Impact of age, tumor characteristics, and treatment on local control and disease outcome in early stage breat cancer : an EORTC translational research project

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CHAPTER 6

Impact of locoregional treatment on the early-stage breast cancer patients: a retrospective analysis

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Abstract

Although adequate locoregional treatment improves local and regional control in early-stage breast cancer, uncertainty still exists about the role of locoregional therapy with respect to survival.

To study the impact of surgery and radiotherapy on locoregional control and survival, we combined the data of three European Organisation for Research and Treatment of Cancer (EORTC) Breast Cancer Group trials including early-stage breast cancer patients with long-term follow-up. Risk ratios (RR) were estimated for locoregional recurrence and overall survival using Cox regression models. All analyses were adjusted for tumor size, nodal status, age, adjuvant radiotherapy, adjuvant chemotherapy and trial.

The combined data set consisted of 3648 patients. The median follow-up period was 11 years. 5.9% of the patients who underwent mastectomy and 10.8% of the patients who underwent breast-conserving therapy had a locoregional recurrence ($P < 0.0001$). The risk of death after breast-conserving therapy was similar compared with mastectomy (RR 1.07, $P = 0.37$). Adjuvant radiotherapy after mastectomy was associated with a lower risk for locoregional recurrence (RR 0.43, $P < 0.001$) and death (RR 0.73, $P = 0.001$). Patients with 1–3 positive nodes benefited the most from radiotherapy after mastectomy. Breast-conserving therapy was associated with an impaired locoregional control. However, breast- conserving therapy was not associated with a worse overall survival. Adjuvant radiotherapy in mastectomised patients was associated with both a significantly superior locoregional control and overall survival. The effect of adjuvant radiotherapy was most profound in patients who had 1–3 positive nodes.

Introduction

It has long been accepted that adequate locoregional therapy can delay or prevent local or regional recurrence in women with early breast cancer. In addition, the detrimental impact of locoregional recurrence on disease outcome has been firmly established [1,2].

Many investigators have studied the role of locoregional control and its impact on disease outcome. The predominating assumption is that locoregional recurrence is an independent prognostic factor that is associated with a poor outcome. However, more aggressive locoregional treatment has not been reported to result in better survival despite improved locoregional control.

Therefore, locoregional recurrence is not regarded as an instigator of subsequent systemic disease. Locoregional therapy is based on surgery and radiation therapy. Trials that studied breast-conserving surgery versus mastectomy have failed to detect a difference in overall survival, despite demonstrating a superior locoregional control after mastectomy [1,3–5]. However, randomised trials that studied the role of adjuvant radiotherapy after mastectomy in patient samples that were at a high risk of recurrence demonstrated superior locoregional control as well as superior overall survival rates after adjuvant radiotherapy [6,10–13]. The fact that radiotherapy may influence disease outcome, but more aggressive surgery may not, is intriguing. The

most recent follow-up of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG 2000 update) demonstrated a significant overall survival difference of 6.0% in favour with patients who underwent mastectomy compared to patients who underwent breast-conserving surgery without radiotherapy at 15 years of follow-up (survival rates of 53 and 47%, respectively).
This effect was observed in 2489 randomised patients. However, in 4463 women randomised between mastectomy and conservative surgery plus radiotherapy, the survival patterns were very similar after 15 years of follow-up (overall survival of 61 and 60.8%, respectively; EBCTCG 2000 update).
Adjuvant radiotherapy trials have demonstrated a beneficial effect for radiotherapy on overall survival after mastectomy in high-risk early breast cancer patients. However, data from the 2000 update of the EBCTCG concerning the effects of radiotherapy on overall survival are still inconclusive, in that the beneficial effect of radiotherapy on breast cancer mortality is balanced by its negative impact on cardiac mortality [6].
We hypothesised that any improvement in survival through locoregional therapy has to be accompanied by an improvement in local control. The rationale behind this is, of course, that locoregional therapy is directed against locoregional disease and not against systemic micrometastases. The combination of data from different trials provides a larger sample size, which increases the possibility of finding small, but clinically relevant, differences between locoregional treatment modalities. Therefore, we conducted a retrospective analysis combining the data of three trials with sufficient follow-up, which enrolled early breast cancer patients who either underwent mastectomy or breast-conserving therapy, to study whether more aggressive surgery would result in better overall survival rates in a large set of early breast cancer patients. It was decided to select patients with T1 and T2 tumors since these patients can generally be treated by either mastectomy or breast-conserving surgery.

