Acta Oncologica, 2008; 47: 682–690

informa
healthcare

ORIGINAL ARTICLE

Breast conserving treatment in Denmark, 1989–1998. A nationwide population-based study of the Danish Breast Cancer Co-operative Group

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Abstract

Background. Randomised studies have shown that breast conserving surgery followed by radiotherapy is associated with a prognosis similar to mastectomy alone. This formed the basis for recommending breast conserving surgery combined with radiotherapy as a standard treatment for suited breast cancer patients in Denmark. *Patients and methods.* To evaluate the results of this treatment, we performed a nationwide population-based follow-up study of patients aged less than 75 years treated in Denmark from 1989 to 1998 based on the database of Danish Breast Cancer Cooperative Group. *Results.* At 15 years of follow-up, the Kaplan-Meier estimate of overall survival was 69% among 3758 patients who received the recommended treatment. Within the first 10 years of follow-up, the cumulative incidences of loco-regional recurrences, distant metastases or other malignant disease, or death as a first event were 9.0, 19.9, and 6.0% respectively, when analysed in a competing risk setting. The risk of loco-regional recurrences was significantly decreased in patients aged 50 years or more and increased with increasing tumour size. There was a pronounced beneficial effect of adjuvant radiotherapy with those not receiving radiotherapy having a hazard ratio of 3.52 (95% CI 2.21–5.61). The effect of resection margins was significant for loco-regional recurrences only in node negative patients. *Conclusion.* In conclusion, the present study shows that results similar to those from randomised clinical trials can be obtained when breast conserving treatment is applied as a standard treatment in an entire population.

For almost a century the surgical treatment of choice for breast cancer was mastectomy regardless of cancer characteristics or patient age. Already in the 1930's, the idea of breast conservation arose but it was not until the beginning of the 1970's that the safety of this approach was tested. A number of randomised clinical trials have shown that breast conserving surgery followed by radiotherapy is associated with a prognosis similar to mastectomy alone [1]. This has also been confirmed in Denmark, in the randomised trial TM-82 [2]. According to this evidence, the Danish Breast Cancer Co-operative Group (DBCG) decided in 1989 to recommend breast conserving treatment as a standard treatment option for suited breast cancer patients in Denmark.

Since patients are selected from specific eligibility criteria to enter clinical trials, the results of a treatment may differ when it is applied to an unselected patient population. The quality of the treatment may also differ when it is applied as a standard technique outside a clinical trial. To address this issue, we here examine the results of breast conserving treatment as

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(Received 18 October 2007; accepted 4 March 2008)

ISSN 0284-186X print/ISSN 1651-226X online
DOI: 10.1080/02841860802032769

applied to the Danish population from 1989–1998. In addition, determinants of risk of recurrence are analysed.

Material and methods

The DBCG was established in 1977 and has since then conducted nationwide clinical trials of adjuvant breast cancer therapy [3]. From Danish hospital departments of surgery, pathology, and oncology, breast cancer patients are reported prospectively to the database of the DBCG with information on date and type of surgery and on prognostic factors allowing allocation to the treatment protocols. For the present analysis, we included information on age, tumour size, number of lymph nodes removed, number of positive lymph nodes, resection margins, hormone receptor status, histological type, grade of malignancy, adjuvant systemic treatment and radiotherapy. Histological type was defined according to the WHO classification [4]. Tumour grade was assessed according to the method of Bloom and Richardson modified by Elston and Ellis [5]. Hormone receptor status was determined by immunohistochemistry and tumours were classified as receptor positive by 10% or more positive tumour cells for estrogen and/or progesterone receptors.

Breast cancer surgery

According to the DBCG guidelines, women are suited for breast conserving surgery if the tumour can be removed with a good cosmetic outcome, a minimum of 5 mm. microscopic tumour free margins, and the woman is willing to accept postoperative radiotherapy to the residual breast. Breast conserving surgery for breast cancer included lumpectomy and dissection of axillary levels I and II. According to the guidelines, the surgeon should intend to have at least 10 mm macroscopic free margins. The surgical procedure was regarded as radical if microscopic free margins of at least 5 mm were achieved. If the tumour was located close to the skin or the pectoral fascia over the pectoral muscle these were removed along with tumour. The tumour bed was marked by metal clips. Up to 1994, at least four lymph nodes were removed. Since then a sufficient axillary clearance included removal of ten or more lymph nodes. Sentinel node biopsy was not performed during the study period.

