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Adjuvant Systemic Treatment and the Pattern of Recurrences in Patients with Breast Cancer

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Abstract—*The aim was to analyze the impact of adjuvant systemic treatment (AST) on the anatomical distribution, the number, and the temporal relationship of the first metastases in 635 patients (pts) with breast cancer. These patients participated in the prospective studies of AST of the Danish Breast Cancer Cooperative Group (DBCG) 77-program. All patients had primary high-risk breast cancer (i.e. node positive or local invasion or tumor size >5 cm). The initial treatment was mastectomy with axillary sampling, followed by postoperative radiotherapy. The types of AST and the number of patients with recurrence were: chemotherapy (CT), 134 pts; levamisole (LEV), 96 pts; tamoxifen (TAM), 154 pts. The pattern of recurrence in these patients was compared with the pattern of recurrence in 251 pts who did not receive AST (controls). Although CT reduced the total number of metastatic sites (P = 0.04), the incidence of liver metastases was increased compared to untreated controls (P = 0.02). The median number of metastatic sites was equal in TAM- and LEV-treated pts compared to controls. The incidence of lung metastases was increased in TAM-treated pts (P = 0.03), and LEV-treated pts had a decreased incidence of lymph node (P = 0.01) and pleural recurrences (P = 0.01) compared to controls. The results may suggest that mechanisms of clonal selection during the metastatic process involve differences in sensitivity to antineoplastic treatments of metastases at various anatomical locations.*

INTRODUCTION

THE modern approach to primary treatment of breast cancer comprises both local and systemic therapy. The use of adjuvant systemic treatments (AST) is based on the concept of tumor dissemination at the time of presentation. Despite many efforts to cure patients by AST, most of the patients still recur, and the gain in survival is limited [1, 2]. While selection of resistant cell clones during AST is probably the major cause of recurrence, the length of survival after recurrence (SAR) is determined by the number and the location of metastases [3–5].

Clonal selection of tumor cells during growth and spread leads to heterogeneity, which is expressed in both histopathological and biochemical tumor characteristics [6, 7]. In clinically advanced breast cancer, this heterogencity is expressed in response rates to antineoplastic treatments which vary with the anatomical locations of metastases [8–10]. However, there is only little information concerning the anatomical distribution of recurrences in patients who received AST [11–13]. Despite the paucity of data regarding variability in response to antineoplastic treatment at different sites, particularly concerning cytotoxics, it must be supposed that the distribution of metastases at the time of initial recurrence varies with and reflects the type of AST.

Since the study of differences in the metastatic pattern in patients receiving different forms of AST may give a hint about where and when a specific treatment fails, we have studied the timing and the distribution of recurrences of patients who were enrolled in the first generation of adjuvant trials of the Danish Breast Cancer Cooperative Group (DBCG).

MATERIALS AND METHODS

Details of the organization of the DBCG have been given elsewhere [14]. All the patients in the present study had a tumor size >5 cm and/or

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positive axillary lymph nodes, and/or skin or deep fascial invasion. They were registered in the DBCG from September 1977 until November 1982, and the primary treatment and follow-up took place at one of four participating oncological centers or at their corresponding medical or surgical departments. After mastectomy and locoregional radiotherapy the patients were divided into two subgroups, with premenopausal and perimenopausal patients in one group, and postmenopausal patients in the other. The former group of patients was randomized to the following adjuvant treatments: A, No further therapy. B, Levamisole, 2.5 mg per kg body weight, given for 2 consecutive days and repeated weekly for 1 year. C, Cyclophosphamide, 130 mg per square meter p.o. days 1–14, every 4 weeks for 12 cycles. D, Cyclophosphamide, methotrexate and 5-fluorouracil (CMF: C, 80 mg per square meter p.o. days 1–14; M, 30 mg per square meter i.v. days 1 and 8; F, 500 mg per square meter i.v. days 1 and 8) every 4 weeks for 12 cycles. The postmenopausal patients were randomized to either treatment A (no further treatment), B (levamisole as the premenopausal patients), or C (tamoxifen at a daily dose of 10 mg × 3 for 48 weeks) [14].