Patients and methods

Selection of the trials
Patients were selected from trials that randomized early-stage breast cancer patients. The European Organisation for Research and Treatment (EORTC) has conducted several large randomised phase III trials concerning the management of breast cancer patients with stage I or stage II/III breast cancers. These trials, EORTC trial 10801, 10854, and 10902 have enrolled a total of over 4018 early breast cancer patients. Median follow-up periods ranged from 6.1 to 13.4 years in these studies. From these trials, all patients who had clinical T1 or T2 tumors at the time of diagnosis were selected. Patient characteristics are listed in Table 1. A brief description of these trials follows below:

EORTC trial 10801 (1980–1986, median follow-up of 13.4 years) was conducted in order to assess the safety of breast-conserving treatment. In this trial, patients were randomised between breast-conserving surgery combined with radiotherapy and radical mastectomy. Six cycles of adjuvant chemotherapy with cyclophosphamide 100 mg/m^2 given orally on days 1–14, methotrexate 40 mg/m^2 given intravenously (i.v.)

on days 1 and 8, and 5-fluorouracil (5-FU) 600 mg/m^2 given i.v. on days 1 and 8, were indicated for all patients under the age of 55 years with positive nodes. No information was collected on hormonal therapy. In this study, 902 patients were randomised [3].

EORTC trial 10854 (1986–1991, median follow-up of 10.8 years) studied the question whether one course of perioperative chemotherapy given directly after surgery yields better results in terms of treatment outcome than surgery alone. Perioperative chemotherapy consisted of one single course of doxorubicin 50 mg/m^2, 5-FU 600 mg/m^2 and cyclophosphamide 600 mg/m^2 (FAC), administered i.v. within 36 h after surgery. Axillary lymph node-positive premenopausal patients in the perioperative chemotherapy group were recommended to receive an extra five cycles of cyclophosphamide, methotrexate and 5-FU (CMF). Node-positive patients, younger than 50 years, who did not receive perioperative chemotherapy, were advised to receive one conventional course of FAC followed by five cycles of CMF after surgery. Patients were stratified for breast-conserving therapy and modified radical mastectomy. Prolonged adjuvant systemic treatment was left to the discretion of the local investigators. 2795 patients were included in this trial [7].

EORTC trial 10902 (1991–1999, median follow-up of 6.1 years) was set up to determine the value of preoperative chemotherapy. Patients were randomised to receive four cycles of chemotherapy either before or after surgery. Chemotherapy consisted of four cycles of 5-FU 600 mg/m^2, epirubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 (FEC) administered i.v., at 3-weekly intervals. In the preoperative chemotherapy group, surgical therapy followed within 4 weeks of the fourth course of chemotherapy. In the postoperative chemotherapy group, the first cycle was given within 36 h after surgery. Stratification was performed for planned type of surgery instead of performed type of surgery. This was done because of the expected effect of preoperative chemotherapy on downstaging of the tumor. A total number of 698 patients were randomised [8].

Selection of data

All of eligible patients from all the trials were included in the analysis, with the exception of patients who underwent preoperative chemotherapy in EORTC trial 10902. These patients would have introduced a selection bias since preoperative chemotherapy influences the choice of locoregional treatment due to tumor downstaging.

