Eur J Cancer Clin Oncol, Vol. 23, No. 12, pp. 1925–1934, 1987.
Printed in Great Britain

0277–5379/87$3.00+0.00

Stage and Pattern of Metastases in Patients with Breast Cancer

CLAUS KAMBY,* CARSTEN ROSE,* BENT EJLERTSEN,† JÖRN ANDERSEN,‡ NIELS E. BIRKLER,§ LENE RYTTER,§ KNUD W. ANDERSEN‖ and KARIN ZEDELER‖

**Department of Oncology ONA, The Finsen Institute, Rigshospitalet, Copenhagen, †Department of Oncology and Radiotherapy R, Odense Hospital, ‡Radium Centre, Aalborg Hospital, §Radium Centre, Aarhus Municipal Hospital and ‖DBCG Secretariat, Copenhagen, Denmark*

Abstract—*This study compares the pattern of metastases in* 228 *patients with initial stage I and* 635 *patients with initial stage II breast cancer. All these patients had recurrence within a median time of follow-up of* 4.9 *years (range* 2.0–7.0 *years). All patients were initially mastectomized, and staging was based on histopathological evaluation of mastectomy specimens. Patients with stage II disease received postoperative radiotherapy;* 67% *also received systemic adjuvant therapy.*

Locoregional recurrences were the most common sites of recurrence in stage I, whereas distant metastases occurred more often in stage II patients. Stage II patients had a significantly higher number of metastatic sites than stage I patients. Among patients with a single site of recurrence the frequency of local or regional recurrence was 62% *in stage I patients compared to* 16% *in stage II patients. When correcting for this difference, which was ascribed to the effect of radiotherapy, the number and the distribution of metastatic sites were almost equal in stage I and II patients. The anatomical distribution of metastatic sites in different periods after mastectomy was almost the same in stage I and stage II patients; extraregional lymph node metastases, however, occurred earlier in stage II than in stage I patients.*

The recurrence-free interval, the survival after recurrence (SAR), and the overall survival were all significantly shorter for stage II than for stage I patients. The reduced SAR for patients with stage II disease hints that tumours of higher stages have a higher rate of progression. The progression time, however, was of the same duration in patients with initial stage I and II breast cancer.

The prognostic significance of the classification of patients with breast cancer according to stage does not seem to discriminate tumours with different biological properties with regard to the rate as well as the pattern of dissemination. Postmastectomy follow-up of patients with stage I and II disease should therefore, follow the same guide-lines. Since the anatomical distribution of metastases was the same in different periods after mastectomy, the screening for recurrent disease should not be directed towards any specific sites in certain periods after initial diagnosis.

INTRODUCTION

THE RECOGNITION of breast cancer as a subclinical systemic disease at the time of primary diagnosis has important implications for the postoperative follow-up programme, since most of the patients are expected to recur, and because the anatomical distribution of recurrences has both prognostic and therapeutic significance [1–6]. Furthermore, analyses of the pattern of metastases at the time of first recurrence can be of value in the understanding of the biology of breast cancer.

Skin, lymph node and bone metastases are the most frequent sites of recurrence, both at the time of first relapse [7–10] and at autopsy [11]. There is, however, only little information concerning both the proportion of metastases in different anatomical locations and the temporal relation of these after diagnosis of the primary tumour [7].

Factors which are responsible for the anatomical distribution and for the extent of metastases are largely unknown; however, patients with oestrogen receptor (OR) positive tumours may have a propensity to have recurrence in bone [9, 12–14], while

Accepted 15 July 1987.
Reprint requests and correspondence to: Claus Kamby, Department of Oncology ONA, The Finsen Institute 49, Strandboulevarden, DK-2100 Copenhagen, Denmark.
Supported by a grant from The Danish Medical Research Council No. 12-6006.

patients with OR negative or low differentiated tumours often have initial recurrence confined to viscera [12–15]. Although not all investigators agree with these findings [16], it seems nevertheless possible that the effect of these and other prognostic factors may exert their influence on the course of the disease through a propensity to cause recurrence in certain sites.

The influence of presenting stages on overall survival are well known. Initial histopathological stage may, however, also influence the survival after recurrence (SAR) [17]. It has been suggested that differences between stages reflect differences between tumours with respect to the metastatic potential (i.e. increasing aggressiveness with increasing stage). It is, however, unknown whether this biological aggressiveness is expressed through a tendency for tumours of higher stages to recur in many sites and/or in specific and more lethal sites.

