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The Influence of Chemotherapy on Survival after Recurrence in Breast Cancer—a Population-based Study of Patients Treated in the 1950s, 1960s and 1970s

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In a population-based study survival after recurrence was compared in three cohorts of patients with a primary diagnosis of breast cancer in 1959, 1969 and 1979, respectively. The use of chemotherapy after recurrence in these cohorts was either none, sporadic or widespread. This allowed a retrospective analysis of the survival impact of chemotherapy. Given the basic assumption that the natural history of breast cancer and the influence of endocrine therapy have not changed significantly during the 20-year period covered by the study, our data suggest that chemotherapy in recurrent breast cancer prolongs survival by 9.5 months in patients who survive more than 2 weeks from the start of treatment for their recurrence.
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INTRODUCTION

ALTHOUGH THE clinical course may be highly variable in patients with recurrent breast cancer (RBC), these patients usually die of their disease. Like endocrine therapy, combination chemotherapy (CT) has been regarded as standard treatment in RBC for many years. It is generally assumed that CT prolongs survival in this situation but it has never been proven conclusively. Similarly, if survival is indeed prolonged by CT, the magnitude of the benefit is also not known. Obviously, the best way to elucidate these problems would be to conduct a prospective trial in which patients with RBC were randomised to receive CT or no CT, respectively. However, no trial of this kind has been reported, and today such a trial would be very difficult or impossible to conduct for ethical reasons.

In the absence of prospective randomised trials, several investigators have tried to assess whether there is a survival gain from CT in RBC, using historical series of patients. The results have been contradictory. Neither Patel *et al.* [1] nor Powles *et al.* [2] were able to demonstrate any improval of survival after the introduction of CT. In contrast, evidence of improvement was found by both Ross *et al.* [3] and Brincker [4]. However, all of these studies were essentially hospital-based with selective series of patients. No population-based study has been reported as yet.

In the present study survival after recurrence was compared in three cohorts of patients with a primary diagnosis of breast cancer in 1959, 1969 and 1979, respectively. Since the use of CT was either none, sporadic or widespread in these three cohorts, this provided an opportunity to analyse the survival impact of CT. In contrast with previous hospital-based studies the present study is population-based since it included all patients with breast cancer from a well-defined geographical area in which the primary treatment was uniform and in which the subsequent treatment of metastatic disease was centralised to a single oncological centre. The basic assumption of the study is that the natural history of RBC and the influence of endocrine treatment has not changed significantly during the 20-year period covered by the study so that any significant changes in survival may be attributed to the introduction of CT.

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MATERIALS AND METHODS

The geographical area covered by the study constitutes the three counties of Funen, Ribe, and southern Jutland plus the eastern part of the county of Vejle. This area had a total population of approximately 1 million inhabitants throughout the study period, corresponding to one fifth of the Danish population. The three study cohorts were identified by cross-checking the files of the Department of Oncology in Odense with the files of the National Danish Cancer Registry. They included all patients with newly diagnosed breast cancer from 1959, 1969 and 1979, respectively, from the geographical area described, thus securing an approximately 99% registration of all newly diagnosed female breast cancer cases in the area according to the documented accuracy of the Danish Cancer Registry [5]. Patients who had no records of recurrent disease, a second malignancy, a sarcoma of the breast, or who died less than 2 weeks after the start of treatment for RBC were excluded from the study.

Consequently, the remaining study population includes patients with RBC (local and distant) with a primary diagnosis of breast cancer within the 3 cohort years specified and subsequent treatment at the Department of Oncology in Odense or elsewhere. All patients without files in the Department of Oncology were traced and their clinical status ascertained as regards recurrent disease, second malignancy, sarcoma of the breast or early death after recurrence. The following data were recorded for the study population at initial diagnosis: age, T- and N-status, extent of primary surgery, axillary lymph node status whenever possible, type of postoperative radiotherapy and type of systemic adjuvant therapy.