Selection of covariates

To study the independent impact of surgery and radiotherapy on locoregional control and overall survival, we included the following covariates; clinical tumor size, pathological nodal status, age, type of surgery, adjuvant radiotherapy, adjuvant chemotherapy, and the trial in which a patient participated. Clinical tumor size was measured taking the largest diameter using callipers. Pathological tumor size, hormone receptor status and tamoxifen use were not taken into account as these tumor- and treatment-related characteristics were poorly reported in some of the trials. Specifications on the radiotherapeutic regimens used differed between the trials and the institutions in which patients were treated. Therefore, it was decided

that any type of radiotherapy given to a patient after surgery should be regarded as adjuvant radiotherapy without specification of radiation fields and doses.

Locoregional treatment
In all of the trials, patients were selected for breast-conserving therapy if a wide local excision could be performed provided that at least a 1-cm margin around the macroscopic dimension of the tumor could be achieved. Patients who received breast-conserving therapy underwent lumpectomy plus axillary lymph node dissection and radiotherapy to the whole breast, with or without a boost. Radiotherapy to the axilla was given in cases of extensive lymph node metastasation (pN1-bii/ pN2) or in cases of positive nodes in level III of the axilla. All patients who underwent mastectomy underwent axillary lymph node dissection. Postoperative radiotherapy to the breast was always indicated after breast-conserving surgery. In EORTC trials 10854 and 10902, postoperative radiotherapy to the chest wall and parasternal lymph node chain after mastectomy was indicated if surgery was considered not to be radical, if the tumor was >5 cm, or if a positive infraclavicular node was found after surgery. In EORTC trial 10801, microscopically-incomplete excision was not a reason for exclusion. Lumpectomy was followed by radiotherapy (50 Gy over a 5-week period), with an additional booster dose of 25 Gy directed to the lumpectomy site via an Iridium-192 implant. If implants could not be used for technical reasons, patients were given an equivalent booster dose with external irradiation. Postoperative irradiation to the chest wall was indicated after a microscopicallyincomplete operation. General guidelines concerning adjuvant radiotherapy were as follows: for patients both after mastectomy or breast-conserving therapy, irradiation of the parasternal lymph node region was indicated for patients with a centrally or medially localised tumor and for patients with a lateral tumor and histologically-proven axillary lymph node metastases. Postoperative radiation was always given in cases in which surgery was considered not to be radical. In cases of breast-conserving surgery, microscopically incomplete or not, the whole breast was irradiated using a dose of at least 50 Gy followed by a boost on the initial tumor of at least 16 Gy.

Statistical methods
To compare different locoregional treatment modalities, type of surgery was divided into two states; breast-conserving therapy (lumpectomy plus axillary lymph node dissection followed by radiotherapy) and (modified) radical mastectomy, with or without radiotherapy. All analyses were performed for overall survival and locoregional recurrence. Survival time was defined as the time between randomisation and death from any cause. A locoregional recurrence was defined as any recurrence in the breast or axilla. Only recurrences, which occurred before the diagnosis of a distant metastasis and/or a new primary tumor, were regarded as a locoregional recurrence as the first event included in the analysis. In EORTC trial 10854, any chemotherapy (1x perioperative FAC) was scored as having received chemotherapy. Cox proportional-hazard regression models [9] were used to estimate the hazard ratios with their 99% confidence intervals (CIs). Since the number of patients is high, a 1% significance level was used. All tests are two-sided. To control for possible differences in the study populations, we added study as a factor in the multivariate Cox regression analysis, after testing the proportional hazards assumption.

	10801	10854	10902	Total
Mastectomy (%)	49	41	71	45
BCT (%)	51	59	29	55
T1 (%)	20	32	17	28
T2 (%)	80	68	83	72
N−(%)	59	54	36	54
N+ (%)	41	46	64	46
⩽50 years (%)	38	40	59	41
>50 years (%)	62	60	41	59
No adjuvant CT (%)	83	41		48
Adjuvant CT (%)	17	59[a]	100	52
No. of deaths	368 (42.5)	672 (26.3)	51 (22.3)	1091 (29.9)
No. of locoregional recurrences	80 (9.2)	223 (8.7)	11 (4.8)	314 (8.6)

CT, chemotherapy; BCT, breast-conserving therapy; peri-Op FAC, perioperative 5-fluorouracil, doxorubicin, cyclophosphamide. *N*−, node-negative; *N*+, node-positive.
[a] 70% of these patients only received 1×peri-OpFAC.

