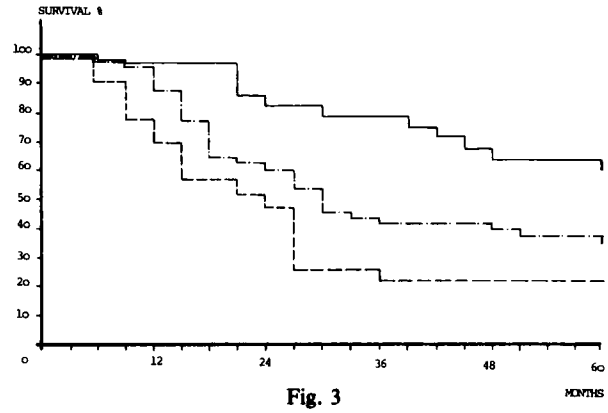

Fig. 3

Fig. 1. Survival by response to radiation therapy. CR (——) and PR (– · –) relative to NR (– – –) ($p<0.001$).

Fig. 2. Survival by T status. T3 (——) and T4abc (– · –) relative to T4d (– – –) ($p<0.05$).

Fig. 3. Survival by N condition. N1 (——) and N2 (– · –) relative to N3 (– – –) ($p<0.01$).

them refused surgery and received hormonal therapy (castration and/or tamoxifen). For women who failed to respond to irradiation chemotherapy was initiated (CMF). The patients have been under observation for at least 5 years with periodic (3 to 6 months) investigation. Women with local recurrence or distant metastases were treated again by systemic therapy and in some cases by palliative irradiation. One woman without recurrence was lost to follow-up between the first and second year and one between the second and third year. One patient died of nephritis after 45 months of observation; autopsy did not show malignant disease.

The site and time of first relapse (either local or distant) was recorded. Overall survival, metastasis-free survival (MFS) and relapse-free survival (RFS) were dated from the start of irradiation till the death, appearance of metastases or local recurrance respectively. Patients with no response were considered to have persistent local disease. Survival curves were calculated and plotted by the method of KAPLAN & MEIER (7). P values for comparison of these curves were derived from log-rank test (9).

Results

Tumor response. The rate of complete response (CR) was 12 per cent; 70 per cent of the patients achieved partial response (PR) and 18 per cent showed either no response (NR, 15%) or progressive disease (PD, 3%).

Table 1

T and N distribution of patients

	T2	T3	T4abc	T4d	Total
N1	0	14	10	5	29
N2	6	16	16	10	48
N3	2	4	13	4	23
Total	8	34	39	19	100

The 5-year survival rate in these 3 groups was 0.83, 0.40 and 0.00 respectively. The survival curves are plotted in Fig. 1. The survival rate for women with persistent local disease was very unfavourable, in spite of the fact, that they received chemotherapy after irradiation.

Duration of premedical history (PMH). The duration of symptoms was extremely variable, ranging from 1 day to 10 years. These estimates by the patients must of course be interpreted with caution. Patients with a shorter duration of symptoms ($\leq$6 months, 67 patients) did better than those with a longer history (>6 months, 33 women). Their 5-year survival rate was 0.42 and 0.29, respectively ($p<0.1$).

Menopausal status. The 25 premenopausal women did a little better than the 75 postmenopausal patients (5-year survival 47% versus 36%, $p<0.8$).

Primary tumor status. The best survival rate was ob-

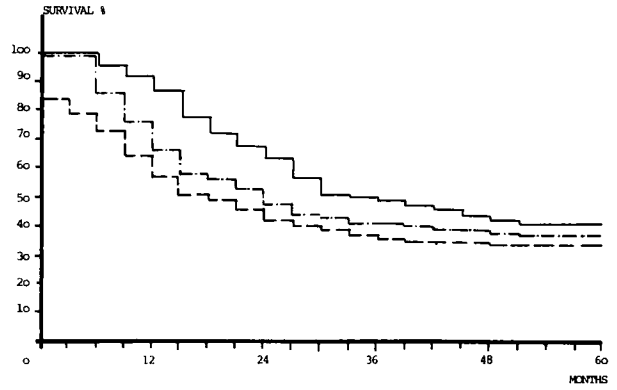

Fig. 4. Overall survival (——), survival without distant metastases (— · —) and survival without local or regional recurrence (– – –) of the whole group. Non-responders were considered to have persistent local disease.

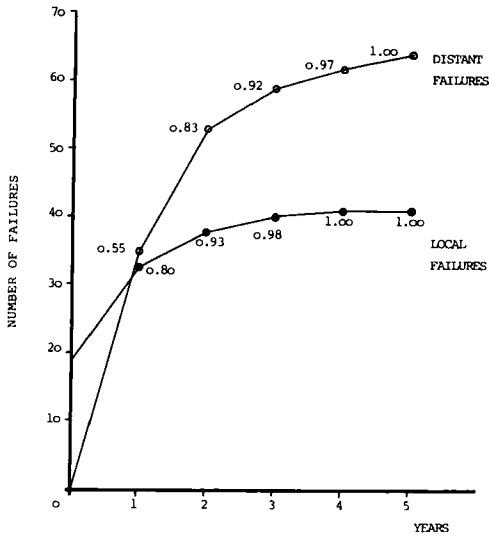

Fig. 5. Cumulative incidence of failures. Total number of metastases 64, persistent local diseases 18, local or regional recurrences 23.