The patients comprised 80% of the patients who were randomized in the DBCG-77 protocols for follow-up and adjuvant treatment (Table 1). Follow-up took place in the autumn of 1984. The median time (range) of follow-up was 4.9 years (2.0–7.0 years). At January 1984, 947 out of the 2468 patients (38%) had left the protocols because of either clinical recurrence (635 patients, 67%), death without clinical recurrence (17%), loss to follow-up (13%), or other primary cancer (3%). Sixty per cent of the patients lost to follow-up were classified as such because of insufficient data—they were no referred to the oncological center at the time of recurrence. These patients are, however, comparable with those with a known cause for having been taken off study with respect to age, menopausal status, degree of anaplasia, size of the primary tumor, and regional lymph node (RLN) status (data not shown).

In case of clinical recurrence information about the anatomical location, the date of detection and subsequent treatment was obtained from the records. Sites of *first recurrence* included all metastatic locations detected within 1 month from diagnosis of the first site of metastasis.The *cumulated sites* of recurrence included the site of first recurrence together with all new sites of recurrence up to the date of follow-up. Details of the primary local treatment and follow-up have been given elsewhere [15, 16].

The sites of metastases were divided and defined as follows: Soft tissue: 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 node recurrence (RLN; regional lymph nodes of the ipsilateral axilla or the periclavicular region). Other lymph node metastases (OLN; lymph nodes other than RLN). Contralateral breast tumors (all carcinomas in the contralateral breast were regarded as recurrence of the primary tumor). Bone metastases required verification by X-rays and, when possible, the bone morphology was recorded as osteoblastic, osteolytic or mixed. The sites of bone metastases were grouped into the following regions: cranium, columna, pelvis, thorax and extremities. Visceral metastases: lung and pleural recurrences (demonstrated by X-ray examinations; solitary 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 metastasis irrespective of the number of tumor deposits within each site.

Comparisons of the distribution of metastases were carried out for the following three groups: (A) pre-/perimenopausal patients who received no AST vs. chemotherapy (CT); (B) postmenopausal patients who received no AST vs. tamoxifen (TAM); and (C) pre- peri- or postmenopausal patients who received no AST vs. levamisole (LEV). Due to an increased rate of recurrence and death, the randomization of premenopausal patients to no adjuvant systemic treatment (control arm) and of all patients to levamisole (17) was stopped in January 1981 and in December 1979, respectively. Because of the early closing of the control and the levamisole arms, the median follow-up times are longer for these patients. As this could possibly precipitate differences in metastatic patterns when comparing the different groups of patients, the incidence of metastases was compared in patients who had recurrence in the first year after mastectomy as well as in the following years. Thus, the incidence of metastases was evaluated in the following three ways: (1) at the time of first recurrence; (2) at the time of follow-up (i.e. cumulated site of metastases), and (3) within the first year after mastectomy.

The incidence of metastases in a specific site was defined as the number of patients with metastases in the site divided by the total number of patients with recurrence. Comparisons were performed using the Chi-square test [18]. Differences in the number of metastatic sites within each group were evaluated, using the rank t test for ordered categories and corrected for ties (Mann–Whitney rank sum test) [19]. The Mantel–Haenszel statistics extended for stratified data were used in order to control the

Table 1. Characteristics of the patients and their primary tumors in the present material compared with the material of the Danish Breast Cancer Cooperative Group—protocol 77 (DBCG-77) (n (%) indicates the number of patients in each group)