Table 1. Patient characteristics (N=3648)

Results

Patient's characteristics

In total, 4018 primary operable breast cancer patients were randomised to one of the trials. Of these patients, 3886 breast cancer patients were deemed eligible. 3648 patients had cT1 or cT2 tumors and were subsequently included in the analysis. At the time of the analysis, the median follow-up period in this subset of patients was 11 years, 1091 patients have died, and 314 patients have developed a locoregional recurrence as their first event. Other patient characteristics are listed in Table 1. 2011 patients (55%) underwent breast-conserving therapy. Breast-conserving therapy consisted of lumpectomy and axillary lymph node dissection followed by adjuvant radiation therapy. 1633 patients underwent a (modified) radical mastectomy. In total, 804 (49%) patients received adjuvant radiotherapy to the chest wall and/or the axilla after mastectomy (Table 2).

Overall analysis

Overall, 5.9% of the patients who underwent mastectomy and 10.8% of the patients who underwent breast-conserving therapy experienced a locoregional recurrence (as the first event) (Chi square test $P < 0.0001$). Overall survival rates were slightly better for patients who underwent breast-conserving therapy, 72.3% versus 67.5%, respectively.

In the multivariate analysis, breast-conserving therapy was significantly associated with a poor locoregional control (Risk Ratio (RR) 2.25, $P < 0.001$, Table 3). Age <50 years at the time of diagnosis was an independent predictor of a poor locoregional control (Table 3). Additional covariates associated with an improved locoregional control were adjuvant radiotherapy and chemotherapy. Although breast-conserving therapy was associated with a poor locoregional control, there was no association with poor outcome in terms of overall survival (BCT: RR 1.07, $P = 0.37$). Significant independent predictors of a poor overall survival were involved axillary nodes, tumor size >2 cm and age >50 years at the time of diagnosis (Table 3). Again, adjuvant radiotherapy and chemotherapy were associated with an improved overall survival. In addition, in 452 patients aged <40 years at the time of diagnosis, breast-conserving therapy was not associated with an impaired locoregional control or overall survival. The RRs for locoregional recurrence and overall mortality after breast-conserving therapy were 1.31 (99% CI 0.49–3.56, $P = 0.48$) and 0.76 (99%CI 0.45–1.29, $P = 0.18$), respectively (Table 4). To study the effect of (prolonged) adjuvant chemotherapy alone, we repeated the analysis excluding

Radiotherapy, *N*	No radiotherapy, *N*	Total, *N*
804 (49%)	829 (51%)	1633

Table 2. Patients who underwent mastectomy to the chest wall and/or axilla

	Locoregional recurrence (as the first event)			Overall survival		
	RR	99% CI	*P* value	RR	99% CI	*P* value
BCT	2.25	1.47–3.44	<0.001	1.07	0.88–1.29	0.37
pN+	1.25	0.91–1.72	0.07	2.38	2.00–2.83	<0.001
T2	1.11	0.80–1.54	0.40	1.54	1.25–1.89	<0.001
Age > 50 years	0.66	0.49–0.89	<0.001	1.18	1.00–1.40	0.01
Adjuvant radiotherapy	0.60	0.38–0.95	0.005	0.77	0.62–0.96	<0.001
Adjuvant chemotherapy	0.63	0.45–0.89	0.001	0.77	0.64-0.93	<0.001
EORTC trial						
10801 versus 10854	1.13	0.78–1.63	0.40	0.76	0.63–0.91	<0.001
10801 versus 10902	1.22	0.51–2.96	0.56	1.09	0.71–1.66	0.61

99% CI, 95% Confidence Interval; EORTC, European Organisation for Research and Treatment of Cancer; RR, relative risk.