Table 2

Risk factors and survival

Factor	5-year survival rate (%)	Median survival (months)
Short history	43	39
Long history	29	29
Premenopause	47	58
Postmenopause	36	31
T2	25	57
T3	57	>60
T4abc	38	27
T4d	11	18
N1	60	>60
N2	33	28.5
N3	22	22.5
Response to irradiation		
CR	83	>60
PR	40	41
NR + PD	0	13
Neg. axill. nodes (post-irrad.)	88	>60
Pos. axill. nodes (post-irrad.)	48	58
Whole group	38	33

Table 3

First site of relapse

	No. of cases
Local	
Breast	5
Axillary lymphs nodes	1
Supraclavicular lymph nodes	4
Infraclavicular lymph nodes	1
Area of surgery	8
Distant	
Skeleton	12
Lung	11
Pleura	4
Brain	1
Liver	2
Total	49

Eighteen patients with persistent local disease are not included.

served in patients with T3 tumors, while the worst was in those with T4d tumors. T4abc cases had intermediate survival rate (Fig. 2). The number of T2 patients was small (n=8) and T2 tumors were, according to definition of stage III, associated with regionally advanced disease. The 5-year survival of these patients was 25 per cent.

Lymph node condition. The degree of lymph node involvement proved to have prognostic value. N1 patients had the best prognosis, N2 women intermediate and those with N3 status the worst prognosis (Fig. 3).

Axillary lymph node condition after irradiation and operation. Irradiation produced objective response in 82 patients. Fifty-four of them were operated, while 28 women either refused surgery or developed early distant metastases. The 5-year survival of the operated group was 60 per cent. A separate analysis was carried out concerning the postirradiation histology of the axillary lymph nodes. No axillary metastases were found in 18 cases while the lymph nodes contained tumor in 36 cases. The node negative patients (p N neg.) had a better 5-year survival than the node positive patients (p N pos.) (88% versus 48%, $p<0.001$).

Data of the whole group. The overall survival, MFS and RFS curves are plotted in Fig. 4; the 5-year rates were 0.38, 0.36 and 0.33, respectively. The risk factors and the relevant survival data are summarized in Table 2. The cumulative incidence of distant and local failures is presented in Fig. 5.

The survival after appearance of distant metastases was short. The mean survival was 9.5 months, ranging from 1

month in patients with liver metastases to 40 months in patients with bone metastases. The first site of failure, either local or distant, is shown in Table 3. In all but two cases, local relapse was followed by distant metastases and the patients died eventually. In two cases solitary local recurrences were removed by surgery and the women have remained free of the disease.

Discussion

A considerable number of women with breast cancer has stage III disease. In our institute the rate of stage III carcinomas was 25 per cent during the 1970's and this figure has not changed during the last decade. Such patients have been said to have a poor prognosis. However, the results presented here demonstrate that subgroups of these patients have very different survival rates which correlates to prognostic variables. There is no dramatic effect of the patient's age on survival but our data show a somewhat better prognosis for premenopausal women. Patients with shorter premedical history had a modest survival advantage. This contrasts to the report of RUBENS et coll. (11) on longer symptoms connected with better prognosis.

A strong correlation was found between survival and the following factors: response to radiation therapy, primary tumor status, pretreatment clinical lymph node condition and postirradiation findings concerning axillary lymph node metastases. The 5-year survival rates were relatively good for patients with complete response after radiation therapy, T3, N1 and operated patients with negative axillary nodes (0.83, 0.57, 0.60 and 0.88, respectively). The 5-year survival for patients with uncontrolled disease was zero. Women with inflammatory carcinoma and with N3 disease showed very poor survival rates (0.11 and 0.22, respectively).

The analysis of the incidence of distant and local failures indicates that more than 80 per cent of the relapses occurred during the first 24 months. LEVENE et coll. (8) and RUBENS et coll. (11) made similar observations on the clinical course of stage III carcinoma. Two extreme groups could be recognized: one rapidly growing metastasizing and one slowly growing non-metastasizing form. Patients with T4d and N3 and advanced N2 condition generally belonged to the first group. Their disease progressed rapidly to a fatal termination.

As most patients with stage III breast cancer certainly have subclinical distant metastases already at the time of diagnosis it seems logical to combine the local treatment with systemic therapy (hormonal and/or cytotoxic). A combined modality approach has also been emphasized by several authors (2, 6, 12). In the present series only patients with uncontrolled disease by irradiation were subjected to postirradiation chemotherapy but the results were unsatisfactory. In a randomized clinical trial SCHAAKE-KONING et coll. (13) reported on a 5-year overall survival rate of 37 per cent for both radiation therapy and radiation therapy + chemotherapy groups. We agree to their conclusion that the routine use of adjuvant chemotherapy is not well established for stage III breast cancer and further studies are needed. The proper combination of local treatment, hormonal treatment and cytotoxic chemotherapy is, however, an important question, which probably could be best elucidated by randomized trials.

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