Radiotherapy techniques

According to the DBCG guidelines, adjuvant radiotherapy should be prescribed to all patients after a lumpectomy. The treatment (target) volume included the thoracic wall with the residual breast. In addition, the target volume included the axillary, periclavicular and parasternal lymph nodes if the patients were aged less than 46 years and had metastases to four or more lymph nodes up to 1995. From 1995, radiotherapy to the regional lymph nodes was prescribed to all premenopausal node positive patients. All patients were simulated with a conventional simulator, i.e. not CT-based. The dose to all fields was 48 Gy in 24 fractions with five fractions per week. Boost doses of 10–16 Gy in 5–8 fractions were given to the tumour bed, including the scar, with margins of 3 cm to a depth of 1 cm from the tumour bed, measured to the metal clips.

Adjuvant medical treatment

Adjuvant medical treatment was prescribed according to the DBCG 89 protocols. Patients with a low risk of recurrence, defined as a tumour less than 5 cm, malignancy grade I for ductal carcinomas in premenopausal women, and node negative, were allocated to the 89a protocol with no adjuvant medical treatment. To the 89a protocol was also allocated hormone receptor negative patients aged 70–74 years with a high risk of recurrence. The 89b protocol has been described in detail elsewhere [6]. Premenopausal, hormone receptor positive patients at high risk of recurrence were randomized to 9 cycles of chemotherapy with Cyclophosphamide, Methothrexate, and 5-Fluouracil (CMF) or ovariectomy. In the 89c protocol high risk, postmenopausal patients with hormone receptor positive or receptor unknown tumours were randomized to tamoxifen 30 mg/day for one year versus for two years versus for six months followed by Megestrolacetate 160 mg/day for another six months [7]. The 89d protocol included high risk patients aged less than 70 years with receptor negative tumours and four treatment arms: 9 series CMF versus 9 series CEF with or without Pamidronate 150 mg twice daily [8].

Patient population

Between 1989 and 1998, 27 688 patients were registered with surgery for breast cancer in the database of the DBCG of whom 5 371 or 19% had a lumpectomy for a carcinoma of the breast. We excluded 450 patients aged more than 75 years at diagnosis, leaving 4 921 patients available for the analysis of overall survival (Table I). For the analysis of recurrence, 639 patients were excluded since they were ineligible for the treatment protocols for the following reasons: patient refusal (n = 115), surgery not according to DBCG guidelines (n = 144), pre-

Table I. Overview of the study population of patients with breast conserving treatment in Denmark, 1989–1998.

Protocol	+ RT*	− RT	RT unknown	No follow-up	No protocol	Total
89-a	2 115	83	50	327	0	2 575
89-b	367	7	0	0	0	374
89-c	548	30	6	0	0	584
89-d	728	21	0	0	0	749
none	0	0	0	0	639	639
Total	3 758	141	56	327	639	4 921

* RT = radiotherapy.

vious malignant disease (n = 106), distant metastases registered within the first two months after surgery (n = 45), bilateral breast cancer (n = 35), misclassification (n = 83), and others (n = 111). In addition, 56 patients were excluded from the analyses due to missing information on radiotherapy. For 327 patients in the low risk group (DBCG 89a), there was no follow-up within the DBCG since one hospital had chosen not to follow these patients, leaving 3 899 patients for analysis in the competing risk setting (Table I). Patients with unknown hormone receptor status (n = 463) were included in the analysis, but treated as a separate category.

With few exceptions, the patients were followed by the hospital departments for 10 years or to first failure in terms of recurrence, another malignancy or death. We identified date, location of recurrences, and end of follow-up without recurrence at 10 years from the database of the DBCG. Information on date of death was retrieved by record linkage to the Central Population Registry which keeps electronically updated data on vital status and on emigration on the entire Danish population. Linkage with the registry is possible by using the civil person registration number, a unique personal identification number given to everybody upon birth or immigration. Follow-up for death was longer than for recurrence, since we had information on deaths occurring after end of follow-up for recurrence. Follow-up ended on October 1, 2005. The median potential follow-up for recurrence was 8.5 years and for death 10.3 years.

