Articles

Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial

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Summary

Background Postmastectomy radiotherapy is associated with a lower locoregional recurrence rate and improved disease-free and overall survival when combined with chemotherapy in premenopausal high-risk breast-cancer patients. However, whether the same benefits apply also in postmenopausal women treated with adjuvant tamoxifen for similar high-risk cancer is unclear. In a randomised trial among postmenopausal women who had undergone mastectomy, we compared adjuvant tamoxifen alone with tamoxifen plus postoperative radiotherapy.

Methods Between 1982 and 1990, postmenopausal women with high-risk breast cancer (stage II or III) were randomly assigned adjuvant tamoxifen (30 mg daily for 1 year) alone (689) or with postoperative radiotherapy to the chest wall and regional lymph nodes (686). Median follow-up was 123 months. The endpoints were first site of recurrence (locoregional recurrence, distant metastases, or both), and disease-free and overall survival.

Findings Locoregional recurrence occurred in 52 (8%) of the radiotherapy plus tamoxifen group and 242 (35%) of the tamoxifen only group ($p<0·001$). In total there were 321 (47%) and 411 (60%) recurrences, respectively. Disease-free survival was 36% in the radiotherapy plus tamoxifen group and 24% in the tamoxifen alone group ($p<0·001$). Overall survival was also higher in the radiotherapy group (385 *vs* 434 deaths; survival 45 *vs* 36% at 10 years, $p=0·03$).

Interpretation Postoperative radiotherapy decreased the risk of locoregional recurrence and was associated with improved survival in high-risk postmenopausal breast-cancer patients after mastectomy and limited axillary dissection, with 1 year of adjuvant tamoxifen treatment. Improved survival in high-risk breast cancer can best be achieved by a strategy of both locoregional and systemic tumour control.

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Introduction

The benefit of adjuvant tamoxifen in postmenopausal breast-cancer patients is well established from several randomised studies.[1–5] Improvements in disease-free and overall survival have been found in both node-negative and node-positive patients. Therefore the standard adjuvant systemic therapy in most postmenopausal breast-cancer patients is tamoxifen, irrespective of locoregional treatment.

An increasing number of patients with small tumours are now treated by conservative approaches, such as lumpectomy plus axillary dissection, and irradiation to residual breast.[6–8] However, total mastectomy is still the treatment of choice in patients with larger and more diffuse local tumours. Whether postoperative radiotherapy would be beneficial to such patients has long been controversial. Several randomised studies have shown a significant decrease in the rate of locoregional recurrence, but no improvement in long-term survival.[7,9,10] Studies on the role of radiotherapy have involved patients who were not receiving adjuvant systemic treatment. The implication of optimum locoregional tumour control in patients also treated with adjuvant chemotherapy has been shown in two randomised studies in high-risk premenopausal patients.[11,12] In these trials, combined adjuvant radiotherapy and adjuvant chemotherapy (cyclophosphamide, methotrexate, and fluorouracil [CMF]) showed a significant improvement in locoregional tumour control, disease-free survival, and overall survival compared with adjuvant chemotherapy alone. Thus, modified radical surgery plus adjuvant chemotherapy cannot sufficiently prevent locoregional recurrences in patients with extensive primary loco-regional disease. Also, the poorer overall survival in patients with higher locoregional recurrence rates indicates that such residual locoregional disease is likely to be a nidus for dissemination of and death from breast cancer.[13,14]

Whether this mechanism also occurs in postmenopausal patients given adjuvant systemic treatment such as tamoxifen is not yet clear.[13,14] The aim of our trial was to assess whether postoperative irradiation is necessary in high-risk postmenopausal

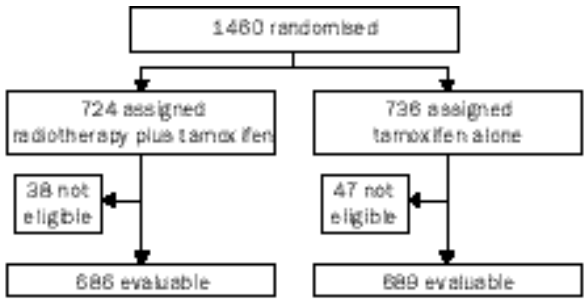

Figure 1: **Trial profile**

patients treated with total mastectomy, axillary dissection, and adjuvant tamoxifen, in terms of locoregional tumour control, disease-free, and overall survival.