The present study was conducted in order to describe and analyse the distribution of metastases in relation to initial stage in human breast cancer.

MATERIALS AND METHODS

From September 1977 until October 1982, a total of 6201 patients with operable breast cancer entered the 77-protocols of the Danish Breast Cancer Cooperative Group (DBCG). The organization of the DBCG has been described elsewhere [18]. Criteria of selection:

1. All patients in the present study participate in the DBCG-77 programme.
2. Primary treatment and follow-up took place at one of the four participating oncological centres or at their regional medical or surgical departments.
3. The confirming diagnosis of recurrent disease and the treatment was undertaken at the oncological centres.

Patient characteristics

Three thousand eight hundred and two (61%) of the 6201 patients who entered the DBCG-77 protocols met the criteria of selection (Table 1A). These patients were comparable to the whole DBCG material with respect to age, menopausal status, size and degree of anaplasia of the primary tumour and RLN status (data not shown). The characteristics of the patients according to stage are shown in Table 1B. The relatively low number of stage I patients (35%) is due to the fact that mainly stage II patients were followed up at the oncological centres. Thus, many stage I patients were not referred to the centre at the time of recurrence.

As of 1 January 1984, 1291 patients (34%) were taken off study because of clinical recurrence (67%), death without recognized clinical recurrence (16%), lost to follow-up (14%) and other primary cancer (3%). The causes were equally distributed between stage I and II patients ($P = 0.10$). Sixty-two per cent of the 183 patients classified as being lost to follow-up were for unknown reasons not referred to the oncological centre at the time of going off study. As the characteristics of these patients are stored in the DBCG database, they were compared to the group of patients with a known cause of coming off study. The two groups were equal with respect to age, menopausal status, tumour size, degree of anaplasia and RLN status (data not shown). The median time of follow-up was 4.9 years (range 2.0–7.0), and the median time of observation after first recurrence was 3.6 years (range 0.8–6.4). As expected, both the RFI and the OS were longer in stage I than in stage II patients ($P < 0.001$).

The primary treatment was total mastectomy a.m. Cady with axillary lymph node sampling [19]. Patients were divided into a high and a low risk group. The low risk patients (in the following referred to as stage I patients) had a tumour less than or equal to 5 cm in diameter, no positive nodes and no invasion of skin or deep fascia. These patients received no further therapy following mastectomy. The remaining high risk patients (in the following referred to as stage II patients) had a tumour larger than 5 cm in diameter and/or positive lymph nodes and/or skin or fascial invasion. These patients were all given postoperative radiotherapy to the chest wall, the axillary and periclavicular areas, equivalent to 1335 rets [18]. After mastectomy, patients with stage II disease were stratified according to menopausal status, and then randomized to different forms of adjuvant treatment, as described elsewhere [20–23].

All patients were seen for physical examination every 3 months until 18 months after mastectomy and every 6 months thereafter. The follow-up took place either at the oncological centre or at the local corresponding departments. Chest X-rays, bone scintigraphy and blood chemistry including liver enzymes were carried out every 6 months for 1 year. Thereafter, chest X-rays were repeated once a year for another 4 years. An abnormal bone scintigramme required bone X-ray survey.

The files of all patients who were taken off study before 1 January 1984 were reviewed. In the case of recurrence, information concerning the sites of metastases was obtained from the records. All metastatic sites detected within 1 month after the diagnosis of the first site of metastases were grouped together and designated as the sites of metastases at first recurrence. Subsequent metastases in other sites and the date of their detection and treatment were also recorded.

The sites of metastases were divided and defined as follows:

Table 1A. Breakdown of patient material. n indicates number (frequency) of patients

	n	%
Randomized in the DBCG protocols	6201	(100)
stage I	3127	(50)
stage II	3074	(50)
Allocated to the present study*	3802	(100)
stage I	1334	(35)
stage II	2468	(65)
Off study before 1 January 1984	1291	(34)
Clinical recurrence	863	(23)
initially stage I	228	(6)
initially stage II	635	(17)

*Criteria of selection: see Materials and Methods.