In 1977 the Danish Breast Cancer Cooperative Group (DBCG) started a nationwide adjuvant trial in breast cancer [6]. This trial focused on both clinical and pathological staging and resulted in a new surgical practice with routine axillary lymph node sampling.

Prior to that time axillary status had been determined mainly by clinical examination. Because of these major changes in diagnostic practice the data on axillary lymph node involvement are difficult to compare.

The following data were recorded at recurrence: disease-free interval, site of recurrent disease (if several sites were involved they were ranked in the following order: visceral, bone, soft tissue, local), number of involved sites, extent of surgery, type of radiotherapy, and type of systemic treatment (if given for at least 2 weeks).

All patients were followed until 1 January 1987; and the recurrent patient from the 1979 cohort until 1 January 1992. Cases in which follow-up data were incomplete in the departemental files were traced via the national registry of civic registration numbers. Such patients were assumed to be alive at 1 January 1987 if they had not been reported dead by 1 March 1987. The distribution of clinical parameters was compared using the χ^2 test. Regarding the cells in the χ^2 test: T-status was (T0 + T1 + T2) vs. (T3 + T4); N-status was N0 vs. (N1 + N2 + N3); lymph node involvement was positive vs. (unknown + negative); primary surgery was unilateral mastectomy vs. other treatment; primary radiotherapy was chest wall with regional lymph nodes vs. other treatment; number of recurrent sites were 1 vs. (2 + 3); adjuvant CT was any vs. none. Survival curves were calculated according to the Kaplan–Meier method, and differences were analysed using Gehan's test.

RESULTS

Table 1 shows the distribution of the 547 cases found via the departmental files and the additional 222 cases found via the Danish Cancer Registry. Among the latter cases the patient records were not available for review in 37 cases (16.6%). Among the 196 cases of RBC 15 cases (7.1%) were not treated at the Department of Oncology. However, their data were obtained from local hospitals and included with the study group for analysis of the effect of CT on survival. Thus, the 196 patients with RBC represent a truly unselected group of such patients.

Table 2 summarises the characteristics of the 196 patients with RBC at the time of initial diagnosis according to cohort year, including age and primary treatment. The T-status shows a trend towards smaller tumours in the latest decade, while the N-status remains unchanged. The histologically verified lymph node involvement increased in the seventies. As regards loco-regional treatment there were no significant changes in the extent of surgery or use of postoperative radiotherapy. No patient from the 1959 cohort had adjuvant treatment, but adjuvant actinic castration was used in 49% of the patients from the 1969 cohort, and adjuvant systemic endocrine or cytostatic treatment was used in 30% of the patients from the 1979 cohort in accordance with the nationwide DBCG protocols, implemented in 1977.

Table 3 shows the characteristics of the 196 patients with RBC at the time of recurrence. There are significantly less patients with a disease-free interval of 61+ months in the 1979 cohort

Table 1. Sources of patients with primary breast cancer in the study, and number of patients in the three cohorts

Cohort	1959	1969	1979	Total
Patients recorded in the Danish Cancer Registry	193	239	337	769
Patients with files in the Department of Oncology	142	156	249	547
With recurrent disease	51	49	81	181
Without recurrent disease	54	73	149	276
Second malignancy	15	15	18	48
Early death	21	17	1	39
Sarcoma	1	2	0	3
Patients without files in the Department of Oncology	51	83	88	222
With recurrent disease	9	6	0	15
Without recurrent disease	19	21	86	126
Second malignancy	12	11	0	23
Early death	7	13	0	20
Sarcoma	0	1	0	1
Records missing	4	31	2	37

Table 2. Characteristics of patients with recurrent breast cancer at the time of initial diagnosis