Methods

Study population

A detailed description of the protocol design and organisation of the Danish Breast Cancer Cooperative Group has been reported.[15]

In our study we included postmenopausal high-risk breast-cancer patients younger than 70 years of age.[1,15] High-risk status was defined as node positive, tumour size greater than 5 cm, invasion to skin or pectoral fascia, or any combination of these characteristics. Postmenopausal status was defined as 5 years or more of amenorrhoea or, for women who had undergone hysterectomy, age over 55 years.

The criteria for entry into the protocol were: no evidence of metastatic distant disease from physical examination, biochemical tests, chest radiography, bone scintigraphy, or bone radiography, and no previous or concomitant other malignant disease. Patients with macroscopic residual tumour were excluded from the trial. Those for whom incomplete excision was apparent only on microscopy were included. The study was approved by the national scientific ethics committee, and verbal informed consent was mandatory. Patients were randomly allocated treatment options by a closed-envelope system through the departments responsible for the systemic treatment and follow-up. This study was nationwide, and inclusion was offered to all eligible Danish women with the exception of patients included in the parallel DBCG 82TM protocol, which addressed the role of tumour removal versus mastectomy.[15]

We recruited patients between October, 1982, and March, 1990. After surgery, patients were randomly assigned radiotherapy plus tamoxifen, tamoxifen alone, or adjuvant chemotherapy (CMF) plus tamoxifen. This report addresses only the role of radiotherapy in addition to adjuvant tamoxifen in postmenopausal patients; the results for CMF plus tamoxifen will be published elsewhere.

	Total number of patients	Radiotherapy plus tamoxifen				Tamoxifen alone			
		Number of patients	Proportion of patients with first recurrence (%)			Number of patients	Proportion of patients with first recurrence (%)		
			Local*	Distant†	Other‡		Local	Distant	Other
Total patients	1375 (100%)	686 (100%)	8	39	13	689 (100%)	35	25	11
Age (years)									
<60	454 (33%)	231 (34%)	8	43	13	223 (32%)	40	24	5
⩾60	921 (67%)	455 (66%)	7	37	14	466 (68%)	33	25	14
Tumour size (mm)									
<21	518 (38%)	260 (38%)	7	32	14	258 (37%)	33	21	12
21–50	679 (49%)	333 (49%)	8	43	13	346 (50%)	37	26	11
>50	161 (12%)	84 (12%)	10	45	13	77 (11%)	34	29	9
Unknown	17 (1%)	9 (1%)				8 (1%)			
Nodes removed									
<8	825 (60%)	413 (60%)	7	38	14	412 (60%)	36	23	12
⩾8	549 (40%)	272 (40%)	8	41	13	277 (40%)	34	27	10
Unknown	1	1				0			
Positive nodes									
None	132 (10%)	68 (10%)	6	28	16	64 (9%)	23	20	11
1–3	794 (58%)	391 (57%)	6	34	12	403 (58%)	31	21	11
>3	448 (33%)	226 (33%)	11	52	14	222 (32%)	46	32	11
Unknown	1	1				0			
Tumour type									
Ductal carcinoma	1168 (85%)	583 (85%)	8	39	13	585 (85%)	36	24	11
Lobular	139 (10%)	71 (10%)	1	44	8	68 (10%)	22	32	13
Medullary	21 (2%)	11 (2%)	9	27	18	10 (1%)	80	0	0
Unknown/others	47 (3%)	21 (3%)				26 (4%)			
Malignancy grade									
I	324 (24%)	163 (24%)	6	32	12	161 (23%)	27	23	16
II	600 (44%)	291 (42%)	9	38	14	309 (45%)	39	24	10
III	215 (16%)	118 (17%)	10	52	13	97 (14%)	42	28	8
Unknown	29	11 (2%)				18 (3%)			
Deep fascia invasion									
No	1130 (82%)	563 (82%)	8	39	12	567 (82%)	32	25	11
Yes	206 (15%)	100 (15%)	6	42	17	106 (15%)	45	22	11
Unknown	39 (3%)	23 (3%)				16 (2%)			
Skin invasion									
No	1176 (86%)	590 (86%)	8	39	12	586 (85%)	35	24	10
Yes	189 (14%)	91 (13%)	8	42	20	98 (14%)	34	27	14
Unknown	10 (1%)	5 (1%)				5 (1%)			
Affected breast									
Right	665 (48%)	340 (50%)	8	39	14	325 (47%)	33	25	10
Left	710 (52%)	346 (50%)	7	39	13	364 (53%)	37	24	11

*Local recurrence alone or with concomitant distant recurrence. †Distant recurrence alone. ‡Other events: dead without recurrence, or other malignant disease.