Statistical analysis

The data were analysed for overall survival, defined from date of surgery until the date of death irrespective of cause. Curves illustrating overall survival were computed unadjusted using the Kaplan Meier method. Differences between the groups were analysed using the log-rank statistic.

The analysis of loco-regional recurrence, defined as a recurrence in the breast or in the ipsilateral axilla or periclavicular nodes, was performed in a competing risks setting [9], because only the first failure was recorded, leaving distant metastases, contra-lateral breast cancer, other malignant disease and death competing types of failure to loco-regional recurrence. With loco-regional recurrence considered as one type of failure, contra-lateral breast cancer, distant metastases and other malignant disease considered as another type of failure, and death without previous events as a third, there were three distinct types of failure. Univariate curves of the cumulative incidences of the three competing failure types were computed for each of the variables listed in Table II, and equality across groups within the variables was tested for each failure type using the log-rank test statistic. Multivariate analyses of the effects of all the variables on the three competing failure types were performed using the Cox proportional hazard regression model. The appropriateness of the goodness of fit was carried out for each type of event, treating the other types as censorings. The assumption of proportional hazards was verified graphically and found fulfilled in all variables, except for histological grade and type and receptor status. The two parameters were entered into the model as stratification variables. Tests for further time dependencies were performed in the stratified model by entering a time dependent component for each covariate, one at a time.

Since the prescription of adjuvant systemic treatment depends on prognostic factors, i.e. node negative patients may receive no adjuvant systemic treatment; there is an inherent interaction between the effects of prognostic factors and treatment. Consequently, similar analyses in the competing risk setting were performed with our study population divided into a cohort of node negative patients (n = 2 232) with no adjuvant systemic treatment, and a cohort of node positive patients (n = 1 250) who received adjuvant systemic treatment.

Results

Figure 1 shows the overall survival curves for the present material according to the five groups presented in Table I. A 15 year survival of 68.7% (95% CI 66.2 to 71.3%) was observed among 3 758 patients who had breast conserving surgery followed

Table II. Breast conserving treatment in Denmark 1989–1998. Patient and tumour characteristics. Events at end of follow-up (10 years) LR = Locoregional recurrence, DM + OMD = Distant metastases and other malignant disease, including contra-lateral breast cancer.

Variable	Categories	LR		DM + OMD		Death (1. Event)		Censored		Total	
Age at diagnosis	–49	144	*9.8%*	252	*17.2%*	31	*2.1%*	1038	*70.9%*	1465	*37.6%*
	50–59	73	*5.7%*	203	*15.8%*	42	*3.3%*	966	*75.2%*	1284	*32.3%*
	60–74	58	*5.0%*	189	*16.4%*	107	*9.3%*	796	*69.2%*	1150	*29.5%*
Tumour size in mm	1–10	49	*4.9%*	102	*10.2%*	41	*4.1%*	807	*80.8%*	999	*25.6%*
	11–15	87	*7.0%*	193	*15.6%*	54	*4.4%*	907	*73.1%*	1241	*31.8%*
	16–20	73	*8.3%*	167	*19.1%*	36	*4.1%*	599	*68.5%*	875	*22.4%*
	21–	66	*8.4%*	182	*23.2%*	49	*6.3%*	487	*62.1%*	784	*20.1%*
Resection margins	free	226	*6.5%*	566	*16.4%*	157	*4.5%*	2506	*72.5%*	3455	*88.6%*
	not free	20	*10.4%*	40	*20.8%*	14	*7.3%*	118	*61.5%*	192	*4.9%*
	unknown	29	*11.5%*	38	*15.1%*	9	*3.6%*	176	*69.8%*	252	*6.5%*
Receptor status	positive	182	*6.7%*	430	*15.8%*	123	*4.5%*	1982	*73.0%*	2717	*69.7%*
	negative	58	*8.1%*	134	*18.6%*	45	*6.3%*	482	*67.0%*	719	*18.4%*
	unknown	35	*7.6%*	80	*17.3%*	12	*2.6%*	336	*72.6%*	463	*11.9%*
Histology	grade I	78	*6.2%*	149	*11.9%*	46	*3.7%*	978	*78.2%*	1251	*32.1%*
grade of malignancy	grade II	91	*7.3%*	242	*19.5%*	60	*4.8%*	846	*68.3%*	1239	*31.8%*
	grade III	53	*8.7%*	138	*22.6%*	39	*6.4%*	382	*62.4%*	612	*15.7%*
	non ductal	44	*6.7%*	83	*12.6%*	27	*4.1%*	507	*76.7%*	661	*17.0%*
	unknown	9	*6.6%*	32	*23.5%*	8	*5.9%*	87	*64.0%*	136	*3.5%*
Nodes removed	1–9	90	*8.5%*	211	*19.8%*	52	*4.9%*	712	*66.9%*	1065	*27.3%*
	10–	185	*6.5%*	433	*15.3%*	128	*4.5%*	2088	*73.7%*	2834	*72.7%*
No. of positive lymph nodes	0	174	*6.6%*	347	*13.1%*	114	*4.3%*	2014	*76.0%*	2649	*67.9%*
	1–3	75	*7.6%*	202	*20.6%*	49	*5.0%*	656	*66.8%*	982	*25.2%*
	4–	26	*9.7%*	95	*35.5%*	17	*6.3%*	130	*48.5%*	268	*6.9%*
Radiotherapy	no	20	*14.2%*	11	*7.8%*	13	*9.2%*	97	*68.8%*	141	*3.6%*
	yes	255	*6.8%*	633	*16.8%*	167	*4.4%*	2703	*71.9%*	3758	*96.4%*
Total		275	*7.1%*	644	*16.5%*	180	*4.6%*	2800	*71.8%*	3899	*100%*

