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THE PATTERN OF METASTASES IN HUMAN BREAST CANCER

Influence of systemic adjuvant therapy and impact on survival

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Abstract

Of the 3802 patients enrolled in the DBCG 77 protocols, 863 developed clinical recurrence within a median follow-up time of 4.9 years (range 2.0–7.0). More than 69% of these had their first recurrence confined to a single anatomical site and 12% had more than two metastatic sites. The most common sites were bone (35%), lung (23%), skin (22%), and regional lymph nodes (16%). The observation period after first recurrence was 3.6 years (range 0.8–6.4). Survival after recurrence was significantly related both to the location and the number of metastases. Patients who were given adjuvant chemotherapy (n=134) had significantly fewer metastatic sites and significantly more frequent liver metastases than untreated patients (n=50). Patients who received adjuvant tamoxifen (n=154) had the same number of metastatic sites, but more often had lung metastases than untreated patients (n=201). These results probably reflect that metastases in different anatomical locations differ with respect to sensitivity to antineoplastic treatments.

Key words: Breast cancer, systemic adjuvant treatment, pattern of recurrence.

The metastatic process involves selection and adaption of circulating tumour cells to grow in different anatomical locations. Experimental studies have shown that the heterogeneous composition of malignant tumours includes both intratumoural heterogeneity of the primary tumour, differences between primary tumour and the metastases, and differences between metastases located in various anatomical sites (8, 18). Clinically, the heterogeneity is reflected by the response rate to antineoplastic treatments, which varies with respect to the location of the metastases (11). Accordingly, the effect of systemic adjuvant treatment (SAT) may vary according to the anatomical site of subclinical disease, and this may influence the subsequent patterns of first recurrence.

The aim of the present study was to describe the pattern of first recurrence in patients treated in accordance with the DBCG-protocols for primary local or regional breast cancer (1). The metastatic pattern was related to the type of systemic adjuvant treatment, and the survival after recurrence was analysed according to the dominating metastatic site.

Material and Methods

The patients were all enrolled in the first generation of adjuvant DBCG trials. Details of this study have been given elsewhere (1). The primary treatment and follow-up took place at one of the 4 participating oncological centres or at their regional medical or surgical departments. The confirming diagnosis of recurrence and the subsequent treatment was undertaken at the oncological centres. A total of 3802 patients (61%) of the 6201 patients who entered the protocols were allocated to the present study.

The primary treatment was total mastectomy with axillary lymph node sampling (6). Patients with tumours 5 cm or less in diameter, no positive nodes, and no invasion of skin and fascia (low-risk patients, stage I) received no further therapy after mastectomy. The remaining high-risk patients (stage II) all received postoperative radiotherapy and were, thereafter, stratified according to menopausal status and randomised to either no further treatment,

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chemotherapy (premenopausal patients only), levamisole (pre- and postmenopausal patients), or tamoxifen (postmenopausal patients only). Adjuvant chemotherapy was given every 4 weeks for 12 cycles with either cyclophosphamide orally or cyclophosphamide orally combined with methotrexate and 5-fluorouracil intravenously. Details of the adjuvant treatment have been presented elsewhere (7, 14, 17).

Information about the anatomical location of metastases was obtained from a review of patient records. Sites of first recurrence included all metastatic locations detected within one month from diagnosis of the first site of metastases. The sites of metastases were divided and defined as follows.

Skin: Local skin recurrence (skin and/or subcutaneous tissue of the ipsilateral mammary region). Other skin recurrence (skin and/or subcutaneous tissue outside the ipsilateral mammary region).

Regional lymph nodes: Recurrence of regional lymph nodes of the ipsilateral axilla or the periclavicular region.

Other lymph nodes: Recurrence of lymph nodes other than regional.

Contralateral breast: All carcinomas in the contralateral breast were regarded as recurrence of the primary tumour.

Bone: Metastases required verification by radiography.

Viscera: Lung and pleural recurrences demonstrated by radiography; pleural effusions required cytological verification. Liver metastases: Demonstrated by ultrasonic or CT-scans. Brain metastases: Confirmed by brain or CT-scans.

Other sites were verified by appropriate investigations.