Cohort	1959	1969	1979
Number of patients	60	55	81
Age in years, mean (range)	54 (31–84)	57 (23–80)	55 (20–89) $P = 0.28$
Initial T-status			
T0	1	0	1
T1	3	6	6
T2	19	23	45
T3	12	13	14
T4	20	8	11
T-unknown	5	5	4
Initial N-status			
N0	30	42	45
N1	16	7	32
N2	6	1	1
N3	3	0	1
N-unknown	5	5	2
Axillary lymph node involvement			
Positive	19	8	53
Negative	15	14	19
Unknown	26	33	9
Primary surgical treatment			
Unilateral mastectomy	57 (95)	52 (95)	79 (98)
Bilateral mastectomy	2 (3)	3 (5)	1 (1)
Tumorectomy	1 (2)	0 (0)	1 (1)
Primary radiotherapy			
Chest wall only	2 (3)	1 (2)	0 (0)
Chest wall + lymph nodes	47 (79)	45 (82)	61 (75)
Other	3 (5)	3 (5)	3 (4)
None	8 (13)	6 (11)	17 (21)
Adjuvant chemotherapy			
Cyclophosphamide	0 (0)	0 (0)	4 (5)
CMF	0 (0)	0 (0)	6 (7)
Levamisole	0 (0)	0 (0)	14 (17)
None	60 (100)	55 (100)	57 (70)
Ajuvant endocrine therapy			
Tamoxifen	0 (0)	0 (0)	9 (11)
Actinic castration	0 (0)	27 (49)	0 (0)
Other	0 (0)	2 (4)	0 (0)
None	60 (100)	26 (47)	72 (89)

Number of patients with percentages in brackets.
CMF, cyclophosphamide, methotrexate, 5-fluorouracil.

Table 3. Characteristics of patients with recurrent breast cancer at the time of recurrence

Cohort	1959	1969	1979
Number of patients	60	55	81
Disease-free interval (months)			
0–12	17 (28)	13 (24)	33 (41)
13–24	12 (20)	13 (24)	26 (32)
25–60	14 (23)	12 (22)	17 (21)
61+	17 (28)	17 (31)	5 (6)
			$P < 0.003$
Site of recurrent disease			
Visceral	16 (27)	19 (35)	30 (37)
Osseous	16 (27)	14 (25)	30 (37)
Soft tissue	22 (37)	19 (35)	14 (17)
Local	6 (10)	3 (5)	7 (9)
			$P = 0.14$
Number of recurrent sites			
1	46 (77)	46 (84)	66 (81)
2	11 (18)	8 (15)	14 (17)
3	3 (5)	1 (2)	1 (1)
			$P = 0.33$
Surgery for recurrent disease			
Excision	22 (37)	15 (27)	19 (23)
None	38 (63)	40 (73)	62 (77)
			$P = 0.22$
Radiotherapy of recurrence			
"Curative"	11 (18)	5 (9)	15 (19)
Palliative	13 (22)	17 (31)	24 (30)
None	36 (60)	33 (60)	42 (52)
			$P = 0.43$
Endocrine therapy			
Tamoxifen	1	13	66
Medroxyprogesterone	0	3	11
Actinic castration	22	1	14
Surgical castration	0	1	1
Oestrogens	9	4	0
Androgens	17	3	0
Prednisolone	34	32	21
Anabolic steroids	8	14	6
Chemotherapy			
Cyclphosphamide	0	2	2
Other monotherapy	3	4	13
CMF	0	3	25
CAF	1	2	45
Other polychemotherapy	1	2	13

Number of patients with percentages in brackets.
CMF, cyclophosphamide, methotrexate, 5-fluorouracil; CAF, cyclophosphamide, doxorubicin, 5-fluorouracil.

than in the two previous cohorts. However, this finding is mainly due to the fact that the average observation time in the 1979 cohort is only 7.5 years against 17.5 and 27.5 years, respectively, in the two preceding cohorts. The sites of recurrence are not significantly different in the three cohorts, but there is a trend towards an increased involvement of viscera and bone. The numbers of involved sites are fairly equal. As for locoregional treatment no differences are apparent. Endocrine treatment is characterised by frequent use of actinic castration and androgens in the 1959 cohort and frequent use of tamoxifen in the 1979 cohort. Only a few of the patients in the 1959 and 1969 cohorts had any CT while combination CT was used extensively in the 1979 cohort.