by radiotherapy. Compared to these patients, survival was not significantly different for the 327 patients with no information on follow-up or for the 56 patients with no information on radiotherapy whereas survival was significantly poorer among the 141 patients not receiving radiotherapy ($p < 0.01$) and the 639 not included in the treatment protocols ($p < 0.01$).

Of the 3 899 patients available for the analysis of recurrence, 38% were less than 50 years old, 26% had tumours $\leq$10 mm in diameter, 79% had ductal carcinomas, 73% had more than 10 lymph nodes removed, 68% were node negative, 89% had free resection margins, and 70% of the tumours were receptor positive (Table II). The treatment included chemotherapy (23%) or tamoxifen (19%) while 96% received adjuvant radiotherapy. Within 10 years of follow-up from diagnosis, 1 099 patients had a first event while 2 800 remained free from recurrence. We observed 275 isolated loco-regional recurrences (192 local and 83 regional), 644 distant metastases or other malignant diseases (408 distant metastases, 148 contralateral breast cancers, and 88 other malignant diseases), and 180 deaths as a first events, corresponding to cumulative incidences of 9.0, 19.9 and 6.0% respectively (Figure 2).

In the multivariate analysis (Table III), the risk of developing a loco-regional recurrence was significantly lower in patients aged more than 50 years at

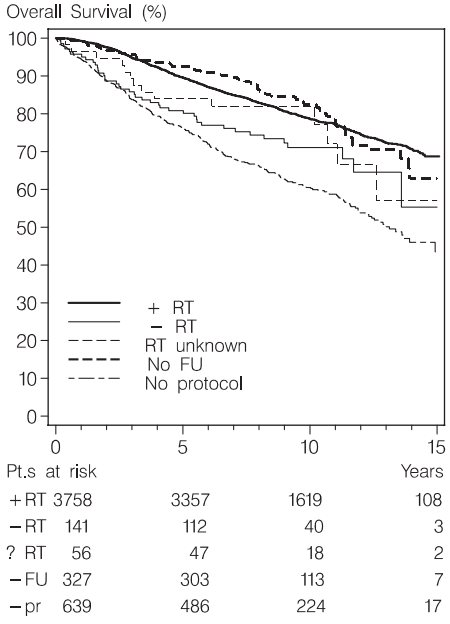

Figure 1. Overall survival (OS) after breast conserving treatment according to allocation and information on follow-up and radiotherapy in Denmark 1989–1998.

