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POSTOPERATIVE RADIOTHERAPY IN HIGH-RISK PREMENOPAUSAL WOMEN WITH BREAST CANCER WHO RECEIVE ADJUVANT CHEMOTHERAPY

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ABSTRACT

Background Irradiation after mastectomy can reduce locoregional recurrences in women with breast cancer, but whether it prolongs survival remains controversial. We conducted a randomized trial of radiotherapy after mastectomy in high-risk premenopausal women, all of whom also received adjuvant systemic chemotherapy with cyclophosphamide, methotrexate, and fluorouracil (CMF).

Methods A total of 1708 women who had undergone mastectomy for pathological stage II or III breast cancer were randomly assigned to receive eight cycles of CMF plus irradiation of the chest wall and regional lymph nodes (852 women) or nine cycles of CMF alone (856 women). The median length of follow-up was 114 months. The end points were locoregional recurrence, distant metastases, disease-free survival, and overall survival.

Results The frequency of locoregional recurrence alone or with distant metastases was 9 percent among the women who received radiotherapy plus CMF and 32 percent among those who received CMF alone ($P<0.001$). The probability of survival free of disease after 10 years was 48 percent among the women assigned to radiotherapy plus CMF and 34 percent among those treated only with CMF ($P<0.001$). Overall survival at 10 years was 54 percent among those given radiotherapy and CMF and 45 percent among those who received CMF alone ($P<0.001$). Multivariate analysis demonstrated that irradiation after mastectomy significantly improved disease-free survival and overall survival, irrespective of tumor size, the number of positive nodes, or the histopathological grade.

Conclusions The addition of postoperative irradiation to mastectomy and adjuvant chemotherapy reduces locoregional recurrences and prolongs survival in high-risk premenopausal women with breast cancer. (N Engl J Med 1997;337:949-55.)

RANDOMIZED clinical trials have established that adjuvant chemotherapy or hormonal treatment prolongs the survival of patients with breast cancer.[1-4] As a result of these studies, large numbers of women with breast cancer now receive one or both of these treatments postoperatively. A number of randomized trials have also shown that overall survival in patients with small tumors was the same whether they were treated with limited surgery plus irradiation or total mastectomy.[5-7] For this reason, many patients are now treated locally with conservative measures, such as lumpectomy plus axillary dissection and irradiation to residual breast tissue; some also receive adjuvant systemic therapy. Total mastectomy, however, is still the treatment of choice for many patients, especially those with more diffuse local disease. The role of radiotherapy after mastectomy has been evaluated in several randomized trials.[6,8,9] Overall, these studies have shown a significant reduction in locoregional recurrences with postoperative irradiation but no improvement in long-term survival, irrespective of nodal status.

Radiotherapy has been evaluated mainly in trials in which chemotherapy was not given. The widespread use of adjuvant chemotherapy calls for a reassessment of radiotherapy, because the efficacy of systemic therapy in preventing local or regional re-

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currence after mastectomy is only moderate,[10] and it is not clear whether local or regional control is required for prolonged survival in patients who also receive adjuvant chemotherapy.

Our aim was to evaluate whether the addition of radiotherapy to total mastectomy with axillary dissection and adjuvant chemotherapy influenced locoregional control of tumors, the likelihood of freedom from distant metastases, and overall survival in high-risk premenopausal patients.

METHODS

Protocol Design

The Danish Breast Cancer Cooperative Group protocol 82b includes premenopausal high-risk patients with breast cancer.[1,11] High-risk status was defined as consisting of one or more of the following: involvement of axillary lymph nodes, a tumor size of more than 5 cm, and invasion of the cancer to skin or pectoral fascia (pathological stage II or III). A woman was considered premenopausal if she had had amenorrhea for less than five years or had had a hysterectomy before the age of 55.

To be eligible for the study a woman had to have no evidence of metastatic disease as determined by physical examination, biochemical tests, chest radiography, bone scintigraphy, or bone radiography and no other previous or concomitant malignant disease. The study was approved by the national ethics committee, and oral informed consent was mandatory. The departments responsible for systemic treatment and follow-up used a closed-envelope system to randomize eligible patients. No stratification into prognostic subgroups was performed before randomization.

