*Acta Oncologica Vol. 30 No. 3 1991*

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# PATTERN OF SPREAD AND PROGRESSION IN RELATION TO THE CHARACTERISTICS OF THE PRIMARY TUMOUR IN HUMAN BREAST CANCER

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**Abstract**

Characteristics of primary breast tumours were related to the extent of dissemination, the anatomical location of metastases, and the rate of progression in 863 patients with recurrent breast cancer. The following features were examined: tumour laterality, location within the breast, size, invasion of skin or fascia, presence of residual cancer tissue (RCT) in the mastectomy specimen, and number of positive lymph nodes. Increasing tumour size, increasing number of nodes, and the presence of local invasion and RCT were all associated with a short duration of survival both from initial diagnosis and from first recurrence. None of the factors were related to either the extent of dissemination or the rate of progression. Patients who had their primary tumours located in the medial or central part of the breast had an increased incidence of mediastinal and pleural recurrences respectively. Primary tumours >5 cm, invasion of skin or fascia, and presence of RCT were all associated with an increased incidence of local recurrences. In addition, both RCT and fascial invasion were associated with increased occurrence of brain metastases. Most differences were explainable on the basis of local and regional lymphodynamics. Since the status of the features examined here all vary with time from tumour inception, it is suggested that the impact on prognosis is related to variations in tumour age from inception to primary diagnosis rather than to qualitative biological differences.

*Key words:* Breast cancer, spread, progression, patterns, relation to primary characteristics.

The rate of dissemination and the anatomical pattern of metastasis are important prognostic factors in patients with recurrent breast cancer (1–3). Moreover, the stage of disease at the time of initial diagnosis is also related to the duration of survival after the first recurrence (4–6). The initial stage of disease is a reflection of features such as tumour size, presence of local invasion, and regional metastasis. It is not known how these characteristics are related to the main prognostic factors of recurrent breast cancer. Theoretically, characteristics of the primary tumour may reflect either the underlying aggressiveness of the tumour or the length of time for which the tumour has been present, i.e. the tumour age (7). However, it may also be hypothesized that signs of poor prognosis are associated with either an increased growth rate and/or a propensity to develop a lethal anatomical pattern of spread (8).

The aim of the present study was to search for any relationships between features of the primary breast cancer and the extent of subsequent metastases, the anatomical location of the metastases, and the rate of progression. Thus, the aim was also to evaluate the possible modes of action of these initial or primary prognostic factors.

## Material and Methods

In the period from September 1977 to October 1981, a total of 6 201 patients with operable breast cancer entered the Danish Breast Cancer Cooperative Group's (DBCG) 77-protocols for primary and adjuvant therapy. Of these, 3 802 patients (61%) met the following 3 selection criteria: 1) The primary treatment and follow-up took place at one of the 4 participating oncological centres or at the regional medical or surgical departments. 2) Recurrences

Submitted 23 April 1990.
Accepted for publication 4 August 1990.

were detected before the 1st of January 1984. 3) The confirmative diagnosis of recurrent disease, and the subsequent treatment, was undertaken by the oncological centres.

The primary diagnosis and treatment comprised tumour excision and subsequent total mastectomy with partial axillary sampling (9). In some departments, the mastectomy was performed a few days after the biopsy. This two-stage procedure involved 31% of the patients.

The patients were grouped into two stages of disease, based on the histopathological features of the primary tumour and the regional nodes. Patients with stage I disease were in the low-risk group of recurrence, while patients with stage II disease were grouped in the high-risk group. The type of adjuvant therapy varied according to the initial stage of disease. Adjuvant loco-regional radiotherapy (equivalent to a CRE-value of 1 335) was given to all patients with either primary tumours $>5$ cm, histologically confirmed positive nodes, or local invasion of skin or deep fascia. These high-risk patients were thereafter randomized to different forms of systemic adjuvant therapy (10, 11). Low-risk patients (without any of the above-mentioned features) did not receive adjuvant therapy.