In Tables 4 and 5 the 196 patients with RBC have been divided into two groups, one consisting of 69 patients who had CT after recurrence (the treatment group), and another consisting of 127 patients who did not (the control group). Table 4 shows the characteristics of the patients at the time of initial diagnosis. There is no significant difference between the two

Table 4. Characteristics at the time of diagnosis in patients treated with and without chemotherapy at recurrence

Treatment	Chemotherapy	No chemotherapy
Number of patients	69	127
Age in years, mean (range)	50 (20–73)	58 (27–89)
		$P = 0.001$
Initial T-status		
T0	1	1
T1	3	12
T2	43	44
T3	12	27
T4	7	32
T-unknown	3	11
		$P = 0.007$
Initial N-status		
N0	38	79
N1	29	26
N2	1	7
N3	0	4
N-unknown	1	11
		$P = 0.10$
Axillary lymph node involvement		
Positive	43 (62)	37 (29)
Negative	19 (28)	29 (23)
Unknown	7 (10)	61 (48)
		$P < 0.001$
Primary surgical treatment		
Unilateral mastectomy	68 (99)	120 (94)
Bilateral mastectomy	1 (1)	5 (4)
Tumorectomy	0 (0)	2 (2)
		$P = 0.36$
Primary radiotherapy		
Chest wall only	0 (0)	3 (0)
Chest wall + lymph nodes	54 (78)	99 (78)
Other	2 (3)	7 (6)
None	13 (19)	18 (14)
		$P = 0.41$
Adjuvant chemotherapy		
Cyclophosphamide	4 (6)	0 (0)
CMF	6 (9)	0 (0)
Adjuvant immunotherapy		
Levamisole	9 (13)	5 (4)
Adjuvant endocrine therapy		
Tamoxifen	3 (4)	6 (5)
Actinic castration	5 (7)	22 (17)
Other	0 (0)	2 (2)
None	61 (88)	97 (76)
		$P = 0.042$

Number of patients with percentages in brackets.
CMF, cyclophosphamide, methotrexate, 5-fluorouracil.

Table 5. Characteristics at the time of recurrence in patients treated with and without chemotherapy at recurrence

Treatment	Chemotherapy	No chemotherapy
Number of patients	69	127
Disease-free interval (months)		
0–12	26 (38)	37 (29)
13–24	20 (29)	31 (24)
25–60	13 (19)	30 (24)
61+	10 (14)	29 (23)
		$P = 0.33$
Site of recurrent disease		
Visceral	26 (38)	39 (31)
Osseous	21 (30)	39 (31)
Soft tissue	17 (25)	38 (30)
Local	5 (7)	11 (8)
		$P = 0.75$
Number of recurrent sites		
One	58 (84)	100 (79)
Two	10 (14)	23 (18)
Three	1 (1)	4 (3)
		$P = 0.37$
Surgery for recurrent disease		
Excision	21 (30)	36 (28)
None	48 (70)	91 (72)
		$P = 0.76$
Radiotherapy of recurrence		
"Curative"	14 (20)	17 (13)
Palliative	19 (28)	35 (28)
None	36 (52)	75 (59)
		$P = 0.42$
Endocrine therapy		
Tamoxifen	52 (75)	28 (22)
Medroxyprogesterone	12 (17)	2 (2)
Actinic castration	16 (23)	21 (17)
Surgical castration	1 (1)	1 (1)
Oestrogens	1 (1)	13 (10)
Androgens	2 (3)	18 (14)
Prednisolone	25 (36)	62 (49)
Anabolic steroids	9 (13)	19 (15)
Any endocrine therapy	66 (97)	109 (86)
Chemotherapy		
Cyclophosphamide	4 (6)	0 (0)
Other monotherapy	20 (29)	0 (0)
CMF	28 (41)	0 (0)
CAF	48 (70)	0 (0)
Other polychemotherapy	16 (23)	0 (0)
Only monotherapy	8 (12)	0 (0)
Any polychemotherapy	61 (88)	0 (0)