We recruited patients from November 1982 to December 1989. After surgery, they were randomly assigned to radiotherapy plus cyclophosphamide, methotrexate, and fluorouracil (CMF); CMF alone; or CMF plus tamoxifen. Because of a higher-than-expected rate of mortality, enrollment in the third subgroup was stopped in June 1986, as described elsewhere.[1] This report will address only the results in the first two groups.

Surgery and Histopathological Analysis

The primary surgical treatment, performed at 79 surgical departments, was total mastectomy and axillary-node dissection.[12] The pectoral fascia was stripped, but neither the major nor the minor pectoral muscles were removed. Axillary dissection included removal of the central axillary lymph nodes involving level I and part of level II. Overall, a median of seven lymph nodes were removed.

The histopathological examination was performed according to a standardized procedure by the 29 pathology departments participating in the trial. Microscopical examination included tumor classification according to the World Health Organization (WHO) standards[13] and histopathological classification according to the system of Bloom and Richardson.[14] Grading of anaplasia was performed only in ductal carcinomas. The pathologist recorded the number of lymph nodes identified in the specimen, as well as the gross tumor size and whether there was invasion of the tumor into skin or deep fascia.

Radiotherapy

Radiation therapy was delivered to the chest wall, including the surgical scar and regional lymph nodes (i.e., supraclavicular, infraclavicular, and axillary nodes as well as internal mammary nodes in the four upper intercostal spaces).[15] The intended dose was a median absorbed dose in the target volume of either 50 Gy, given in 25 fractions over a period of 5 weeks, or 48 Gy, given in 22 fractions over a period of 5½ weeks, according to report 29 of the International Commission on Radiation Units and Measurements.[15] The recommended field arrangement involved the use of an anterior photon field against the supraclavicular, infraclavicular, and axillary regions and an anterior electron field against the internal mammary nodes and the chest wall. The use of posterior axillary fields was advised in patients in whom the ratio of the anterior to posterior diameter was too large to limit the maximal absorbed dose to 55 Gy (given in 25 fractions) or 53 Gy (given in 22 fractions). Most of the patients were treated at the six departments that used a linear accelerator, but 64 patients (7.5 percent) were treated at small departments that used 250-kV x-ray machines and the McWhirther technique.[16] In these patients the minimal intended dose was 36 Gy given in 20 fractions over a period of four weeks. Compliance with radiotherapy was high; only 32 patients (3.8 percent) did not receive the planned treatment.

Adjuvant Systemic Therapy

A combination of cyclophosphamide (600 mg per square meter of body-surface area), methotrexate (40 mg per square meter) and fluorouracil (600 mg per square meter) was given intravenously every four weeks, with the first cycle beginning two to four weeks after surgery. Patients who were randomly assigned to radiotherapy plus CMF started radiotherapy within one week after the first cycle of chemotherapy. They completed the treatment within five weeks and, after a rest of one to two weeks, continued with the CMF regimen, which was repeated every four weeks. Thus, for these patients the planned chemotherapy consisted of eight cycles of CMF, whereas the patients who were assigned to CMF without radiotherapy were given a total of nine cycles of CMF. Compliance with chemotherapy was the same in both groups, and at least 85 percent of the patients received the planned number of CMF cycles.

Follow-up

The patients were followed with clinical examination at regular intervals for up to 10 years and further tested only if they had symptoms or evidence of recurrent disease.

Statistical Analysis

All diagnostic, therapeutic, and follow-up data were validated and processed by the Danish Breast Cancer Cooperative Group's data center.[11,17] The protocol did not call for an interim analysis, but the study was monitored regularly by the data center for excess mortality in either treatment group. To optimize the quality of the data, all events recorded by the data center through June 1992 were cross-checked with hospital records throughout the country to ensure correct recording of the site or sites of the first relapse.

Locoregional recurrence was defined as the appearance of local or regional tumor (in the chest wall, axilla, or supraclavicular or infraclavicular area) alone or together with distant metastases (diagnosed within one month after the initial finding of recurrence). Any recurrence that occurred after the first relapse was not included. Disease-free survival was defined as the duration of survival without locoregional recurrence or distant metastases, cancer in the opposite breast, or other malignant disease. Overall survival was calculated as the length of time until death, irrespective of cause. The lengths of time until treatment failure were measured from the date of mastectomy.