The number of metastatic sites was defined as the number of the above mentioned anatomical locations with metastases irrespective of the number of tumour lesions deposited within each site. The dominant site of metastatic disease was designated as recurrence in one of the three main sites of metastases, namely viscera, bone, or soft tissue in decreasing order of priority.

The incidence of metastases in a specific site was defined as the number of patients with metastases at the site divided by the total number of patients with recurrence. Comparisons were performed by using the χ^2-test, and the differences in the number of metastatic sites were evaluated by using the rank t-test (2, 5). Odds ratios (OR) with 95% confidence interval were used to describe the direction and the magnitude of differences between occurrences of metastases in patients given systemic adjuvant treatment compared to untreated controls. An OR near or equal to one indicates an equal incidence of metastases in 2 groups. A great OR indicates a greater incidence of metastases in treated patients compared to the untreated ones. The survival after recurrence was analyzed by the actuarial life-table method, and the differences between survival curves were evaluated by the log-rank test (16). A 2-tail p-value of less than 0.05 was considered significant.

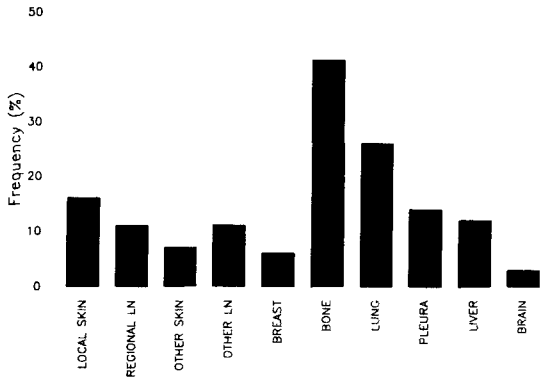

Fig. 1. Anatomical distribution of metastases in 635 (100%) patients with recurrence after stage II breast cancer.

Table 1

Distribution of the total number of patients and the study population according to stage, menopausal status, and type of systemic adjuvant therapy

	No. of patients	No. of patients with recurrence
Stage I	1 334	228
Stage II	2 468	635
Premenopausal		
No systemic adjuvant therapy	146	50
Levamisole	90	38
Chemotherapy	671	134
Postmenopausal		
No systemic adjuvant therapy	679	201
Levamisole	186	58
Tamoxifen	696	154
Total	3 802	863

Results

Of the 3802 patients 36% were premenopausal, and 26% >50 years. The distribution of patients according to stage, menopausal status, and systemic adjuvant treatment is presented in Table 1. The median follow-up time was 4.9 years (range 2.0–2.7), and 863 patients have developed recurrence before the follow-up date (Jan. 1, 1984).

Pattern of metastases. The most common anatomical sites of recurrence were bone (35%), lung (23%), local skin (22%), and regional nodes (16%). The anatomical distribution of metastases was related to whether radiotherapy was given post-operatively or not (10). Thus, the most common locations of metastases in patients with stage I disease were locoregional. Bone, lung, and pleura metastases were most common in patients with stage II disease (Fig. 1). Of the patients 69% had their first recurrence confined to a single anatomical site, whereas 12% had more than 2 metastatic sites.

Concerning the dominant site of metastases, 79% recurred in a single anatomical site, 18% in 2 sites, and 3% in 3 sites. Most patients had their dominant site of metas-

