Pergamon

European Journal of Cancer, Vol. 34, No. 3, pp. 315–323, 1998

Printed in Great Britain
0959-8049/98 $19.00+0.00

PII: S0959-8049(97)10035-1

Original Paper

Eight-year Results of a Prospective Non-randomised Study on Therapy of Small Breast Cancer

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In this report, the results of the first controlled clinical trial on breast cancer in Germany, begun in 1983, are presented after a median follow-up of 8 years. Four-year results have been previously published. In pT1 N0 M0 breast cancer, mastectomy as the standard treatment was to be compared with tumorectomy plus radiotherapy to the remaining breast tissue. The study design, originally planned as a comprehensive cohort study including randomised and non-randomised patients, had to be changed into a prospective observation study due to the low randomisation rate. 1036 out of 1119 recruited patients were evaluable. After a median follow-up of 97 months, 237 events (local recurrence, regional recurrence, distant metastases, contralateral breast cancer or death of the patient without previous recurrence) occurred. With the exception of death without recurrence, the events were evenly distributed among the two treatment groups. The 8-year local recurrence rate of the whole patient population is 8.8%. Out of all prognostic factors examined, only tumour size and grade had a significant influence on recurrent disease. Event-free survival decreased in cases with 'uncertain' tumour margins, whereas the width of the margin has no influence on disease recurrence. Based on 151 deaths observed so far, there was no significant difference in overall survival between the two treatment groups. The 8-year results of this study are in accordance with the 4-year results reported previously and with those of other breast-conserving treatment trials. There was no significant difference between the two treatment groups with regard to event-free and overall survival. Incomplete tumorectomy had a negative influence on recurrence. © **1998 Elsevier Science Ltd. All rights reserved.**

Key words: small breast cancer, mastectomy, breast-conserving treatment, prognostic factors
Eur J Cancer, Vol. 34, No. 3, pp. 315–323, 1998

INTRODUCTION

At the beginning of the 1980s, in the Federal Republic of Germany, breast-conserving treatment (BCT) was not considered to be a standard primary treatment for breast cancer. In 1983 to promote BCT, a controlled clinical trial was performed in Germany. 69 university and community hospitals joined the German Breast Cancer Study Group (GBSG) in order to move the treatment of breast cancer in Germany a step forward. The background and design of the study were described in detail in a report of the 4-year results [1]. In this paper we will present the results after a median follow-up of 8 years.

PATIENTS AND METHODS

The trial, originally intended as a randomised treatment comparison, was actually planned as a comprehensive cohort study [2, 3], including eligible patients refusing randomisation because of a treatment preference. This decision was driven by the expected problems of getting consent to randomisation [1].

All women with pathological stage I breast cancer were candidates for the study. Inclusion criteria were: histological diagnosis of invasive carcinoma, maximal tumour diameter

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Received 26 Apr. 1997; revised 26 Aug. 1997; accepted 22 Sep. 1997.

2 cm, histologically tumour-free axillary lymph nodes (minimum number of nodes examined: $n = 6$), no distant metastases, consent of the patient to participate in the study, to allow data processing by the statistical centre and quality control by the reference centres.

The following characteristics were exclusion criteria: no tumour-free margin, tumour infiltration in skin or pectoralis major muscle, pathohistological diagnosis of Paget's disease, inflammatory carcinoma or cystosarcoma phylloides, supra- or infraclavicular lymph node metastases, synchronous carcinoma of the opposite breast, sequential breast cancer or carcinoma of other organs, pregnant or breast-feeding patients, patients in reduced general condition (Karnofsky Index $\leq 50\%$), other diseases which prevented both treatment modalities in question, patients with macromastia on whom homogeneous breast irradiation could not be applied.

Therapeutic procedures

Surgery. The surgical technique has been previously described in detail [1]. The tumour had to be removed with histologically free margins. The axillary lymph node status, being an important inclusion criterion, was obtained by a lower axillary dissection. Level III was only removed when a suspicious lesion was found on palpation.

Histological work-up. Of special importance was the diagnosis of tumour size as well as the statement of a tumour-free margin. Also, axillary lymph node involvement had to be excluded. At least six lymph nodes had to be in the axillary specimen. Oestrogen and progesterone receptor analysis was performed: a level of ≥ 20 fmol/mg cytosol protein was regarded as being positive. Histological tumour grade was determined as described by Bloom and Richardson [4].

Radiotherapy. Radiotherapy (with 1 MV Cobalt-60 or 4–6 MV linear accelerator photons) was started 2–6 weeks after surgery. Five fractions of 2 Gy per week and a total dose of 50 Gy (reference dose) in 25 fractions (5–6 weeks) were applied to the whole breast. An electron boost of 10–12 Gy (reference dose) in fractions of 2 Gy was delivered to the primary tumour bed (311 patients). If electrons were not available, the total reference dose to the breast was changed to 60 Gy (422 patients) [5].

Systemic treatment. The patients did not receive any adjuvant systemic treatment.

Quality control

Treatment and work-up of the patients, according to the rules of the protocol, were supervised by reference centres for each discipline. The protocol on how the quality of radiotherapy, the evaluated parameters and the results were observed has been published before [6].

Post-therapeutic follow-up

Patients were followed at regular intervals to secure detection of any kind of recurrence at the earliest time possible. Patients were clinically examined every 3 months during the first 2 years after operation, every 6 months for the following 3 years, and annually from the sixth year onwards. Laboratory investigations were performed together with each clinical examination. The first postoperative mammogram was taken 3 months following breast-conserving treatment, and 6 months after mastectomy; it was repeated every 6 months for the first 2 years, and in yearly intervals thereafter. Chest X-rays as well as abdominal ultrasound were done twice a year, and bone scans were performed annually.