The recording of only the first recurrence and not of subsequent recurrences (local, regional, or distant) implies that an estimation of the time to locoregional recurrence would be categorized as an analysis of competing risks. However, the effects of radiotherapy on locoregional recurrence and distant metastases cannot be assessed separately. Any analysis of locoregional recurrence therefore involves analyzing the time to the first recurrence (at any site) and the percentages of patients with locoregional recurrences and distant metastases. The latter are analyzed as simple proportions because the lengths of follow-up and the way censoring was performed in the two groups were similar.[18] These values were compared by chi-square tests and risk ratios. We used the life-table method to estimate the probability of treatment failure for the end points of disease-free survival and overall survival, and we used the log-rank test for comparison.

We used a multivariate Cox proportional-hazards analysis to

evaluate prognostic variables and treatments with respect to disease-free survival and overall survival. Statistical analysis was performed by the likelihood-ratio test. Because of the lack of proportionality, the analysis was stratified with respect to histopathological findings: ductal, lobular, or medullary carcinoma. Furthermore, the last two histopathological types could not be graded with respect to anaplasia,[14] but in the multivariate analysis they were designated as grade I anaplasia. The Cox model was further applied to test whether radiotherapy significantly affected the prognostic variables.

All the estimated P values are two-tailed. Statistical analysis was performed with the SAS 6.11 program package.

Treatment effect was evaluated according to the intention-to-treat principle, and all the patients were included in their randomization group irrespective of whether they completed the planned treatment. The date for the evaluation of recurrence and survival was September 1, 1996, so that the median potential follow-up was 114 months (range, 78 to 167).

RESULTS

Of the 1789 patients who underwent randomization, 81 (34 assigned to radiotherapy plus CMF and 47 assigned to CMF alone) were subsequently found to be ineligible by the data center and were excluded. The reasons for exclusion were the patient's inclusion in another protocol, the occurrence of distant metastases, the presence of other malignant conditions, or the patient's refusal to participate in the study. These patients were included only in the analysis of survival. Of the remaining 1708 premenopausal patients, 852 were randomly assigned to postmastectomy irradiation plus CMF and 856 to CMF alone. Table 1 gives the characteristics of the patients.

TABLE 1. FREQUENCY OF LOCOREGIONAL RECURRENCES OR DISTANT METASTASES IN WOMEN TREATED WITH RADIOTHERAPY AND CMF OR CMF ALONE AFTER MASTECTOMY.

VARIABLE	NO. OF PATIENTS	RADIOTHERAPY AND CMF				CMF ALONE			
		NO. OF PATIENTS	LOCOREGIONAL RECURRENCES*	DISTANT METASTASES†	OTHER EVENTS‡	NO. OF PATIENTS	LOCOREGIONAL RECURRENCES*	DISTANT METASTASES†	OTHER EVENTS‡
			percent				percent		
All patients	1708	852	9	34	6	856	32	26	4
Age (yr)									
<40	323	156	11	38	4	167	44	26	1
40–49	934	459	8	32	4	475	29	26	4
50–59	451	237	10	35	11	214	30	25	7
Tumor size (mm)									
<21	674	339	6	28	5	335	25	21	5
21–50	772	402	10	37	6	370	35	30	4
>50	234	99	12	38	8	135	42	25	4
Unknown	28	12				16			
No. of nodes removed									
0–3	255	122	10	34	7	133	40	17	5
4–9	1042	531	8	33	5	511	32	26	5
>9	409	198	9	35	6	211	27	30	3
Unknown	2	1				1			
No. of positive nodes									
None	135	58	3	19	2	77	17	17	4
1–3	1061	545	7	30	5	516	30	23	4
>3	510	248	14	46	8	262	42	34	5
Unknown	2	1				1			
Frequency of positive nodes (%)									
<34	715	360	5	24	4	355	21	22	5
34–67	446	217	7	38	7	229	37	25	3
>67	532	269	15	42	8	263	44	31	5
Unknown	15	6				9			
Histopathological classification of tumor§									
Ductal	1461	741	10	33	6	720	34	25	5
Lobular	162	69	4	43	7	93	22	31	1
Medullary	45	21	5	19	10	24	25	21	0
Unknown or other	40	21				19			
Grade of anaplasia (ductal carcinoma only)									
Grade I	363	182	6	23	5	181	29	17	3
Grade II	701	361	7	37	6	340	31	29	7
Grade III	351	176	18	39	5	175	46	28	4
Unknown	46	22				24			

*This category includes local failure alone or with concomitant distant failure.