Table 1: **Characteristics of patients by treatment and type of recurrence**

Site of first recurrence	Radiotherapy plus tamoxifen (n=686)	Tamoxifen only (n=689)	All patients (n=1375)
Distant metastases only	269 (39%)	169 (25%)	438 (32%)
Locoregional only	30 (4%)	203 (29%)	233 (17%)
Distant metastases and locoregional	22 (3%)	39 (6%)	61 (4%)
All recurrences	321 (47%)	411 (60%)	732 (53%)

Table 2: **Site of first recurrence by treatment**

Procedures

The surgical and histopathological procedures were carried out as previously described.[11] The primary surgical treatment at 76 different surgical departments was total mastectomy and axillary-node dissection. The pectoral fascia was stripped, but neither the major nor the minor pectoral muscles were removed. Axillary dissection incuded removal of the central axillary lymph nodes involving level I and part of level II. Overall, a median of seven lymph nodes were removed.

For histopathology, the 30 participating pathological departments followed a standard procedure. Microscopic examination included tumour classification according to WHO, and for ductal carcinomas according to Bloom and Richardson's grading for malignant disease. The number of lymph nodes removed was identified in the axillary specimen, and tumour size and invasion into skin or deep fascia was also recorded. Oestrogen-receptor status was obtained in less than half of the patients, and we did no further analysis of this variable.

Radiotherapy was directed towards the chest wall, which included the surgical scar and regional lymph nodes (the supraclavicular, infraclavicular, and axillary nodes, and internal mammary nodes in the four upper intercostal spaces).[5] The intended dose was either a median absorbed dose in the target volume of 50·0 Gy in 25 fractions in 35 days, or 48·0 Gy in 22 fractions in 38 days.[5] The recommended procedure was to use an anterior photon field against the supraclavicular and axillary region, and an anterior electron field against the internal mammary nodes and the chest wall. The protocol recommended use of posterior axillary fields for patients with large anterior to posterior diameter to limit the maximum absorbed dose to 55·0 Gy in 25 fractions, or 52·8 Gy in 22 fractions. Most patients were treated at six departments with a linear accelerator. However, 69 patients (10% of the patients who were randomly assigned radiotherapy) were treated at small departments with 250 kV X-rays, by the McWhirther technique, as previously described.[16] In these patients the lowest intended dose was 36·0 Gy in 20 fractions in 4 weeks. Compliance to radiotherapy was high, and only 30 (4%) patients did not complete the treatment.

Patients received adjuvant tamoxifen 30 mg daily for 1 year. Tamoxifen was started 2–4 weeks after surgery, and was given concomitantly with postoperative radiotherapy in the patients assigned this treatment.

Patients were followed up with clinical examinations regularly for 10 years. If the women had any indication of recurrent disease they underwent further investigations. Death of patients after 10 years were recorded from the national population register.

Statistical analyses

All diagnostic, therapeutic, and follow-up data were validated and processed by the data centre.[15] All events recorded by the data centre up to July, 1992, were cross-checked against hospital records throughout the country, to ensure that the site where the first recurrence occurred was correctly recorded.[17]

We planned to include patients for a 5-year period, with an estimated inclusion of at least 750 patients altogether in the planned three groups. With the assumption of an improvement of 15% in 5-year survival (eg, from 60% to 75%), the probability that such change would be detected with significance of p=0·05 was greater than 95%. To avoid unwanted side-effects, the trial was regularly monitored by the

