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Survival after First Recurrence in Breast Cancer

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Abstract—*The aim of the present study was to evaluate the significance of primary stage, histopathological grade, disease-free survival and site of first relapse on survival after first recurrence. The study included* 1621 *female breast cancer patients admitted between* 1970 *and* 1975. *The patient material was analysed by unifactorial life table methods and the multifactorial Cox regression analysis. The primary stage and histopathological grade maintained a significant prognostic value also after relapse. Survival after first recurrence was dependent on the disease-free interval and site of first relapse, too. If the disease-free survival was over* 5 years, 44% *of the patients were still alive after* 7 years *from recurrence. Of the patients with a disease-free survival shorter than* 2 years, *only* 10% *were alive after* 7 years *from recurrence. Survival was significantly better after locoregional relapse than after distant relapse, but the difference levelled off within* 7 years. *The prognosis of axillary relapse was best and that of liver and brain metastases poorest. Regression analysis confirmed the importance of primary stage, site of recurrence and histopathological grade as prognostic variables for survival after first recurrence.*

INTRODUCTION

BREAST cancer is a very heterogeneous disease [1]. Therefore it is important to know the individual prognostic factors to be able to estimate the survival. Recently, many reports have been published on prognostic factors in breast cancer, but not too much attention has been paid to the prognostic factors for survival after first recurrence. Cutler *et al.* showed that disease-free survival, site of relapse and number of sites involved influence survival after recurrence [2]. Devitt, too, documented the effects of site and disease-free interval. Furthermore he found that primary stage was an important factor for survival after first relapse [3]. Pater *et al.* have made an observation in their multivariate analysis that histological subtype and primary stage did affect survival after recurrence [4].

The aim of the present study was to evaluate the significance of the main prognostic factors, i.e. primary stage and grade, on overall survival and survival after first recurrence. The importance of disease-free survival and site of first recurrence was evaluated, too. This paper serves to clarify the importance of these factors in estimating the survival after first recurrence.

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MATERIAL AND METHODS

Patients

The study included 1621 female breast cancer patients admitted between 1970 and 1975 to the Department of Radiotherapy and Oncology, Helsinki University Central Hospital. 1486 patients (92%) were without distant metastases at referral. The tumors were verified histologically (operable) or cytologically (inoperable). The patients ranged in age from 19 to 89 years (mean 58 years). 482 patients (30%) were premenopausal and 1139 (70%) postmenopausal. The criterion for postmenopause was that the periods had ceased before breast cancer was diagnosed. Subdivision into only two groups on the basis of menstrual status was used because of the difficulty of exactly defining the lower limit for a stage of ongoing menopause.

As a non-random sample of the whole material, histopathological specimens taken in 1970 and 1975 were re-examined and graded by two pathologists according to the WHO classification [5]. Of the 492 specimens taken, 413 were available. These were considered a representative sample of the whole material. There were 51 cases of uncommon histology (e.g. intraductal and lobular carcinoma) which were not graded. This is a common practice, because some of the grading criteria cannot be

applied to them and because in these cases the histological type overrules the prognostic value of grading.

Upon termination of the follow-up on 31 December 1982, 658 patients (41%) were alive and 963 (59%) were dead. Breast cancer was the cause of death in 78% of patients who died.

Staging and follow-up

At the time of diagnosis, the examinations performed included physical examination, blood count, liver function tests and chest X-ray. Radioisotopic scans were not primarily performed during 1970–75.

The material was distributed into clinical stages according to the TNM classification (1978). On 34 cases the data on tumor size or axillary involvement were incomplete. Thus they were not classified into TN classes, but were evaluated for prognosis.

After primary treatment, follow-up was uniform, all patients being examined 3-monthly during the first year, 4-monthly during the second, 6-monthly during the next three years, 9-monthly during the next five years and, finally, once a year for the rest of their lives. Apart from the above examinations, the patients were instructed to contact an oncologist if needed.

Physical examination, blood count, liver function tests and chest X-ray were repeated at each follow-up examination. Appropriate radiological, radioisotopic and surgical examinations were carried out whenever recurrence was suspected or clinically evident. Since the late 70s, radioisotopic liver and bone scans were performed in association with the first relapse.

First relapse was defined as the relapse first observed within the follow-up system, and this was not changed even though more sophisticated examinations performed later would have disclosed metastases also in other sites. Very few patients displayed completely simultaneous multiple recurrences.

Primary treatment

The most common operative method was modified radical mastectomy (1039 patients, 66%). 429 patients (27%) were subjected to simple mastectomy. A breast saving local excision was done in 110 patients (7%).