†This category includes distant failure alone.

‡Other events were other malignant disease and death without recurrence.

§The WHO classification was used.[13]

TABLE 2. TYPES OF FIRST RECURRENCES OR EVENTS.

TREATMENT	NO. OF PATIENTS	DISTANT METASTASES ALONE	LOCOREGIONAL RECURRENCE		OTHER EVENTS*	CENSORED OBSERVATIONS†
			ALONE OR WITH DISTANT METASTASES	ALONE		
			number of patients (percent)			
Radiotherapy + CMF	852	287 (34)	75 (9)	44 (5)	50 (6)	440 (52)
CMF alone	856	219 (26)	277 (32)	221 (26)	37 (4)	323 (38)
All patients	1708	506 (30)	352 (21)	265 (16)	87 (5)	763 (45)

*Other events were other malignant disease and death without recurrence.

†Censored observations indicate patients without recurrences or other events.

By the time of the analysis (median follow-up, 114 months), the disease had recurred in 858 patients (Table 2) and 842 patients had died. The probability of disease-free survival was significantly higher in the group that received radiotherapy plus CMF than in the group treated only with CMF (Fig. 1 and Table 3). The type of first recurrence differed significantly in the two groups ($P<0.001$): Locoregional recurrence was significantly more frequent in the group treated with CMF alone, whereas distant metastases were more frequent in the group treated with radiotherapy plus CMF (Table 2). The relative risk of locoregional recurrence as a first event among patients treated with CMF alone was 3.7 (95 percent confidence interval, 2.9 to 4.7), and the relative risk of distant metastases as a first event was 0.8 (95 percent confidence interval, 0.7 to 0.9). The estimated overall survival after 10 years was 54 percent (95 percent confidence interval, 51 to 58 percent) in the group assigned to radiotherapy plus CMF, as compared with 45 percent (95 percent confidence interval, 42 to 48 percent) in the group assigned to CMF alone (Fig. 2).

Our results confirm that tumor size, the number of pathologic nodes, and the grade of anaplasia are the major prognostic factors in breast cancer (Tables 1 and 3). We could not identify any subgroups in which the effect of radiotherapy was particularly beneficial.

We estimated that locoregional recurrences were the only cause of a first relapse in 80 percent of patients who received only CMF postoperatively, whereas in the group given radiotherapy and CMF, 41 percent of the patients who relapsed with locoregional recurrences also had distant metastases (31 of 75 patients) (Table 2). Table 1 shows that the addition of irradiation to chemotherapy reduced the frequency of locoregional recurrence to about one-fourth that found in the groups that did not receive radiotherapy. Table 1 also shows that the frequency of locoregional recurrences increased with the size of the tumor, the number of positive nodes, and the grade of anaplasia, irrespective of treatment.

The results of multivariate Cox regression analyses, with any type of recurrence or death or death from any cause used as end points, are shown in Table 4. The size of the primary tumor, the frequency and number of positive lymph nodes, the histopathological grade, the use of radiotherapy, and age were all significant independent predictors of outcome. No significant interactions between radiotherapy and these prognostic signs were found — that is, the beneficial effect of radiotherapy on both disease-free and overall survival applied to all subgroups.

DISCUSSION

Our results indicate that the addition of radiotherapy to adjuvant chemotherapy after total mastectomy and axillary dissection reduces locoregional recurrences and improves survival. Previous studies of radiotherapy, which included only small numbers of patients (approximately one-fifth the number enrolled in the present study), showed improvement in the control of locoregional tumors[19-26] and suggested improvement in survival.[23-26]

Although our protocol carefully described recommendations for the surgical procedure,[12] there might have been important variations in the extent of the surgery performed among the 79 departments that enrolled patients in the study. Our surgeons found relatively few lymph nodes in the axilla (median, seven nodes), but the number also relies on the pathologist who counted the lymph nodes in the specimen. The fact that 255 patients had fewer than four nodes removed weakens our analysis of the influence of having more than three positive nodes in the study group. Although we included the frequency of positive nodes in the analysis of prognostic factors, the importance of the number of nodes removed is difficult to assess, since in some patients many nodes