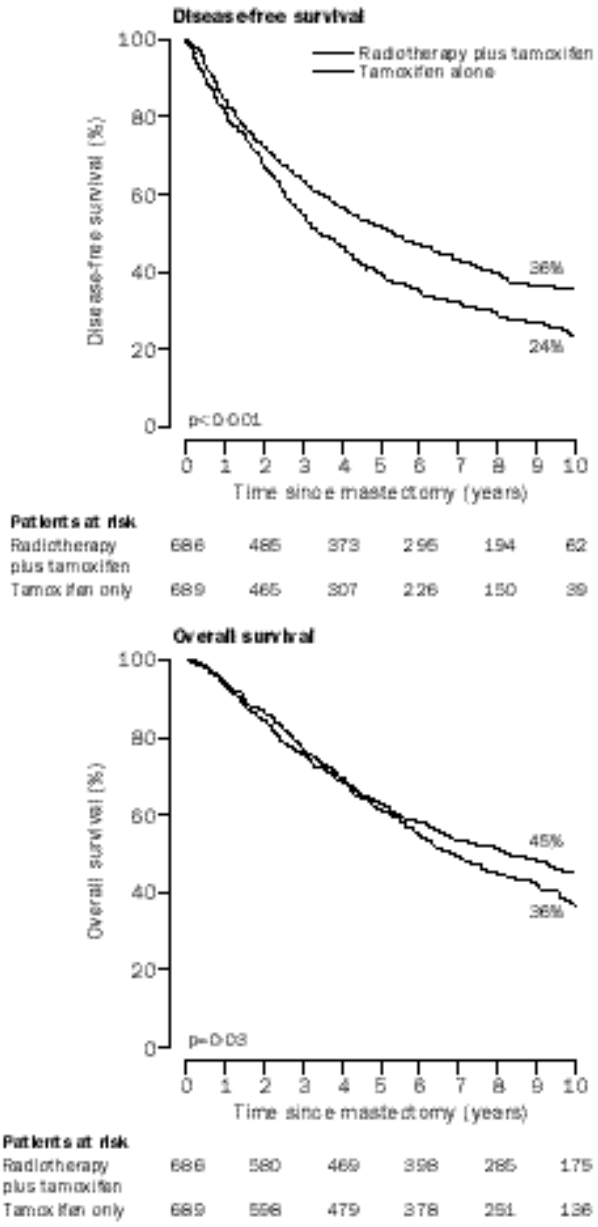

Figure 2: **Effect of radiotherapy on disease-free survival and overall survival**

data centre and the Danish Breast Cancer Cooperative Group steering committee, and recruitment was continued beyond the planned number of patients.

The effect of treatment was assessed by intention to treat, and patients were included in their randomisation group, whether or not they had completed the planned treatment.

The primary endpoint was survival (all deaths from any cause were included in the analysis). The definition of the endpoint of locoregional recurrence was first site of failure (chest wall, axilla, supra/infraclavicular), alone or together with distant metastases (diagnosed within 1 month). Any recurrence occurring after first relapse was not recorded. Disease-free survival was defined as freedom from locoregional or distant recurrence, cancer in opposite breast, other malignant disease, or death without recurrence. All time estimates were done with the date of mastectomy as the baseline. The date for assessment of recurrence and survival was Sept 1, 1996.

The recording of first site of recurrence only implies competing risks for locoregional and distant recurrence, because patients who receive radiotherapy have a substantially lower risk of local recurrence.[8,18] The effect of radiotherapy on

	Disease-free survival (%)				Overall survival (%)			
	5-years value*		10-years value*		5-years value*		10-years value*	
	RT+T	T alone	RT+T	T alone	RT+T	T alone	RT+T	T alone
Total patients	52	40	36	24	63	62	45	36
Age (years)								
<60	47	39	33	27	61	61	43	36
⩾60	54	41	37	23	64	62	46	37
Tumour size (mm)								
<21	60	46	43	28	74	69	52	44
21–50	50	38	31	21	57	59	42	32
>50	35	30	29	22	49	47	30	29
Nodes removed								
<8	52	40	37	24	64	60	46	36
⩾8	51	41	34	24	61	64	44	37
Positive nodes								
None	69	67	43	40	79	84	56	55
1–3	61	48	44	31	70	68	55	44
>3	31	19	18	6	45	42	24	17
Tumour type								
Ductal carcinoma	51	39	35	23	62	60	44	35
Lobular	56	45	39	26	70	69	54	42
Medullary	45	20	45	20	55	40	55	20
Malignancy grade								
I	68	48	44	29	77	69	55	43
II	50	37	34	21	62	59	44	32
III	30	27	25	18	38	48	26	29
Deep fascia invasion								
No	52	42	36	26	64	62	45	38
Yes	49	33	31	15	58	60	41	28
Skin invasion								
No	53	41	37	24	65	62	47	38
Yes	41	37	23	22	51	61	31	27
Breast affected								
Right	51	42	35	25	62	65	45	40
Left	52	39	36	23	63	59	44	33

*Kaplan-Meier estimates. RT=radiotherapy; T=tamoxifen.

Table 3: **Effect of radiotherapy on disease-free survival and overall survival**

locoregional recurrence cannot be assessed separately from its effect on distant recurrence. Analysis of locoregional recurrence therefore includes analysis of the time to first recurrence (in any site) and of the proportions of patients with recurrence at the different sites. The proportions are presented by the frequencies, because the follow-up times and censoring in the two groups are similar.[18] The frequencies were analysed by the χ^2 test. Overall survival and disease-free survival were estimated by the Kaplan-Meier method. The log-rank test was used to compare the treatment groups.

