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Postsurgical Adjuvant Chemotherapy with or without Radiotherapy in Women with Breast Cancer and Positive Axillary Nodes: a South-Eastern Cancer Study Group (SEG) Trial

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In a prospective study of 622 women with breast cancer, those with one to three histologically positive axillary lymph nodes were randomised after mastectomy to receive cyclophosphamide 100 mg/m^2 orally on days 1–14, methotrexate 40 mg/m^2 intravenously on days 1 and 8, and fluorouracil 600 mg/m^2 intravenously on days 1 and 8 every 28 days for six cycles (CMF × six), or for twelve cycles of the same chemotherapy (CMF × 12). Those with ≥ four positive nodes were randomised to one of these two groups or to 5000 cGy of postmastectomy regional radiotherapy (RT) followed by six cycles of the same chemotherapy (RT + CMF × six). With about 10 years median follow-up, there was no significant difference in survival or disease-free survival among the three groups. There was evidence of decreased locoregional recurrence in patients with ≥ four nodes who received RT + CMF × six (relative risk 0.53, $P = 0.067$). Multivariate analysis indicated that the presence of ≥ four positive nodes (negatively) and the percentage of ideal (full) dose of CMF received (positively) were the strongest factors predictive of survival. This study shows no advantage for 12 over six cycles of CMF chemotherapy in women with breast cancer and positive axillary nodes. There was a suggestion of decreased locoregional recurrence but no improvement in survival with radiotherapy for women with ≥ four positive nodes.
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INTRODUCTION

In 1976 the South-Eastern Cancer Study Group (SEG) initiated a trial (76 BRE303) to study the optimal duration of adjuvant chemotherapy with cyclophosphamide, methotrexate and 5-fluorouracil (CMF) and the role of postmastectomy radiotherapy given in addition to CMF. This report presents the results of that trial with a median follow-up of about 10 years. Preliminary analyses have been published [1, 2, 3].

PATIENTS AND METHODS

Patient selection

Non-pregnant women were eligible if they had undergone radical or modified radical mastectomy within the previous 60 days for breast cancer T1a, T2a, T3a, T1b or T2b and No, N1a or N1b and Mo disease and had one or more histologically positive axillary lymph nodes, ≥ 1500/μl granulocytes, ≥ 100 000/μl platelets, bilirubin ≤ 0.2 mg/dl, BUN ≤ 25 mg/dl or creatinine ≤ 1.2 mg/dl, no active infection, and had signed informed consent. Patients with previous malignancy, chemotherapy, hormonal therapy or radiotherapy for breast cancer, and those unavailable for follow-up were not eligible. Before randomisation, their disease was assessed by history and physical examination with TNM staging, chemistry profile (including BUN, creatinine, bilirubin, AST, lactate dehydrogenase, alkaline phosphatase and calcium), complete blood count, urinalysis, chest X-ray, and liver and bone scintigraphs (with X-rays to confirm benign changes in any suspicious areas). Oestrogen and progesterone receptor assays were recommended but not required.

Randomisation and stratification

Randomisation was done by telephone to the SEG statistical office only after patient characteristics had been verbally transmitted. Treatment was assigned from computer-generated lists using stratification for the treating institution, the number of histologically positive axillary nodes (1–3 vs. ≥ 4), menopausal status (premenopausal vs. postmenopausal), type of mastectomy (radical vs. modified radical) and elapsed number of days from operation to onset of therapy (< 28 vs. ≥ 28 days).

Treatment

Surgical treatment was a total mastectomy with (radical) or without (modified radical) removal of the pectoralis muscles and complete axillary dissection which included at least 10 lymph nodes in the operative specimen. Postmastectomy radiotherapy consisted of 5000 cGy given over 5 weeks to chest wall of the operative site and to the regional lymph node sites including the ipselateral axilla, internal mammary region, and supraclavicular area. Patients with one to three positive axillary nodes were assigned to groups 1 or 2; those with ≥ four positive nodes were assigned to groups 1, 2, or 3.