Table 1B. Characteristics of the patients at the time of initial diagnosis and the subsequent adjuvant therapy (including radiotherapy)

	Stage I		Stage II	
	n	(%)	*n*	(%)
Total No. of patients	1334	(100)	2468	(100)
Age (years)				
<50	343	(26)	633	(26)
50–59	331	(25)	613	(25)
≥60	660	(49)	1222	(49)
Menopausal status:				
pre/perimenopausal	460	(34)	907	(37)
postmenopausal	870	(65)	1561	(63)
unknown	4	(1)	0	(0)
Primary tumour, size (cm):				
<2	183	(14)	123	(5)
2–5	1126	(84)	1757	(71)
>5	0	(0)	564	(23)
unknown	25	(2)	24	(1)
No. of positive nodes:				
0	1334	(100)	427	(17)
1–3	0	(0)	1367	(55)
≥4	0	(0)	673	(27)
unknown	0	(0)	1	(1)
Degree of anaplasia:*				
I	368	(28)	539	(22)
II	519	(39)	1196	(48)
III	148	(11)	399	(16)
not graded	299	(22)	334	(14)
Systemic adjuvant therapy:				
none	1334	(100)	825	(33)
chemotherapy	0	(0)	671	(27)
levamisole	0	(0)	276	(11)
tamoxifen	0	(0)	696	(28)

*Ductal carcinomas only.

I *Soft tissue:* local skin recurrence (the skin and or subcutaneous tissue of the ipsilateral mammary region). Other skin recurrence (the skin and/or subcutaneous tissue outside the ipsilatral mammary region). Regional lymph node metastases (RLN, recurrence in the regional lymph nodes of the ipsilateral axilla or the periclavicular regions). Other lymph node metastases (OLN, lymph nodes other than RLN). Contralateral breast metastases (all carcinomas in the contralateral breast were regarded as recurrences of the primary tumour).

II *Bone* metastases (verified by X-ray examination).

III *Visceral* metastases metastases: lung and

pleural recurrences (demonstrated by X-ray examination; solitary pleural effusions required cytological verification). Liver metastases (demonstrated by ultrasonic or CT scans). Brain metastases (confirmed by brain or CT scans). Other metastastic sites (verified by appropriate methods). When the number of sites is calculated, the presence of recurrence in each of the above-mentioned anatomical locations counts for one, irrespective of the number of tumour deposits within each site.

The period of follow-up was defined as the time from the date of mastectomy until the date of evaluation (autumn 1984). The recurrence-free interval (RFI) and the overall survival (OS) were calculated from the date of mastectomy until the date of recurrence (RFI) or death (OS). The survival after recurrence (SAR) was defined as the time from the date of first recurrence until death.

The RFI and the SAR were used as rough estimates of the growth rate. Differences in these between stage I and II patients could be due to differences in the extent and the pattern of metastases and, consequently, also in the treatment of recurrent disease. The growth rate was, therefore, additionally estimated as the time interval from recurrence in a single distant site until detection of other distant metastases. This interval was designated the time to progression (TTP).

The frequency of metastases in stage I and II patients was compared, using the chi square test. Odds ratios (ORs), with 95% confidence limits in parentheses [24], were used to describe the difference in the incidence of metastases between stage I and II patients. An OR near or equal to 1 indicates an equal incidence of metastases in the two groups. Differences in the incidence of metastases in different sites were evaluated, using the incidence in stage I as a reference. A great OR indicates a greater incidence of metastases in stage II compared to stage I patients. Comparisons of the number of metastatic sites were performed, using the rank *t*-test for ordered categories and corrected for ties (Mann–Whitney rank sum test) [25]. The Mantel–Haenszel statistics, extended for stratified data, were used in order to control the possible confounding effect of differences in the number of metastatic sites [26]. Actuarial life table analyses were performed on data concerning RFI, OS, SAR and TTP. The log-rank test was used to evaluate the differences in recurrence and survival rats [27]. A two-tailed *P*-value of less than 0.05 was considered significant.

RESULTS

Pattern of metastases

Clinical recurrences were found in 228 of the 1334 stage I (17%) and in 635 of the 2468 stage II patients (26%) (Table 1A). Among these 863 patients, most patients had recurrence in a single anatomical site at the time of first recurrence (72%). The most common sites of recurrence were bone (35%), lung (23%), local skin (22%) and RLN (16%).