A multivariate Cox's proportional-hazards regression model was applied to assess whether radiotherapy had different effects on disease-free and overall survival in subgroups of some of the prognostic variables (ie, interactions between treatment effect and prognostic variables). The multivariate analyses included size of primary tumour, number of lymph nodes removed, number of positive lymph nodes, histopathological tumour type, malignancy grade, and radiotherapy. Patients with any missing values for prognostic variables were excluded from the analysis. All variables were investigated with respect to interaction with radiotherapy. Estimation used the SAS procedure PROC PHREG with backward elimination (version 6.12).

Tests to analyse the time-changing effects of an explanatory variable and log (–log) S plots were used to check the proportional-hazard assumptions. The hazard rates of the tumour types were not proportional. Therefore, the Cox's regression was stratified by tumour type. This solution implies that no effect of tumour type was estimated. Also, the hazard rates for the two treatment groups were not proportional. Stratification for this variable was not a solution, since the effect of treatment is the main interest. Instead, all analyses were divided into two components: an analysis of overall survival within 4 years after surgery; and an analysis of overall survival from 4 years after surgery and onwards. The same approach was used for disease-free survival within 2 years after surgery; and an analysis from 2 years and onwards. Plots and piecewise constant models provided the background for choosing the cut-off points, such that the proportional-hazard assumptions were met. We emphasise that the cut-off points should not be taken too strictly; analysis with the time divided to allow an equal number of events to occur in each separate time period (2·3 years for disease-free survival, and 3·8 years for overall survival) gave similar results.

The level of statistical significance was set to 5%. All the estimated p values are two-tailed. Statistical analysis used SAS (version 6.12).

Results

1460 patients were randomly assigned treatment, but 85 (38 in the radiotherapy plus tamixofen group and 47 in the tamoxifen only group) were subsequently found not to be eligible by the data centre and excluded. The reasons for exclusion were inclusion in other protocols, concomitant distant metastases, other malignant diseases, or refusal by the patient. These non-eligible patients were not followed up, and only survival data are available. Thus, 1375 patients were included in the analysis (figure 1). The median age was 62 years (range 42–69), and median tumour size was 25 mm (range 2–130). The characteristics of the patients in relation to treatment and type of recurrence are given in table 1.

The median follow-up time for patients alive at time of evaluation was 119 months (range 77–166), and the median time to death among those who died was 46 months (1–160). At the time of analysis, 732 patients had developed recurrence (table 2), and 819 had died: with recurrence (274 radiotherapy plus tamoxifen, 338

Site of first recurrence	Radiotherapy plus tamoxifen	Tamoxifen only	All patients
No recurrence	637	444	1081
Site*			
Chest wall	31 (16)	123 (17)	154 (33)
Axillary nodes	9 (2)	73 (8)	82 (10)
S/I nodes	7 (2)	29 (8)	36 (10)
Axilla and chest wall	3 (1)	9 (2)	12 (3)
Axilla and S/I nodes	0	5 (2)	5 (2)
Chest wall plus S/I nodes	2 (1)	3 (2)	5 (3)
All recurrences	52 (22)	242 (39)	294 (61)

S/I=supra/infraclavicular nodes. *Numbers in parentheses=numbers with concurrent distant metastases.

Table 4: **Frequency and localisation of local recurrences by treatment**

tamoxifen) or without recurrence (111 *vs* 96). The site of first recurrence differed significantly between the two treatment groups (p<0·001). Locoregional recurrence was significantly more frequent in the group treated with tamoxifen alone. Overall, the frequency of locoregional recurrence as first site of recurrence was 8% in the radiotherapy plus tamoxifen group and 35% in patients who received adjuvant tamoxifen alone. Distant metastases, however, were more frequent in the group treated with radiotherapy plus tamoxifen (tables 1 and 2).

Although the patients treated with radiotherapy had their first recurrence more frequently at a distant site, this increased frequency was not enough to counterbalance the high rate of locoregional recurrence in the tamoxifen only patients. Therefore, when all sites of recurrence were evaluated as the probability of disease-free survival, patients who received radiotherapy plus tamoxifen had significantly better disease-free survival than patients treated with tamoxifen alone (36 *vs* 24%, figure 2).

Overall survival revealed a significant benefit with a 9% difference after 10 years (figure 2). Thus, the estimated overall survival after 10 years was 45% (95% CI 41–49), for radiotherapy plus tamoxifen, and 36% (95% CI 33–40) for patients treated with tamoxifen alone. The decentralised randomisation procedure caused 85 non-eligible patients to be randomised, however, inclusion of these patients in the overall-survival analysis did not influence the result.