Statistics

Due to the low rate of randomisation, the study had to be analysed as a prospective observation study. Event-free survival time (EFS) was defined as the period between the date of diagnosis and the first occurrence of one of the following events: local recurrence, regional recurrence, distant metastases, contralateral breast cancer and death of the patient without previous recurrence. Metachronous carcinomas of other organs were not regarded as an event for EFS.

For univariate analyses, EFS rates were calculated according to Kaplan–Meier [7]. The relative risks between different groups defined by prognostic factors with corresponding 95% confidence intervals (CI) were determined by using a univariate Cox regression model [8]. The P values were based on the log-rank test [9]. Event-specific recurrence rates for the first event of failure were estimated by using the methodology of cumulative incidence rates [10, 11]. The first event was classified as local recurrence (with or without simultaneous failure in other locations), distant failure (including regional recurrence, distant metastases, and a second primary in the contralateral breast) or death without recurrence.

A simultaneous assessment of the effects of treatment and prognostic factors was performed within a multiple regression analysis using the Cox model [8]. In the first analysis after four years [1], those factors were included in the model which had a significant effect on univariate analyses and/or were unequally distributed among the two treatment groups. In this analysis, the same factors together with the treatment modality were included in a Cox model. From this model, estimates of relative risks with corresponding 95% confidence intervals and P values based on Wald tests [10] were calculated. The same methodology was employed to analyse overall survival (OS) which was defined as the period between the date of diagnosis and death from any cause. Event-specific analysis of the simultaneous influence of treatment and prognostic factors on the first event of failure in the classification mentioned above were performed by using the Cox model for competing risks [12]. All tests of significance were two-tailed, and a P value of ≤ 0.05 was considered to indicate statistical significance.

Not all patients followed the close observation schedule as postulated in the protocol. At the time of the data cut-off date (August, 1995), the last follow-up of 357 patients was dated earlier than January 1994. For these cases, we contacted the residents' registration offices to obtain their survival status. This additional information was used only for the calculation of OS; for calculation of EFS, we used the last follow-up report.

RESULTS

Patient accrual

Between November 1983 and November 1989, a total of 1119 patients were recruited. Of those, only 72 patients (6.4%) were randomised. The other patients were treated according to their individual treatment preference. Therefore, the study is analysed as a prospective observational study. 83 patients were removed from the study since they did not fulfil the protocol's inclusion criteria [1]. This resulted in a total of 1036 evaluable patients from 69 institutions of whom 733 (71%) had BCT and 303 (29%) had mastectomy. Between

1983 and 1988, the percentage of patients treated with BCT hardly changed (percentages per year between 68% and 73%). In 1989, the last year of accrual, the percentage increased to 78%.

Table 1 shows the distribution of various prognostic factors. Despite the very strict selection criteria, the two treatment groups were still heterogeneous regarding the distribution of the prognostic factors. Patients with smaller tumours (up to 10 mm) as well as younger patients were more often treated with BCT. Also, the number of premenopausal patients was higher in this group. Due to the heterogeneous age distribution and the correlation between age and hormone receptor status, the number of patients showing a positive hormone receptor status was higher in the mastectomy group. In approximately 20% of the whole patient population, hormone receptors were not examined. This was mainly due to a small tumour size where pathohistological diagnosis was considered to be more important than hormone receptor analysis.

There was a high correlation between tumour grading and hormone receptor status: 90% of grade I tumours were receptor positive compared with only 40% of grade III tumours. There was also a correlation between tumour grading and age as well as between age and tumour size.

Event-free survival

After a median follow-up of 97 months, 237 events (recurrences/deaths) were observed. Among these were 118 patients with progressive disease who were still alive at the time of evaluation, 84 patients had died of breast cancer and 35 patients died without any evidence of a breast cancer recurrence.

Table 1. *Patient and tumour characteristics*

Variables		Total $n = 1036$ n (%)	Mastectomy $n = 303$ n (%)	BCT $n = 733$ n (%)
Age (years)	≤ 45	254 (25)	31 (10)	226 (30)
	46–60	415 (40)	107 (35)	305 (42)
	> 60	367 (35)	105 (55)	202 (28)
Menopausal status	pre	374 (37)	50 (19)	326 (45)
	post	645 (63)	243 (81)	402 (55)
	unknown	7 (1)	2 (1)	5 (1)
Tumour size	≤ 10 mm	272 (26)	60 (20)	212 (29)
	11–20 mm	726 (74)	242 (80)	520 (71)
	unknown	2 (1)	1 (< 1)	1 (< 1)
Oestrogen receptor status	≥ 20 fmol/mg	512 (62)	127 (68)	335 (59)
	< 20 fmol/mg	318 (38)	84 (32)	234 (41)
	unknown	206 (20)	42 (14)	164 (22)
Progesterone receptor status	≥ 20 fmol/mg	502 (62)	168 (66)	334 (60)
	< 20 fmol/mg	309 (38)	86 (34)	223 (40)
	unknown	225 (22)	49 (16)	176 (24)
Histological tumour type	sol/comb/oth	735 (71)	214 (71)	521 (71)
	lobular	48 (10)	39 (10)	68 (9)
	com/crib	70 (7)	20 (7)	50 (7)
	tub/pap/muc	97 (9)	29 (9)	68 (9)
	medullar	36 (3)	10 (3)	26 (4)
Tumour grade	I	350 (34)	100 (33)	250 (34)
	II	556 (54)	171 (57)	385 (53)
	III	124 (12)	31 (10)	93 (13)
	unknown	6 (1)	1 (< 1)	5 (1)

sol, solid; comb, combination; oth, other; com, comedo; crib, cribriform; tub, tubular; pap, papillary; muc, mucinous.