TABLE 3. ESTIMATED DISEASE-FREE SURVIVAL AND OVERALL SURVIVAL.*

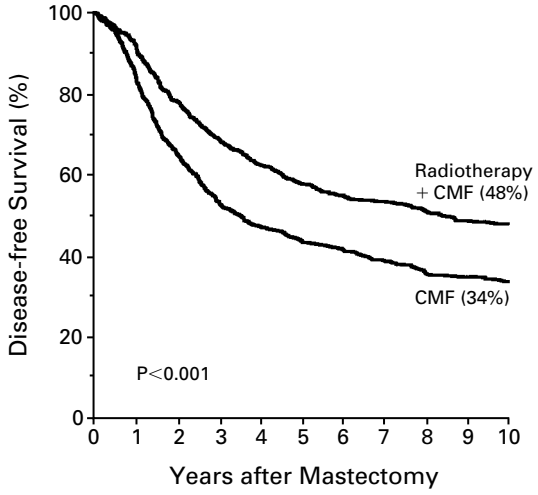
VARIABLE	10-YR ACTUARIAL DISEASE-FREE SURVIVAL		10-YR ACTUARIAL OVERALL SURVIVAL	
	RADIOTHERAPY + CMF	CMF ALONE	RADIOTHERAPY + CMF	CMF ALONE
	percent			
All patients	48	34	54	45
Age (yr)				
<40	44	26	55	38
40–49	54	36	59	48
50–59	40	34	45	45
Tumor size (mm)				
<21	57	45	67	58
21–50	43	28	47	38
>50	37	22	40	33
No. of nodes removed				
0–3	42	38	58	48
4–9	50	32	55	45
>9	46	34	49	45
No. of positive nodes				
None	74	62	82	70
1–3	54	39	62	54
>3	27	14	32	20
Frequency of positive nodes (%)				
<34	65	49	70	63
34–67	44	31	51	46
>67	27	15	37	20
Histopathological classification of tumor†				
Ductal	48	32	54	43
Lobular	36	41	45	53
Medullary	65	54	66	65
Grade of anaplasia (ductal carcinoma only)				
Grade I	63	47	71	62
Grade II	46	29	52	40
Grade III	35	20	39	27

*The numbers of patients in each group are given in Table 1. In univariate analyses all differences between subgroups were significant except for the difference between subgroups in the number of nodes removed for both disease-free and overall survival and the difference between subgroups in the histopathological classification of tumor for disease-free survival.

†The WHO classification was used.[13]

were removed because they were clinically involved, whereas in others many nodes were removed by a careful surgeon.

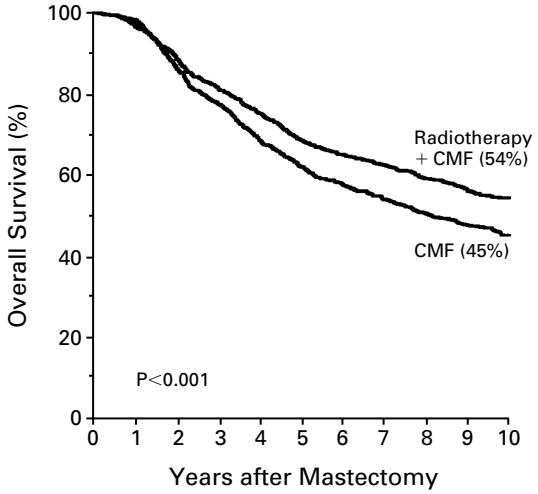
The problem of local recurrence is not related solely to the management of the axilla, since more than half of the recurrences were on the chest wall.[15] Recurrences on the chest wall and in the axilla (without concomitant distant metastases) were treated with curative intent. Most patients who did not receive radiotherapy were treated with resection of the recurrent tumor followed by radiotherapy, whereas patients who had received radiotherapy were treated with surgery alone. The significant difference in overall survival between the group treated with radiotherapy plus CMF and the group given CMF alone indicates that second-line treatment cannot compensate for inadequate primary therapy.