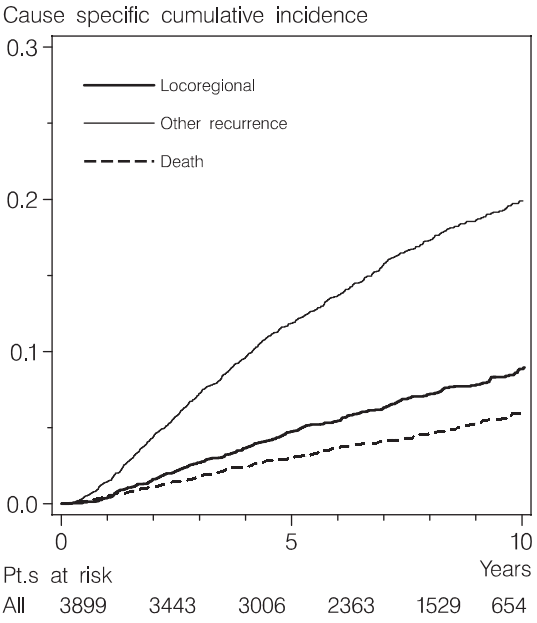

Figure 2. Cumulative incidence of loco-regional recurrences, other recurrences (distant metastases and other malignant disease, including contra-lateral breast cancer) and death as first event after breast conserving treatment in Denmark 1989–1998.

diagnosis, increased significantly with increasing tumour size, and with unclear resection margins (not free or unknown). The risk was also higher among patients with metastases to four or more lymph nodes though the association did not reach formal statistical significance (p = 0.07). Having adjusted for the influence of these prognostic factors, there was a pronounced beneficial effect of adjuvant radiotherapy, those not receiving radiotherapy having a HR of 3.52 (95% CI 2.21–5.61). The risk of developing distant metastases or other malignant disease as a first event was also significantly increased with tumour size and number of positive lymph nodes while no significant associations were found for age, resection margins, or radiotherapy. The risk of death as a first event increased significantly with increasing age at diagnosis, number of positive lymph nodes, and not receiving radiotherapy but was not significantly associated with tumour size or resection margins.

In the separate analyses of node negative and positive patients, the cumulative 10-year risks were 8.6% for loco-regional recurrences, 15.9% for distant metastases or other malignant disease, and 6.3% for death as a first event among 2 232 node negative patients with no adjuvant treatment (Figure 3). Equivalent estimates for the 1 250 node positive patients were 9.9%, 28.2% and 6.5% respectively (Figure 4). In the separate multivariate analyses (Tables IV and V), it became clear that the effect of the resection margins not being free was

Table III. Hazard ratios (HR) with confidence intervals (CI) for loco-regional recurrence, other recurrences (distant metastases and other malignant disease, including contra-lateral breast cancer, DM+OMD) and death as first event in 3 899 women with breast conserving treatment in Denmark, 1989–1998.

	Loco-regional		DM+OMD		Death, 1. event	
Variable	HR	95% CI	HR	95% CI	HR	95% CI
Age	*p = 0.002*		*p = 0.21*		*p < 0.0001*	
−49 yrs.	1		1		1	
50–59 yrs.	0.60	(0.45–0.80)	1.01	(0.83–1.21)	1.64	(1.03–2.62)
60–74 yrs.	0.60	(0.44–0.82)	1.17	(0.97–1.42)	5.52	(3.66–8.31)
Tumour size	*p = 0.02*		*p < 0.0001*		*p = 0.37*	
1–10mm	0.73	(0.51–1.04)	0.75	(0.59–0.96)	0.87	(0.57–1.32)
11–15mm	1		1		1	
16–20mm	1.27	(0.93–1.74)	1.23	(1.00–1.51)	0.99	(0.65–1.51)
21– mm	1.22	(0.87–1.70)	1.40	(1.14–1.72)	1.28	(0.86–1.91)
Resection margins	*p = 0.04*		*p = 0.64*		*p = 0.41*	
free	1		1		1	
not free	1.31	(0.82–2.08)	1.05	(0.76–1.46)	1.38	(0.79–2.41)
unknown	1.60	(1.08–2.38)	0.86	(0.62–1.21)	0.81	(0.41–1.59)
Removed lymph nodes	*p = 0.29*		*p = 0.0005*		*p = 0.49*	
1–9	1		1		1	
10–	1.15	(0.89–1.49)	1.35	(1.14–1.60)	1.12	(0.81–1.56)
Pos. lymph nodes	*p = 0.07*		*p < 0.0001*		*p = 0.05*	
0	1		1		1	
1–3	1.05	(0.80–1.39)	1.54	(1.28–1.84)	1.31	(0.92–1.85)
4–	1.66	(1.08–2.55)	3.12	(2.46–3.96)	1.84	(1.07–3.14)
Radiotherapy	*p < 0.0001*		*p = 0.21*		*p = 0.0002*	
Yes	1		1		1	
No	3.52	(2.21–5.61)	0.68	(0.38–1.25)	2.96	(1.66–5.28)