Table 3. Multivariate Cox regression analysis all patients (N = 3648)

	Locoregional recurrence (as the first event)			Overall survival		
	RR	99% CI	*P* value	RR	99% CI	*P* value
BCT	1.31	0.49–3.56	0.48	0.76	0.45–1.29	0.48
pN+	1.03	0.48–2.21	0.94	2.75	1.63–4.63	<0.001
T2	1.43	0.70–2.92	0.20	1.77	1.04–3.01	<0.01
Adjuvant radiotherapy	1.04	0.34–3.20	0.92	1.63	0.84–3.15	0.06
Adjuvant chemotherapy	0.78	0.35–1.73	0.42	0.67	0.39–1.15	0.06
EORTC trial						
10801 versus 10854	2.01	0.71–5.78	0.09	0.70	0.42–1.18	0.08
10801 versus 10902	1.10	0.13–9.24	0.91	1.08	0.42–2.78	0.83

99% CI, 95% Confidence Interval; EORTC, European Organisation for Research and Treatment of Cancer; RR, relative risk.

Table 4. Multivariate Cox regression analysis patients younger than or equal to 40 years (N = 452)

patients who received perioperative chemotherapy. Breast-conserving therapy remained the strongest predictive factor for locoregional recurrence (RR 2.31, P < 0.001). In addition, young age remained a significant predictor of poor locoregional control and the effect of adjuvant radiotherapy on locoregional control remained unchanged (data not shown). In the overall survival multivariate analysis, nothing changed except for the fact that age lost its prognostic significance (data not shown).

Mastectomy with or without radiotherapy

Forty-nine percent of patients who underwent mastectomy subsequently received radiotherapy. Adjuvant radiotherapy after mastectomy decreased locoregional recurrence rates independent of the TNM stage, patient's age, and whether they received adjuvant chemotherapy (RR 0.43, P < 0.001) (Table 5). Furthermore, it was the only independent predictor of a better locoregional control among these covariates. In addition, patients who received radiotherapy had a lower risk of dying (RR 0.73, P = 0.001) compared with patients who did not receive adjuvant radiotherapy (Table 5).

Adjuvant chemotherapy was also independently associated with a better outcome in terms of decreased mortality (RR 0.77, P = 0.01). Independent predictors for a poor overall survival were a positive nodal status and tumor size >2 cm.

	Locoregional recurrence (as the first event)			Overall survival		
	RR	99% CI	*P* value	RR	99% CI	*P* value
Adjuvant radiotherapy	0.43	0.23–0.80	<0.001	0.73	0.57–0.94	0.001
pN+	1.25	0.68–2.28	0.34	2.40	1.83–3.15	<0.001
T2	1.40	0.69–2.87	0.22	1.49	1.07–2.08	0.002
Age > 50 years	0.67	0.39–1.17	0.06	1.11	0.87–1.43	0.28
Adjuvant chemotherapy	0.89	0.47–1.67	0.64	0.77	0.59–1.00	0.01
EORTC trial						
10801 versus 10854	1.08	0.56–2.11	0.76	0.87	0.66–1.14	0.18
10801 versus 10902	0.52	0.12–2.27	0.25	1.11	0.65–1.90	0.63

Table 5. Multivariate Cox regression analysis mastectomized patients (N = 1633)

	Locoregional recurrence (as the first event)			Overall survival		
	RR	99% CI	*P* value	RR	99% CI	*P* value
(a) 1–3 positive nodes						
Adjuvant radiotherapy	0.28	0.09–0.85	0.003	0.48	0.31–0.75	<0.001
T2	2.04	0.40–10.28	0.26	1.77	0.94–3.31	0.02
Age > 50 years	0.46	0.14–1.47	0.08	0.98	0.62–1.54	0.90
Adjuvant chemotherapy	0.52	0.15–1.79	0.18	0.68	0.42–1.08	0.03
EORTC trial						
10801 versus 10854	0.77	0.22–2.69	0.59	0.69	0.43–1.12	0.05
10801 versus 10902	0.89	0.09–8.48	0.89	1.04	0.43–2.50	0.92
(b) 4 or more positive nodes						
Adjuvant radiotherapy	0.48	0.16–1.40	0.08	1.15	0.77–1.73	0.37
T2	0.88	0.17–4.37	0.84	1.14	0.60–2.14	0.60
Age > 50 years	1.28	0.40–4.04	0.59	1.05	0.68–1.63	0.76
Adjuvant chemotherapy	0.57	0.45–5.57	0.36	0.76	0.50–1.16	0.39
EORTC trial						
10801 versus 10854	0.57	0.15–2.17	0.27	0.87	0.53–1.41	0.46
10801 versus 10902	0.44	0.05–4.15	0.35	0.61	0.24–1.55	0.17