The site of the first recurrence as well as the distribution of events among the treatment groups (crude rates) are shown in Table 2. There was no difference between the treatment groups with regard to the events observed. The somewhat larger number of deaths without recurrent disease and second contralateral primary in the mastectomy group is due to the higher mean age of these patients. 30 out of 35 patients who died without previous recurrence were older than 60 years. The 8-year EFS rate of the whole patient population was 0.75 with a 95% CI of 0.72–0.78.

Table 3 shows the results of the univariate analyses on the influence of the various prognostic variables on EFS. The influence of tumour size and grade was significant. In patients with a tumour diameter greater than 1 cm there was a 1.76-fold risk of developing an event. Patients with grade II or III tumours had a similar EFS; the risk of recurrence, however, was approximately 1.6-fold higher when compared with grade I disease. Patients' age, hormone receptor status and histological subtype showed either no or only a weak influence on EFS.

The treatment modalities were analysed together with tumour size, grading and the patients' age in a Cox regression model (Table 4). Again, tumour size and grading were shown to be significant prognostic factors, whereas age was only of borderline prognostic relevance. This analysis demonstrates a slight but non-significant advantage for BCT for EFS. This result also appears from the univariate comparison of the EFS rates as displayed in Figure 1. Consequently, no superiority can be shown for either one of the therapeutic modalities at the time of follow-up.

In an additional analysis, we examined event-specific effects of treatment and prognostic factors separately on the occurrence of local recurrence, distant failure (in regional lymph nodes, distant location and contralateral breast cancer) and death without previous recurrence as the first event of failure. Event-specific recurrence rates according to treatment are displayed in Figure 2(a) and (b). The 8-year local recurrence rate was approximately 9% in both treatment arms. The results of the multivariate analysis using the Cox model for competing risks are listed in Table 5. Compared with the results of the analysis of the effects on the composite outcome variable EFS as displayed in Table 4 they indicate the following: there is no uniform age effect on the different events. With regard to the composite outcome EFS, patients younger than 46 years and patients older than 60 years had an increased risk compared to the middle group. Table 5 shows that younger patients have an increased risk of local recurrence and older patients have an increased risk of death without recurrence. In general, the results concerning the

Table 2. *Localisation of primary recurrence in different treatment groups*

Primary recurrence	Mastectomy (%)	BCT (%)	Total
No recurrence	212 (70.0)	555 (75.7)	767
Local	21 (6.9)	55 (7.5)	76
Local + regional/distant	2 (0.7)	8 (1.1)	10
Regional	3 (0.9)	7 (1.0)	10
Distant + regional/distant	25 (8.3)	66 (9.0)	91
Second primary contralateral	7 (2.3)	8 (1.1)	15
Death without recurrence	18 (5.9)	17 (2.3)	35
Death (recurrence unknown)	15 (5.0)	17 (2.3)	32
Total	303 (100)	733 (100)	1036

Table 3. *Univariate analyses of the effects of prognostic factors on event-free survival (EFS)*

Variables		No. of patients included	Estimated relative risk	Confidence interval	*P* value (log-rank test)
Age (years)	≤ 45	1036	1.00	—	0.09
	46–60		0.74	[0.53–1.02]	
	> 60		0.98	[0.71–1.35]	
Menopausal status	pre	1029	1.00	—	0.85
	post		0.97	[0.75–1.27]	
Tumour size	≤ 10 mm	1034	1.00	—	0.001
	11–20 mm		1.76	[1.26–2.46]	
Oestrogen receptor status	≥ 20 fmol/mg	830	1.00	—	0.64
	< 20 fmol/mg		0.93	[0.70–1.25]	
Progesterone receptor status	≥ 20 fmol/mg	811	1.00	—	0.47
	< 20 fmol/mg		1.11	[0.83–1.48]	
Histological tumour type	sol/comb/oth	1036	1.00	—	0.056
	lobular		0.75	[0.48–1.20]	
	com/crib		0.75	[0.43–1.31]	
	tub/pap/muc		0.51	[0.29–0.89]	
	medullar		0.49	[0.18–1.31]	
Tumour grade	I	1030	1.00	—	0.006
	II		1.57	[1.16–2.12]	
	III		1.72	[1.12–2.64]	

sol, solid; comb, combination; oth, other; com, comedo; crib, cribriform; tub, tubular; pap, papillary; muc, mucinous.

Table 4. *Effects of treatment and prognostic factors on event-free survival (EFS) estimated by a Cox regression model (*1028 *patients with complete data*/234 *events)*

Variables		Estimated relative risk	Confidence interval	*P*-value (Wald test)
Age (years)	≤ 45	1.00	—	0.07
	46–60	0.72	[0.51–1.00]	
	> 60	0.97	[0.69–1.37]	
Tumour size	≤ 10 mm	1.00	—	0.003
	11–20 mm	1.68	[1.19–2.36]	
Tumour grade	I	1.00	—	0.019
	II	1.51	[1.11–2.05]	
	III	1.64	[1.06–2.56]	
Treatment	Mastectomy	1.00	—	0.32
	BCT	0.86	[0.65–1.15]	

effects on the event of death without documented recurrence have to be interpreted with caution. First, the rather small number of 34 may show unstable results. Second, there may be some misclassification in this group because all patients without a known and documented recurrence are included, and an autopsy was not performed in every case. There was no treatment effect with respect to risk for local recurrence as well as distant failure. With the strong effect of age on death without recurrence and the different age distribution in the two treatment arms, we performed an additional analysis of the effects on recurrence-free survival, where, in contrast to EFS, the 34 events 'death without recurrence' were censored and not counted as events. The treatment effect was again adjusted for age, tumour size and tumour grade. Here, the relative risk of BCT compared with mastectomy was estimated as 0.93 (95% CI 0.68–1.29, $P = 0.67$).