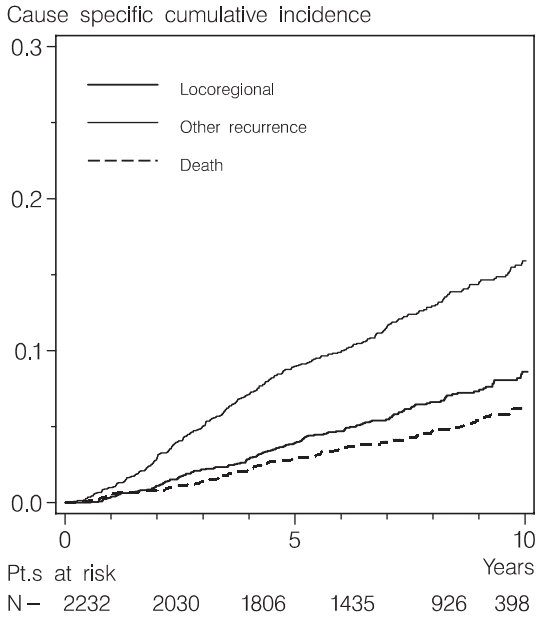

Figure 3. Cumulative incidence of loco-regional recurrences, other recurrences (distant metastases and other malignant disease, including contra-lateral breast cancer) and death as first event after breast conserving treatment among node negative patients with no adjuvant treatment in Denmark 1989–1998.

limited to the risk of a loco-regional recurrence among node negative patients. Otherwise, the effects of the prognostic factors and radiotherapy were similar to the overall analysis (Table III).

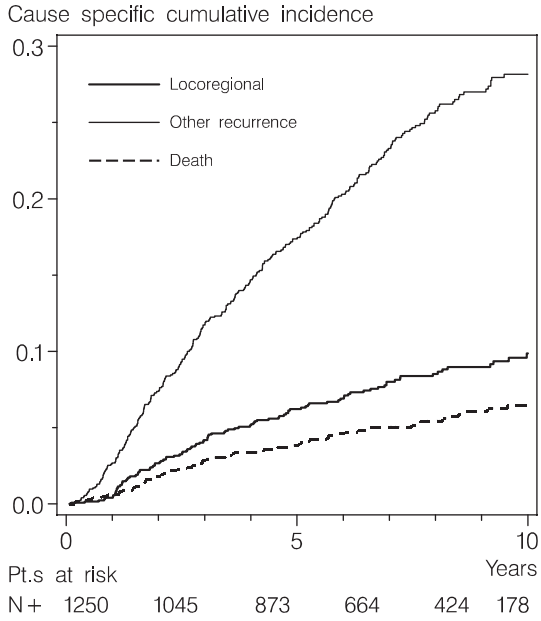

Figure 4. Cumulative incidence of loco-regional recurrences, other recurrences (distant metastases and other malignant disease, including contra-lateral breast cancer) and death as first event after breast conserving treatment in among node positive patients in Denmark 1989–1998.