Patients were randomly assigned to one of three groups:

(1) Chemotherapy for six cycles consisting of cyclophosphamide 100 mg/m^2 orally on days 1–14, methotrexate 40 mg/m^2

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intravenously on days 1 and 8, and 5-fluorouracil 600 mg/m^2 intravenously on days 1 and 8. This cycle was repeated every 4 weeks for a total of six cycles.

(2) Chemotherapy identical to that in group 1 but given for a total of 12 cycles.

(3) Radiotherapy, as described above, followed by six cycles of chemotherapy. The chemotherapy was identical to that in group 1 except that the first two cycles were given with a 25% dose reduction. The latter four cycles were given in doses identical to those in group 1.

Dosage adjustments for the chemotherapy were as follows: Chemotherapy was held and subsequent doses were reduced by 25% if the granulocyte nadir fell to 750–1500/μl or platelet nadir to 50 000–100 000/μl. Radiotherapy was also discontinued. Both were resumed when the blood counts rose above those levels. If the granulocyte nadir fell below 750/μl or the platelet nadir fell below 50 000/μl, chemotherapy was withheld and subsequent doses were reduced by 50%. Radiotherapy was also discontinued. Both were resumed when the granulocyte count rose above 1500/μl and the platelet count rose above 100 000/μl. Doses of methotrexate were reduced by 25% if the serum creatinine rose to 1.2–2.0 mg/dl and by 50% if it rose above 2.0 mg/dl. Doses of methotrexate were reduced by 25% if ulcerative mucositis occurred and by 50% if there was mucositis severe enough to prevent eating. Doses of chemotherapy were reduced by 25% if severe nausea and vomiting occurred which could not be controlled by antiemetics.

Statistical methods

Patients who remained free of recurrent disease were considered responders and those who developed recurrent disease, failures. Relapses were classified as locoregional only, locoregional and distant, and distant only. This analysis includes information on 622 patients treated on the study from 1976 to 1983. An additional 23 patients were randomised but not treated on the study and were not followed by the statistical office. We do not have information on their survival [8 patients from group 1 (3.8%), 2 from group 2 (2.9%), 12 from group 3 (6.3%, $P = 0.292$)]. Because of slow accrual of patients with ≥ four positive axillary nodes and because preliminary analysis showed no differences between the three groups, group 2 was closed to patients with ≥ four nodes in February 1980, so that more patients with ≥ four nodes would enter groups 1 and 3. The median duration of follow-up is 10 years.

The statistical analysis was based only on all eligible randomised cases, unless otherwise noted. Survival analysis was calculated from the date of study entry until death or loss to follow-up. Disease-free survival was measured from the date of study entry until one of the following endpoints:

(1) Date last known disease-free (these cases are censored).
(2) Date relapse occurred.
(3) The date of death disease-free (these cases are censored).
(4) The date of death due to disease when exact date of relapse is unknown (these cases are very few and equally distributed between the arms of the study).

Survival and disease-free curves were plotted using the method of Kaplan and Meier [3]. Comparisons between the curves were made with the logrank test [4] of significance. The Cox proportional hazards model was used for multivariant analysis [5]. Chi square statistics were used for other comparisons of treatments for differences in proportions. All P values were two-sided; a P value of ≤ 0.05 was considered to be significant. All comparisons were established with a β error of 0.20. In the ≥ four node group the study had a 65% power to detect a difference of 20% in recurrence and an 80% power to detect a 40% difference in recurrence.