	Present material		DBCG-77	
	n	(%)	*n*	(%)
Total no. of patients	2468	(100)	3074	(100)
Age (yrs)				
<50	633	(26)	795	(26)
50–59	613	(25)	781	(25)
≥60	1222	(49)	1498	(49)
Menopausal status				
Pre-/perimenopausal	907	(37)	1143	(37)
Postmenopausal	1561	(63)	1931	(63)
Primary tumor size (cm)				
≤2	123	(5)	157	(5)
3–5	1757	(71)	2175	(71)
>5	564	(23)	714	(23)
Unknown	24	(1)	28	(1)
Positive nodes (no.)				
0	427	(17)	542	(18)
1–3	1367	(55)	1693	(55)
≥4	673	(27)	838	(27)
Unknown	1	(1)	1	(1)
*Degree of anaplasia**				
I	539	(22)	708	(23)
II	1196	(48)	1498	(49)
III	399	(16)	479	(16)
Not graded	334	(14)	389	(13)
Systemic adjuvant therapy				
None	825	(33)	1032	(34)
Chemotherapy	671	(27)	845	(27)
Levamisole	276	(11)	333	(11)
Tamoxifen	696	(28)	864	(28)

*Ductal carcinomas only.

possible confounding effect for differences in the number of sites and period of recurrence [20]. Odds ratios (OR) with 95% confidence limits (95% CL) [18] were calculated in order to estimate differences in the incidence of recurrence at a specific site. An OR >1 reflects an increased incidence of recurrence in patients receiving AST compared to controls. Recognizing that the use of multiple statistical tests increases the likelihood of a type 1 error (i.e. rejection of true null hypothesis), differences between the AST and the control group of patients with respect to occurrence of metastases in a specific anatomical site were only considered significant when ORs for the three methods of evaluation were all >1 or <1, and with at least one test being *statistically* significant. A two-tailed P value of less than 0.05 was considered significant.

RESULTS

The results of AST from the DBCG-77 program have been presented previously [15, 17, 21–23].

A total of 635 patients had clinical recurrence. Of these, adjuvant cytotoxic therapy was given to 134 (21%), levamisole to 96 (15%), and tamoxifen to 154 patients (24%). The remaining 251 patients (40%) did not receive AST (controls).

Pattern of metastases

The occurrence of metastases in various anatomical locations in the group of patients receiving AST was almost equal to the corresponding groups of controls. However, the incidence of liver metastases was higher among patients who received adjuvant CT; $P = 0.038$ (OR, 3.59, 95%; CL, 1.11–11.61). The incidence of lung metastases was higher among patients who received adjuvant tamoxifen compared to untreated controls; $P = 0.030$ (OR, 1.61, 95%; CL, 1.02–2.58). Moreover, among patients with recurrence, the incidence of recurrences of lymph nodes other than regional was reduced in patients who received either CT ($P = 0.014$) or LEV ($P = 0.016$), compared to the corresponding groups of controls. In addition, the incidence of pleural recurrences was reduced among patients