Discussion

The purpose of the present study was to examine the results of breast conserving treatment in Denmark from the introduction in 1989 through the following ten years with treatment according to the DBCG 89 protocols for the various treatment modalities. Surgery as well as radiotherapy can be regarded as local therapies as opposed to chemotherapy and endocrine therapy which constitute systemic therapy. To assess the effect of local therapies, the most relevant effect measure is local failure, i.e. local or loco-regional recurrences. Similarly, the relevant measure of failure of systemic therapy is distant metastases or death. Our main interest was to address the local control of breast cancer. Since only the first event has been recorded in the DBCG database, we analysed the data in a competing risk setting, estimating the risk of local recurrence as a first event, taking into account all causes. This technique enabled us to compare our results with those of the randomised clinical trials and to separate the effects of the local therapies alone from those combined with systemic therapy.

In the most recent overview analysis by the EBCTCG [10], the cumulative risk of an isolated local recurrence was 10% after 10 years among node negative patients treated with breast conserving surgery plus radiotherapy in a total of 6 097 randomised patients. This agrees well with our estimate of a cumulative risk of a local recurrence as a first event of 8.6% at 10 years in a material of 2 232 node negative patients who did not receive adjuvant systemic therapy but almost all adjuvant radiotherapy. The overview analysis [10] included 1 214 node positive patients randomised to radiotherapy or control with a cumulative risk at 10 years of an isolated local recurrence of 13.1% in the radiotherapy group. In our material of 1 250 node positive patients, the cumulative risk of a local recurrence as a first event was 9.9% at 10 years in patients who received radiotherapy as well as systemic therapy. Although based on small numbers, our population based results on the effect of adjuvant radiotherapy with an approximately 3-fold reduction in risk of a local recurrence is equivalent to the results obtained from the randomised trials.

One of the main conclusions from the overview analysis [10] was that avoidance of four local recurrences would result in avoidance of one breast cancer death after 15 years. In our material, the overall survival after 15 years of follow-up was 69% in 3 758 patients who received radiotherapy and of whom 32% were node positive. The equivalent figure from the overview analysis was an overall survival of 65% at 15 years among those randomised

Table IV. Hazard ratios (HR) with confidence intervals (CI) for loco-regional recurrence, other recurrences (distant metastases and other malignant disease, including contra-lateral breast cancer, DM+OMD) and death as first event in 2 232 node negative breast cancer patients without adjuvant systemic treatment in Denmark, 1989–1998.

	Loco-regional		DM+OMD		Death, 1. event	
Variable	HR	95% CI	HR	95% CI	HR	95% CI
Age	*p=0.0004*		*p=0.07*		*p<0.0001*	
–49 yrs.	1		1		1	
50–59 yrs.	0.50	(0.33–0.74)	1.16	(0.84–1.61)	1.58	(0.68–3.65)
60–74 yrs.	0.49	(0.32–0.74)	1.43	(1.04–1.97)	6.95	(3.29–14.7)
Tumour size	*p=0.002*		*p=0.002*		*p=0.32*	
1–10mm	0.61	(0.39–0.95)	0.64	(0.47–0.87)	0.70	(0.43–1.16)
11–15mm	1		1		1	
16–20mm	1.28	(0.82–1.98)	1.21	(0.89–1.66)	0.85	(0.47–1.51)
21– mm	1.59	(0.99–2.55)	1.16	(0.81–1.64)	1.16	(0.81–1.64)
Resection margins	*p=0.01*		*p=0.40*		*p=0.31*	
free	1		1		1	
not free	1.93	(1.03–3.63)	1.22	(0.69–2.15)	1.58	(0.68–3.66)
Unknown	1.87	(1.11–3.15)	0.73	(0.42–1.26)	0.59	(0.21–1.61)
Removed lymph nodes	*p=0.90*		*p=0.05*		*p=0.63*	
1–9	1		1		1	
10–	1.02	(0.72–1.45)	1.28	(1.00–1.64)	0.90	(0.58–1.39)
Radiotherapy	*p<0.0001*		*p=0.95*		*p=0.0002*	
yes	1		1		1	
No	4.13	(2.19–7.80)	1.03	(0.45–2.33)	4.14	(1.94–8.86)

Table V. Hazard ratios (HR) with confidence intervals (CI) for loco-regional recurrence, other recurrences (distant metastases and other malignant disease, including contra-lateral breast cancer, DM+OMD) and death as first event in 1 250 node positive breast cancer patients receiving adjuvant systemic treatment in Denmark, 1989–1998.