The histological evaluation of the diagnostic biopsy and the mastectomy specimen was performed in accordance with standardized guidelines. Macroscopic procedures comprised recording of tumour laterality, localization, size (longest diameter). Microscopic procedures comprised recording of presence of invasion of skin (epidermis and/or dermis) or the deep fascia, and presence of residual cancer tissue (RCT) in the margins of the biopsy cavity. All lymph nodes in the mammary axillary process and in the axilla were examined morphologically.

*Follow-up.* All patients were seen for physical examination every 3 months until 18 months after mastectomy, and every 6 months thereafter. Chest x-ray examination, bone scintigraphy, and blood chemistry, including liver enzymes, were carried out every 6 months for one year. Thereafter, chest x-ray examination was repeated once a year for another 4 years. An abnormal bone scintigram required bone x-ray survey.

The files of all patients who were taken off study before January 1984 were reviewed in the autumn of 1984. All metastatic sites detected within one month after diagnosis of the first site of metastasis were grouped together and designated as the sites of metastases at the time of first recurrence. Subsequent metastases in other sites and the date of their detection were recorded. These sites together with the sites of first recurrence were grouped together and designated as the cumulated sites of recurrence.

*Metastases.* The occurrence of metastases was recorded in the following locations: local skin (skin and/or subcutaneous tissue of the ipsilateral mammary region), other skin (skin and/or subcutaneous tissue outside the ipsilateral mammary region), regional lymph nodes (RLN; regional lymph nodes of the ipsilateral axillary or the periclavicular region), other lymph nodes (lymph nodes other than RLN), contralateral breast (all carcinomas in the contralateral breast were defined as recurrences of the primary tumour), bone (verified by x-rays), lung and pleura (demonstrated by x-ray examination; solitary pleural effusions required cytological verification), liver (demonstrated by ultrasound or CT-scans), and brain (confirmed by brain or CT-scans). The number of metastatic sites was defined as the number of the above-mentioned anatomical locations with metastasis, irrespective of the number of tumour deposits within each site.

The distribution of metastases was compared in patients who differed with respect to the following characteristics: tumour laterality and location within the breast, tumour size, presence of local invasion (skin or fascia) and RCT, and number of positive axillary nodes (Table 1). Occurrence of metastases in each of the anatomical locations was compared separately for each characteristic. The influence of RCT was evaluated both in the total group of patients and in a subgroup of patients, who had been treated with diagnostic biopsy and mastectomy as a one-stage procedure.

The occurrence of metastases was evaluated in the following five circumstances: 1) At the time of first recurrence (i.e. all patients). 2) Among patients with only a single metastasis at the time of recurrence. 3) At the time of follow-up (i.e. all patients). 4) Among patients with only a single metastasis at the time of follow-up 5) Among patients with recurrence within the first year after mastectomy.

These modes of evaluation were chosen from logical considerations: a strong association between a specific metastatic site and a pathoanatomical feature is presumed to appear early after primary treatment, as a single site of first recurrence and as a single recurrence during observation after initial recurrence.

Odds ratios (OR) were calculated in order to estimate the magnitude and the direction of differences in the frequency of metastases in various sites. An odds ratio $>1$ reflects an increased incidence of recurrence in patients with a specific pathoanatomical feature compared to a reference feature. Reference features were: tumour size $<3$ cm (low risk), $<5$ cm (high risk); 1–3 positive nodes; outer quadrant tumours; lower quadrant tumours; tumour located other than centrally; no local invasion (skin and fascia); no RCT (Table 1).