Locoregional recurrences were most often seen in stage I patients ($P < 0.05$), whereas distant metastases were seen significantly more often in stage II patients (Fig. 1). The number of metastatic sites was significantly higher in stage II than in stage I patients (Table 2). Moreover, 62% of the stage I patients with a single site of recurrence has this confined to the locoregional area compared to 16% of the stage II patients ($P < 0.0001$). These differences are conceivably due to the effect of postoperative radiotherapy, which was given to stage II patients only.

The effect of radiotherapy on the pattern of metastases was excluded by restricting the analysis to patients with distant metastases (i.e. exclusion of patients with locoregional recurrences only). This leaves 106 stage I and 558 stage II patients for further analysis. Both the median number of metastastic sites ($P = 0.98$) and the anatomical distribution was comparable in stage I and II patients (Fig. 2).

The incidence of metastases in the liver constituted the only anatomical site, which showed a significant difference beween stage II (14%) and stage I (6%) patients (OR: 2.6; 95% CL: 1.2–6.0) (Fig. 2). The administration of adjuvant chemotherapy to stage II patients may have affected this, since ORs were 4.48 (1.88–10.70) and 2.19 (0.93–5.11) for patients who were given and not given postoperative chemotherapy, respectively.

Temporal pattern of metastases

Among the 863 patients with clinical recurrence, 33% occurred during the first year, 34% during the second year, 17% during the third year and 16% during the fourth to the seventh years after mastectomy. The proportion of metastases in different sites was nearly unchanged from year to year after mastectomy (Figs. 3 and 4). There was, however, a tendency for patients with bone or lung metastases to recur later, while patients with pleural, liver or brain metastases recurred earlier than patients without these metastases (Fig. 4).

The distribution of patients with metastases at various sites according to stage and period of detection after mastectomy is presented in Table 3. There was a tendency for stage II patients to have recurrence in earlier periods after mastectomy than was the case for stage I patients. The difference was, however, only significant with respect to the occurrence of metastases in OLN ($P = 0.01$).

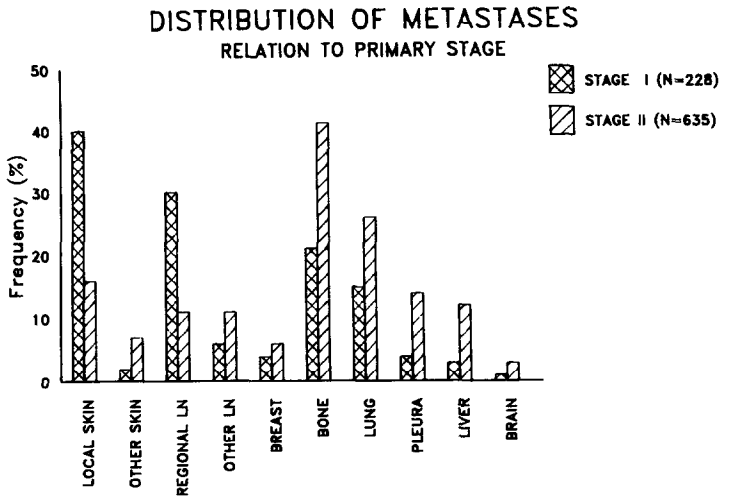

Fig. 1. Distribution of patients according to primary stage and anatomical location of first recurrence.

Table 2. Distribution of patients according to the number of metastatic sites at first recurrence. n (%) *indicates the number of patients in each group*

No. of metastatic sites	Stage I n = 228 (100)	Stage II n = 635 (100)
1	181 (79)	437 (69)
2	36 (16)	120 (19)
3	9 (4)	56 (9)
≥4	2 (1)	22 (3)

P = 0.009 (rank t-test).

apy (E: 38%) and C + E: 37%, with no difference between the stages.

Thirteen and 72 patients developed subsequent distant metastases during the period of follow-up, for stage I and stage II patients, respectively. The actuarial rate of progression was higher in stage II (43%) than in stage I (24%). The difference was not statistically significant (Table 4).