Our results indicate that major prognostic factors in primary breast cancer were tumour size, number of affected nodes, and grade of cancer, and that the effect of irradiation seemed to be beneficial (tables 1 and 3).

From the data in table 2 we calculated that 84% of locoregional recurrences occurred as the only site of first relapse in patients who received tamoxifen only, whereas 42% of patients in the radiotherapy group with locoregional recurrence also had concomitant distant metastases. Table 1 shows that the addition of radiotherapy to systemic treatment was generally associated with a frequency of locoregional recurrence, about 25% of that found in the tamoxifen-only group.

Most of the recurrences occurred on the chest wall in both treatment groups but in general the proportion of recurrences at any site was lower with radiotherapy than without (table 4). Supraclavicular and infraclavicular-node recurrences were associated with distant metastasis in many cases whether or not radiotherapy was given. Axillary and chest-wall recurrences more commonly occurred alone, especially in patients who had not undergone radiotherapy.

A median of seven lymph nodes were removed altogether from all the patients in the study. However, the nodes removed did not influence the 10-year disease-free or overall survival, or the long-term beneficial effect of radiotherapy (tables 1 and 3).

Some of the patients had more advanced primary-tumour characteristics (tumour size greater than 5 cm, with fascia or skin involvement) than normally included in such trials (n=224 radiotherapy group *vs* 220 tamoxifen only). After exclusion of patients with such features, the effect of radiotherapy on disease-free survival (37 [32–42] *vs* 25 [21–30]%, p<0·01) and

	Any recurrence within 2 years (n=1282)		Death within 4 years (n=1282)	
	Relative risk (95% CI)	p	Relative risk (95% CI)	p
Crude estimates				
T alone*	1·00*		1·00	
RT+T	0·87 (0·71–1·06)	0·17	1·05 (0·86–1·27)	0·63
Tumour size (mm)				
<21*	1·00		1·00	
21–50	1·36 (1·07–1·74)	0·01	1·37 (1·09–1·72)	0·01
>50	2·47 (1·79–3·42)	<0·001	2·03 (1·48–2·78)	<0·001
Nodes removed				
<8*	1·00		1·00	
⩾8	0·55 (0·41–0·75)	<0·001	0·49 (0·37–0·67)	<0·001
Positive nodes				
0*	1·00		1·00	
1–3	2·20 (1·26–3·82)	0·01	2·49 (1·44–4·32)	0·01
>3	5·06 (2·91–8·77)	<0·001	5·88 (3·40–10·2)	<0·001
Malignancy grade				
I*	1·00		1·00	
II	2·06 (1·49–2·85)	<0·001	1·77 (1·32–2·38)	<0·001
III	3·22 (2·25–4·60)	<0·001	3·14 (2·27–4·34)	<0·001
Radiotherapy according to number of nodes removed				
<8 nodes removed				
T*	1·00		1·00	
RT+T	0·69 (0·52–0·90)	0·01	0·85 (0·66–1·09)	0·21
⩾8 nodes removed				
T*	1·00		1·00	
RT	1·04 (0·75–1·43)	0·83	1·41 (1·03–1·92)	0·03

RT=radiotherapy; T=tamoxifen. *Reference group. The Cox analysis was stratified for histopathological type (ductal, medullary, lobular). Patients with unknown tumour size, unknown nodal status, or histopathology other than ductal, lobular, or medullar, or no grade if ductal, were excluded from analysis.

Table 5: **Cox's proportional hazards models by time periods since surgery**

	Any recurrence after 2 years (n=879)		Death after 4 years (n=877)	
	Relative risk (CI)	p	Relative risk (CI)	p
Crude estimates				
T alone	1·00		1·00	
RT+T	0·66 (0·55–0·79)	<0·001	0·67 (0·55–0·83)	<0·001
Adjusted estimates				
Positive nodes				
0–3	1·00		1·00	
>3	2·18 (1·80–2·64)	<0·001	1·97 (1·58–2·45)	<0·001
Radiotherapy				
T alone	1·00		1·00	
RT+T	0·64 (0·54–0·77)	<0·001	0·68 (0·55–0·83)	<0·001

Footnote as for table 5.

Table 6: **Cox's proportional hazard model by time periods since surgery**

overall survival (47 [42–52] *vs* 40 [35–44]%, p<0·07) was maintained among the patients with less advanced tumours.

Figure 2 shows that the curves for overall survival overlap then diverge, suggesting that the underlying hazard ratio changes with time since surgery. Such results are also apparent in the results of the Cox's proportional hazards model by time periods, where the estimates of early (table 5) and late (table 6) treatment effects differ.

