PERGAMON

European Journal of Cancer 37 (2001) 1537–1544

European Journal of Cancer

www.ejconline.com

Time trends in the results of breast conservation in 4694 women

I. Fredriksson[a,*], G. Liljegren[b], L.-G. Arnesson[c], S.O. Emdin[d], M. Palm-Sjövall[e], T. Fornander[f], J. Frisell[g], L. Holmberg[h]

[a]*The Karolinska Institute, Department of Surgery, Stockholm Söder Hospital, Stockholm, Sweden*

[b]*Department of Surgery and Center for Assessment of Medical Technology in Örebro (CAMTÖ), Örebro Medical Center Hospital, Örebro, Sweden*

[c]*Department of Biomedicine and Surgery, University Hospital, Linköping, Sweden*

[d]*Department of Surgery, University Hospital, Umeå, Sweden*

[e]*Department of Oncology, University Hospital, Lund, Sweden*

[f]*Department of Oncology, Stockholm Söder Hospital, Stockholm, Sweden*

[g]*Department of Surgery, Huddinge University Hospital, Stockholm, Sweden*

[h]*Regional Oncologic Center, University Hospital, Uppsala, Sweden*

Received 18 December 2000; received in revised form 21 March 2001; accepted 2 May 2001

Abstract

In a population-based cohort of 4694 women with invasive breast cancer, operated upon with breast conserving surgery (BCS) in 1981–1990 and followed through to 1997, we studied how this technique had been adopted into clinical practice, especially with reference to the use of radiotherapy (RT). Our main aim was to see whether there was a drift in the risk of local recurrence and breast cancer death over time. During the 30 151 person-years of observation in the cohort, there were 582 local recurrences, 456 breast cancer deaths and 438 deaths due to other causes. Postoperative RT was given to 70.2%, but usage increased over the period. The women not receiving RT were mostly elderly, but also in women <70 years, 20.4% did not receive RT. The risk for local recurrence after RT were 7.6 and 17.8% at 5 and 10 years, respectively. Without RT, more than 30% had a local recurrence at 10 years. Thus, the choice not to irradiate failed to target women at a low risk. In a multivariate Cox analysis taking tumour size, nodal status, age at operation and RT into account, there was a trend for a higher risk of local recurrence in the later time period, relative hazard 1.5 (95% confidence interval (CI) 1.0–2.1). Corrected survival was 93.3 and 85.2% at 5 and 10 years, respectively.

Keywords: Breast cancer; Conservative treatment; Cohort study; Local recurrence; Radiotherapy

1. Introduction

Breast conserving surgery (BCS) for invasive breast cancer was introduced in Sweden in the late 1970s [1,2]. During the 1980s, the technique became the treatment of choice for early breast cancer, especially in areas with population-based mammographic screening. This development was prompted by published results from randomised clinical trials [3,4], screening trials [5–7], the subsequent introduction of screening and clinical trials of BCS in Sweden [8]. The dominant surgical tradition in Sweden has been a radical approach with clear margins, as in a formal segmental or sector resection [9]. The treatment protocols have recommended postoperative radiotherapy (RT) as routine after BCS in all patients outside trials.

We conducted a cohort study of women who underwent BCS for invasive breast cancer, focusing on whether the wider adoption of the technique had led to a shift in indications and patient management, especially RT, that would be detrimental to the main outcomes of local recurrence or breast cancer-corrected survival. During a 10-year period, we identified 4694 women operated upon with BCS for the study in four of Sweden's six healthcare regions.

* Corresponding author. Tel.: +46-8-616-2349; fax: +46-8-616-2309.

E-mail address: irma.fredriksson@kirurg.sos.sll.se (I. Fredriksson).

0959-8049/01/$ - see front matter
PII: S0959-8049(01)00168-X

2. Patients and methods

2.1. Coverage

Data were collected from four of Sweden's six healthcare regions, covering 63.8% of the Swedish population. The period of inclusion lasted from 1 January 1981 through to 31 December 1990.

2.2. Inclusion and exclusion criteria

Women who had undergone BCS aimed at radical excision of the breast tumour were eligible. Women with a previous cancer, distant metastases at the time of diagnosis, undergoing a surgical procedure not aiming at microscopic radicality, or undergoing preoperative adjuvant treatment were excluded. Women reoperated upon with a mastectomy due to involved margins or node-positive disease were also excluded.