Survival after recurrence (SAR)

When considering all sites of recurrences together, the SAR was longer in stage I than in stage II patients ($P < 0.0001$). Table 5 shows that

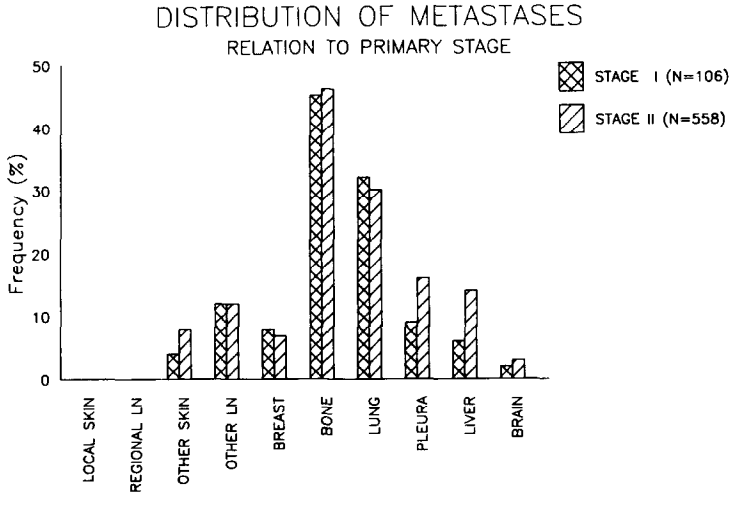

Fig. 2. Distribution of patients according to primary stage and distant anatomical location of first recurrence (i.e. patients with locoregional recurrences only have been excluded from analysis).

Time to progression

Thirty-three per cent (76 patients) of the stage I and 60% (380 patients) of the stage II patients had a single distant site of metastasis at the time of first recurrence. The treatments of these patients comprised chemotherapy (C: 39%), endocrine therapy

the prolonged SAR of stage I patients applied to patients with recurrence in most anatomical sites. The initial stage had, however, no significant influence on SAR in patients with extraregional skin, other lymph nodes, pleural, liver and brain metastases (Table 5).

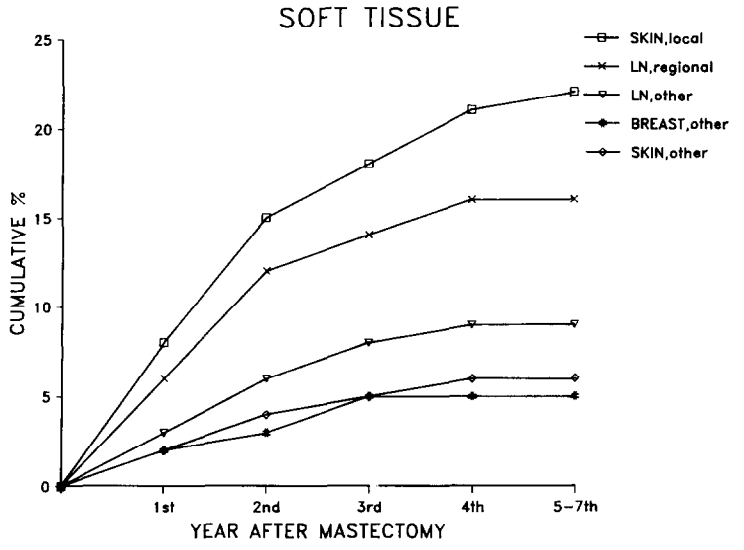

Fig. 3. Cumulative incidence of soft tissue recurrences according to the period (year) of recurrence after mastectomy. Percentages express the fraction of the total number of patients with recurrence.

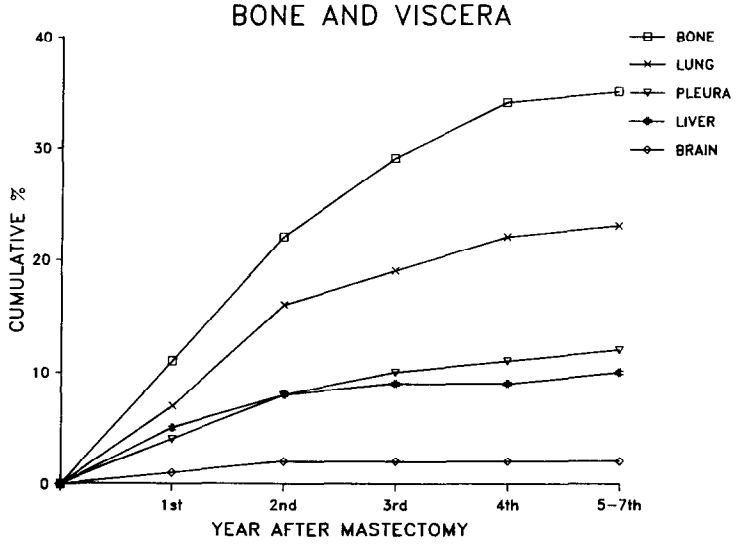

Fig. 4. Cumulative incidence of distant metastases according to the period (year) of recurrence after mastectomy. Percentages express the fraction of the total number of patients with recurrence.