*Treatment of recurrent disease.* Low-risk patients with loco-regional recurrence received radiotherapy. Patients with distant metastases were followed up and treated according to uniform and protocolled guidelines. Premenopausal patients were castrated and received a 3-drug chemotherapy with cyclophosphamide, doxorubicin and 5-flourouracil. Postmenopausal patients below the age of 65 years received tamoxifen and chemotherapy combination with cyclophosphamide, methotrexate or doxorubicin, and 5-fluorouracil. Patients above the age of 65 years of

**Table 1**

*Study parameters, reference features, and number of patients*

| Study parameters | Stage* | Stratifications | | | Number of evaluable patients | Hereof with recurrence |
|---|---|---|---|---|---|---|
| | | Reference feature | vs. | Variable | n | n (%) |
| Tumor size | L | <3 cm | vs. | 3–5 cm | 1 309 | 225 (17) |
| | H | <5 cm | vs. | ⩾5 cm | 2 444 | 629 (26) |
| Local invastion | | | | | | |
| skin | H | absent | vs. | present | 2 466 | 635 (26) |
| fascia | H | absent | vs. | present | 2 450 | 635 (26) |
| Residual cancer | L&H | absent | vs. | present | 3 289 | 863 (23) |
| Number of positive regional lymph nodes | H | 1–3 | vs. | ⩾4 | 2 040 | 568 (28) |
| Location of the primary tumour | | | | | | |
| laterality | L&H | right | vs. | left | 3 802 | 863 (23) |
| location within the breast | L&H | lower | vs. | upper | 3 688 | 833 (23) |
| | | lateral | vs. | medial | | |
| | | peripheral | vs. | central | | |

*As defined in Material and Methods (L: low risk; H: high risk).

age received endocrine therapy only. Thus, patients who received chemotherapy were followed up 1–2 times every month, whereas patients who received endocrine therapy only were seen every second month.

*Statistical methods.* The use of multiple statistical tests increased the likelihood of a type I error (i.e. rejection of a true null hypothesis). We therefore decided that differences between pathoanatomical variables with respect to occurrence of metastases in different sites only were to be considered significant when ORs for all five modes of evaluation were >1 or <1 (i.e. all having the same direction). Moreover, it was required that at least one of the 5 ORs should be statistically significant.

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 parameters of tumour growth rate. In addition, the rate of progression was estimated from life-table analysis as the interval from initial recurrence in a single distant site until detection of other distant metastases (other events were ignored).

Comparison of the frequency of metastases was performed by the $\chi^2$-test or the rank t-test (Mann-Whitney rank sum test) for ordered categories. The Mantel-Haenszel $\chi^2$ statistics and odds ratios extended for stratified data were used in order to control for the possible confounding effect of differences in the number of sites with metastases, tumour size, number of positive nodes, and stage (e.g. when analyzing the effect of tumour size on the location of metastases, the statistics have been adjusted for the effect of number of sites and number of positive nodes) (12). Previous studies have shown that the type of systemic adjuvant therapy have only minor influence on the distribution of metastases at first recurrence (3). The potential confounding effect of adjuvant therapy was therefore not included in the stratified Mantel-Haenszel analyses.

Actuarial life-table analysis has been performed on all data concerning RFI, OS, SAR, and progression rates. The log-rank test was used to evaluate differences between survival and progression rates. A two-tailed p-value of $<0.05$ was considered significant.

## Results

*Patient characteristics.* As of the 1st of January 1984, 1 291 (31%) of the 3 802 patients had been taken off study. A clinical recurrence was detected in 863 patients (73%). The other causes of off study were death without clinical recurrence (18%), loss to follow-up (6%), or another primary cancer (3%). Twenty-six per cent of the patients were <50 years of age, and 36% were pre- or perimenopausal at the time of primary diagnosis. The median number of regional nodes removed by axillary sampling was 4.5 (25–75% fractiles: 3.1–7.2). More than 5 nodes were removed in 57% of the patients. Systemic adjuvant treatment was given to 67% of the high-risk patients (chemotherapy (41%), tamoxifen (42%), and levamisole (17%)).