2.3. Identification of subjects

In two healthcare regions, data were collected from regional breast cancer registers containing prospective data about stage of disease, types of treatment and recurrences. These breast cancer registers are updated continuously by matching with the Swedish Cancer Registry [10]. The validity of the Cancer Registry had been tested previously [11] and was for this study rechecked by applying a series of controls, selected for the performance of a nested case–control study for a detailed analysis of the local recurrences. In the 1355 selected controls, 2.2% of the registered breast conserving operations were found to be mastectomies. To check the regional registers, we also conducted a search in the computerised patient administrative system (PAS) that is mandatory for each hospital and codes admission diagnoses and performed operations. All in- and outpatient treatments after the primary operation were checked if due to local recurrence. The revalidation of the registers indicated that the number of local recurrences was underestimated by less than 5% (leading to little impact on the estimated rates) and the number of follow-up years was overestimated by at the most 2%. As the errors were not sizeable in any specific time period, treatment group or age group, they should not confound the results.

In the remaining two regions, which did not have regional breast cancer registers at that time, a search was conducted in PAS. All patients recorded as having undergone a segmental or sector resection, a wide excision or a partial mastectomy were considered for inclusion and their medical records were retrieved and read.

In the period 1981–1990, a total of 29 652 women were diagnosed with breast cancer in these four healthcare regions. During the same period, we identified 4753 patients that were eligible for this study. The medical records of 59 patients could not be found and a total of 4694 patients were included in the study. Their distribution over the years and in relation to the total number of women diagnosed with breast cancer is shown in Fig. 1.

There were four randomised studies of mammographic screening going on in Sweden up until 1985. After 1985, a population-based mammographic screening programme was successively introduced. In the nested case–control study from the cohort, 38.6% of the controls had their tumour detected by a screening mammography.

2.4. Surgical procedures

BCS in Sweden has been performed as a segmental or sector resection [9] so that the tumour-bearing portion of the breast is removed by dissection of the breast parenchyma in the plane of Scarpa's fascia down to the pectoral muscle. Excision of the fascia has been recommended as part of the procedure. The skin incisions and the choice to excise overlying skin have varied. The great majority of centres participating in screening programmes have used wire [12] or coal dye [13] preoperative localisation of non-palpable tumours. All centres have used specimen radiography to ensure complete excision of such tumours.

The indications for BCS during the study period changed over time. In the early 1980s, BCS were mainly offered T1N0M0-patients. Successively from 1985, conservative surgery became generally accepted also for node-positive patients with tumours up to and including 30 mm. Of the included patients with data on histopathological tumour diameter, 1.8% had a tumour size >30 mm.

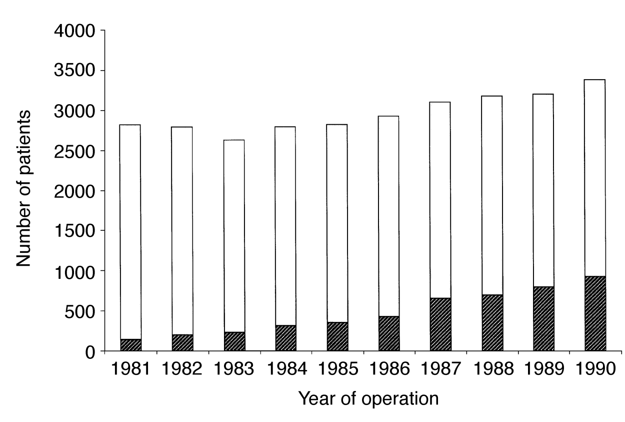

Fig. 1. Patients included in the study (operated upon with breast conserving surgery (BCS)) in relation to all patients diagnosed with breast cancer in four of Sweden's six health care regions, by year.

In the beginning of the observed period, it was common for a woman with an unclear tumour margin to be offered a mastectomy. All patients undergoing mastectomy on this indication were excluded from the study. In the latter part of the period, it was more common for patients with a unifocal, well-defined tumour and an unclear margin to be offered a re-excision of the margins and postoperative radiotherapy; such patients were included in this study.

The routine for axillary dissection has been to dissect levels I and II [14] through a separate incision unless the primary breast tumour was situated high up in the axillary tail. The standard procedure has been to dissect from the axillary vein down to the axillary tail of the breast parenchyma, clearing all the tissue from the thoracic wall down to the latissimus dorsi.