Table 1. Patient characteristics

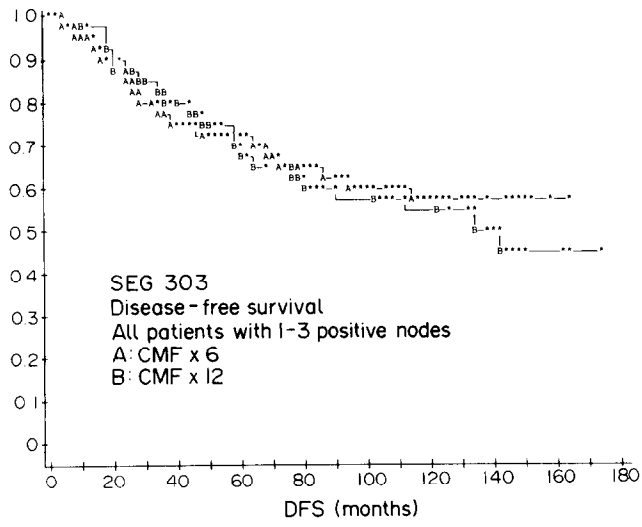
	CMF × six	CMF × 12	RT + CMF
Total	295	210	139
Nodal status			
1–3	162	149	2
≥ 4	133	61	137
Menopausal status			
Pre	118	89	53
Post	177	121	86
Type of mastectomy			
Radical	56	44	26
Modified radical	239	166	133
Time from surgery			
< 28 days	92	67	38
≥ 28 days	203	143	101
TMN Stage			
T1	58	48	19
T2	173	116	70
T3	38	28	30
Other or missing	26	18	20
Age			
< 40 years	64	39	35
≥ 40 years	231	171	104
Median	51.3	49.9	51.7
Race			
White	212	155	84
Non-white	83	55	55

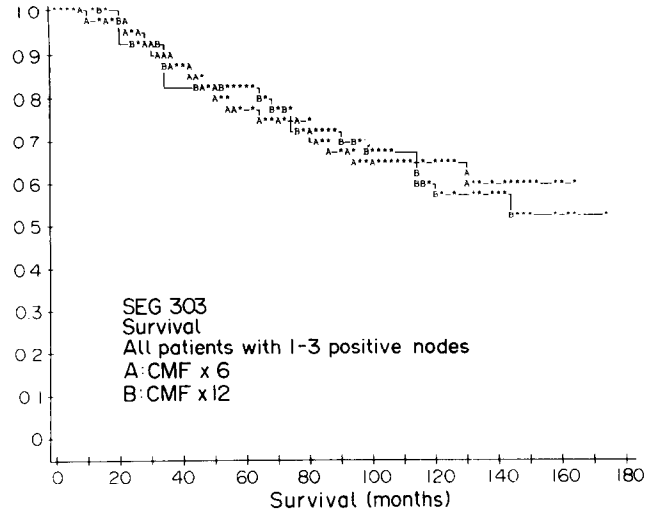
Follow-up

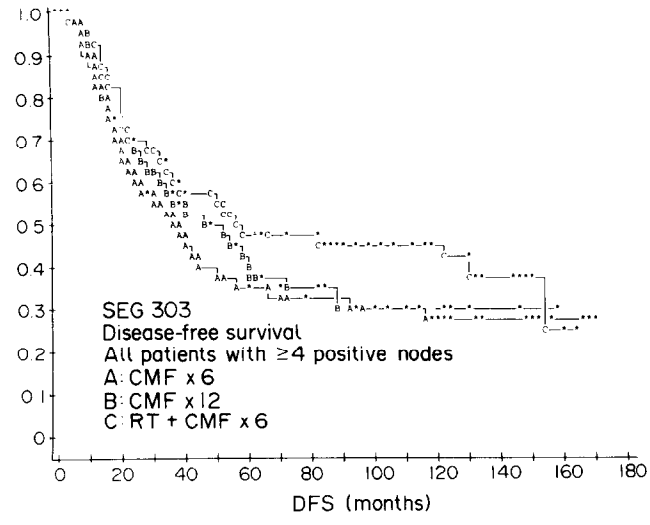
Patients were seen and blood counts obtained weekly during the first cycle of chemotherapy, before each subsequent cycle, and at least every 6 months after completing treatment. Those who received radiotherapy had blood counts done twice weekly during treatment. Clinical examination with chemistry profile was done at 6-month intervals after completing therapy. Annual chest X-ray was done as well as a liver scintigraph 1 year after entry onto the study and annual bone scintigraph for 3 years after entry onto the study. Restaging, as done at the time of entry onto the study, was requested at the time of recurrence of disease so that distinction could be made between locoregional only, locoregional and distant, or distant relapse. Biopsy of recurrent lesions was encouraged. The statistical office requested follow-up information on each patient from the responsible physician every 6 months after completing therapy.