*Survival.* The median time of follow-up was 4.9 years (range 2.0–7.0). The laterality and the location of the primary tumour had no significant influence on the duration of either RFI, OS or SAR. Increasing tumour size was associated with a significantly shorter RFI and OS, but not SAR. Moreover, at the time of first recurrence there was

**Table 2**

*Recurrence-free survival (RFI), overall survival (OS), and survival after recurrence (SAR) according to pathoanatomical features of the primary tumor. (Abbreviations: SPT = size of the primary tumor; RLN = positive regional lymph nodes; RCT = residual cancer tissue in the mastectomy specimen)*

| | No. of patients | 3-year actuarial survival rate (%) | | |
|---|---|---|---|---|
| | | RFI | OS | SAR |
| SPT (cm) | | | | |
| low risk | | | | |
| <3 cm | 590 | 84 | 93 | 63 |
| 3–5 cm | 606 | 79 * | 90 | 55 |
| =5 cm | 113 | 72 | 87 | 47 |
| high risk | | | | |
| <3 cm | 527 | 81 | 91 | 31 |
| 3–5 cm | 994 | 69 * | 79 * | 20 |
| ⩾5 cm | 923 | 57 | 68 | 20 |
| RLN (No.) | | | | |
| high risk | | | | |
| 0 | 426 | 78 | 85 | 29 |
| 1–3 | 1367 | 74 * | 84 * | 28 * |
| ⩾4 | 673 | 46 | 60 | 14 |
| RCT | | | | |
| Present | 1723 | 67 * | 79 * | 28 * |
| Absent | 1566 | 80 | 87 | 38 |
| Skin invasion | | | | |
| Present | 316 | 54 * | 67 * | 19 |
| Absent | 2150 | 69 | 79 | 22 |
| Fascial invasion | | | | |
| Present | 572 | 63 * | 74 * | 26 * |
| Absent | 1878 | 68 | 79 | 21 |

*p < 0.05 (log rank)

**Table 3**

*Distribution of metastases at first recurrence*

| | Patients | |
|---|---|---|
| | n | (%) |
| Soft tissue | 409 | (47) |
| Skin | | |
| local | 191 | (22) |
| other | 51 | (6) |
| Lymph nodes | | |
| regional, | | |
| axillary | 113 | (13) |
| periclavicular | 41 | (5) |
| regional, NOS* | 140 | (16) |
| other, | | |
| contralat. axilla | 31 | (4) |
| contralat. periclavicular | 14 | (2) |
| contralat. neck | 10 | (1) |
| ipsilat. neck | 20 | (2) |
| mediastinal | 18 | (2) |
| other nodes, NOS | 80 | (9) |
| Contralateral breast | 46 | (5) |
| Bone | 304 | (35) |
| Viscera | 361 | (42) |
| Lung | 202 | (22) |
| Pleura | 100 | (12) |
| Liver | 82 | (10) |
| Brain | 21 | (2) |
| Total No. of patients with recurrence | 863 | (100) |

NOS* = not otherwise specified.

an (insignificant) trend towards a shorter survival for patients with large tumours. The 3-year rates of SAR were 57% and 25% for low and high-risk patients respectively ($p < 0.0001$). A large number of positive nodes, fascial invasion and RCT was significantly associated with a decreased length of RFI, OS, and SAR (Table 2).

*Number of metastatic sites.* Seventy-one per cent of the patients had first recurrence confined to a single site. Two sites were involved in 18%, while 11% had more than two sites with metastases. The number of sites was not associated with either laterality of the primary tumour, size, local invasion, RCT, or number of positive nodes. Lower quadrant tumours were associated with recurrences in more sites than upper quadrant tumours; subgroup analysis showed that this was due to an increased number of metastases in patients with medial tumours compared to patients who had tumours situated laterally ($p = 0.026$).

*Anatomical location of metastases.* The most common sites of first recurrence were bone and lung followed by local recurrences (Table 3). The location of metastases varied according to initial stage, since postoperative radiotherapy was given to the high-risk patients only. Thus, low-risk patients most often had loco-regional recurrence (68%), while distant metastases were seen more often in the high-risk group (63%).