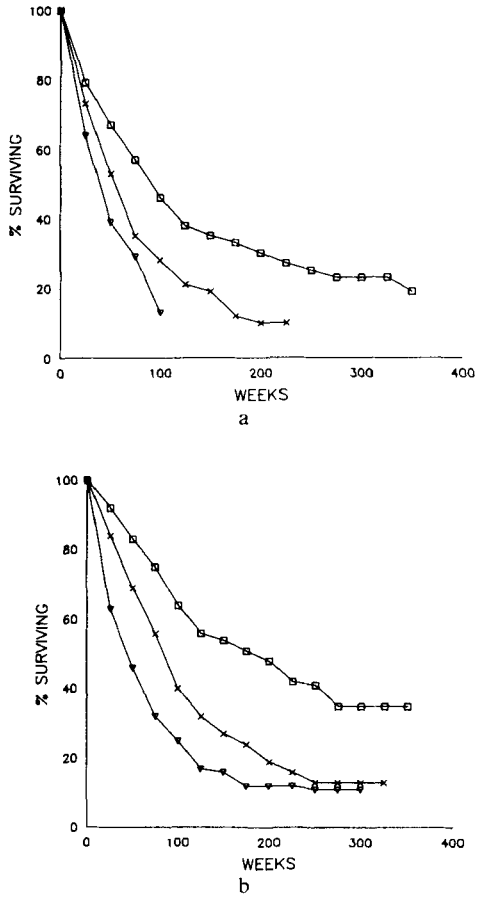

Fig. 2. a) Survival after first recurrence in relation to number of main site with metastases. □ 1 site (n=678); 2 sites (n=157); ▼ 3 sites (n=28). b) Survival after first recurrence in relation to dominant site of recurrence. □ soft tissue (n=277); × bone (n=225); ▼ viscera (n=361).

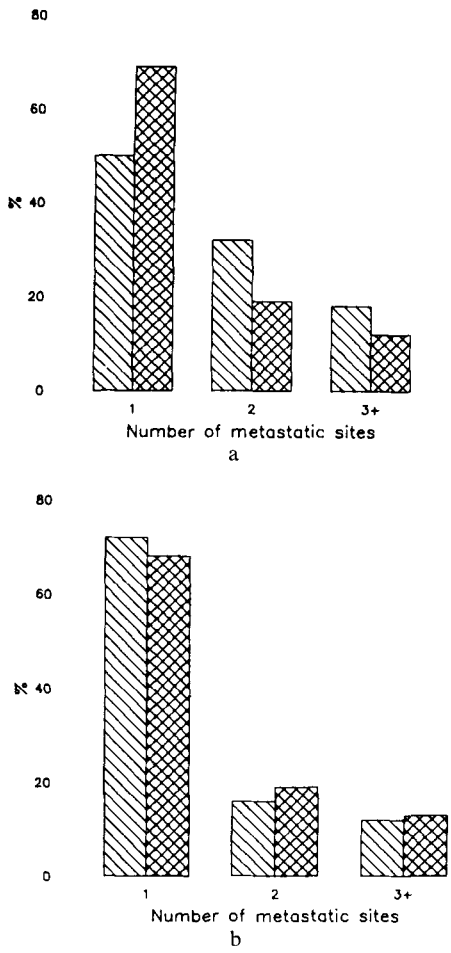

Fig. 3. Number of metastatic sites according to type of systemic adjuvant therapy; n (=100%) indicates the total number of patients in each group. a) Chemotherapy (▩ n=134). Control (▧ n=50). b) Tamoxifen (▩ n=154). Control (▧ n=201).

tases in either soft tissue (32%) or bone (26%), while 42% of the patients had metastases in all 3 main sites.

Survival after recurrence. The observation period after first recurrence was 3.6 years (range 0.8–6.4). The survival after recurrence was significantly related to the main location of recurrent disease, and it decreased with increasing degree of dissemination ($p<0.0001$) (Fig. 2).

Extent of metastases. The median number of metastatic sites was approximately the same in patients given tamoxifen as in untreated controls ($p=0.57$). However, the group of patients who received chemotherapy had a significantly decreased number of metastatic sites ($p=0.04$) (Fig. 3).

Distribution of metastases. When considering the main site of metastases the distribution was approximately the same in patients given systemic adjuvant treatment as in untreated controls (Table 2). However, as regards the anatomical sites of metastases, differences emerged between treated and untreated patients (Fig. 4). Liver metastases thus occurred approximately 3.6 times more often in patients given adjuvant chemotherapy and lung metastases about 1.6 times more often in patients given tamoxifen than in untreated controls ($p<0.05$). Moreover, as can be seen from the figure, other lymph node metastases (non-regional) occurred significantly less often in patients given adjuvant chemotherapy.