RESULTS

Of the 622 patients, 597 met all eligibility requirements. Patient characteristics are shown in Table 1. The median number of courses of chemotherapy received was six for groups 1 and 3 and 12 for group 2. The percentage of group 1 who received six courses of chemotherapy was 83% and of group 3 was 81%; 78% of group 2 received 12 courses. If the optimal dose is defined as the total amount of drug received/total targeted dose at each course times the number of courses received, the proportion of







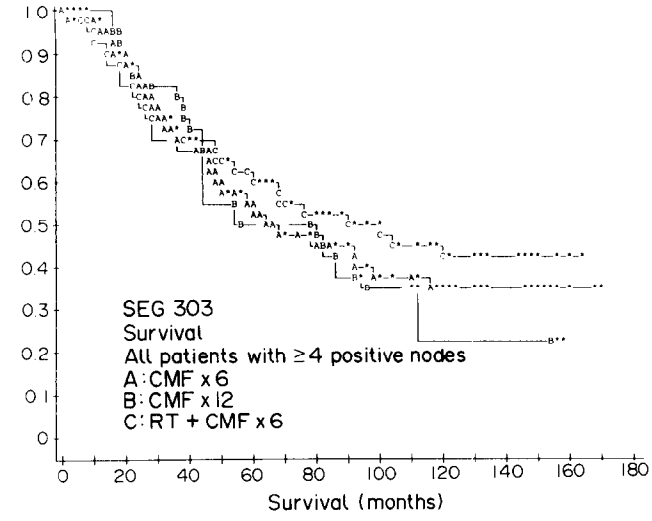


Fig. 1. Disease-free survival

Fig. 2. Survival

Relapses: 1–3 6 months 53/155 12 months 55/147
≥ 4 6 months 75/122 12 months 34/54 RT + 6 months 57/117

		P (logrank)
1–3	6 vs. 12 months	0.74
≥ 4	6 vs. 12 months	0.56
	6 vs. RT + 6 months	0.07
	12 vs. RT + 6 months	0.32
	Overall	0.18

Deaths: 1–3 6 months 48/155 12 months 46/147
≥ 4 6 months 66/122 12 months 32/54 RT + 6 months 53/117

		P (logrank)
1–3	6 vs. 12 months	0.85
≥ 4	6 vs. 12 months	0.93
	6 vs. RT + 6 months	0.33
	12 vs. RT + 6 months	0.39
	Overall	0.55

patients who received ≥ 85% of optimal dose was 51% of group 1, 27% of group 2 and 43% of group 3. The median time from mastectomy to initiation of chemotherapy was 37 days in groups 1 and 2, and 97 days in group 3.

There is no significant difference in the proportion of relapses in patients with one to three nodes who were randomised to groups 1 or 2 or in patients with ≥ four nodes who were randomised to groups 1, 2 or 3 (Fig. 1). There is a suggestion of a decreased recurrence in patients with ≥ four nodes who received radiotherapy followed by chemotherapy (group 3); given the rather small number of recurrences, however, the difference is not a significant one. There is no significant difference in survival in patients with one to three nodes randomised to groups 1 or 2 or in those with ≥ four nodes randomised to groups 1, 2 or 3 (Fig. 2).

There was no significant difference in the proportion of relapses in patients who underwent a radical vs. a modified radical mastectomy, in those who started chemotherapy < 28 vs. ≥ 28 or more days after mastectomy and between premenopausal and postmenopausal women. Patients with four to six, seven to 12, and ≥ 13 positive nodes are equally distributed among groups 1, 2 and 3. In previous reports, premenopausal patients with one to three nodes who received 12 cycles of chemotherapy had superior survival to those who received six cycles. In this analysis with 5 additional years of follow-up, there is no difference (17/68 deaths vs. 20/66 deaths), $P = 0.48$ (Fig. 3).