During the 1980s, the treatment protocols recommended axillary dissection for all patients with an invasive breast cancer, but they did not stipulate a specific number of nodes to be investigated. The introduction of mammographic screening and adjuvant treatment programmes from 1985 onwards successively heightened the awareness of the importance of an adequate axillary dissection for proper tumour staging. Early in the period, some patients with axillary lymph node metastases were reoperated upon with mastectomy; such patients were excluded from this study.

2.5. *Radiotherapy*

According to treatment protocols, radiotherapy was recommended as the standard treatment after BCS. Yet, at two hospitals participating in this study, generally, patients were not recommended radiotherapy during the major part of the observed period. All centres that used radiotherapy delivered two tangential fields in 25–29 fractions of 2 Gy up to a total dose of 50–58 Gy, spread over a total treatment period of 33–39 days. For node-positive patients, the target volume included residual breast, axillary, supraclavicular and infraclavicular nodes. The target volume included only residual breast for node-negative patients. Boost has generally not been used in Sweden.

2.6. *Adjuvant systemic therapy*

Adjuvant systemic therapy was seldom used before 1985. After 1985, the larger central hospitals generally began to use CMF (cyclophosphamide, methotrexate and 5-fluorouracil) for premenopausal women with node-positive disease. From 1985 and at full scale from about 1987, adjuvant tamoxifen therapy has been used for postmenopausal women in International Union Against Cancer (UICC) stage II; during these initial years of tamoxifen use, oestrogen receptor status did not generally guide treatment recommendations.

2.7. *Endpoints*

The healthcare regions participating in this study had similar routines for follow-up. In the first 2 years, patients were seen three to four times a year, thereafter every 6 months up to 5 years. Yearly mammography was recommended. After 5 years, the routines varied, but especially at the beginning of the period, patients were recommended annual mammography up to 10 years after operation. Since the introduction of screening, all patients have been strongly recommended to comply with the screening programme after their hospital-based check-ups had ended. Most patients have also been referred to their general practitioner for further clinical examinations after 5 years.

The date was recorded of the first report of a morphologically-verified local recurrence, axillary recurrence, contralateral breast cancer, clinically- or morphologically-verified distant recurrence, or death. The date of each woman's latest clinical examination was also recorded.

Local recurrence was defined as the appearance of any new breast tumour, invasive or cancer *in situ*, in the operated breast parenchyma or in the overlying skin, prior to or at the same time as distant metastases. Recurrence in the axilla was recorded separately. Recurrence in the supraclavicular nodes was classified as distant metastases. A clinically- or morphologically-verified distant recurrence or death in breast cancer not preceded by relapse were defined as events in distant disease-free survival. Thus, also patients with previous local recurrences were still eligible as contributors to these analyses.

Breast cancer as an underlying or contributory cause of death was considered to be an event in the analysis of corrected survival. Data concerning cause of death were collected from the medical record. If cause of death were given with uncertainty, or not given in the medical record, it was checked by matching with the National Causes of Death Register. Swedish law requires that cause of death always get reported to the National Causes of Death Register. The cause of death was determined in a way that has been tested in a review of Swedish mammography trials and found accurate [15]. Patients could be followed through to 1997, which gave a median follow-up time of 6 years (range: 0–16.8 years) and a total of 30 151 follow-up years in the cohort.

2.8. *Covariates*

This study focuses primarily on the calendar period of operation, patient's age, and whether radiotherapy was given or not. Axillary nodal status and histopathological tumour diameter (if more than one tumour, the diameter of the largest tumour was used) were also recorded. All details of the treatment protocol were obtained for 3890 patients. Data on histopathological tumour diameter were lacking for 194 patients. In one of the regions where data were collected from regional breast cancer registers, the use of radiotherapy had not been registered for part of the observed period; information about radiotherapy or not was therefore lacking in 804 patients.

2.9. Statistical analysis

The calendar period of operation was divided into five strata; the early strata covered up to 3 years because the frequency of these operations was comparatively low in the beginning of the 1980s. The probability of remaining free from local recurrence or distant metastases and the overall and corrected survival probabilities were estimated with the life-table method. The 5- and 10-year results are given together with the standard error of a life-table estimate. The differences between survival curves were tested with a log rank test [16]. The simpler stratified analysis clearly showed that comparisons between time periods may be subject to various confounding factors. In an attempt to study the joint effect of the different variables and at least partially deconfound the comparisons of time periods, Cox proportional hazards models were computed and relative hazards with 95% confidence intervals (CI) were estimated.