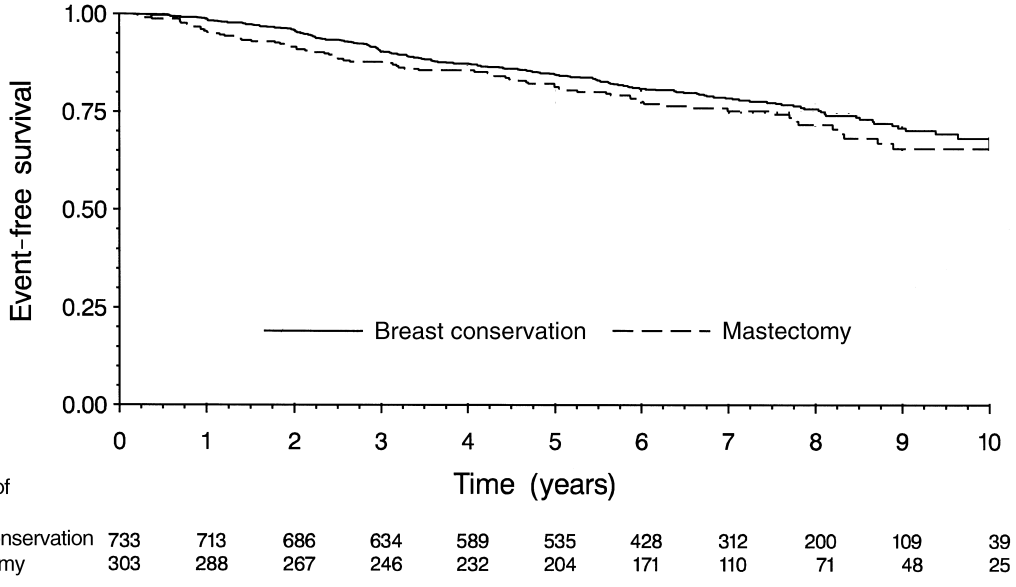


Figure 1. Event-free survival (EFS) by treatment.

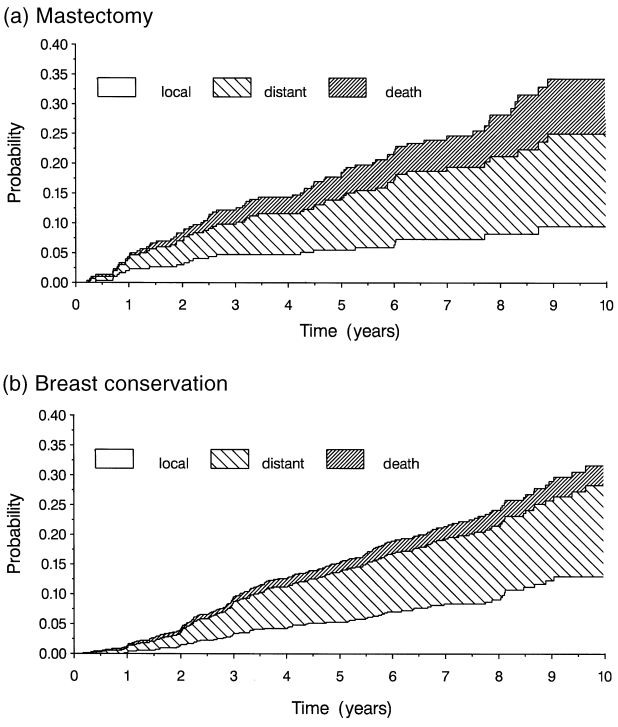


Figure 2. Cumulative incidence rates for local recurrence, regional or distant metastases and death without previous recurrence by treatment: (a) mastectomy; (b) breast conservation.

Table 6. Event-free survival (EFS) according to type of hospital in patients with breast-conserving treatment (727 patients with complete data/159 events)

Variables		Estimated relative risk	95% confidence interval	*P* value (Wald test)
Type of hospital	University (13 hospitals)	1.00	—	0.11
	Non-university (56 hospitals)	0.74	[0.51–1.07]	
Percentage of patients treated with mastectomy	≤ 15% (26 hospitals)	1.00	—	0.34
	> 15% (43 hospitals)	1.17	[0.85–1.61]	
Tumour-free margin	Uncertain	1.00	—	0.041
	0–2 mm	0.47	[0.22–0.98]	
	3–5 mm	0.35	[0.16–0.74]	
	> 5 mm	0.41	[0.20–0.82]	
Age (years)	≤ 45	1.00	—	0.66
	46–40	0.85	[0.59–1.22]	
	> 60	0.88	[0.58–1.35]	
Tumour size	≤ 10 mm	1.00	—	0.008
	11–20 mm	1.72	[1.15–2.57]	
Tumour grade	I	1.00	—	0.06
	II	1.41	[0.98–2.05]	
	III	1.77	[1.06–2.93]	