Figs 1, 2, and 3 illustrate the influence of the primary characteristics on the anatomical location of metastases. Generally, the location of recurrences was similar in different groups (i.e. an OR equal or near to one). However, the impact of tumour size on the location of metastases was not the same in the two risk groups. In the low-risk group, there was an increased incidence of bone metastases (OR: 1.49–6.47) and a decreased occurrence of contralateral breast tumours (OR: 0.17–0.51) in patients who had tumours of 3–5 cm, compared with patients with smaller tumours (Fig. 1A). In high-risk patients with tumours >5 cm local recurrences were observed more often than in patients with smaller tumours (OR: 1.09–2.80) (Fig. 1B). Patients with more than 3 positive nodes more often had bone metastases (OR: 1.16–1.92) and less often lung metastases (OR: 0.52–0.83) than did patients with fewer nodes. Other sites of metastases were equally distributed in the two node groups (Fig. 1C).

Patients who had invasion of either the skin or fascia developed local recurrence significantly more often than patients without these features (OR: 1.82–2.46 and 1.09–2.24 respectively) (Figs 2A and B). The incidence of brain

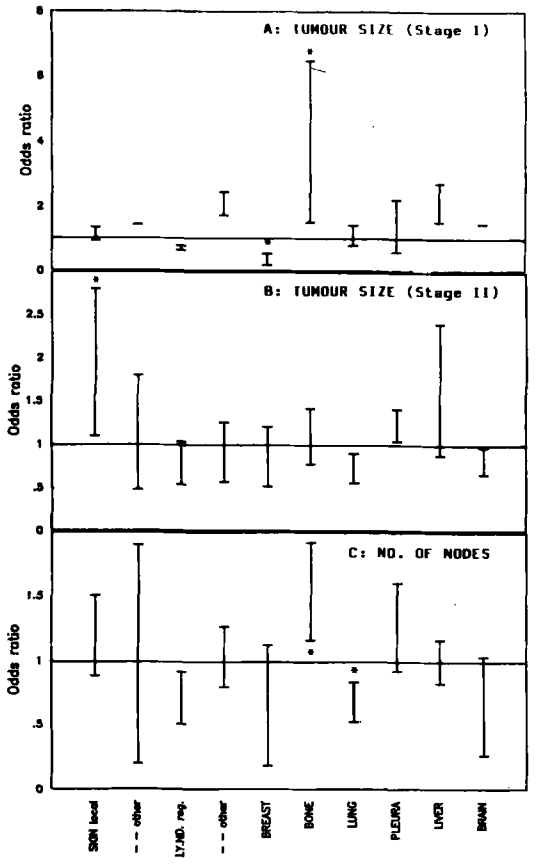


Fig. 1. Range of odds ratios (ORs) for tumour size and number of positive nodes according to anatomical location of metastases. The range of ORs is for the five modes of investigation (see Material and Methods). The asterisks (*) indicate that at least one of the ORs was statistically significantly different from one. An OR > 1 indicates an increased incidence of metastases compared to that of patients with the base-line feature (A: tumour size < 3 cm (stage I: low-risk patients); B: tumour size <cm (stage II: high-risk patients); C: 1–3 positive nodes).