3. Results

3.1. Indications for operation and use of radiotherapy

Mean tumour size and the proportion of node-positive patients increased modestly over the studied period, indicating some successive broadening in the indications for BCS i.e. a greater mean T-size was allowed and more node-positive patients (Table 1). Looking at age groups, the distribution of tumour diameter and nodal status also indicates a broadening in the criteria for offering BCS to the youngest patients. On average, patients 80 years of age or over had been offered BCS for larger tumours. Mean age at the primary operation was 58.5 years (S.D. = 13.1), and remained constant during the observed period. The use of BCS increased successively in all age groups, but the proportions of women <50 years and >70 years were higher in the earlier years. The proportion of patients with unknown axillary status decreased over time from approximately 15–8%. Axillary dissection was avoided most often in patients over 70 years of age. The overall proportion of patients treated with postoperative radiotherapy was 70.2%. The patients who did not receive radiotherapy were mainly elderly, but as much as 20.4% (628/3077) of the women <70 years of age were not given postoperative irradiation.

3.2. Local recurrences

During the follow-up period, 582 patients out of 4694 (12.4%) developed a local recurrence. The overall risk of local recurrence was 9.2% at 5 years and 21.1% at 10 years. Nearly 50% of the local recurrences (253/556 with complete data of radiotherapy) were recruited from the women not treated with radiotherapy in conjunction with the primary tumour. There was no clear time trend in the probability of remaining free from local recurrence (Table 2). Younger patients had a higher risk of local recurrence. The probability of local recurrence was markedly lower after radiotherapy, but the risk was still as much as 7.6% at 5 years and 17.8% at 10 years. Of the patients without radiotherapy, more

Table 1
Characteristics of the 4694 patients operated upon with breast conserving surgery for invasive breast cancer in the time period of 1981–1990

	Number	Mean T-size[a] (mm)	Proportion of N+ (%)	Proportion of N? (%)	Proportion of RT+[b] (%)	Proportion of pats <50 years (%)	Proportion of pats >70 years (%)
Time period							
⩽1983	565	12.9	10.4	14.7	68.2	30.8	20.7
1984–1986	1077	13.8	13.9	10.7	62.6	30.1	18.6
1987–1988	1339	14.0	16.1	9.3	69.4	29.0	17.8
1989	791	14.7	17.4	7.7	77.0	25.9	17.3
1990	922	14.1	18.0	7.7	75.9	24.2	14.5
Total	4694	14.0	15.5	9.7	70.2	28.0	17.6
Age group (years)							
<40	312	15.0	22.8	2.2	84.2		
40–49	1002	14.4	17.3	4.6	84.9		
50–59	1118	13.8	17.2	4.9	81.3		
60–69	1327	13.0	13.4	5.4	73.5		
70–79	699	13.8	11.9	18.4	43.4		
⩾80	236	17.8	13.6	62.3	6.8		
Total	4694	14.0	15.5	9.7	70.2		

N+, node-positive; RT+, given radiotherapy; pats, patients; N?, unknown axillary status.
[a] Based on 4500 patients.
[b] Based on 3890 patients.

than 30% had experienced a local recurrence at 10 years. Those with positive lymph nodes tended to do worse at 10 years (Table 2).

3.3. Distant disease-free survival

Distant metastatic disease developed in 588 of the 4694 women (12.5%). At 5 and 10 years, the estimated survival-free from distant recurrences was 90.6 and 81.6%. Patients who had experienced a local recurrence had a higher risk of distant metastases than those without a local recurrence (68.7% estimated survival-free compared with 84.3% at 10 years).

3.4. Corrected and overall survival

During the study period, 894 patients died. Breast cancer was responsible for 51.0% (456 patients) of all deaths. The life-table estimates for corrected survival in the whole cohort were 93.3 and 85.2% at 5 and 10 years, respectively. The corresponding figures for overall survival were 87.6 and 72.0% at 5 and 10 years, respectively. Life-table analysis showed no time trend in the risk of breast-cancer specific mortality (Table 3). The risk of breast cancer death was highest among the youngest and the oldest patients. The probability of death from breast cancer was markedly higher in patients who experienced a local recurrence.