Treatment results according to type of hospital

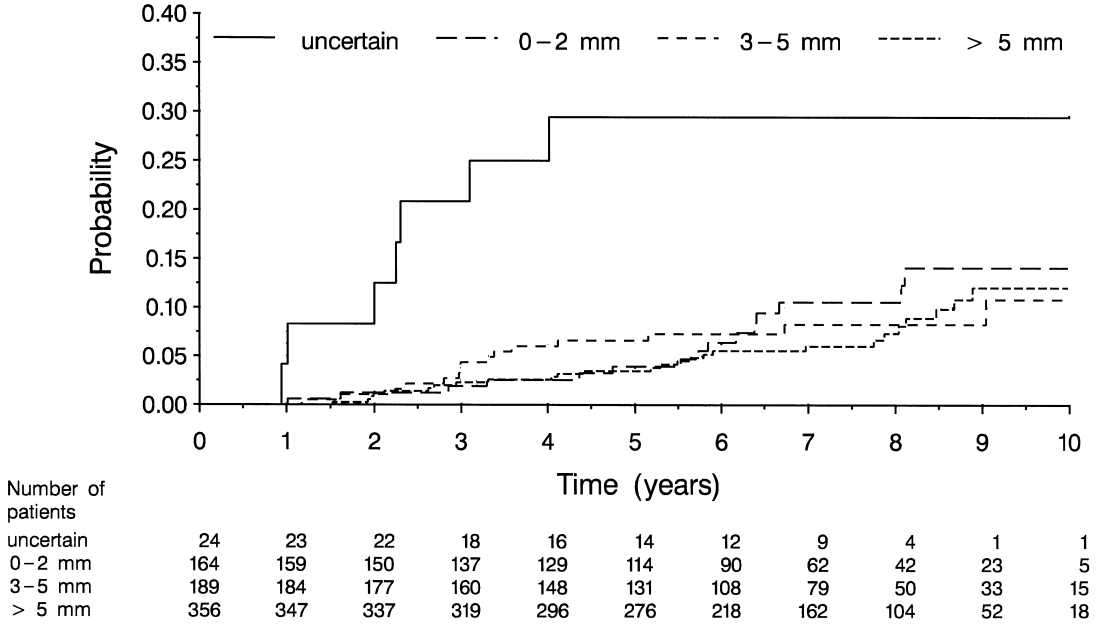
We further investigated whether there was a difference in the outcome following BCT between large specialised centres (university hospitals) and smaller institutions (community hospitals). Therefore, we examined the risk of recurrence and/or death for patients treated with BCT according to the type of the hospital. Table 6 shows the different variables which were included in a Cox regression model. In addition to patient's age, tumour size and grading, the hospital type (184 patients from 13 university hospitals, 852 patients from 56 non-university centres), the hospitals' experience with breast-conserving treatment (depending on the percentage of patients treated with mastectomy in this study, i.e. 371 patients from 26 centres with ≤ 15% mastectomy, 665 patients from 43 centres with > 15% mastectomy, 17 centres with 159 patients did not include any patients treated by mastectomy) and the extent of tumour-free margins were included. Neither the percentage of patients treated with mastectomy nor the type of hospital showed any significant influence on treatment outcome. As stated earlier, some of the centres did not use a boost as part of the radiotherapy. The local recurrence rate was slightly increased in these patients, but this result was not significant (data not shown).

Effect of tumour-free margin in patients treated with BCT

Also included in Table 6 is the estimated effect of the extent of tumour-free margin on EFS in patients treated with BCT. The small subgroup of patients in whom the reference

Table 5. Event-specific effects related to treatment and prognostic factors on the occurrence of local recurrence, distant failure (including regional recurrence, distant metastases and contralateral breast cancer), and death without previous recurrence as first event by a Cox regression model for competing risks (1028 patients with complete data/234 events)

		Local recurrence 85 events			Distant failure 115 events			Death without recurrence 34 events		
Variables		Estimated relative risk	Confidence interval	*P* value	Estimated relative risk	Confidence interval	*P* value	Estimated relative risk	Confidence interval	*P* value
Age (years)	≤ 45	1.00	—	0.043	1.00	—	0.75	1.00	—	0.0001
	46–60	0.61	[0.37–1.01]		0.84	[0.53–1.33]		0.76	[0.13–4.63]	
	> 60	0.49	[0.27–0.89]		0.88	[0.53–1.46]		9.38	[2.13–41.3]	
Tumour size	≤ 10 mm	1.00	—	0.48	1.00	—	0.022	1.00	—	0.018
	11–20 mm	1.20	[0.72–2.00]		1.79	[1.09–2.94]		5.67	[1.35–23.8]	
Tumour grade	I	1.00	—	0.46	1.00	—	0.055	1.00	—	0.47
	II	1.38	[0.84–2.28]		1.62	[1.03–2.54]		1.49	[0.70–3.17]	
	III	1.27	[0.61–2.66]		1.95	[1.06–3.62]		1.99	[0.53–7.47]	
Treatment	Mastectomy	1.00	—	0.70	1.00	—	0.81	1.00	—	0.12
	BCT	0.91	[0.55–1.50]		0.95	[0.63–1.44]		0.58	[0.29–1.15]	



Number of patients										
uncertain	24	23	22	18	16	14	12	9	4	1	1
0–2 mm	164	159	150	137	129	114	90	62	42	23	5
3–5 mm	189	184	177	160	148	131	108	79	50	33	15
> 5 mm	356	347	337	319	296	276	218	162	104	52	18

Figure 3. Cumulative incidence rates for local recurrence of patients in the breast conservation group by extent of tumour-free margin.

pathologist after re-examination of the specimen was 'uncertain' about the presence of a margin of normal breast tissue around the tumour had a worse prognosis than those with a clear margin. The extent of the margin, however, did not have any influence on EFS.