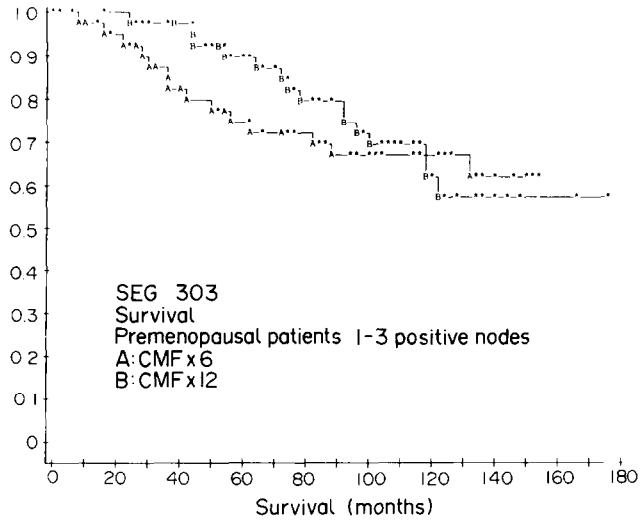


Fig. 3. Survival of premenopausal patients with one to three positive nodes: CMF × six, 17/68 deaths; CMF × 12, 20/66 deaths; $P = 0.048$.

A multivariate analysis of prognostic factors adversely affecting survival was performed using the Cox proportional hazards model. The percentage of optimal dose actually received (as defined above) was analysed. For the 23 patients who relapsed during therapy, the percentage of optimal dose received was calculated using full dosage of the number of cycles actually received as the denominator. We do not have information on exact tumour size to include that factor. Menopausal status ($P = 0.517$), time from surgery to adjuvant therapy ($P = 0.717$), type of mastectomy ($P = 0.730$) and treatment received ($P = 0.730$ and $P = 0.121$) had no significant effect on survival (separate analyses were peformed for both chemotherapy and radiotherapy; neither had a significant effect on survival). The factor most strongly predictive of survival was the presence of ≥ four positive nodes ($P = 0.001$); the other factor strongly predictive of survival was the percentage of ideal dose received ($P = 0.013$). Non-white race was also a predictor of survival ($P = 0.018$) but may be confounded by the larger tumour size in this group and this may or may not be an independent factor. The finding of percentage of ideal dose received to be strongly predictive of survival differs from findings in previous reports where only a binomial separation of dosage was tested (≥ 85 vs. 85% of ideal dose) and no multivariate analysis was done.

Table 2 displays sites of relapse. If isolated locoregional recurrences are examined there were fewer locoregional recurrences in patients who received 12 instead of six cycles of chemotherapy but the numbers are small and 95% confidence intervals overlap somewhat. No significant difference was observed in those with ≥ four nodes. When all locoregional recurrences are examined, no significant difference was observed in patients with one to three nodes who received 6 vs. 12 months of chemotherapy. In those with ≥ four nodes, about half as many locoregional recurrences were observed in those who received radiotherapy and chemotherapy. The difference was not a significant one (relative risk 0.53, $P = 0.067$); the number of locoregional recurrences seen in this study is simply too small to detect confidently a small but real difference in the rate of locoregional recurrence.

DISCUSSION

Our results indicate no advantage for treatment with 12 as compared with 6 months of adjuvant chemotherapy, either for relapse-free survival or for overall survival. This result confirms those of the Milan group [5]. Other prospective comparisons [6] of different durations of adjuvant chemotherapy have similarly indicated no advantage for the longer regimens. Multivariate analysis indicates that one disease-related factor, ≥ four positive nodes, was most strongly predictive of survival. The other factor strongly predictive of survival was treatment-related, i.e. the percentage of ideal dose received. Although the fraction of