Table 2
Life-table estimates with standard errors of the mean (SEM) showing probability of remaining free from local recurrence in a cohort of 4694 patients operated upon with breast conserving surgery (BCS) for invasive breast cancer in the time period of 1981–1990

	5 years		10 years	
	%	SEM	%	SEM
Time period				
⩽1983	92.6	1.2	87.0	1.6
1984–1986	89.8	1.0	81.0	1.5
1987–1988	89.9	0.9	65.6	5.0
1989	91.3	1.1	–	–
1990	91.6	1.2	–	–
Age group (years)				
<40	84.0	2.2	75.8	3.1
40–49	88.3	1.1	74.2	2.1
50–59	92.6	0.8	83.0	1.7
60–69	92.3	0.8	82.4	1.7
70–79	92.2	1.1	79.8	3.2
⩾80	90.3	2.3	77.8	6.4
Radiotherapy				
Yes	92.4	0.5	82.2	1.2
No	81.6	1.2	67.2	2.2
Lgll (lymphoglandulae)				
N?	90.3	1.6	80.0	3.2
N−	91.2	0.5	80.9	1.0
N+	89.5	1.2	72.4	3.4

N−, node-negative; N+, node positive; N?, unknown axillary status.

For overall survival, the results were somewhat worse in the first time period, 84.6% at 5 years compared with 88.0% when the operation was performed in 1990. Radiotherapy was associated with higher survival figures at 10 years. Overall survival was 78.5% when radiotherapy was given and 57.7% for the non-irradiated, but this estimate is influenced by the selection of whom to irradiate, as is clearly depicted in Table 1.

3.5. Cox proportional hazards analysis

As expected from the distribution of covariates, clear differences were found between the univariate and the multivariate analysis and we have thus chosen to present data from the multivariate models (Tables 4 and 5). In the analysis of time periods and local recurrence (Table 4), there was a definite trend for results to be somewhat worse in the later period, relative hazard (RH) 1.5 (1.0–2.1) for 1990 versus 1981–1983. This time trend also applied to corrected survival (Table 5). For the age groups, the multivariate model showed a diminishing risk of local recurrence with increasing age. In the estimates of corrected survival, women under 40 years of age did worse than other age groups. A

Table 3
Life-table estimates with standard errors of the mean (SEM) showing probability of corrected survival in a cohort of 4694 patients operated upon with breast conserving surgery (BCS) for invasive breast cancer in the time period of 1981–1990

	5 years		10 years	
	%	SEM	%	SEM
Time period				
⩽1983	93.9	1.0	87.8	1.5
1984–1986	93.5	0.8	85.1	1.4
1987–1988	93.4	0.7	82.2	3.4
1989	93.1	1.0	–	–
1990	91.9	1.2	–	–
Age group				
<40	87.5	2.0	75.0	3.2
40–49	91.7	0.9	85.8	1.5
50–59	94.2	0.7	87.9	1.4
60–69	95.3	0.6	87.0	1.5
70–79	93.8	1.0	80.8	3.1
⩾80	90.0	2.4	84.3	4.0
Radiotherapy				
Yes	93.4	0.5	85.4	1.0
No	92.4	0.8	83.2	1.8
Lgll (lymphoglandulae)				
N?	92.5	1.4	85.5	2.7
N−	95.2	0.4	88.9	0.8
N+	84.4	1.4	64.8	3.2
Local recurrence				
Yes	89.0	1.3	75.4	2.4
No	94.0	0.4	87.2	0.8

N−, node-negative; N+, node positive; N?, unknown axillary status.

comparison between women receiving RT and those who did not revealed that radiotherapy had a clearly protective effect on the risk of local recurrence. The analysis of RT also showed statistically significant effects on overall survival [RH 0.7 (0.6–0.8)] but not on corrected survival. Nodal status and tumour size were of importance for corrected survival. Nodal status did not affect the risk of local recurrence, whereas risk of local recurrence tended to rise with increasing tumour size. Local recurrence was associated with an increased risk of distant disease [RH 1.8 (1.5–2.2)] and of death by breast cancer [RH 1.9 (1.5–2.4)].

4. Discussion

It was surprising that nearly 30% of the patients had not received adjuvant radiotherapy. The non-irradiated patients in a randomised study [8] were only approximately one sixth of this group. During the 1980s, it was widely accepted that postoperative RT should become routine after BCS. The notion that a higher age implied a lower risk of ipsilateral breast recurrence was not widely publicised or discussed. The treatment recommendations did not exclude women over 70 years of age for RT.