Number of patients with percentages in brackets.
CMF, Cyclophosphamide, methotrexate, 5-fluorouracil; CAF, cyclophosphamide, doxorubicin, 5-fluorouracil.

groups as regards primary locoregional treatment. However, the mean age is 50 years in the treatment group against 58 years in the control group ($P = 0.001$). The data on T-status indicates that smaller tumours occurred in the CT-treated group, whereas there was no difference as regards the N-status. Axillary lymph node involvement is significantly more pronounced in the CT-treated group, while the number of unknown cases is much lower. Since the CT-treated patients belong mainly to the 1979 cohort, more patients in the treatment group than in the control group had preceding adjuvant chemotherapy. Similarly, more patients in the control group than in the treatment group had preceding adjuvant actinic castration.

Table 5 demonstrates that the characteristics of the two groups were not significantly different at the time of recurrence as regards site of recurrence, locoregional treatment and disease-free interval, though there is a slight trend for a shorter time to recurrence in the treatment group. In the latter group each patient had an average of 1.7 endocrine regimens against 1.3 such regimens in the control group. The endocrine treatments were given simultaneously with the CT treatment in 65% of the patients, up to 1 year before in 17%, between 1 and 2 years before in 10% and more than 2 years before in 4%. Three percent had no endocrine treatment. Similarly, in the treatment group each patient had an average of 1.7 CT regimens against none in the control group.

Figure 1 shows overall survival from diagnosis in all 769 patients with primary breast cancer from the original three cohorts. While survival is similar in the 1959 and 1969 cohorts, it is significantly better in the 1979 cohort ($P < 0.005$). This is most probably due to the introduction of adjuvant systemic treatment as a consequence of the nationwide DBCG trial, initiated in 1977. Similar differences are apparent from the trial data reported by the DBCG [7] and corroborated by an independent analysis of the national data by the Danish Cancer Registry [6].

As regards survival after recurrence, Fig. 2 demonstrates that there are no significant differences between the 196 patients in the three cohorts ($P = 0.49$). Survival is significantly worse in patients with known initial axillary lymph node involvement compared with no involvement, while the survival in the patients with unknown status is intermediate (data not shown). Survival after recurrence following adjuvant endocrine treatment is similar to survival after no adjuvant endocrine treatment (data not shown). However, when comparing the CT-treated group with the control group, median survival is 17 months in the control group against 26.5 months in the CT-treated group, showing a significant overall survival benefit of 9.5 months (Fig. 3). In addition, the same data have been analysed with stratification according to recurrence before or after 2 years. The survival advantage is consistently in favour of the CT-treated patients with median survivals of 21 vs. 12 months and 39 vs. 22 months for recurrences before and after 2 years, respectively. Interestingly, Fig. 4 shows that survival after recurrence is shorter in patients having had previous adjuvant chemo- or immunotherapy. This difference is significant ($P = 0.006$) even though the number of patients with this adjuvant therapy is small (Table 4). Nevertheless, this finding is also corroborated by trial data reported by the DBCG [8]. In addition, the influence of various other parameters on survival after recurrence was analysed (data not shown). As expected, patients without initial axillary lymph node involvement did better than patients with axillary involvement [4, 9]. The initial T-status showed a trend towards longer survival in the patients with T 0–2 tumours compared with patients with T 3–4 tumours. Similarly, patients with local or soft tissue recurrences did better than patients with visceral or bone recurrences [10, 11]. Patients with two involved sites did worse than patients with only one involved site. Finally, patients with a disease-free interval of 61+ months did better than patients with shorter disease-free intervals [12, 13]. Age at recurrence did not predict length of survival.