The variables of independent significant importance for the early effects were all those investigated, namely size of primary tumour, number of lymph nodes removed, number of positive lymph nodes, and cancer grade, but not radiotherapy. For the long-term effects, the number of positive lymph nodes, and radiotherapy, were the only variables of independent significant importance.

Interactions between radiotherapy and each of the other variables, including tumour type, were investigated. Significantly different (p<0·01, χ^2 test) effects of radiotherapy in the subgroups were found only for number of nodes removed, and only with respect to death within 4 years. Table 5 shows the short-term effect of radiotherapy for the subgroup of patients with up to seven nodes removed, and the short-term effect of radiotherapy for the subgroup of patients with more than seven nodes removed. In the first few years after treatment, only patients with fewer than eight nodes removed had any benefit from radiotherapy, whereas for patients with many nodes removed, radiotherapy was of no benefit and in some had a negative effect. However, with longer follow-up (table 6), the effects of radiotherapy were the same irrespective of how many nodes were removed—ie, radiotherapy was of benefit for the long-term survival in all groups of patients.

Discussion

We found that the addition of radiotherapy to 1 year of adjuvant tamoxifen after mastectomy and limited axillary dissection improved local control and disease-free and overall survival. The pattern of relapses in irradiated versus non-irradiated patients was similar to that in high-risk premenopausal patients, although the systemic therapy is different.[11] The only difference between premenopausal and postmenopausal patients is in the timing of the improvement in overall survival; it is delayed in postmenopausal patients. There is no obvious explanation for this discrepancy. Differences in tumour biology, with generally more receptor-positive tumours in postmenopausal patients, and differences in the effects of the systemic treatments between the premenopausal and postmenopausal trials, could influence the time course of the disease.

The recommended surgical procedure was identical to that used in the premenopausal study,[11] since the two trials were done in parallel over the same period and the patients were operated on in the same departments. There might be important variations among the 76 departments that allocated patients to the study in how radical the surgery was. However, such variations would not undermine the conclusion that optimum locoregional control is necessary for maximum long-term survival to be achieved.

The extent and quality of surgery may influence the need for postoperative radiotherapy. In this study, few lymph nodes (median seven) were removed from the axilla. A significant interaction between number of nodes removed and radiotherapy was observed in patients who survived less than 4 years (table 5). However, the number of nodes removed (<8 vs ⩾8) did not significantly influence long-term survival among patients who had radiotherapy. This finding could indicate that patients who had many nodes removed would not initially benefit from the addition of radiotherapy. However, because there was a close correlation between the number of positive nodes and the number of nodes removed, the finding is more likely to indicate that radiotherapy had less effect on survival within 4 years in patients with more advanced disease.

The problem of local recurrence is not related only to the management of the axilla, because more than half of the recurrences occurred on the chest wall (table 4).[5] The frequency of chest-wall recurrences is influenced by the quality of surgery—the margins to the primary tumour and the completeness of excision of breast tissue in relation to the pectoral fascia and skin flaps. Although this information is not available, some might argue that the positive effect of radiotherapy is a result of compensation for suboptimum surgery, rather than a true additional contribution to the locoregional tumour eradication.

Patients with more advanced primary tumours may benefit most from radiotherapy,[14] but as in premenopausal patients,[19] we also observed a substantial improvement in disease-free and overall survival in postmenopausal patients with less advanced tumours. The Cox's analysis showed that there was no significant difference in the benefit of radiotherapy between patients with small tumours and patients with larger tumours, and for the outcome in patients with few positive nodes and many positive lymph nodes.

We gave tamoxifen for 1 year, which was the standard duration when the trial started. At present, 5 years of adjuvant tamoxifen seems to be superior.[20,21] Tamoxifen greatly decreases the size of locoregional tumours but in the majority of patients this effect did not result in persistent tumour control despite continued tamoxifen therapy.[22] However, whether longer periods of tamoxifen treatment would decrease the apparent benefit from radiotherapy is unclear. Preliminary results from the third treatment group with CMF plus tamoxifen showed that more aggressive systemic therapy improved neither locoregional control nor overall survival compared with treatment with tamoxifen alone.[23] The addition of CMF to treatment with tamoxifen did result in a disease-free

survival rate similar to that for radiotherapy plus tamoxifen because there were fewer distant recurrences. The overall survival for the patients treated with CMF plus tamoxifen was not significantly different from that achieved with radiotherapy plus tamoxifen, or tamoxifen alone. Thus, more aggressive systemic therapy may not replace effective locoregional treatment, but, on the contrary, both effective locoregional and systemic therapy are necessary to obtain maximum disease control.