Figure 3 shows the local recurrence rate according to the extent of tumour-free margin. Compared with patients with a clear margin, the small subgroup of patients with an uncertain tumour-free margin has an increased risk of local recurrence. The effect of the tumour-free margin on the event-specific hazard rates was further analysed with a Cox model for competing risks which included the factors age, tumour size and tumour grade for adjustment. The relative risk of local recurrence of the patient groups uncertain versus certain margin was estimated as 4.8 (95% CI 2.15–10.92, $P < 0.0001$). In patients with a clearly tumour-free margin, no influence of the extent of the margin on the risk of local recurrence may be shown (3–5 mm versus 0–2 mm: relative risk 0.93 with 95% CI 0.45–1.92, > 5 mm versus 3–5 mm: relative risk 0.82 with 95% CI 0.43–1.57).

Overall survival (OS)

After a median follow-up of 97 months, we observed 151 deaths. The causes of death were: 84 patients died from breast cancer (BCT group: 62 (8.5%), mastectomy group: 22 (7.3%)), 35 patients died with no evidence of recurrent dis-

Table 7. Univariate analyses of the effects of prognostic factors on overall survival (OS)

Variables		No. of patients included	Estimated relative risk	Confidence interval	*P* value (log-rank test)
Age (years)	≤ 45	1036	1.00	—	< 0.001
	46–60		0.95	[0.60–1.50]	
	> 60		1.87	[1.23–2.84]	
Menopausal status	pre	1029	1.00	—	0.016
	post		1.53	[1.08–2.18]	
Tumour size	≤ 10 mm	1034	1.00	—	0.002
	11–20 mm		1.96	[1.27–3.04]	
Oestrogen receptor status	≥ 20 fmol/mg	830	1.00	—	0.44
	< 20 fmol/mg		1.15	[0.81–1.63]	
Progesterone receptor status	≥ 20 fmol/mg	811	1.00	—	0.08
	< 20 fmol/mg		1.37	[0.96–1.96]	
Histological tumour type	sol/comb/oth	1036	1.00	—	0.042
	lobular		0.41	[0.19–0.87]	
	com/crib		0.79	[0.40–1.54]	
	tub/pap/muc		0.51	[0.25–1.04]	
	medullar		0.53	[0.17–1.67]	
Tumour grade	I	1030	1.00	—	0.007
	II		1.57	[1.07–2.31]	
	III		2.17	[1.31–3.61]	

sol, solid; comb, combination; oth, other; com, comedo; crib, cribriform; tub, tubular; pap, papillary; muc, mucinous.

Table 8. Effects of treatment and prognostic factors on overall survival (OS) estimated by a Cox regression model (1028 patients with complete data/150 deaths)

Variables		Estimated relative risk	Confidence interval	*P* value (Wald test)
Age (years)	≤ 45	1.00	—	0.001
	46–60	0.97	[0.61–1.54]	
	> 60	2.02	[1.29–3.17]	
Tumour size	≤ 10 mm	1.00	—	0.008
	11–20 mm	1.83	[1.17–2.86]	
Tumour grade	I	1.00	—	0.003
	II	1.57	[1.07–2.31]	
	III	2.50	[1.48–4.24]	
Treatment	Mastectomy	1.00	—	0.43
	BCT	0.87	[0.62–1.23]	

ease (BCT: 17 (2.3%), mastectomy: 18 (5.9%)) and 32 patients (BCT: 17 (2.3%), mastectomy: 15 (5.0%)) died with unknown cause of death—in these cases, the information about death of the patient was obtained from the registration office. Table 7 shows the results of univariate analyses on the effects of various prognostic factors. Age, menopausal status, tumour size, tumour grade and histological tumour type had significant effects on OS. The univariate significant effects of menopausal status and histological tumour type disappeared in a multivariate analysis. Therefore, for the simultaneous evaluation of treatment and prognostic factors on OS, we used a Cox model with the same variables as for the analysis of EFS (Table 8). The influence of age, tumour size and tumour grade was significant. Patients older than 60 years had a 2-fold increase in their risk of death when compared with the two groups of younger age. Tumour size exceeding 10 mm leads to a 1.8-fold increase in risk of death compared with smaller tumours. In contrast to grade I, grade II and III were associated with a 1.6-fold and 2.5-fold increase in the risk of death. Again, there was no significant treatment effect. The estimated survival rates by treatment are displayed in Figure 4. The 8-year survival rate of the whole patient population was 0.86 with a 95% confidence interval of 0.84–0.88.

DISCUSSION

This study was the first nationwide trial on breast cancer treatment which was ever conducted in West Germany. In a previous publication [1], we explained why the trial had to be conducted as a prospective observation study. With the exception of the low rate of randomised patients, this study fulfils all quality criteria of a prospective controlled clinical trial [13]. Using the Cox regression model, we compared EFS and OS after breast-conserving treatment and mastectomy by adjusting for the most important prognostic factors and factors differing in distribution between the two groups.

Our 8-year results for EFS are very much in accordance with the 4-year results previously reported [1] and with those from randomised trials on breast-conserving treatment [14–22]. This applies especially to the treatment comparison which so far shows no difference between radical operation and BCT with respect to EFS. The result that the treatment modalities are similar with respect to OS is presented here for the first time. There appears to be a minimal trend in favour of BCT. The 8-year EFS rate of 0.75 and the 8-year OS rate of 0.86 confirm the good prognosis of the patient population selected for this study. The rate of local recurrences of 8.8% in 8 years indicates good local tumour control in our patients with breast-conserving treatment. Due to the large variety in inclusion criteria and in the application of surgery and radiotherapy, the recurrence rate in the breast at 8–10 years ranges between 4 and 20% in the randomised studies mentioned above [23].