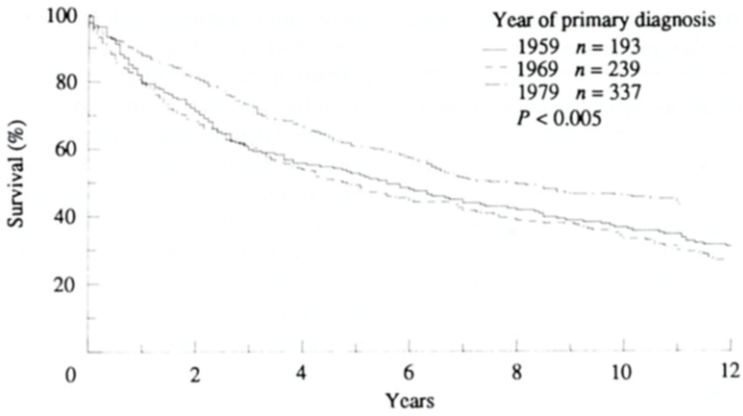

Fig. 1. Overall survival from primary diagnosis of breast cancer in patients from Funen and southern Jutland according to year of diagnosis.

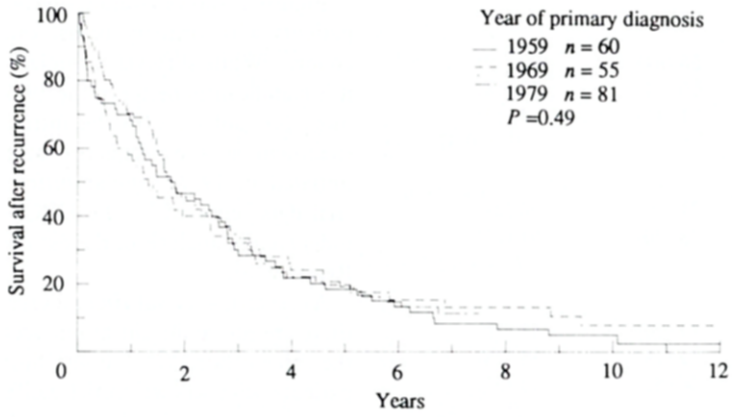

Fig. 2. Survival after recurrence according to primary year of diagnosis.

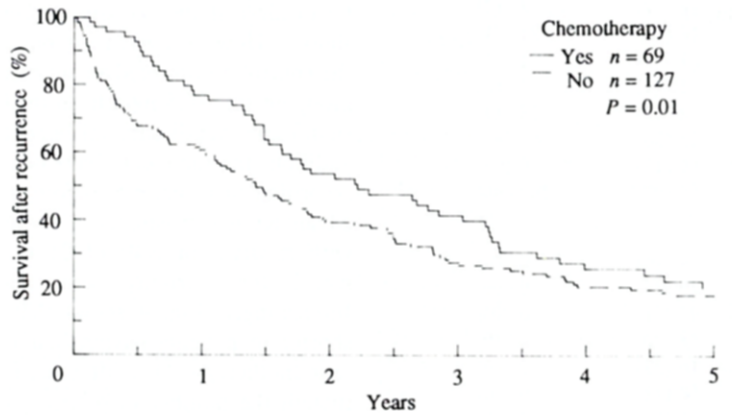

Fig. 3. Survival after recurrence according to chemotherapy or no chemotherapy at recurrence.

DISCUSSION

As stated in the introduction, the basic assumptions of the present study are that the natural history of RBC has not changed over the years and that the influence of endocrine therapy has remained constant during the period covered by the study. For the interpretation of these results it is important to clarify two problems: (1) is it sufficiently well documented that the patients from the three cohorts are comparable as regards extent of disease at diagnosis and primary treatment? (2) Are the patients who had CT after recurrence comparable with the patients who did not?