The monitoring of late complications such as lymphoedema and shoulder movements was planned prospectively. Although these data are incomplete, further registration of treatment-related morbidity in long-term survivors is in progress. Studies of chest radiographs have shown that tamoxifen may increase the risk of radiation-induced lung fibrosis, but whether such findings are clinically relevant in our patients needs to be further investigated.[24]

The internal mammary nodes were included in the target with anterior electron fields in most patients. Therefore, the extent of ischaemic heart disease and mortality have been evaluated. In a preliminary analysis (median follow-up almost 10 years), no evidence of excess cardiac mortality or morbidity was observed in the patients who underwent radiotherapy.[25] Furthermore, there has been no excess of deaths in patients with left-sided tumours (table 3).

We recorded only the site of first recurrence, and information about subsequent recurrences is not available. Nevertheless, there is a striking similarity between our results and the detailed analysis of the Stockholm trial.[26,27] In that study about half of the patients were postmenopausal (older than 55 years of age), and only a third were node-positive. These characteristics obviously result in better 5-year and 10-year survival than in our study, in which the patients were older and almost all had positive lymph nodes. However, the effect of adjuvant radiotherapy on node-positive patients in the Stockholm trial who did not receive adjuvant systemic therapy, was very similar to our findings, when the site of first recurrence was used as the endpoint. The Stockholm trial showed a 5-fold decrease in local recurrences after radiotherapy, and the analysis of all (accumulating) recurrences showed a strong correlation between locoregional control and subsequent distant recurrences, implying that primary locoregional tumour is very important for survival.

Since only the first site of recurrence was monitored, interpretation of patterns of treatment failure is difficult (table 2). Obviously, radiotherapy resulted in a substantial improvement in locoregional control, but also in an increased frequency of distant metastases as first site of recurrence. The latter was, however, probably not a true indication of a higher distant-recurrence rate in the radiotherapy group, but simply a consequence of the lower rate of locoregional recurrences. The patients who did not receive radiotherapy, however, would have a high incidence of locoregional recurrences that may conceal the true frequency of distant metastases, since that might increase as a result of secondary dissemination from a residual locoregional nidus.

The survival benefit achieved in this study differs from the conclusion of the latest overview analysis,[7] in which adjuvant radiotherapy was found to decrease the number of local recurrences significantly, but to have no impact on survival in node-positive patients. A drawback of the overview analyses[7,9] is the inclusion of early trials, in which the radiation dose and technique were below current standards[10,27,29] and which could lead to poor tumour control and increased late morbidity and therefore mortality.[10] The accumulating results from later trials point toward an important gain in both disease-free and overall survival if sufficient locoregional treatment is applied.[10,26,28] An overview analysis of these contemporary trials alone may, therefore, yield better guidance for future therapeutic strategy.

Our findings further support the evidence that optimum treatment of high-risk breast cancer can be achieved only if therapy is aimed at both locoregional and systemic tumour control. Postoperative radiotherapy seems to be necessary in high-risk postmenopausal patients treated with adjuvant tamoxifen to secure both sufficient locoregional control and maximum long-term survival with the current surgical approach. However, the balance between absolute survival gain from radiotherapy and treatment-related morbidity needs to be continuously supervised and redefined according to changes in primary surgery and adjuvant systemic therapy, along with improvement in the biological criteria for defining high-risk patients.

Contributors

M Overgaard contributed to the study design, recruitment, and clinical management and follow-up of patients, analysis and discussion of data, and wrote the guidelines for radiotherapy and the paper. M-B Jensen did the statistical analyses and contributed to the writing of the paper. J Overgaard contributed to the study design, analysis and discussion of the data, and the writing of the paper. P S Hansen did the quality control of events recorded by the data centre and did the cross-check with the hospital records throughout the country. C Rose and C Gadeberg contributed to the study design, recruitment, clinical management and follow-up of patients, and were responsible for reporting of radiotherapy data. M Andersson, C Kamby, and M Kjær contributed to recruitment, clinical management and follow-up of patients, and were responsible for reporting of radiotherapy data. B B Rasmussen was responsible for guidelines for pathology description and reporting, and analysis of these data. M Blichert-Toft contributed to the study design coordination, and wrote the guidelines for surgery. H T Mouridsen contributed to the study design, study coordination, management of the data centre, recruitment, clinical management and follow-up of patients. All investigators contributed to critical revision of the paper.

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