DISCUSSION

The majority of the patients had their first manifestation of recurrent disease confined to a single anatomical site, often located in the skin, lymph nodes, bone and lung. With increasing time from mastectomy, the incidence of metastases in these sites increased along with a corresponding steady increase in the incidence of metastases in other sites. Thus, after a median time of follow-up of 3.6 years, the distribution of metastases between different anatomical sites were still the same.

The incidence and the distribution of metastases obtained in the present multicentre study are comparable to what was found in a single-centre study of intensively investigated patients with first recurrence of breast cancer [28, 29]. In contrast to the present study, that study included patients with stage III and IV breast cancer, and ultrasonography of the liver was performed routinely in all patients [29]. These discrepancies may explain why liver metastases were found more often than in the present study (15% vs. 10%).

Since adjuvant radiotherapy was not given to patients with stage I disease, these patients frequently had locoregional recurrences. These recurrences were generally the only sites of recurrence in stage I, while stage II patients had a greater number of metastatic sites as well as distant metastases. The low incidence of locoregional recurrences in patients given radiotherapy is well documented in the literature [30, 31].

This study shows that the anatomical distribution

Table 3. Distribution of patients according to period of recurrence after mastectomy, anatomical site of metastasis at first recurrence and stage (n *indicates the number of patients in each group, and percentages are calculated from the total number of patients in each stage with recurrence in the site in question*)

Site of metastasis	Stage	Year from mastectomy: 1st *n*	(%)	2nd *n*	(%)	3rd *n*	(%)	4–7th *n*	(%)
Skin (local)	I	29	(32)	32	(35)	13	(14)	17	(19)
	II	38	(38)	34	(34)	13	(13)	15	(15)
Skin (other)	I	0	(0)	2	(50)	0	(0)	2	(50)
	II	18	(38)	11	(23)	12	(26)	6	(13)
Lymph nodes (regional)	I	25	(37)	21	(31)	9	(13)	13	(19)
	II	25	(35)	29	(40)	12	(17)	6	(8)
Lymph nodes (other)	I	1	(8)	3	(23)	6	(46)	3	(23)
	II	24	(36)	22	(33)	13	(19)	8	(12)
Contralateral breast	I	4	(44)	1	(11)	3	(33)	1	(11)
	II	12	(32)	11	(30)	9	(24)	5	(14)
Bone	I	10	(21)	16	(33)	9	(19)	13	(27)
	II	82	(32)	82	(32)	55	(21)	37	(14)
Lung	I	7	(21)	11	(32)	6	(18)	10	(29)
	II	55	(33)	67	(40)	21	(13)	25	(15)
Pleura	I	3	(30)	3	(30)	2	(20)	2	(20)
	II	31	(34)	28	(31)	16	(18)	15	(17)
Liver	I	1	(17)	5	(83)	0	(0)	0	(0)
	II	38	(50)	23	(30)	13	(17)	2	(3)
Brain	I	1	(50)	0	(0)	1	(50)	0	(0)
	II	5	(26)	9	(47)	3	(16)	2	(11)

Table 4. Time to progression. Actuarial cumulative proportion of stage I and II patients who, after having experienced a single site of distant recurrence, developed additional distant metastases

Stage	Total No. of patients	No. of events	Actuarial proportion*	*P*
I	76	13	24%	0.29
II	380	72	43%	

*At 3 years.

and the number of metastases was almost the same in stage I and II patients, when correction was made for the protective effect of postoperative radiotherapy on the recurrences in the locoregional areas. Adjuvant systemic treatment was given to 67% of the stage II patients. As this might change the natural history of the disease it has been subjected to a separate analysis [23]. Thus, the increased incidence of liver metastases in stage II compared to stage I patients was probably influenced by the administration of adjuvant chemotherapy to 27% of the patients with stage II disease [23].