Table 6.
A. Multivariate Cox regression analysis mastectomized patients with 1-3 positive nodes (N = 507)
B. Multivariate Cox regression analysis mastectomized patients with 4+ positive nodes (N = 381)

Subgroup analyses were undertaken in order to study whether the effect of adjuvant radiotherapy after mastectomy could be demonstrated in node-positive, as well as node-negative, breast cancer patients. Node-positive patients benefited in terms of an improved locoregional control (RR 0.36, 99% CI 0.17–0.77, P = 0.001). However, in node-negative patients, radiotherapy was not associated with a better locoregional control (RR 0.56, 99% CI 0.22–1.45, P = 0.12). In terms of overall survival, node-positive patients who received radiotherapy had better overall survival rates than patients who did not (RR 0.70, 99% CI 0.52–0.94, P = 0.002). This could not be shown in the node-negative patient group in which no advantageous effect of adjuvant radiotherapy could be demonstrated (RR 0.87, 99% CI 0.56–1.34, P = 0.40). In patients who underwent mastectomy and had 1–3 positive nodes, radiotherapy was associated with significantly improved survival rates (RR 0.48, 99% CI 0.31–0.75, P = <0.001, Table 6a). However, in patients with four or more positive nodes, no significant association between radiotherapy and overall survival was found (Table 6b).

Discussion

The central question regarding locoregional therapy (i.e. surgery and radiotherapy) for early breast cancer remains; that is, whether more aggressive locoregional treatment significantly reduces long-term mortality from breast cancer. For example, the EORTC trial 10801 [3], which randomised between modified radical mastectomy and breast-conserving surgery demonstrated a significant difference in terms of local control in favour of the modified radical mastectomy arm after a long-term follow-up. The respective local control rates were 87% after radical mastectomy and 77% after breast-conserving therapy at 13 years of follow-up. However, overall survival was not significantly different between the arms. To study both treatment modalities in a large non-randomised sample, we combined the data of three controlled clinical trials conducted by the EORTC Breast Cancer Group studying different treatment regimens in early breast cancer patients. As mentioned before, the analyses in this study are based upon non-randomised comparisons. In our series, the most important predictor of locoregional recurrence was undergoing breast-conserving surgery. This is a striking finding considering the fact that breast-conserving therapy is well established in the management of early-stage breast cancer. The underlying cause for this effect may be due to inadequate surgical margins, which are known to impair local control after breast-conserving surgery [14–16]. Unfortunately, we were not able to retrieve this information from the case report forms, so a definite answer to this question cannot be given. However, the increased risk for locoregional recurrence after breast-conserving therapy did not result in an increased risk for worse overall survival. This is in accordance with the results of the randomised trials comparing breast-conserving surgery and mastectomy [3-5], as well as with the meta-analyses conducted by the EBCTCG. This underlines the fact that the majority of early locoregional recurrences after breast-conserving therapy are associated with a poor prognosis, but are not instigators of the subsequent systemic spread [1,17]. In addition, late recurrences and second ipsilateral primary tumors can be treated well with salvage mastectomy and have a much less detrimental effect on prognosis compared with early recurrences. Although the median follow-up of this analysis was 11 years, this period may be to short to detect a survival benefit if the impact of more aggressive surgery on survival occurs after a longer follow-up, i.e. 15–20 years. Therefore, it must be stressed that the impact of surgery on outcome in breast cancer has to be followed-up in the future. Breast cancer at a young age, i.e. younger than 35/40 years at the time of diagnosis, is often associated with a poor prognosis [18–21]. In addition, young breast cancer patients have been reported to be at a higher risk of local recurrence, especially after breast-conserving therapy [22,23]. In line with these data, our results also demonstrate that young age, i.e. lower than 50 years, is associated with a poor locoregional control. Remarkably, in our analysis, breast-conserving therapy was not associated with a higher risk for locoregional recurrence or death in women younger than or equal to 40 years. Patients that underwent mastectomy and subsequently received adjuvant radiotherapy were at a lower risk for locoregional recurrence in our analysis and this resulted in a lower risk of death as well. Two randomized trials in high-risk breast cancer patients conducted by the Danish Breast Cancer Study Group and one Canadian trial have previously demonstrated a survival benefit for adjuvant radiotherapy after mastectomy [10–12].