Table 2. Sites of initial relapse

Number of positive nodes	Distant only		Locoregional and distant		Locoregional only		All local regional		None	Total
	No.	%	No.	%	No.	%	No.	%	No.	No.
1–3										
6 months	33	21	1	1	19	12	20	13	102	155
12 months	43	29	4	3	8	5	12	8	92	147
Total	76	25	5	2	27	9	32	11	194	302
≥ 4										
6 months	47	39	5	4	25	20	30	25	47	122
12 months	20	37	3	6	8	15	11	20	20	54
RT + 6 months	60	51	3	3	12	10	15	13	60	117
Total	127	43	11	4	45	15	56	19	127	293

	Overall P
All locoregional recurrence	
One to three nodes (13 vs. 8%)	0.181
≥ four nodes (25 vs. 20 vs. 13%)	0.067
Isolated locoregional recurrences	
One to three nodes (12 ± 5 vs. 5 ± 4%)	0.038
≥ four nodes (20 vs. 15 vs. 10%)	0.089

patients who received full doses or nearly full doses of chemotherapy is small (27–51% in different groups), the findings are consistent with the importance of dose intensity or of administration of full doses of chemotherapy.

The other findings of interest relate to postmastectomy radiotherapy. Survival was not at all different in patients with ≥ four nodes who received radiotherapy. There was a suggestion of a radiotherapy effect with fewer locoregional recurrences ($P = 0.067$). This difference is not significant by conventional tests of significance; a study with a larger number of recurrences would be required to detect a true reduction in locoregional recurrence of this magnitude. The expense and toxicity of postmastectomy radiotherapy [7], as well as its modest effect in reducing locoregional recurrence when given in addition to chemotherapy, do not support its routine use. Limiting its use to groups of patients at higher risk of recurrence after mastectomy and chemotherapy than those in this study would seem judicious.

In summary, the results of this prospective study indicate no advantage for 12 as compared with 6 months of adjuvant CMF chemotherapy in women with breast cancer and positive axillary nodes. There is a suggestion of a decrease in locoregional recurrence from postmastectomy regional radiotherapy given before 6 months of CMF chemotherapy, but there was no effect on survival. A study with a larger number of recurrences would be needed to detect a true reduction in locoregional recurrence of the magnitude seen in this one.

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Vincristine is Associated with the Risk of Azoospermia in Adult Male Survivors of Childhood Malignancies

Jukka Rautonen, Aarne I. Koskimies and Martti A. Siimes

Of 55 males, currently above 18 years of age, diagnosed with and treated for different malignancies in childhood between 1960 and 1985 at a single institution, 28 (51%) were azoospermic. The age of the patient, testicular irradiation, four different therapeutic agents (L-asparaginase, cyclophosphamide, doxorubicin, vincristine) and one combination (MOPP, nitrogen mustard, vincristine, procarbazine, prednisone) were each associated with the risk of azoospermia. However, in multivariate analysis vincristine had the statistically most significant independent effect on the risk of azoospermia, the risk being 5-fold (95% confidence limits 1.3–18.8, $P = 0.02$) that in patients who had not received vincristine. The risk of azoospermia in patients who had received cyclophosphamide was 3.4-fold (0.95–12.3, $P = 0.06$) and in those who had received testicular irradiation it was 8.2-fold (0.75–90.9, $P = 0.09$) that of others. Normospermia (22% of patients) was not incompatible with any of the more commonly used modes of therapy. We conclude that vincristine may have a previously unrecognised important role in causing azoospermia, possibly irreversible, when administered in childhood or adolescence.
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INTRODUCTION

TESTICULAR IRRADIATION and various chemotherapeutic agents used in the treatment of malignant diseases are known to cause temporary or even permanent disturbances in spermatogenesis [1–12]. However, most studies have included only patients who received treatment as adults, and very little is known about fertility in adult male survivors of malignancies of childhood [13–17]. Since the toxic effect of any agent or treatment modality may be different on a prepubertal or pubertal as opposed to a mature testis, it is crucial to assess the toxic effects of individual agents in the pediatric population as well. Unfortunately the simultaneous use of many drugs makes this task difficult. We have attempted to overcome this difficulty by using statistical multivariate methods, not used in previous studies, to identify