Stage II and III patients were routinely irradiated post-operatively. Postoperative radiotherapy was not given to 271 patients (17%). Radiotherapy was carried out with a Cobalt 60 unit (81%), and by conventional X-rays (19%). Detailed information about the treatment methods has been published previously [1].

Secondary treatment

For patients presenting with recurrence only in locoregional sites, radiotherapy was the treatment of choice. In a small part of patients radiotherapy was preceded by surgical excision of local or regional recurrences. Patients showing new manifestations of the disease in distant sites were treated using various modalities. The majority of premenopausal patients underwent ovariectomy or radiological castration. In general, hormonal manipulations followed by single agent chemotherapy represented the treatment of choice in the beginning of the 70s. Later on, different forms of combination chemo- and hormonal therapy were more regularly applied to patients with progressive disease. Sometimes, palliative radiotherapy was used to relieve symptoms.

Statistics

The survival curves were constructed by the life table method from the date of primary operation, using the BMDP-81 computer programs [6]. The Mantel–Haenszel test (log rank) was used to evaluate the overall difference between survival curves. The P values quoted in the curve comparisons were derived from a chi-square for homogeneity, not for trend. The Cox life table regression analysis (program 2L of BMDP-81) was used in a forward stepwise mode to assess the simultaneous effects of multiple prognostic factors. The inclusion criterion was $P \leq 0.1$. Separate regression analyses were made (and compared) for the total material (without histopathological grade) and for the years in which histopathological grade was available (with and without grade). Disease-free survival was tried both as a continuous and a categorical variable, categorized as described in the legends to figures. The cut-off points of 2 and 5 years were chosen subjectively, in part on the basis of earlier publications, as representing aggressive, rapidly growing tumors on the one hand and slowly growing tumors on the other [4].

The significance of differences between proportions in the tables was tested by the two-tailed z test, using the weighted mean of the proportions.

RESULTS

Significance of stage and histopathological grade on recurrence.

Distribution into stages (clinical staging) and number of relapses are presented in Table 1. The nodal status was verified in 66% of patients by axillary evacuation and histology. In 34%, axillary status was confirmed only clinically or by biopsy. The difference in the number of relapses was significant between stage I and II and highly significant between stage II and III.

Table 1. *Number of relapses by stage*

Stage	Number of relapses	Percent	
I	125/285	44	
			$P < 0.05$
II	412/819	51	
			$P < 0.001$
III	244/348	70	
IV	–/135		

The histopathological grade was reassessed in 362 patients admitted in 1970 and 1975. Distribution of histopathological grades and number of relapses are shown in Table 2. In grade I patients the recurrence rate was only half that of grade III patients. Table 3 gives a cross-tabulation of grade and stage.

Survival

The survival rates in various stages differed highly significantly from each other (unifactorial $P < 0.001$). The survival curve for stage IV was strikingly lower than that for other stages. Only 19% of these patients survived 2 years (Fig. 1).

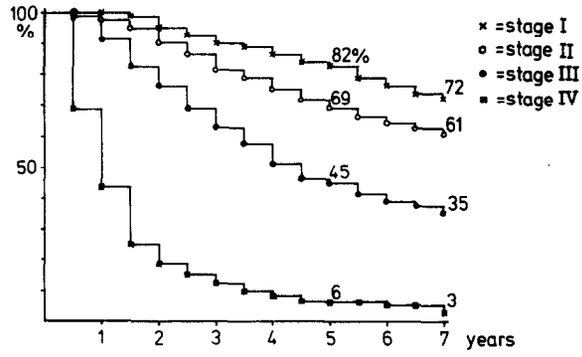

Fig. 1. *Corrected survival curves by stage (stage I*: n = 285, *stage II*: n = 819, *stage III*: n = 348, *stage IV*: n = 135). *The numbers in the figure indicate survival probability.*

Table 2. *Distribution of relapses by histopathological grade*

Histopathological grade	Number of relapses	Percent	
I	16/46	35	
			$P = 0.01$
II	115/204	56	
			$P < 0.05$
III	77/112	69	

Table 3. *Cross-tabulation of grade and stage*

Histopathological grade	Stage I		II		III	
	n	%	n	%	n	%
I	9	20	30	65	7	15
II	35	17	124	61	45	22
III	9	8	76	68	27	24

The survival rates in various grades (assessed in 362 patients) differed highly significantly from each other (unifactorial $P < 0.001$). In grade III, mortality was higher than in other grades during the 4 years following initial treatment, but thereafter mortality appeared to be somewhat more evenly distributed among the grades (Fig. 2).