The impressive results of the MILAN-I-trial are in accordance with the 1994 GAO meta-analysis of all monocentre and multicentre trials. In a commentary by J. Abrams [21], monocentre studies are associated with a better overall outcome. In comparison with the MILAN-I-trial, Marubini and associates [24] report a 40% increase of in-breast recurrences in the MILAN observation study following the MILAN-I-trial. The two main reasons for that observation were the increasing number of surgeons performing breast-conserving treatment as well as more generous patient eligibility criteria for quadrantectomy plus axillary dissection and radiotherapy

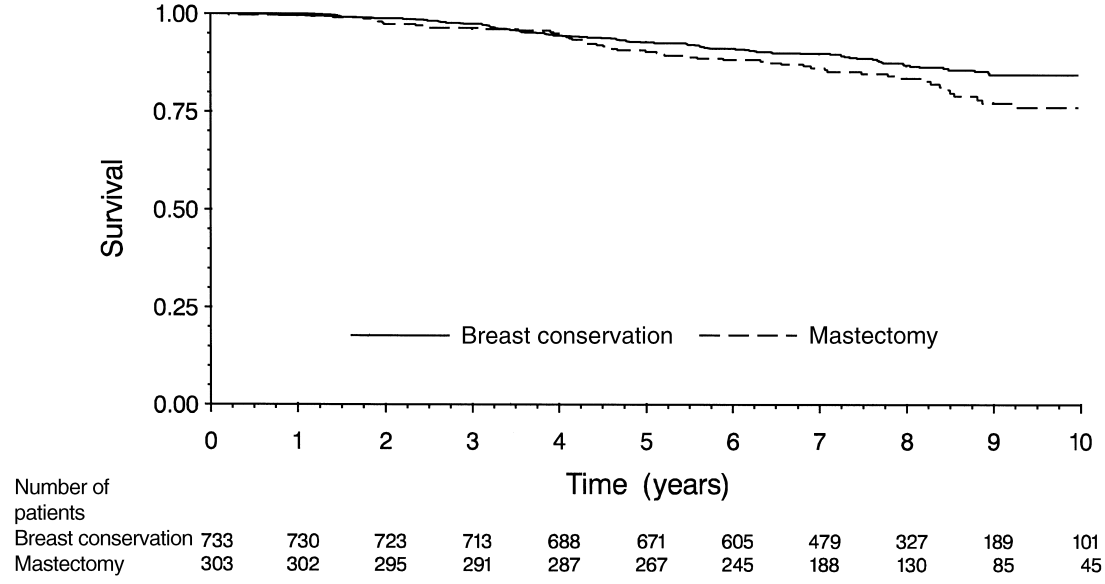


Figure 4. Overall survival (OS) by treatment.

(QUART). Even though overall survival was not affected, the increase in local recurrence clearly demonstrates that treatment quality improves under the conditions of a properly performed clinical trial.

The extent of the margin of normal tissue around the tumour is still a matter of debate [15–20, 25, 26]. Veronesi claims a necessary margin of 2–3 cm, whereas Fisher considers a 'microscopically free margin' sufficient for local tumour control. Our results indicate that the extent of the margin does not have an influence on the risk of local recurrence, whereas the small group of patients with an 'uncertainly free' tumour margin showed a significantly higher recurrence rate. This also agrees with the findings of Renton and associates [26] and Gage and associates [27]. However, in other studies [19, 20] there was no increase in local recurrence rate following incomplete tumour removal in comparison with total excision of the lesion [15].

For all our cases, the essential histological examinations were supervised by the reference centre of pathology. This made differentiated analyses possible confirming the central importance of tumour grade. In this context, the significance of the different components for histological grading was the subject of an additional analysis [28].

The results of our study on quality of life (QOL) have also been reported previously [1]. They correspond with the findings of an overview comprising several small and heterogeneous trials comparing QOL after mastectomy and breast-conserving treatment in early breast cancer by Kiebert and associates [29]. Apart from a better body image in patients treated with BCT, psychological adjustment and QOL in general is similar after either one of the treatment modalities. We can confirm the statement of Fallowfield and associates [30] that 'the key to successful adaptation of the treatment for breast cancer appears to be closely related to the woman's opportunity to participate in the choice of surgical treatment'.

In this study of the German Breast Cancer Study Group, radical and breast-conserving treatment in early breast cancer was compared in a large, homogeneous predominantly non-randomised patient population. On the basis of this prospective study, breast-conserving treatment was established in Germany. Size and histological grade of the tumour were shown to be the most important prognostic variables with regard to event-free and overall survival. A microscopically free tumour margin also played an important role especially with regard to the risk of local recurrence. Based on a median follow-up of 97 months, nearly identical results regarding event-free as well as overall survival could be observed for both treatment modalities.