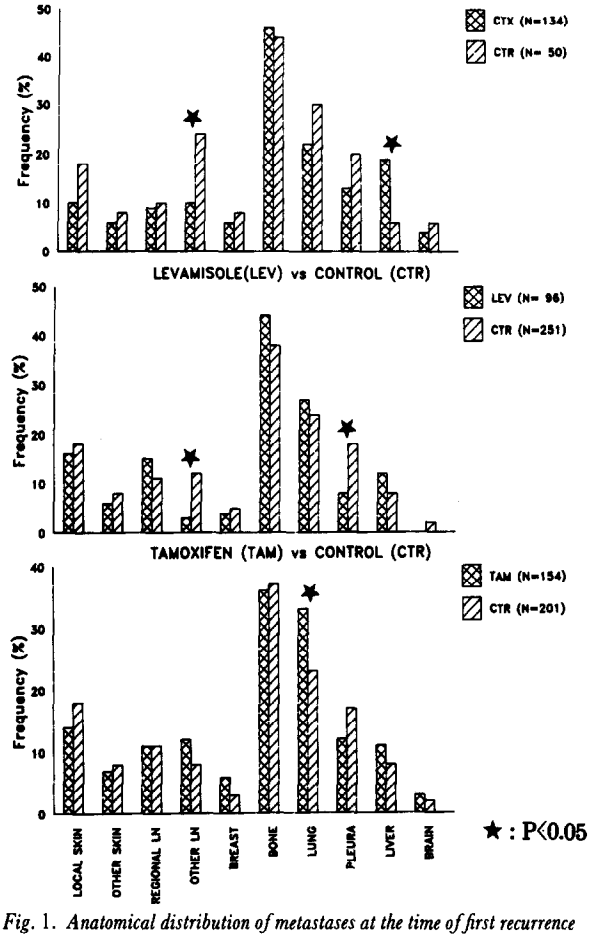

Fig. 1. Anatomical distribution of metastases at the time of first recurrence according to type of adjuvant systemic treatment. The heights of the columns reflect the frequency of metatases among the total number of patients with recurrence (n).

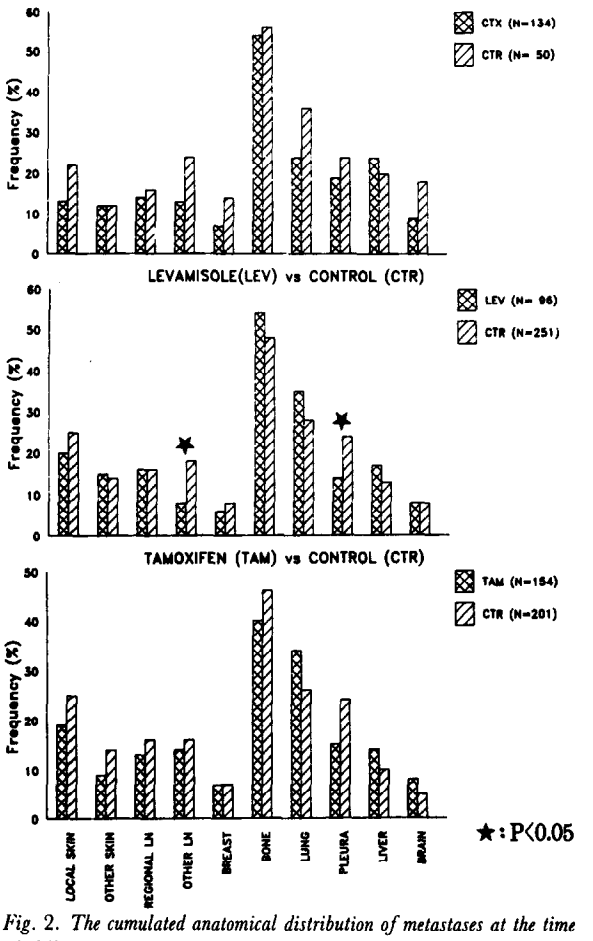

Fig. 2. The cumulated anatomical distribution of metastases at the time of follow-up according to type of adjuvant systemic treatment. For interpretation, see legend to Fig. 1.

who received LEV; $P = 0.013$ (OR 0.41, 95%; CL, 0.19–0.87) (Fig. 1). The same differences and the same directions were found when only considering patients recurring within the first year after mastectomy. However, statistical significance was not achieved due to the lower number of patients (data not shown).

During the clinical course these differences diminished, but the direction remained unchanged. Only the incidence of extraregional lymph node metastases and pleural recurrences was still significantly lower in the group of patients treated with LEV (Fig. 2).

Number of metastatic sites

Most patients had recurrence in a single anatomical site, and the median number of metastatic sites was approximately the same in patients given LEV or TAM compared to controls. The group of patients who received CT, however, had a significantly lower number of metastatic sites at the time of first recurrence (Table 2).

Since the total number of metastatic sites was reduced by adjuvant CT, the risk of getting a recurrence in a certain site may be correspondingly reduced. When controlling for the difference in the number of metastatic sites, the statistically significant lower rate of extraregional lymph node metastases among cytotoxically treated patients disappeared ($P = 0.18$), while the P value for differences in frequency of liver metastases decreased from $P = 0.038$ to $P = 0.016$.