Survival after first recurrence

Survival after first recurrence by primary stage and histopathological grade. Survival after first recurrence was influenced by the primary stage (Fig. 3). The difference between the survival of different stages was highly significant (unifactorial $P < 0.001$). 15% of all the patients were still alive 7 years after first recurrence.

Figure 4 shows that the survival curves after recurrence according to grade (assessed in 208 patients) are not identical. The higher the grade was, the earlier the patients died. The difference between the survival of different grades was nearly significant (unifactorial $P < 0.05$).

Significance of disease-free interval on survival after first occurrence. The patients with recurring disease were distributed into three groups: disease-free survival less than 2 years (56%), 2–5 years (29%)

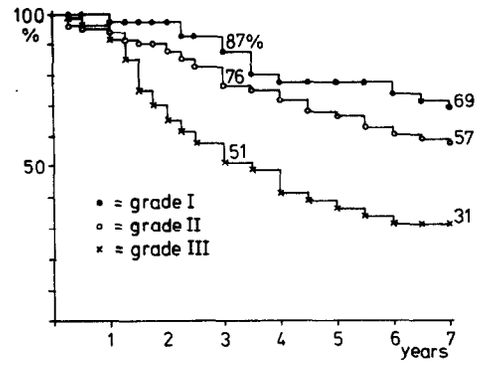

Fig. 2. *Corrected survival curves by grade (grade I*: n = 46, *grade II*: n = 204, *grade III*: n = 112). *The numbers in the figure indicate survival probability.*

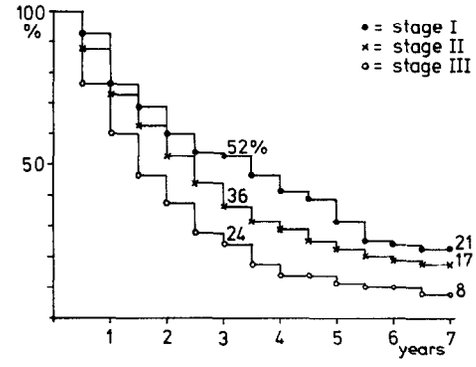

Fig. 3. *Survival after first recurrence by stage (stage I*: n = 121, *stage II*: n = 421, *stage III*: n = 244). *The numbers in the figure indicate survival probability.*

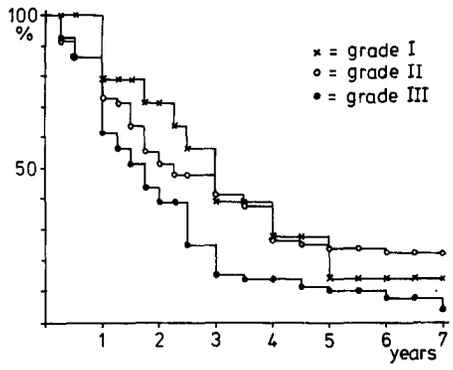

Fig. 4. Survival after first recurrence by grade (grade I: n = 16, grade II: n = 115, grade III: n = 77).

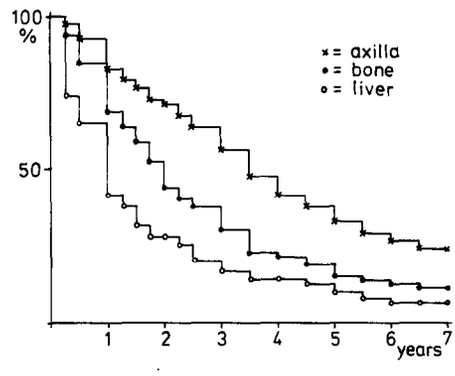

Fig. 6. Survival after first recurrence by site.

and over 5 years (15%). Figure 5 illustrates the relation between the duration of disease-free interval and survival after recurrence; the tendency for longer survival with a longer disease-free interval is evident. The difference between the survival rates of these groups was highly significant (unifactorial $P < 0.001$).

Survival after first recurrence by site of relapse. Survival after first recurrence varies greatly depending on the site of relapse (Table 4 and Fig. 6). Patients with locoregional relapses had a better prognosis than those with distant metastases. The

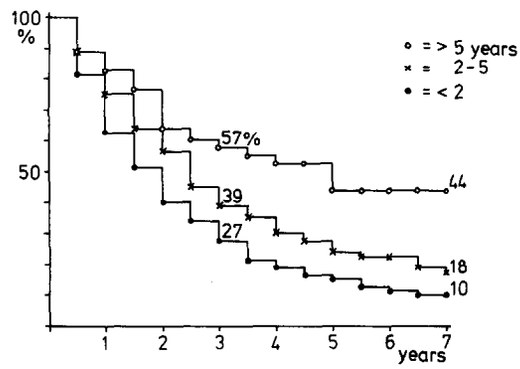

Fig. 5. Significance of disease-free interval on survival after first recurrence (group I: n = 450, group 2: n = 238; group 3: n = 121). The numbers in the figure indicate survival probability.