However, the quality of surgery in these trials was very poor, especially the management of the axilla, resulting in recurrence rates exceeding 20% after 10 years. Therefore, radiotherapy may have compensated for inadequate surgery in these trials. In addition, results from a meta-analysis performed by the EBCTCG demonstrated a trade-off effect due to an increase in cardiac-related mortality after adjuvant radiotherapy, which equalled the decrease in breast cancer-related mortality induced by radiotherapy [6]. It has been proposed that the detrimental effects of radiotherapy are mainly attributable to older trials (conducted before 1975) that used obsolete radiotherapy regimens causing excessive damage to the heart (EBCTCG 2000 update). In our analysis, patients were included who had participated in trials conducted between 1980 and 1999. The median follow-up was 11 years at the time of the diagnosis and our results show a definite favourable effect for radiotherapy after mastectomy in terms of overall survival. This suggests that, in this series, in which the radiotherapeutic regimen that was given to patients varied widely, adjuvant radiotherapy directed at either the chest wall or the axilla resulted in an absolute gain in survival. However, adjuvant radiotherapy only contributed to locoregional control and overall survival in node-positive patients. In the node-positive group, an association between radiotherapy and a favourable outcome was seen, especially in patients with 1–3 positive nodes as opposed to patients with four or more positive lymph nodes. This remarkable finding is in accordance with the results from the Danish radiotherapy trials [7,8] in which patients with limited nodal involvement benefited more from adjuvant radiotherapy than patients with extensive nodal disease. A possible explanation for this difference is that node-positive patients benefit from radiotherapy due to the local eradication of residual tumor cells. In patients with four or more positive lymph nodes, systemic spread of tumor cells may be much more extensive compared with patients with 1–3 positive nodes and therefore locoregional therapy will not have a significant impact on survival in these patients.

This stresses the need for trials studying the management of the axilla. The EORTC Breast Cancer Group is currently conducting a trial in which sentinel node-positive patients are randomised between axillary lymph node dissection and radiotherapy [24].

Many investigators have tried to divide locoregional recurrences into a category that are merely associated with distant disease and a category that are the instigators of distant disease [25–35]. Although these were retrospective analyses, a short disease-free interval between primary therapy and adverse primary tumor characteristics have been identified as predictors for poor outcome after locoregional recurrence. In addition, a small locoregional recurrence (<1 cm) was associated with a favourable prognosis, suggesting an advantageous effect for early detection [31]. Finally, it must be emphasised that this is was a non-randomised, retrospective analysis and, therefore, our results should be interpreted with caution and be considered hypotheses rather than conclusions. Nevertheless, the apparent lack of benefit of mastectomy in young patients, in terms of locoregional control, and the lack of benefit in the general population, in terms of overall survival, once again raises the question of whether breast cancer patients should receive more aggressive surgery. In addition, the differences in the efficacy of radiotherapy between patients with only a few involved nodes (1–3) and those with more involved nodes (54) have to be evaluated more thoroughly. However, any recurrence, either an associative factor or

an instigator of distant spread, is an emotionally devastating event for the patient [36]. Therefore, any treatment strategy against breast cancer should include an adequate local therapy in order to avoid unnecessary locoregional recurrences. The fact that an adequate local therapy may improve survival provides further support for this argument.

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