Discussion

The study confirms that most patients recur in a single anatomical site, and that the most common locations of distant metastases are bone, lung, pleura, and liver (9). A thorough knowledge of the anatomical site of metastases at the time of first recurrence is important for clinical, therapeutic and scientific reasons: Clinically, since the survival after recurrence depends on both the extent and the anatomical distribution of metastases (15), which also was confirmed by the present study. Therapeutically, since many centres currently prefer to treat patients with isolated loco-regional recurrence with surgery and/or ra-

Table 2

Distribution of patients according to main site of metastasis and type of systemic adjuvant therapy. n indicates the total number of patients in each group

	Chemotherapy				Tamoxifen			
	Yes		No		Yes		No	
Main site of metastasis	n 134	% (100)	n 50	% (100)	n 154	% (100)	n 201	% (100)
Soft tissue	44	(33)	21	(42)	57	(37)	86	(43)
Bone	62	(46)	22	(44)	56	(36)	75	(37)
Viscera	67	(50)	29	(58)	79	(51)	94	(48)

diotherapy. Moreover, a thorough evaluation of all measurable disease may serve as a base-line criterion before prospective therapeutic studies (3). Scientifically, because clinical research regarding factors influencing metastatic pattern should rely on valid information on the anatomical location of metastases.

Since response rates to antineoplastic treatment of advanced breast cancer are known to vary with the location of metastases (11), the use of systemic adjuvant treatment may be expected to change the pattern of first recurrence. The present study was conducted in order to investigate this hypothesis. The study showed no relation between the pattern of metastases and systemic adjuvant treatment when only the dominant site of metastasis was considered. When the occurrence of metastases in different anatomical locations was considered, however, patients who had received adjuvant chemotherapy had liver metastases more often and non-regional lymph node recurrences less often; moreover, patients receiving adjuvant tamoxifen more often had lung metastases. Furthermore, the number of metastatic sites was lower in patients receiving chemotherapy.

From the literature there is only little evidence of an altered incidence of metastases in different anatomical sites from studies reporting results of systemic adjuvant treatment of breast cancer. Generally studies document the first site of recurrence either as loco-regional and distant or as dominant site of metastases, and they do not specify the anatomical distribution of metastases (4, 12, 13). The present study shows the necessity of detailed information on the presence of recurrence in the individual anatomical sites.

The results presented here agree with experimental data, which show that metastases in various sites differ with respect to sensitivity to antineoplastic treatment. When selecting and combining drugs for future adjuvant trials one should consider the possible role of site specific differences of response rates. This can be done either by studying the site specific response rates in patients with advanced breast cancer or, as was done here, by analyzing the pattern of recurrence in comparable groups of patients receiving different forms of SAT.

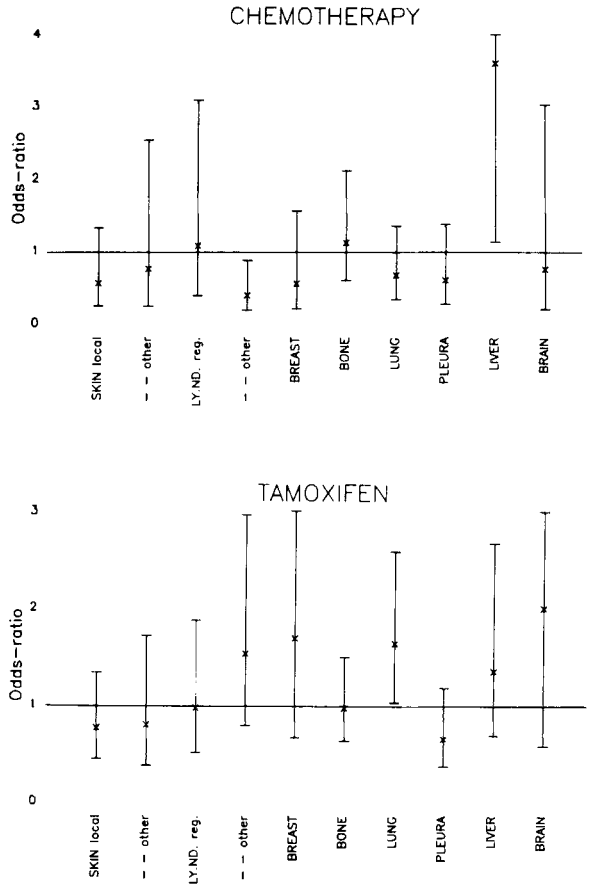

Fig. 4. Odds ratio (with 95% confidence intervals) of the occurrence of metastases in different anatomical locations in patients receiving adjuvant chemotherapy or tamoxifen compared to untreated patients. An odds ratio equal to one indicates equality of the occurrence of metastases in treated and untreated patients.

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