Overview studies of RT after BCS have shown limited impact on survival after breast cancer [17] — especially in patient groups where a majority has stage I disease. Two recent studies of RT after mastectomy have shown that irradiation significantly reduces locoregional recurrences and improves overall survival [18,19]. We noticed quite low overall survival estimates for those not receiving radiotherapy. When we corrected for age and tumour size, the difference between the irradiated and non-irradiated diminished, possibly due to deconfounding of some selection criteria for RT. In this non-randomised

Table 4
Relative hazards (RH) with 95% confidence intervals (CI) from a multivariate Cox proportional hazards analysis of prognostic factors for local recurrence in 3890[a] women operated upon with breast conserving surgery (BCS) for invasive breast cancer in the time period 1981–1990

	Local recurrence RH (95% CI)
Time period	
⩽1983	1.0
1984–1986	1.2 (0.9–1.6)
1987–1988	1.4 (1.1–1.9)
1989	1.5 (1.0–2.1)
1990	1.5 (1.0–2.1)
Age group	
<40	2.2 (1.6–3.0)
40–49	1.7 (1.4–2.2)
50–59	1.0
60–69	0.8 (0.6–1.0)
70–79	0.6 (0.5–0.8)
⩾80	0.6 (0.4–1.0)
Radiotherapy	
Yes	0.3 (0.3–0.4)
No	1.0
Lgll (lymphoglandulae)	
N?	0.9 (0.7–1.3)
N−	1.0
N1–3+	1.2 (1.0–1.6)
N>3+	1.1 (0.6–2.1)
T-size (mm)	
1–10	0.8 (0.7–1.0)
11–20	1.0
21–30	1.0 (0.8–1.4)
>30	1.3 (0.7–2.3)

N−, node-negative; N+, node positive; N?, unknown axillary status; N1–3+, 1–3 nodes positive; N>3+, >3 nodes positive.
[a] Data about radiotherapy were lacking for 804 patients.

Table 5
Relative hazards (RH) with 95% confidence intervals (CI) from a multivariate Cox proportional hazards analysis of prognostic factors for corrected survival in 3890[a] patients operated upon with breast conserving surgery (BCS) for invasive breast cancer in the time period of 1981–1990

	Corrected survival RH (95% CI)
Time period	
⩽1983	1.0
1984–1986	0.9 (0.7–1.2)
1987–1988	1.0 (0.7–1.4)
1989	1.1 (0.7–1.6)
1990	1.3 (0.8–1.9)
Age group (years)	
<40	1.9 (1.3–2.7)
40–49	1.3 (0.9–1.7)
50–59	1.0
60–69	1.0 (0.7–1.3)
70–79	1.2 (0.9–1.8)
⩾80	1.2 (0.7–2.1)
Radiotherapy	
Yes	0.9 (0.7–1.2)
No	1.0
Lgll (lymphoglandulae)	
N?	1.2 (0.8–1.8)
N−	1.0
N1–3+	2.5 (2.0–3.2)
N>3+	5.2 (3.6–7.6)
T-size (mm)	
1–10	0.6 (0.4–0.8)
11–20	1.0
21–30	1.9 (1.5–2.5)
>30	2.7 (1.7–4.3)
Local recurrence	
Yes	1.9 (1.5–2.4)
No	1.0

N−, node-negative; N+, node positive; N?, unknown axillary status; N1–3+, 1–3 nodes positive; N>3+, >3 nodes positive.
[a] Data about radiotherapy were lacking for 804 patients.

setting, where indications for RT were not prospectively controlled, it is impossible to draw valid conclusions about its impact on survival.

Irrespective of the impact on survival, one wonders if RT would not have saved many of the non-irradiated patients from local recurrences without involving substantial side-effects. Inadequate selection mechanisms have also been observed in patients in a North American series [20]. A recently published study on the appropriateness of primary therapy for early-stage breast cancer based on data from the US National Cancer Institute showed a drop in appropriate treatment associated with increased use of BCS [21]. Omission of RT, axillary dissection or both, increased from 10% in 1989 to 19% at the end of 1995. Our study has shown non-protocol treatment (one or many of the variables omission of radiotherapy, axillary dissection or a tumour size >30 mm) of 32% in the observed period, but in contrast to the US study, a successively increasing compliance with the treatment protocols.