	Loco-regional		DM+OMD		Death, 1. event	
Variable	HR	95% CI	HR	95% CI	HR	95% CI
Age	*p=0.03*		*p=0.92*		*p<0.0001*	
–49 yrs.	1		1		1	
50–59 yrs.	0.60	(0.38–0.95)	0.95	(0.73–1.24)	1.93	(1.00–3.75)
60–74 yrs.	0.56	(0.32–0.99)	1.00	(0.74–1.36)	4.40	(2.34–8.27)
Tumour size	*p=0.61*		*p=0.003*		*p=0.46*	
1–10mm	1.06	(0.52–2.16)	0.97		1.55	
11–15mm	1		1	(0.63–1.52)	1	(0.66–3.66)
16–20mm	1.37	(0.81–2.31)	1.46	(1.07–2.01)	1.57	(0.77–3.18)
21– mm	1.33	(0.78–2.26)	1.67	(1.23–2.26)	1.68	(0.86–3.28)
Resection margins	*p=0.48*		*p=0.48*		*p=0.63*	
free	1		1		1	
not free	0.99	(0.48–2.08)	1.09	(0.72–1.65)	1.44	(0.68–3.11)
unknown	1.53	(0.77–3.04)	0.74	(0.44–1.27)	0.97	(0.34–2.82)
Removed lymph nodes	*p=0.048*		*p=0.005*		*p=0.04*	
1–9	1		1		1	
10–	1.56	(1.00–2.42)	1.45	(1.12–1.88)	1.76	(1.03v3.01)
Positive lymph nodes	*p=0.07*		*p<0.0001*		*p=0.26*	
1–3	1		1		1	
4+	1.53	(0.96–2.44)	2.10	(1.63–2.70)	1.40	(0.78–2.50)
Radiotherapy	*p=0.02*		*p=0.07*		*p=0.046*	
Yes	1		1		1	
No	2.67	(1.21–5.90)	0.40	(0.15–1.08)	2.63	(1.02–6.83)

to radiotherapy in a total of 7 311 patients of whom 17% were node positive. These figures indicate that our treatment strategy may have saved a considerable number of breast cancer deaths over the years.

Numerous studies have addressed the influence of patient and tumour characteristics on the risk of recurrence after breast conserving treatment. Most of the findings in the present study agree well with those of others [11–16], in particular with respect to the higher risk of local recurrence in younger women. The age factor has been of major concern since particularly young women are likely to prefer breast conservation. In a previous analysis of the DBCG material, Kroman et al. [17] found a 5-fold higher risk of local recurrence in the breast within 5 years of diagnosis among women aged less than 35 years compared with women aged 45–49 years. Despite this, no overall difference in 10 year survival was observed among women who received breast conserving treatment compared with women who underwent radical mastectomy regardless of age at diagnosis before age 50.

The multivariate analyses showed that the effect of the resection margins not being free was limited to the risk of developing a loco-regional recurrence as a first event among node negative patients. Patients with unknown margin status had a recurrence rate similar to patients with positive margins indicating that these patients did not receive optimal surgery. The findings on resection margins agree well with those of others [18,19]. Radiotherapy should not compensate for insufficient surgery, but studies indicate that radiotherapy can reduce the risk of local relapse among selected patients with close or positive margins [20,21]

The strength of the present study is that the results derive from an entire population where the intent was to apply a well defined treatment programme over a period of 10 years. We were able to account for all patients and follow them to death through our population-based registries. The overall survival of patients not treated according the DBCG protocols was significantly poorer than that of the patients who were included and treated according to the protocols. Reviewing the criteria for protocol exclusion, the poorer survival is likely to be explained by some of the patients having distant metastases at diagnosis and others suffering from medical conditions with a high risk of death from other causes than breast cancer. Patients with severe co-morbidities have been shown to have a significantly poorer survival than patients without co-morbidity even adjusting for age and stage [22]. However, it is unlikely that the exclusion of these patients should have affected the comparison of our results with those of randomised clinical trials, since such patients would also be excluded from the randomised clinical trials.

Conclusion

The present study confirms that results equivalent to those from randomised trials can be obtained when breast conserving treatment is applied as a standard treatment in an unselected population like the Danish.

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