Radiotherapy + CMF	852	643	505	429	308	102
CMF	856	537	382	327	216	74

Figure 1. Kaplan–Meier Estimates of Disease-free Survival among Women Treated with Radiotherapy plus CMF and CMF Alone.

Values in parentheses are disease-free survival at 10 years.



Radiotherapy + CMF	852	755	641	555	392	188
CMF	856	738	587	494	329	163

Figure 2. Kaplan–Meier Estimates of Overall Survival among Women Treated with Radiotherapy plus CMF and CMF Alone.

Values in parentheses are overall survival at 10 years.

TABLE 4. COX MULTIVARIATE PROPORTIONAL-HAZARDS ANALYSIS OF THE RELATIVE RISK OF ANY TYPE OF RECURRENCE OR DEATH OR OF DEATH FROM ANY CAUSE.*

VARIABLE	ANY TYPE OF RECURRENCE OR DEATH		DEATH	
	P VALUE	RR (95% CI)	P VALUE	RR (95% CI)
Tumor size (<21 mm, 21–50 mm, >50 mm)†	<0.001	1.43 (1.30–1.58)	<0.001	1.49 (1.35–1.65)
No. of positive nodes (0, 1–3, >3)†	<0.001	1.57 (1.36–1.81)	<0.001	1.75 (1.50–2.05)
Frequency of positive nodes (<34%, 34–67%, >67%)†	<0.001	1.44 (1.30–1.58)	<0.001	1.38 (1.24–1.53)
Grade of anaplasia (I, II, III)†	<0.001	1.44 (1.31–1.59)	<0.001	1.52 (1.37–1.70)
Age of 40 to 49 yr (vs. <40 yr and 50–59 yr)	<0.001	0.73 (0.64–0.83)	<0.001	0.76 (0.66–0.87)
Radiotherapy + CMF (vs. CMF alone)	<0.001	0.59 (0.51–0.67)	<0.001	0.71 (0.62–0.82)

*The analysis included 1584 patients. Patients whose tumor size was unknown, whose nodal status was unknown, whose histopathological stage was other than ductal, lobular, or medullary, and whose grade of anaplasia (for ductal carcinoma) was unknown were excluded from the analysis. RR denotes relative risk, and CI confidence interval.

†A stepwise comparison was made.

The type and dose intensity of adjuvant chemotherapy are also important.[4,27] The dose intensity with 8 or 9 cycles of CMF (given at four-week intervals) that was used in this trial is lower than the usual course of 12 cycles[4] — a number that was also used in the previous Danish Breast Cancer Cooperative Group trial (protocol 77).[1] This reduction may decrease overall survival, but it is not likely to change our conclusion. The fact that patients given combined treatment received only eight cycles of CMF, with a long interval between the first and third cycles, might have reduced the benefit of radiotherapy plus CMF. The guidelines for irradiation after mastectomy were based on experience from previous trials involving protocol 77,[15] but CMF was given simultaneously with radiotherapy in protocol 77, whereas it was given sequentially in the present trial to decrease the early and late reactions in normal tissues.[28]

Recording of short-term and long-term complications was planned prospectively in all patients, but the data are incomplete and we continue to record long-term complications. We can roughly estimate cardiotoxicity by comparing the survival rates after radiotherapy among patients with cancer of the left breast and those with cancer of the right breast. There is no evidence of a higher rate of death among patients with left-sided tumors, after a median follow-up of almost 10 years. Longer follow-up and more detailed analysis of the actual dose to the heart are needed before final conclusions can be made on this end point.

The decentralized randomization procedure resulted in the enrollment of 81 ineligible patients. However, the inclusion of these patients did not influence overall survival rates (the 10-year actuarial value being 54 percent in the group assigned to radiotherapy plus CMF and 44 percent in the group assigned to CMF alone, $P<0.001$).

Our study strongly indicates that optimal results of the treatment of high-risk breast cancer can be achieved only by controlling both locoregional and systemic tumors. With current surgical methods of treatment, radiotherapy seems required for adequate locoregional control in high-risk premenopausal patients. However, the optimal balance between surgery, radiotherapy, and adjuvant chemotherapy in high-risk patients with breast cancer has not yet been found.

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