Regarding the comparability of the three cohorts, the initial T-status reflects a tendency towards more T-2 tumours in the 1979 population at the expense of T-3 and T-4 tumours. Whether this represents an increased awareness of the disease in the patients or a tendency towards more accurate staging cannot be determined. In the 1979 population the axillary lymph node involvement is far more pronounced, while the number of patients with unknown status is rather low. However, this is almost certainly a result of the improved pathology technique and recommended sampling of lymph nodes following the introduction of the nationwide DBCG protocols in 1977. Thus,

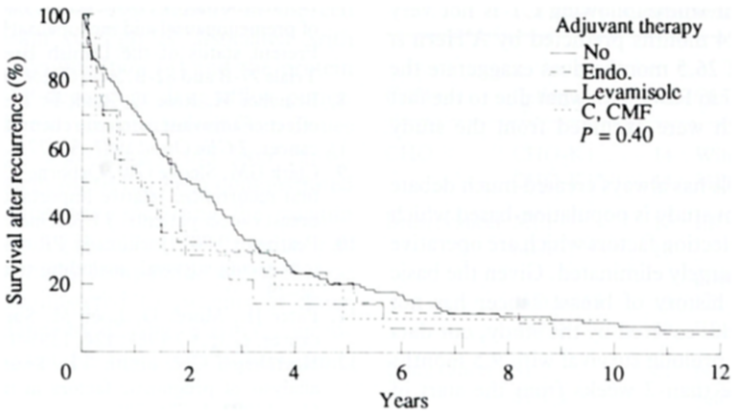

Fig. 4. Survival after recurrence according to previous adjuvant therapy.

in the 1959 and 1969 cohorts the rather high proportion of patients with unknown status merely reflects node-positive patients who have not been diagnosed. In the survival data the curve representing node-unknown patients is located between the curves' node-positive and node-negative patients, but more close to the node-positive curve, probably because of a considerable number of unidentified node-positive patients. No changes took place from 1959 to 1979 in Denmark as regards efforts to diagnose breast cancer earlier. Therefore, in spite of the fluctuations of the TNM data mentioned above it seems unlikely that the extent of the disease at diagnosis should have changed significantly during this period. In accordance with this view, the primary locoregional treatment remained unchanged during the 20-year period covered by the study, as shown in Table 2. Consequently, it seems reasonable to assume that the patients from the three cohorts are comparable, both as regards extent of disease at diagnosis and primary treatment.

Regarding the comparability of patients with and without CT after recurrence, the only major difference between these two groups is the mean age at diagnosis which was 50 years in the CT group against 58 years in the group without CT ($P = 0.001$). This difference appears to be without clinical significance since no influence of age on survival after recurrence could be demonstrated. The pattern of T-status and axillary lymph node involvement is as discussed above, which favours the CT group with smaller tumours while the lymph node involvement has the opposite effect. As shown in Tables 4 and 5, there are no significant differences between the two groups concerning primary and secondary locoregional treatment, disease-free interval, site of recurrence or number of recurrent sites. The no CT group is favoured by slightly less involvement of viscera and bones than of soft tissue and local recurrences, and a tendency towards increased time to recurrence.

During the period covered by the study, follow-up was unchanged with a clinical examination once a year as the basic procedure. However, the detection of recurrent disease is usually a result of patients' complaints rather than routine procedures [14]. Time to recurrence was somewhat shorter in the CT group, but only to the extent that could be explained by the shorter observation, since these patients belong mainly to the 1979 cohort. This fact and the rather uniform distribution of site of recurrence makes it fairly improbable that significant lead time bias is involved.

Since adjuvant actinic castration was widely used in the 1969 cohort and adjuvant CT was introduced in the 1979 cohort the two groups are significantly different as regards previous adjuvant treatment because CT after recurrence was also not used routinely until the 1979 cohort. Thus, CT after recurrence tends to be associated with previous adjuvant CT, while no CT after recurrence tends to be associated with previous adjuvant actinic castration. Since previous CT appears to be associated with a lower effect of subsequent CT, the difference between the treatment group and the control group might be expected to favour the survival of the latter group. Nevertheless, the CT-treated group had a superior survival.

Figure 1 shows a significant improval of overall survival of the 1979 cohort in accordance with the nationwide introduction of adjuvant systemic treatment of breast cancer in 1977. At the same time, Fig. 2 shows that survival after recurrence is not significantly different between the three cohorts. This indicates that the overall survival gain apparent in Fig. 1 is due mainly to systemic treatment *before* recurrence. Nevertheless, Fig. 3 shows that median survival after recurrence appears to have been improved with 9.5 months by the use of CT.