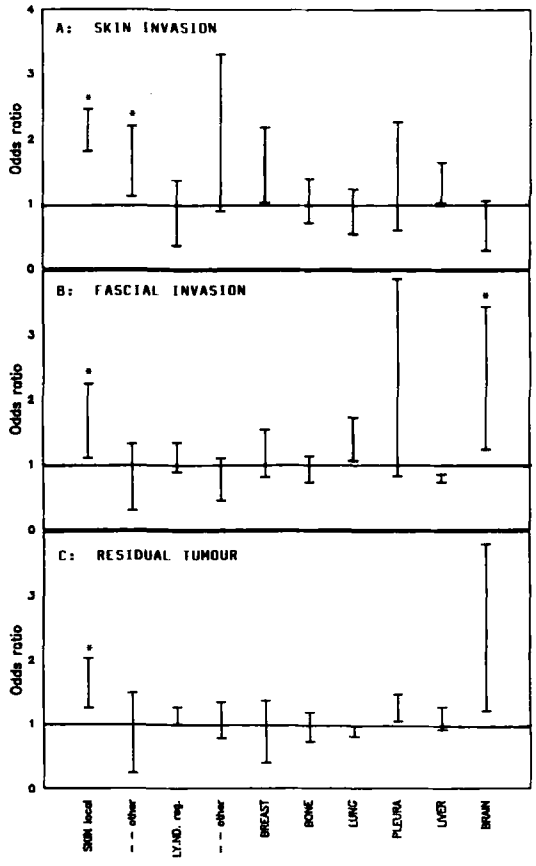


Fig. 2. Range of odds ratios (ORs) for the presence of skin invasion, fascial invasion and residual cancer tissue (RCT) according to anatomical location of metastases. For interpretation, see legend to Fig. 1. The base-line features were: no invasion of skin (A), no invasion of fascia (B), and no RCT (C).

metastases was increased in patients with fascial invasion (OR: 1.23–3.45), and 'other skin' metastases occurred more often in patients who had initial skin invasion (OR: 1.11–2.20). The presence of fascial invasion was not associated with increased incidence of 'other skin' metastases (Fig. 2B). The presence of RCT was associated with an increased incidence of local recurrences (OR: 1.25–2.03). The prevalence of metastases in other sites did not differ significantly in patients with and without RCT. It is noteworthy, however, that the ORs for brain metastases were in the range of 1.17–3.80 (Fig. 2C).

The laterality of the primary tumour had no influence on the anatomical location of metastases (data not shown). The ORs for the different locations of the primary tumours showed that recurrence in pleura and lung occurred less often in patients who had their primary tumours located in the upper and medial part of the breast (Figs 3A and B). Other lymph node metastases (other than regional—axillary or supraclavicular) were noted more often in patients who had medially situated primary tumours (OR: 1.08–3.30). Tumours of the contralateral breast and pleural recurrences occurred more often in patients who had their primary tumours located in the central part of the breast (Fig. 3C).

*Rate of progression.* A total of 456 of the 863 patients with recurrence had their metastases confined to a single distant site. The anatomical distribution of these metastases was similar to the location of metastases in patients with initial recurrence in more than one site (data not shown). The systemic treatment of the 456 patients with an initial single site of recurrence was chemotherapy (CT) in 9%, endocrine therapy (ET) in 38%, CT + ET in 37%, and other treatments in 16% of the patients. The different types of treatment were equally distributed among patients from the various groups of primary tumour characteristics.

Follow-up of patients with only a single distant metastasis showed that 24% of the low-risk patients and 43% of the high-risk patients developed additional recurrences within 3 years ($p = 0.29$). The time to additional recurrence after an initial single metastasis was analyzed

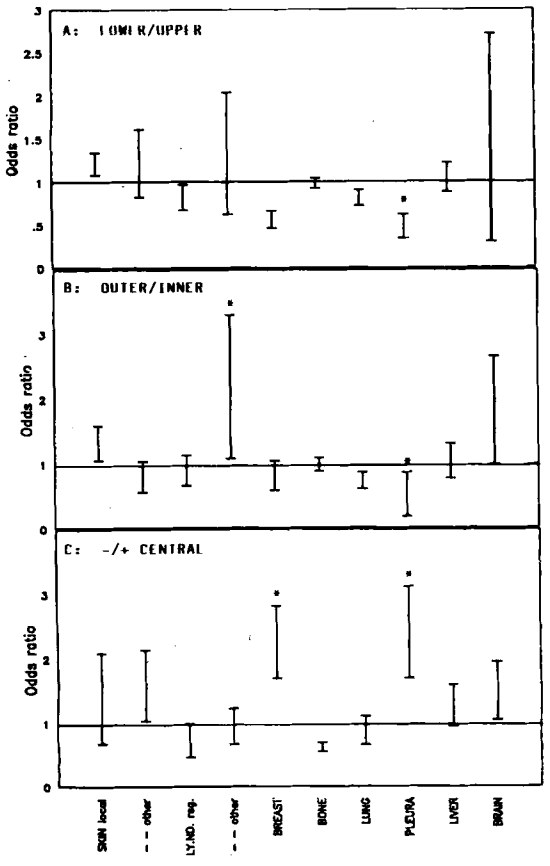


Fig. 3. Range of odds ratios (ORs) for location of the primary tumour according to the anatomical location of metastases. For interpretation, see legend to Fig. 1. The base-line features were: lower quadrant tumours (A), outer quadrant tumours (B), and peripherally (not centrally) located tumours (C).