Period of recurrence

The majority of the patients had their initial recurrence within the first 2 years after mastectomy. When considering patients with recurrence, the RFI was almost the same in systemically patients treated and in controls (Table 3). The frequency of recurrences in different anatomical sites was almost equal when comparing patients who had recurrence in different periods after mastectomy. Thus, the different incidences of metastases in certain sites in patients given AST were not attended by a tendency to occur earlier or later than in other metastatic sites. The only exception to this was that the LEV group of patients developed metastases to extraregional lymph nodes later than to other sites (Table 4).

Bone metastases

The distribution of bone metastases according to

Table 2. Number of patients according to the number of metastatic sites at first recurrence and the types of systemic adjuvant treatment (n (%) *indicates the number of patients in each group*)

Metastatic sites	Chemotherapy		Levamisole		Tamoxifen	
	No	Yes	No	Yes	No	Yes
1	25 (50)	93 (69)	169 (67)	70 (73)	144 (72)	105 (68)
2	16 (32)	26 (19)	48 (10)	17 (18)	32 (16)	29 (19)
3	5 (10)	10 (7)	26 (10)	7 (7)	21 (10)	13 (8)
≥4	4 (8)	5 (4)	8 (3)	2 (2)	4 (2)	7 (5)
n	50 (100)	134 (100)	251 (100)	96 (100)	201 (100)	154 (100)
P (rank *t* test)	0.04		0.37		0.57	

Table 3. Distribution of patients with recurrence according to type of adjuvant treatment and period (year) of recurrence after mastectomy (n (%) *indicates the number of patients in each group*)

Period of recurrence (year after mastectomy)	Chemotherapy		Levamisole		Tamoxifen	
	No	Yes	No	Yes	No	Yes
1st	11 (22)	37 (28)	76 (30)	35 (36)	76 (38)	65 (42)
2nd	20 (40)	51 (38)	89 (36)	27 (28)	69 (35)	52 (34)
3rd	9 (18)	35 (26)	44 (18)	14 (15)	35 (18)	15 (10)
4th–7th	10 (20)	11 (8)	31 (12)	20 (21)	21 (11)	22 (14)
n	50 (100)	134 (100)	251 (100)	96 (100)	201 (100)	154 (100)
P (rank *t* test)	0.27		0.82		0.49	

Table 4. Distribution of patients according to type of systemic therapy, site of metastasis, and to the period of recurrence after mastectomy. n *indicates the number of patients in each group, and percentages are calculated from the total number of patients in each stratum*

Adjuvant treatment	Site(s) of recurrence	Period of recurrence after mastectomy (years) 1 *n* (%)	2 *n* (%)	≥3 *n* (%)	Total *n* (=100%)	*P**
Chemotherapy	Other lymph nodes	1 (7)	7 (50)	6 (43)	14	0.19
	Liver	9 (36)	10 (40)	6 (24)	25	0.16
	All	37 (28)	51 (38)	46 (34)	134	—
Levamisole	Other lymph nodes	0 (0)	0 (0)	3 (100)	3	0.04
	Pleura	3 (28)	2 (25)	3 (38)	8	0.97
	All	35 (36)	27 (28)	34 (35)	96	—
Tamoxifen	Lung	21 (41)	18 (35)	12 (24)	51	0.94
	All	65 (42)	52 (34)	37 (24)	154	—

*Rank *t* test.

the number, localization and radiological morphology was the same in patients given adjuvant CT compared to untreated patients (Table 5). In contrast, osteolytic bone metastases occurred more often in patients treated with LEV, and metastases localized in the spine were more often noted in patients treated with TAM compared to the corresponding groups of controls.