In the multivariate models, the risk of local recurrence was higher in the later time period. The multivariate analysis controlled for period-based differences in the distributions by age, tumour size, lymph nodes and use of RT. Deconfounding may not be complete for lymph node status, since diagnostic work-up of the axilla may have been more sensitive in the later part of the 1980s. However, lymph node status does not seem to be a major risk factor for local recurrence and should not decisively disturb the trend for local recurrence. Patients with positive margins were reoperated upon with mastectomy in the beginning of the period, and more often with a re-excision in the later years. This is an example of the broadening in the indications for conservative surgery, but it can not solely be the explanation of the worsening results since these women were few. The time period as a variable otherwise reflects a complex underlying pattern of changing indications for surgery and adjuvant therapy, increasing sub-specialisation in surgery, the introduction of screening, increased quality of clinical mammography and the successive introduction of breast clinics with a multidisciplinary approach to breast cancer treatment ensuring that more and more patients receive proper management. Thus, we postulate that the multivariate model's trend for the local recurrence rate reflects these other factors. Our results rule out any greatly increased risk from a considerably more widespread use of BCT. However, the relative hazard of 1.5 does imply an excess risk of approximately 3.5%, given that the baseline risk at 1981–1983 was 7% at 5 years. This excess is clinically relevant. Wider indications for BCT and the omission of RT seem to outweigh the possible benefit of other changes in management over time.

It was discouraging to discover a 10-year estimate of local recurrences of 17.8% even when RT had been used. A risk of less than 1% per year has been stipulated as an important quality criteria [22]. Iscoe and colleagues [23] showed that ipsilateral breast relapses are more common in routine treatment compared with trial series; which our results underline. In our study by Liljegren and colleagues [24] where more strict selection criteria were used (i.e. women with unifocal tumours visible on mammography operated with a standardised sector resection, level I–II axillary dissection and peri-operative X-ray of the specimen), a lower risk of local recurrence was observed.

The analysis of risks by age group showed the expected pattern as regards both local and distant recurrences and breast cancer death [25–29].

Our study indicates that the patients with local recurrence may be those who have a more aggressive breast cancer disease. However, since those not irradiated are a selected group and accounted for approximately 50% of those with local recurrences, the difference in survival between those with and without a local recurrence, respectively, may be partially confounded.

In summary, our results point to several problems of general interest in breast cancer treatment: even when controlled for tumour stage and age, in spite of the increasing compliance with treatment protocols, results tended to become worse when BCS was adopted more widely. The quality expected from randomised trials was not achieved. The reasons for this need to be further studied, since the underlying factors may include characteristics of the decision and management process, which can be influenced. The proportion of women who were not irradiated was surprisingly high, especially among those over 70 years of age. It was not unexpected that those who were not irradiated were selected on the basis of comorbidity, for example, but the selection process failed to target a group with a low risk of local recurrence. Any decision not to irradiate must be rationally based on knowledge about the risk factors for local recurrence and such strategies are now incorporated into the Swedish treatment recommendations. Our data once more corroborate the notion that a local recurrence is associated with a high risk to develop distant disease, either due to a generally more aggressive disease or to a dissemination from the local recurrence itself.

Acknowledgements

This study was performed as a collaborative effort under the Swedish Breast Cancer Study Group. Financial support was provided by the Swedish Cancer Society.

References

1. Cedermark B, Askergren J, Alveryd A, *et al*. Breast-conserving treatment for breast cancer in Stockholm, Sweden, 1977 to 1981. *Cancer* 1984, **53**, 1253–1255.