It may be asked why Fig. 3 shows a significant survival difference in favour of CT when Fig. 2 does not show a clear-cut survival improvement for the 1979 cohort in which CT was used fairly routinely after recurrence. However, 18 out of the 116 courses of CT summarised in Table 3 were, in fact, administered to patients belonging to the 1959 and 1969 cohorts. Furthermore, most patients in the 1979 cohort had more than one type of CT, presumably with decreasing effect, so that the survival benefit is unlikely to be proportional merely with the number of courses. Another reason that Fig. 2 does not show a survival improvement for the 1979 cohort after recurrence could be that patients with recurrence after adjuvant chemotherapy may be expected to benefit less from subsequent chemotherapy [8]. As shown in Fig. 4, this assumption appears to be true since survival after recurrence was significantly shorter in patients with previous adjuvant chemotherapy.

Our finding of a survival benefit of 9.5 months with CT in RBC is very similar to that found by Ross *et al.* [3] using a hospital-based series of patients from three different decades. In contrast, neither Patel *et al.* [1] nor Powles *et al.* [2] could find any convincing evidence of a survival benefit from CT in RBC, also using hospital-based series of patients. A'Hern *et al.* [15] used a different approach with pooled data from 50 reported trials of CT in RBC. By comparing response rates and medians for survival they estimated that medians for survival of 18 and 24 months would correspond to response rates of 20 and 40–60%, respectively. The latter figure is in agreement with response rates normally observed with CT in RBC, and a median survival

of 26.5 months in the present study following CT is not very different from the figure of 24 months predicted by A'Hern *et al.* [15]. In fact, our figure of 26.5 months does exaggerate the survival expectations after CT in RBC somewhat due to the fact that patients with early death were excluded from the study population.

The use of historical controls has always created much debate [16, 17]. However, the present study is population-based which means that a number of the selection factors which are operative in hospital-based studies are largely eliminated. Given the basic assumption that the natural history of breast cancer has not changed during the two decades covered by the study, our data suggest that CT in RBC does prolong survival with 9.5 months in patients who survive more than 2 weeks from the start of treatment for their recurrence.

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Selective Reversal of Vinblastine Resistance in Multidrug-resistant Cell Lines by Tamoxifen, Toremifene and their Metabolites

Julie Kirk, Sue Houlbrook, Nicholas S.A. Stuart, Ian J. Stratford, Adrian L. Harris and James Carmichael

In this study we describe the effects of tamoxifen, toremifene and their 4-hydroxy and *N*-desmethyl metabolites on the toxicity of a range of drugs to human breast and lung cancer and to Chinese hamster ovary cell lines, determined using a tetrazolium-based semi-automated colorimetric assay. Vinblastine resistance was completely abolished in an *mdr*1-transfected lung cancer cell line (S1/1.1), indicating that P-glycoprotein-mediated multidrug resistance can be fully reversed by anti-oestrogens. A substantial (14- to 39-fold) enhancement of vinblastine toxicity to highly multidrug-resistant (MCF-7^{Adr}) cells expressing P-glycoprotein was also observed in the presence of tamoxifen, toremifene and their metabolites, while *m*-amsacrine, cisplatin and melphalan toxicity was unaffected.

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INTRODUCTION

TUMOURS TREATED with chemotherapeutic drugs may become resistant not only to subsequent treatment with the same drug, but to treatment with structurally and functionally dissimilar natural products such as anthracyclines, epipodophyllotoxins and vinca alkaloids [1]. This phenomenon, known as multidrug resistance (MDR), is a major clinical problem, rendering a wide range of drugs redundant in the treatment of some tumours. MDR is frequently associated with overexpression of the *mdr*1 gene product [2], the 170 kD P-glycoprotein (Pgp). Cellular