DISCUSSION

The risk of developing clinical metastases in a specific anatomical site depends on several factors. The number of tumor cells released into the bloodstream from the primary tumor or other metastases and the magnitude of local hemodynamic perfusion probably play the most important roles [24, 25]. The general condition of both the host and the

Table 5. Distribution of patients according to radiological morphology, localization, and the number of regions with bone metastases (n (%) *indicates the number of patients in each group*)

	Chemotherapy				Levamisole				Tamoxifen			
	No		Yes		No		Yes		No		Yes	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Pts with bone metastases (no.)	22	(100)	62	(100)	97	(100)	43	(100)	75	(100)	56	(100)
Morphology (X-rays)												
Osteolytic	26	(87)	90	(83)	86	(66)	46	(75)*	60	(59)	50	(64)†
Osteosclerotic	4	(13)	11	(10)	33	(25)	11	(18)	29	(29)	21	(27)
Mixed	0	(0)	7	(6)	12	(9)	4	(7)	12	(12)	7	(9)
Unknown	6	(–)	16	(–)	28	(–)	4	(–)	22	(–)	31	(–)
Localization												
Columna and/or cranium	16	(72)	40	(65)	57	(59)	25	(58)	41	(55)	42	(75)*
Pelvis	9	(41)	37	(60)	48	(49)	17	(40)	39	(52)	26	(46)
Extremities	5	(23)	22	(35)	24	(25)	10	(23)	19	(25)	21	(38)
Thorax	4	(18)	18	(29)	22	(23)	13	(30)	18	(24)	15	(27)
Unknown	2	(9)	1	(2)	8	(8)	1	(2)	6	(8)	0	(0)
No. of bone regions with metastases‡												
1	10	(45)	27	(44)	49	(51)	26	(60)	39	(52)	27	(48)
2	7	(32)	17	(27)	24	(25)	9	(21)	17	(23)	14	(25)
3	2	(9)	9	(15)	7	(7)	7	(16)	5	(7)	9	(16)
≥4	1	(5)	8	(13)	9	(9)	0	(0)	8	(11)	6	(11)
Unknown	2	(9)	1	(2)	8	(8)	1	(2)	6	(8)	0	(0)

*$P < 0.05$.

†Percentage of the total number of evaluable bone regions.

‡Defined in the text.

specific anatomical site may, however, also play a role [26–28].

The detection of metastases should be regarded as the end-result of a process which involves a series of interactions, where different clones of tumor cells are selected and adapted to survive and grow in different sites [6, 29]. Clinically, clonal selection during metastasis may be reflected by site-specific differences in the rate of response to antineoplastic treatment [8–10]. The present study was conducted in order to investigate whether this is also reflected in the pattern of recurrences following AST.

When selecting and combining drugs for adjuvant trials one should consider the possible role of site-specific differences of response rates [6, 30]. This can be done by either studying the site-specific response rates in patients with advanced breast cancer or by analyzing the pattern of recurrence in comparable groups of patients receiving different forms of AST.

The DBCG-77 program showed a significant decrease in the recurrence rates as well as a prolonged survival for premenopausal patients who received either adjuvant cyclophosphamide alone or the CMF combination when compared to untreated controls [21]. A prolonged survival for patients given CT may be a consequence of cure of a subpopulation of patients and/or a less strained pattern of disease among patients who develop recurrence. The present study shows that the beneficial survival effect was attended by a significant decrease in the number of metastatic sites among patients with a recurrence. It is still too early to calculate the fraction of patients who are actually cured by CT. The gain in survival may, however, rely on the decreased number of metastatic sites among patients with recurrence, since this is known to be inversely correlated with the length of survival [4, 16]. The anatomical distribution of metastases was the same in the group of patients treated with CT compared to controls, apart from the higher incidence of liver metastases in CT-treated patients vs. controls (19% vs. 3%). This finding suggests that future regimens of adjuvant CT should include drugs which have shown a high rate of response in patients with liver metastases.

Adjuvant treatment with LEV led to both a shorter RFI and a shorter survival compared to controls [17]. However, the poorer prognosis for patients who received adjuvant LEV was not based on a larger number of metastatic sites or occurrence of metastases in more lethal regions. In contrast, distant metastases both in lymph nodes and in pleura occurred less often in these patients when compared with controls. Furthermore, since LEV is a non-specific immunostimulant, it is interesting to note that the extraregional lymph nodes metastases occurred significantly less often than in controls, both at the time of first recurrence and at the time of follow-up (14% vs. 24%).