patients with axillary recurrences in particular survived longer. Survival after carcinoma of the opposite breast was better than after other sites of relapse. This was due to the fact that carcinomas of the opposite breast were 90% new primaries according to histopathology. The survival rates were similar after bone and lung metastases, two-thirds of the patients dying within 3 years. The prognosis of patients with liver or brain metastases was poorest, only one-third being alive after 1 year. The survival rates of patients with axillary, bone and liver metastases were significantly different (unifactorial $P < 0.001$). The median survival of patients with axillary, bone and liver metastases was 40, 22 and 10 months, respectively.

Multifactorial analyses of survival after first recurrence. In the regression analysis, primary stage and site of relapse were the two most important prognostic variables affecting survival after first recurrence ($P < 0.001$). This was the case both when disease-free survival to the first recurrence was used as a continuous variable and when it was used as a categorical variable. The effect of site manifested primarily as the beneficial effect on survival of recurrence in the axilla only, as compared to recurrence in other sites (see also Fig. 6).

Recurrence in the brain and in the liver both significantly and unfavorably affected survival af-

Table 4. Survival after recurrence by site of first relapse

Site of recurrence	n	Percentage of surviving patients 6 mo	1 year	2 years	3 years	5 years	7 years
Chest wall	150	90	68	47	35	24	18
Homolateral axilla	131	92	82	71	56	33	23
Homolateral supra clavicular fossa	26	85	69	32	18	5	0
Opposite breast	51	98	96	78	58	49	36
Bone	171	85	69	45	30	15	12
Lung	153	83	68	45	27	11	9
Liver	75	65	31	27	16	10	5
Brain	19	53	42	21	15	0	0
Other	33	81	69	37	37	22	17

ter recurrence but in this material they were not the most important prognostic variables. Table 5 shows the regression coefficients and their standard errors for the most important variables for the entire series. When disease-free survival to first recurrence was treated as a continuous variable, it did not meet the criterion ($P \leq 0.1$) for a prognostic variable in the model. However, when disease-free survival was categorized into three groups (under 2 years, 2–5 years and over 5 years), the two longer disease-free times to a significant degree favorably affected survival after first recurrence (improvement p in the model for the entire series 0.003 and 0.043, respectively). Entering of histopathological grade into the model (Table 6) did not abolish the importance of stage and site but it did diminish the significance of the effect of these variables. Grade emerged as the third most important prognostic variable.

Table 5. *Values of statistically significant regression coefficients from the stepwise Cox regression analysis of the entire material*

Variable	Coefficient	Standard error
Primary stage	0.3220	0.0620
Site of recurrence		
Axilla	−0.5454	0.1147
Opposite breast	−0.8370	0.2067
Liver	0.4823	0.1297
Brain	0.6426	0.2481
Disease-free interval*		
> 5 years	−0.8069	0.1560
2–5 years	−0.2953	0.0891

* Contrasted to disease-free interval < 2 years.

Table 6. *Values of statistically significant regression coefficients from the stepwise Cox regression analysis of the subset with histopathological grade*

Variable	Coefficient	Standard error
Grade III (poorly* differentiated)	0.6738	0.1669
Primary stage	0.3150	0.1411
Site of recurrence		
Axilla	−1.0899	0.2618
Opposite breast	−1.3455	0.4292
Disease-free interval†		
> 5 years	−0.7467	0.3352
2–5 years	−0.5676	0.1923

* Contrasted to grade I.

† Contrasted to disease-free interval < 2 years.

DISCUSSION

The present study was designed to identify factors that would influence the prognosis after first recurrence in breast cancer. The material included more stage I and stage II cases and less stage III cases than an earlier material from our department [7]. Because of the retrospective character of the study it has been impossible to avoid some biases in the definition of exact stage and other clinical details. But an increase in earlier stages has been described by other authors as well [8–10]. This may be due to people today knowing more about cancer.

The overall recurrence rate was similar to that in a patient material from Western Finland in the 1970s [11], but the number of relapses in stage I was exceptionally high. This was probably due to a staging error, the axilla not being evacuated in 62% of the patients in this group. According to Haagensen, 29% of the clinically negative nodes involved a histologically verified metastasis [12]. The prognostic value thereof is significant [13]. Forty-two percent of stage I patients had not been irradiated postoperatively and the number of locoregional relapses was particularly high in this group.