The number of patients with recurrence was highest within the first years after primary treatment. This finding is confirmed by other studies [7, 32, 33]. Therefore, if one wishes to detect recurrences early, the most rational routine follow-up of patients with breast cancer should be most frequent in the first couple of years after mastectomy. The anatomical distribution of metastases was almost the same when different periods of time of mastectomy were compared. Accordingly, Bruce *et al.* [33] found that the distribution of locoregional and distant metastases was almost equal in stage I and II in different periods up to 5 years after mastectomy. The follow-up and screening for recurrent disease after mastectomy should not, therefore, be directed towards any specific sites in any specific periods. It should be noted, however, that the present and other studies [7, 28, 29, 32] have found that liver metastases occurred relatively earlier and bone metastases relatively later than metastases in other sites. Finally, since the temporal relation of the distribution of metastases in various sites was the same in stage I and II patients, there is no reason to stratify the postoperative screening programme after mastectomy according to the initial stage of the disease.

Staging procedures at the time of initial diagnosis of breast cancer comprise determination of the size of the primary tumour, presence of local tumour invasion, and determination of the number of positive RLN [18]. As the dissemination of breast cancer increases with time from the inception of the tumour

Table 5. Three-year survival rates after recurrence (SAR) according to site of metastases and stage of disease

Site	Stage	No. of patients	No. of deaths	SAR* %	P†
Skin (local)	I	97	42	65	0.001
	II	130	108	19	
Skin (other)	I	18	14	36	0.237
	II	82	68	16	
Lymph nodes (regional)	I	77	38	53	0.001
	II	93	78	23	
Lymph nodes (other)	I	21	18	22	0.084
	II	95	85	11	
Contralateral breast	I	12	3	82	0.012
	II	50	36	35	
Bone	I	73	49	32	0.010
	II	308	255	19	
Lung	I	49	36	27	0.017
	II	190	157	16	
Pleura	I	27	25	11	0.670
	II	125	109	13	
Liver	I	15	15	6	0.500
	II	103	101	4	
Brain	I	12	12	8	0.750
	II	54	50	5	

*Three-year survival rates; percentages derived from life-table analyses.
†Log-rank test.

the status of these factors also increases and, therefore, staging procedures shoud be regarded as a stratification of patients according to the age of the primary tumour. Different prognoses for patients with tumours of different stages may just be a consequence of this.

It is not known why patients with breast cancer have varying degrees of dissemination (i.e. different stages) at the time of presentation. Factors influencing the time of delay [34, 35] or the rate of tumour growth [36] may play a role. Different stages could, however, additionally distinguish and reflect tumours with different aggressiveness. This may be expressed in differences in either (1) the rate of progression or growth, (2) the extent of dissemination or (3) the anatomical distribution of metastases. The existence of an increased rate of progression in tumours of higher stages is supported by studies which have shown that the initial stage also influences the SAR [3, 37, 38]. The present study confirms these findings, since the SAR in stage I patients with any site of recurrence was longer than that of stage II patients. Differences in SAR according to stage might, however, also be related to differences in the extent of disease or to differences in the treatment between stage I and II patients. We have, therefore, also estimated the growth rate as the time to progression in patients with a single site of distant metastasis, since these patients had both the same extent of disease and received the same treatment. When evaluating the growth rate in this manner, no differences were found between stage I and II tumours. Moreover, this and other studies show [8,10,33,39,40] that different biological properties of stage I and II breast tumours are not expressed either in differences of the extent of dissemination or the anatomical pattern of spread.

In conclusion, the rate and the pattern of dissemination is comparable in stage I and II breast cancers. The prognostic difference for patients with tumours of different stages is probably due to differences in the age of the tumour at the time of primary diagnosis. These findings, together with the finding of a constant and uniform increase in the occurrence of metastases in various anatomical sites, have practical implications for the intensity and the composition of the post-mastectomy screening programme. Thus, follow-up should be most frequent in the first couple of years after primary diagnosis and should include examinations for the most common sites of recurrence (i.e. soft tissue lesions and bone metastases). There is no reason for stratifying the screening programme according to initial stage, and there is no need for confining any specific investigations to certain periods after mastectomy.

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