In the DBCG-77 program, the rate of recurrence for patients who received adjuvant TAM was reduced compared to controls [22, 23]. The present study shows that patients treated with TAM had metastases in the lungs more often than did controls at the time of first occurrence. This finding had, however, no significant impact on survival, since the same length of survival time applied to TAM-treated and untreated patients [22, 23].

This study confirms that the bone system is the most common site of metastasis in patients with node-positive breast cancer [31, 32]; these metastases are usually osteolytic [32, 33], and they are predominantly located in the spine [33, 34]. The reason why some bone metastases initially show osteolysis whereas others show osteosclerosis or mixed morphology on radiographs is not known. The conversion from osteolysis to osteosclerosis may be regarded as a response to antineoplastic treatment [35]. Moreover, bone metastases in patients given adjuvant CMF are probably more likely to be osteosclerotic than the bone metastases in untreated patients [36]. This study as well as previous findings [32] cannot, however, confirm this. It is not clear why osteolytic bone metastases were more frequent in patients treated with levamisole, and it is curious that patients treated with tamoxifen more frequently had their bone metastases located in the spine than did the controls.

Retrospective studies have shown that the incidence of metastases in the central nervous system (CNS) was increased in patients who had received cytotoxic therapy for either advanced disease [11] or as adjuvant therapy [12]. The incidence of CNS metastases was not influenced by AST in this study, but the number of patients who actually had recurrence in the CNS is small. Accordingly, in a retrospective study of 178 patients [13] there was no effect of adjuvant CT (mostly CMF) on the anatomical distribution of metastases at first recurrence. The results of the current study should be interpreted with caution, since the use of multiple statistical tests increases the likelihood of a type 1 error (i.e. rejection of a true null hypothesis). Therefore, the results need verification, e.g. by analyzing the results of other trials of adjuvant therapy of breast cancer.

There is only little evidence of an altered incidence of metastases at specific anatomical sites arising from reports of adjuvant therapy of breast cancer. These reports generally document the first site of recurrence as locoregional and distant, but do not specify the anatomical distribution of metastases. The Milan group [36] found a decreased rate of failure in both locoregional and distant sites in patients treated with CMF compared to control patients. The reduced relapse rate was, however, particularly noted for the locoregional sites, and extended analyses showed that the incidence of patients with solitary lung and bone metastases was greatest among treated patients [39]. The Ludwig Breast Cancer Study Group found that the addition of CMF to adjuvant endocrine therapy of postmenopausal patients reduced the number of distant metastases [37], whereas the distribution of metastases in locoregional and distant sites was the same in premenopausal patients who had received either CMF and prednisone or CMF alone [38]. Howell *et al.* [40] reported that adjuvant CMF reduced the incidence of recurrence in skin and lymph nodes, whereas the incidence of different distant sites was equal when compared to untreated patients.

Adjuvant TAM usually decreases the rate of recurrence in both locoregional and in distant sites [41–44], although one study has shown a tendency towards a greater reduction in the incidence of distant metastases [44]. Contrary to the results of the DBCG study [22], Klefstrom *et al.* [45] reported a beneficial survival effect in patients receiving adjuvant LEV. Moreover, their study showed that the frequency of distant metastases was decreased more than that of locoregional recurrences in the group of patients treated with levamisole [45].

The present study confirms the presumption that the action of AST is based on an unspecified antineoplastic effect as well as on a site-specific effect on subclinical metastases in various anatomical locations. This was illustrated in CT-treated patients, in whom the total number of metastatic sites was decreased, despite the fact that liver metastases occurred more often. The data presented here agree with experimental results which show that metastases in various sites differ with respect to sensitivity to antineoplastic treatment. Improved results of future regimens of AST may be anticipated, if drugs with different spectra of efficacy are combined. However, today there are not sufficient data to allow a more general hypothesis regarding variability in response to antineoplastic treatment at different sites. Thus, further clinical studies of the present type and of patients treated for advanced breast cancer are needed to elucidate this.

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