Mortality in stage III and IV was high within the first year after mastectomy compared to stage I and II, but more evenly distributed in the latter stages (Fig. 1). The same result has been reported by Langlands [14]. In our material the gradation of peak hazard in stages was very similar to that reported by Langlands *et al.* and displayed in their Fig. 2. The reason for the steep fall in the survival curves for stage III and IV was the fact that the disease was more advanced at referral, and these stages included less permanently recovered patients than stage I and II. It was interesting to notice that a small part of patients with distant metastases, too, survived many years. The natural history of their disease must have been slow (histopathologically non-aggressive tumor or a good host-tumor relationship). A good response to therapy could be one explanation. The survival curves of different stages were similar to those previously reported. The results of Blanco and Bunting were slightly poorer for all stages [15,16]. In the patient material of Nikkanen, stage III only exhibited a poorer survival compared to the present material [11]. Our material has been collected some years later than the above, which may partly explain the slightly better survival. The secondary treatment methods, too, varied greatly, which may affect the results. The 5-year survivals of different grades were also better in the present study than in Bunting's and Bloom's material [16,17]. Stage and grade are significant, independent prognostic factors [16,17]. A sample of the present material was

graded and the results obtained indicated the same. The stages were quite evenly distributed into histopathological grades, although there were slightly more stage I patients in grade I and stage III patients in grade III (Table 3). The survival curves of grade I, II and III differed highly significantly from each other (unifactorial analysis).

The stage maintained its prognostic value after relapse, even though the differences between the survival curves were greater at the primary stage (Figs 1 and 2). This was due to the primary curves including the patients who recovered. Stage reflects the biological character of the tumor or host-tumor relationship. These characteristics still exist after relapse. A low-stage tumor grows slowly, while a high-stage disease causes a more rapid death. The histopathological grade, which also reflects the biological character of the disease, is of prognostic significance even after relapse, although it appears to be of greater significance for primary prognosis (Figs 2 and 4). Primary stage and grade both influence the disease-free survival [1]. If the disease-free survival was over 5 years, 44% of the patients were still alive after 7 years from recurrence. Of the patients with a disease-free survival shorter than 2 years, only 10% were alive after 7 years from recurrence. The natural history of breast cancer is very heterogeneous. Only after 20 years from initial treatment the mortality of surviving breast cancer patients approaches that of the normal population [14].

The site of relapse significantly affected survival after recurrence. The prognosis of locoregional relapse was significantly better than that of distant relapse. The same result has been reported by Nikkanen [11]. The disease-free survival before locoregional recurrence was short [1], but survival after relapse was long. This could not be explained by the biological nature of the disease. The better prognosis might be due to these relapses being easier to treat. The patients developing axillary recurrences had a better prognosis than those who recurred in the chest wall. This finding is in line with Patanaphan *et al.* [18]. The poor prognosis after relapse in the supraclavicular fossa could be a statistical error due to the small size of the group, or the prognostic significance of this relapse was the same as that of a distant metastasis. The difference between the survivals after locoregional and distant metastasis levelled off within 7 years. This is due to the fact that a distant metastasis usually follows quite soon after a local relapse [11,12,19,20]. Survival after carcinoma of the opposite breast (relapses and new primaries) was better than after other sites of relapses. In fact, 90% of the carcinomas of the opposite breast were histopathologically new primaries. The liver and brain metastases exhibited the poorest prognosis. This result has been reported by other researchers as well [2,4,21,22]. It is due to the fact that the above organs are vital and partly because aggressive tumors tend to metastasize thereto [1]. Furthermore, these relapses respond poorly to the treatment. Survival after lung and bone metastases was similar in the present work. Cutler has reported prognosis to be better after lung metastases, Devitt reporting the opposite [2,3].

Because this investigation was designed in part to give information about the usefulness of the presently employed standard follow-up program, special attention was paid to the definition of first recurrence. On the other hand, since we wanted to evaluate a routine follow-up program as well as prognosis in relation to the first recognized recurrence, we did not consider it justified to alter the definition of first recurrence on the basis of more sophisticated examinations performed perhaps some weeks or even months after detection of the first signs of recurrence. In our material, very few patients displayed completely simultaneous multiple recurrences.

Survival after first recurrence was dependent on the primary stage, histopathological grade, site of relapse as well as on the disease-free survival. These factors are not all independent. Disease-free survival is affected by the stage and grade. Histologically aggressive or high-stage tumors metastasize more frequently to 'bad sites', but this may be true of grade I and stage I tumors as well [1]. Site of relapse is affected also by currently unknown factors.

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