according to the status of all the pathoanatomical features examined here. The 3-year cumulated progression rates were in the range of 20–52%. There were no statistically significant differences between any of the groups ($p = 0.24–0.99$).

## Discussion

The present study was a search for relationships between the status of prognostic factors at the time of initial diagnosis and the temporal and anatomical pattern of (the subsequent) dissemination. In agreement with the findings of others, numerous positive nodes (6, 13) and a large tumour size (4, 7) were associated with a significant reduction of SAR. Furthermore, the study shows that the presence of both fascial invasion and RCT is also related to a decreased duration of SAR.

The status of all these factors increases with age of the tumour, i.e. the time from tumour inception to primary diagnosis. Tumours with signs of poor prognosis are thus supposed to be older than tumours with more favourable prognostic signs. As demonstrated in Table 4 one could regard these features as chronological prognostic factors (14, 15), and consequently one could consider the influence on prognosis as a lead time phenomenon. Alternatively, biological or qualitative prognostic factors are features which reflect tumours that differ with respect to either the rate of growth or the pattern of spread (8).

The reduction in the duration of SAR in patients with local or regional advanced tumours may indicate that differences in initial stage (or risk group) define tumours which differ biologically (13). However, the present study shows that neither the growth rate nor the extent of disease is related to the status of the primary pathoanatomical features. This is supported by studies, which showed no significant association between the growth rate and stage, node status, and tumour size (16–18). Therefore, if the pathoanatomical factors examined here influence prognosis via a biological (or qualitative) mode of action, it may be through propensities to develop metastases in certain sites (Table 3).

*Tumour size, node status.* It was expected that patients with signs of poor prognosis mainly would develop metastases in more lethal sites than would patients who had more favourable prognostic signs. We found an increased incidence of bone metastases in patients who had signs of poor prognosis (either large primary tumours or more than three positive nodes). Moreover, there was a decreased incidence of lung metastases in patients with signs of short survival (more than three positive nodes). Both of these findings are incompatible with the hypothesis proposed above, since patients with bone metastases have a relatively good prognosis, while patients with visceral recurrences have a shorter survival (3, 19).

The finding of increased incidence of local recurrences in patients with large primary tumours is in agreement with other studies (20–22). If biological factors exist in the 'soil' of a target tissue (i.e. the skin), one would expect an increase in the number of both local and 'other skin' metastases. However, the incidence of recurrence in 'other skin' was similar in patients with small and large primary tumours. It seems probable, therefore, that the association of local recurrences and tumour size is due to other than biological factors.

Increasing tumour size is associated with an increase in the extent of regional lymph node metastases, which may lead to an obstruction of the lymphatics, followed by a decrease of the lymphatic flow. Metastasizing tumour cells are probably trapped in the lymphatics of the mastectomy flaps. Thus, local recurrences may develop from these cells (23). Moreover, the increased incidence of local recurrences in patients with larger tumours probably also depends on an increased risk of leaving tumour extensions behind during mastecomy. Thus, increasing tumour size might entail an increased risk of cutting through the tumour extensions with a consequent risk of seeding of tumour cells.