2. Tejler G, Aspegren K. Complications and hospital stay after surgery for breast cancer: a prospective study of 385 patients. *Br J Surg* 1985, **72**, 542–544.
3. Veronesi U, Saccozzi R, Del Vecchio M, *et al*. Comparing radical mastectomy with quadrantectomy, axillary dissection, and radiotherapy in patients with small cancers of the breast. *N Engl J Med* 1981, **305**, 6–11.
4. Fisher B, Bauer M, Margolese R, *et al*. Five-year results of a randomized clinical trial comparing total mastectomy and segmental mastectomy with or without radiation in the treatment of breast cancer. *N Engl J Med* 1985, **312**, 665–673.
5. Verbeek AL, Hendriks JH, Holland R, Mravunac M, Sturmans F, Day NE. Reduction of breast cancer mortality through mass screening with modern mammography. First results of the Nijmegen project, 1975–1981. *Lancet* 1984, **1**, 1222–1224.
6. Collette HJ, Day NE, Rombach JJ, de Waard F. Evaluation of screening for breast cancer in a non-randomised study (the DOM project) by means of a case–control study. *Lancet* 1984, **1**, 1224–1226.
7. Tabar L, Fagerberg CJ, Gad A, *et al*. Reduction in mortality from breast cancer after mass screening with mammography. Randomised trial from the Breast Cancer Screening Working Group of the Swedish National Board of Health and Welfare. *Lancet* 1985, **1**, 829–832.
8. Holmberg L, Liljegren G, Adami H, Graffman S. Sector resection with or without postoperative radiotherapy for stage I breast cancer: a randomized trial. The Uppsala-Orebro Breast Cancer Study Group. *J Natl Cancer Inst* 1990, **82**, 277–282.
9. Aspegren K, Holmberg L, Adami HO. Standardization of the surgical technique in breast-conserving treatment of mammary cancer. *Br J Surg* 1988, **75**, 807–810.
10. National Board of Health and Welfare TCR. *Cancer Incidence in Sweden*. Stockholm, Socialstyrelsen: Allmänna förlaget, 1960.
11. Mattsson B, Wallgren A. Completeness of the Swedish Cancer Register. Non-notified cancer cases recorded on death certificates in 1978. *Acta Radiol Oncol* 1984, **23**, 305–313.
12. Frank HA, Hall FM, Steer ML. Preoperative localization of nonpalpable breast lesions demonstrated by mammography. *N Engl J Med* 1976, **295**, 259–260.
13. Raininko R, Linna MI, Rasanen O. Preoperative localization of nonpalpable breast tumours. *Acta Chir Scand* 1976, **142**, 575–578.
14. Siegel BM, Mayzel KA, Love SM. Level I and II axillary dissection in the treatment of early-stage breast cancer. An analysis of 259 consecutive patients. *Arch Surg* 1990, **125**, 1144–1147.
15. Nystrom L, Larsson LG, Rutqvist LE, *et al*. Determination of cause of death among breast cancer cases in the Swedish randomized mammography screening trials. A comparison between official statistics and validation by an endpoint committee. *Acta Oncol* 1995, **34**, 145–152.
16. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep* 1966, **50**, 163–170.
17. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. *Lancet* 2000, **355**, 1757–1770.
18. Overgaard M, Hansen PS, Overgaard J, *et al*. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. *N Engl J Med* 1997, **337**, 949–955.
19. Ragaz J, Jackson SM, Le N, *et al*. Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. *N Engl J Med* 1997, **337**, 956–962.
20. Lazovich DA, White E, Thomas DB, Moe RE. Underutilization of breast-conserving surgery and radiation therapy among women with stage I or II breast cancer. *Jama* 1991, **266**, 3433–3438.
21. Nattinger AB, Hoffmann RG, Kneusel RT, Schapira MM. Relation between appropriateness of primary therapy for early-stage breast carcinoma and increased use of breast-conserving surgery. *Lancet* 2000, **356**, 1148–1153.
22. Blamey RW. The British Association of Surgical Oncology Guidelines for surgeons in the management of symptomatic breast disease in the UK (1998 revision). BASO Breast Specialty Group. *Eur J Surg Oncol* 1998, **24**, 464–476.
23. Iscoe NA, Naylor CD, Williams JI, *et al*. Temporal trends in breast cancer surgery in Ontario: can one randomized trial make a difference. *Cmaj* 1994, **150**, 1109–1115.
24. Liljegren G, Holmberg L, Bergh J, *et al*. 10-Year results after sector resection with or without postoperative radiotherapy for stage I breast cancer: a randomized trial. *J Clin Oncol* 1999, **17**, 2326–2333.
25. de la Rochefordiere A, Asselain B, Campana F, *et al*. Age as prognostic factor in premenopausal breast carcinoma. *Lancet* 1993, **341**, 1039–1043.
26. Fowble BL, Schultz DJ, Overmoyer B, *et al*. The influence of young age on outcome in early stage breast cancer. *Int J Radiat Oncol Biol Phys* 1994, **30**, 23–33.
27. Nixon AJ, Neuberg D, Hayes DF, *et al*. Relationship of patient age to pathologic features of the tumor and prognosis for patients with stage I or II breast cancer. *J Clin Oncol* 1994, **12**, 888–894.
28. Veronesi U, Marubini E, Del Vecchio M, *et al*. Local recurrences and distant metastases after conservative breast cancer treatments: partly independent events. *J Natl Cancer Inst* 1995, **87**, 19–27.
29. Liljegren G, Lindgren A, Bergh J, Nordgren H, Tabar L, Holmberg L. Risk factors for local recurrence after conservative treatment in stage I breast cancer. Definition of a subgroup not requiring radiotherapy. *Ann Oncol* 1997, **8**, 235–241.