1. The German Breast Cancer Study Group (GBSG). Therapy of small breast cancer—Four-year results of a prospective non-randomized study. *Breast Cancer Res Treat* 1995, **34**, 1–13.
2. Olschewski M, Scheurlen H. Comprehensive cohort study: an alternative to randomized consent design in a breast preservation trial. *Methods of Information in Medicine* 1985, **24**, 131–134.
3. Schmoor C, Olschewski M, Schumacher M. Randomized and non-randomized patients in clinical trials: experiences with comprehensive cohort studies. *Stat Med* 1996, **15**, 263–271.
4. Bloom HJS, Richardson WW. Histological grading and prognosis in breast cancer. *Br J Cancer* 1957, **11**, 339–377.
5. Sauer R, Schauer A, Rauschecker HF, *et al.* Therapy of small breast cancer: a prospective study on 1036 patients with specific emphasis on prognostic factors. *Int J Radiat Oncol Biol Phys* 1992, **23**, 907–914.
6. Seegenschmiedt MH, Sauerbrei W, Sauer R, *et al.* Quality control review for radiotherapy of small breast cancer: analysis of 708 patients in the GBSG I trial. *Strahlentherapie und Onkologie* 1993, **169**, 339–350.
7. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958, **53**, 457–481.
8. Cox DR. Regression models and life tables (with discussion). *J Royal Stat Soc B* 1972, **34**, 187–220.
9. Peto R, Pike MC, Armitage P, *et al.* Design and analysis of clinical trials requiring prolonged observation of each patient. Part I. *Br J Cancer* 1976, **34**, 585–612. Part II. *Br J Cancer* 1977, **35**, 1–39.
10. Kalbfleisch JD, Prentice RL. *The Statistical Analysis of Failure Time Data*. New York, Wiley, 1980.
11. Marubini E, Valsecchi MG. *Analysing Survival Data from Clinical Trials and Observational Studies*. Chichester, Wiley, 1995.
12. Kay R. Treatment effects in competing-risks analysis of prostate cancer data. *Biometrics* 1986, **42**, 203–211.
13. Liberati A, Himel HN, Chalmers TC. A quality assessment of randomized control trials of primary treatment of breast cancer. *J Clin Oncol* 1986, **4**, 942–951.
14. Blichert-Toft M, Rose C, Andersen JA, *et al.* Danish randomized trial comparing breast conservation therapy with mastectomy: six years of life-table analysis. *J Natl Cancer Inst Monogr* 1992, **11**, 19–25.
15. Arriagada R, Lê MG, Rochard F, Contesso G for the Institut Gustave-Roussy Breast Cancer Group. Conservative treatment versus mastectomy in early breast cancer: patterns of failure with 15 years of follow-up data. *J Clin Oncol* 1996, **14**, 1558–1564.
16. Veronesi U, Volterrani F, Luini V, *et al.* Quadrantectomy versus lumpectomy for small size breast cancer. *Eur J Cancer* 1990, **26**, 671–673.
17. Veronesi U, Salvadori B, Luini A, *et al.* Breast conservation is a safe method in patients with small cancer of the breast. Long-term results of three randomised trials on 1,972 patients. *Eur J Cancer* 1995, **31A**, 1574–1579.
18. Fisher B, Anserson S, Redmond CK, Wolmark N, Wickerham DL, Cronin WM. Re-analysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. *N Engl J Med* 1995, **333**, 1456–1461.
19. Van Dongen JA, Bartelink H, Fentiman IS, *et al.* Randomized clinical trial to assess the value of breast-conserving therapy in stage I and II breast cancer, EORTC 10801 Trial. *J Natl Cancer Inst Monogr* 1992, **11**, 15–18.
20. Straus K, Lichter A, Lippman M, *et al.* Results of the National Cancer Institute Early Breast Cancer Trial. *J Natl Cancer Inst Monogr* 1992, **11**, 27–32.
21. Abrams JS, Phillips PH, Friedman MA. Meeting highlights: a reappraisal of research results for the local treatment of early stage breast cancer. *J Natl Cancer Inst* 1995, **87**, 1837–1845.
22. Jacobson JA, Danforth DN, Cowan KH *et al.* Ten-year results of a comparison of conservation with mastectomy in the treatment of stage I and II breast cancer. *N Engl J Med* 1995, **332**, 907–911.
23. Morrow M, Harris JR, Schnitt SJ. Local control following breast-conserving surgery for invasive cancer: results of clinical trials. *J Natl Cancer Inst* 1995, **87**, 1669–1673.
24. Marubini E, Mariani L, Salvadori B, *et al.* Results of a breast cancer surgery trial compared with observational data from routine practice. *Lancet* 1996, **347**, 1000–1003.
25. Veronesi U. How important is the assessment of resection margins in conservative surgery for breast cancer? *Cancer* 1994, **74**, 1660–1661.
26. Renton SC, Gazet JC, Ford HT, *et al.* The importance of the resection margin in conservative surgery for breast cancer. *Eur J Surg Oncol* 1996, **22**, 17–22.
27. Gage I, Schnitt, SJ, Nixon AJ, *et al.* Pathologic margin involvement and the risk of recurrence in patients treated with breast-conserving therapy. *Cancer* 1996, **78**, 1921–1928.
28. Schumacher M, Schmoor C, Sauerbrei W, *et al.* The prognostic effect of histological tumor grade in node-negative breast cancer patients. *Breast Cancer Res Treat* 1993, **25**, 235–245.
29. Kiebert GM, De Haes JCJM, Van de Velde CJH. The impact of breast-conserving treatment and mastectomy on the quality of life of early-stage breast cancer patients: a review. *J Clin Oncol* 1991, **9**, 1059–1070.

30. Fallowfield LJ, Hall A, Maguire GP, Baum M. Psychological outcomes of different treatment policies in women with early breast cancer outside a clinical trial. *BMJ* 1990, **301**, 575–580.

Acknowledgements—This study was sponsored by the Ministry of Research and Technology (BMFT) of the Federal Republic of Germany; the long-term follow-up is supported by the Deutsche Forschungsgemeinschaft.

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U. Siekmann/Th. Gesenhus	Krankenanstalten Konstanz, Konstanz
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