**Table 4**

*Prognostic factors*

| Type | Mode of action | Clinical method of investigation |
|---|---|---|
| Chronological | Identification of tumours which differ with respect to age (from inception to primary diagnosis) | None |
| Biological | Identification of tumours which differ with respect to | |
| | growth rate | Progression time |
| | pattern of metastases | Number of involved sites<br>Anatomical location |

*Invasion of skin and fascia.* The initial presence of skin invasion was associated with an increased incidence of skin recurrences. These recurrences were found locally as well as in 'other skin', which supports the theory that the propensity to invade skin reflects tumours with a potential of site-specific metastasizing. This pattern did not apply to tumours which invaded the deep fascia. These tumours recurred significantly more often in the brain.

*Residual cancer.* In another DBCG-study, the presence of RCT was significantly associated with a reduction in RFI (24). The study only included patients who were treated with biopsy and mastectomy as a one-stage procedure. The present study also included patients who, for various reasons, were treated with biopsy and a delayed mastectomy (days). Rapid dissemination of RCT in patients with delayed mastectomy could be a possible explanation of the poor prognosis for these patients. Moreover, rapid dissemination could be related to the type of biopsy (although excisional biopsy was always intended, some patients might have received incisional biopsy). We are not able to distinguish the type of biopsy (excisional vs. incisional). However, the exclusion of patients with delayed mastectomy did not alter the present results, neither with respect to the survival nor to the pattern of spread. Therefore, we do not think that the poor prognosis for patients with RCT is associated with a rapid dissemination in connection with the diagnostic biopsy, as suggested by Andersen et al. (24).

As expected, the presence of RCT was associated with subsequent development of local recurrences. Except for brain metastases, however, other sites were equally distributed in patients with and without RCT. It is suggested that the influence on prognosis of RCT may be of the biological type: RCT-positive tumours have specific growth features, which are associated with an increased incidence of brain metastases, which in turn is associated with a decreased duration of SAR.

*Tumour location in the breast.* All parts of the breast are drained via both the medial and the lateral lymphatics. Although the lateral route is quantitatively dominant even for the medial and the central part of the breast, there are some differences between the different parts. Thus, the proportion of the lymph that takes the medial route is somewhat larger in the medial and central parts of the breast compared to the lateral (25). These differences may influence distributions of metastases from tumours which are located in different parts of the breast. The study shows that centrally and medially located primary tumours recurred more often in the pleura and in lymph nodes ('other than regional') respectively. The majority of the latter was located in the mediastinum. The findings of pleural and mediastinal metastases in patients with medially and centrally located tumours are thus in accordance with the direction of the lymphatic drainage (26, 27).

In this study we have focused on the pattern of metastasis and the progression of metastatic disease in relation to the status of prognostic factors established at the time of primary diagnosis. Since we only studied the effect of prognostic factors in patients with metastatic disease, it is not possible to evaluate the mode of action of prognostic factors with respect to the metastatic potential of the primary tumours.

The present material has been followed up to 7 years after the primary diagnosis. When considering the relatively long clinical course of breast cancer, this period seems rather short. This implies that the study population is dominated by patients with signs of poor prognosis. If the distribution of metastases varies with time from primary diagnosis, a short period of observation might invalidate the results. Analyses of the present material have shown a similar distribution of metastases in different periods after mastectomy (19). Accordingly, many other studies have shown that the temporal pattern of metastasis is unaltered or similar up to 15 years after primary diagnosis (28–31). Thus, as there are no indications from the literature which support that metastatic distributions change with time from initial diagnosis, we do not think that a longer period of follow-up would alter the present results.

In conclusion, the clinical course of metastatic breast cancer, estimated as the rate of progression and pattern of dissemination, was in most cases unassociated with the

status of the pathoanatomical features of the primary tumour. The status of all these factors increases with time from tumour inception. Apart from differences in metastatic potential, the mode of action on prognosis is supposed to be due to differences in the age of the tumour at the time of initial diagnosis. Therefore, pathoanatomical features of the primary tumour may be regarded as chronological rather than qualitative or biological prognostic factors.

## ACKNOWLEDGEMENTS

The authors wish to thank Tove Nørgaard, PhD, Department of Pathology, FAC Hillerød, for advice and critical comments. This work was supported by a grant from the Danish Medical Research Council, No. 12-8047.

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