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Cosmetic Outcome and Breast Morbidity in Breast-Conserving Treatment

Results from the Danish DBCG-82TM National Randomized Trial in Breast Cancer

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A total of 266 recurrence-free breast cancer patients from the randomized DBCG-82TM breast conservation trial were called in for a follow-up investigation to study the impact of surgical and radiation treatment factors on the cosmetic and functional outcome after breast conservation. The patients were interviewed and examined after a median follow-up time of 6.6 years, and 194 of them (73%) regarded the cosmetic result as excellent or good. Morbidity assessments showed that breast fibrosis, skin telangiectasia, and breast retraction were significantly associated with a less satisfactory cosmetic result. On univariate analysis, it was found that treatment with a direct anterior electron field produced more morbidity and inferior cosmetic outcomes compared with tangential photon treatment, while increasing breast size was associated with increased breast retraction and breast fibrosis. Treatment characteristics that emerged as independent prognostic factors of a poor cosmetic outcome on multivariate analysis were the use of a direct anterior electron field (OR = 2.15, CI 1.25–3.70) and adjuvant systemic therapy (OR = 2.13, 1.22–3.71). A significant but relatively low level of concordance was found between the patients' and the clinician's evaluations of cosmetic results but self-assessments of breast morbidity and psychological distress were significantly related to the observed treatment-induced side effects after breast-conserving treatment, indicating that subjective perceptions and observations as reported by the patients are relevant for the identification of treatment factors that impact on normal tissue reactions.

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Breast-conserving treatment (BCT) for breast cancer has been shown to obtain identical survival figures to those for mastectomy in large, randomized, multicenter trials, including the Danish Breast Cancer Cooperative Group's DBCG-82TM trial (1–4). Based on these results, BCT has now been accepted as a relevant treatment option in breast cancer patients. However, patients may suffer from long-term adverse reactions affecting cosmesis and functional outcome in the breast and shoulder that could be related to both surgical procedures and radiation techniques. To throw light on some of the factors that may impact on late effects after BCT, a follow-up study was undertaken by including patients from a randomized breast conservation trial (DBCG-82TM protocol).

MATERIAL AND METHODS

The protocol design has been described elsewhere (2, 4). Briefly, between 1982 and 1990 a total of 905 patients entered a randomized trial to compare breast conservation therapy with mastectomy (DBCG-82TM protocol). Four hundred and fifty patients received BCT consisting of a complete tumor excision, axillary dissection and radiation treatment according to the protocol guidelines. No difference in recurrence-free survival or overall survival was

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observed between the two groups (2), which has been confirmed in a recent update (4). Only patients in the BCT arm are reported here.

Surgery

The surgical breast-conserving procedure consisted of either a segmental resection of peripherally located tumors or a complete excision of tumors with central location. Early in the trial, a radial incision was recommended. However, this was later abandoned in favor of a concentric incision. Tumor-free margins at gross examination were assured in both procedures and later confirmed microscopically. In 7% of cases, microfoci of cancer cells were demonstrated in specimen margins. Axillary dissection was generally performed through a separate transverse incision with removal of the lymph nodes including levels I and II, but some patients with tumor in the upper lateral quadrant had 'en bloc' dissection of the axillary contents and the breast segment.

Radiation treatment

Radiotherapy was prescribed to the residual breast as a median target absorbed dose of 50 Gy delivered in 25 fractions, 5 fractions per week over a period of 5 weeks, but in one institution 26 patients (10%) received 48 Gy in 22 fractions, 4 fractions per week over a period of 5.5 weeks.

The protocol recommended supervoltage (6–10 MV) radiotherapy with tangential fields to the entire breast with a margin of at least one centimeter to the residual breast tissue. Wedges or tissue compensators were used to minimize dose inhomogeneity. Individual breast outlines and dose plans were obtained with or without CT scans according to the standard planning policy in the different participating centers.

A boost of minimum 10 Gy to the surgical scar and primary tumor bed was delivered as a daily fraction of 2 Gy with either tangential photons or a single electron field.

In three of the participating departments, it was perceived that treatment complications to the underlying lung could be reduced by using electron beam techniques with wax compensation. For this reason the treatment protocol allowed a single direct anterior electron field (6–20 MeV) to be used with a prescribed median absorbed dose of 50 Gy and the 85% isodose curve at the pleural surface as assessed by ultra sonography.

High-risk patients (tumor diameter >5 cm, and/or invasion to the skin or pectoral facia, and/or involvement of axillary lymph nodes) received an additional direct anterior photon field (6–16 MV) to cover the regional lymph nodes in the axilla, supraclavicular fossa, infraclavicular region, and internal mammary chain. Also, 18% of low-risk patients (31/172) received axillary radiotherapy if an en bloc dissection of the axilla/breast segment had been performed. The prescribed dose was 50 Gy in 25 fractions. A posterior boost was applied if the maximum absorbed dose exceeded 55 Gy.

Adjuvant systemic treatment

High-risk patients, as described above, were offered adjuvant systemic treatment in addition to locoregional radiotherapy. Premenopausal patients ($n=70$) were given sequential CMF, while postmenopausal patients received tamoxifen 30 mg for 12 months ($n=27$). CMF consisted of eight cycles of cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2, and 5-FU 600 mg/m^2, all given intravenously on day one every 4 weeks.

Follow-up and outcome variables

From the original group of 450 patients undergoing BCT, a total of 343 women who were recorded as recurrence-free and alive were invited to participate in the study. This included a single follow-up interview with a study-specific questionnaire in order to obtain self-assessments of several cosmetic and functional outcome measures as well as to obtain information on body perception and the need for reconstructive surgery. In addition, standard breast photography and a clinical examination were performed. The interview and the examination were conducted by the same oncologist after a median follow-up time of 6.6 years (range 3.5–10.5 years).

Of the patients invited to join the study, 266 (78%) agreed to take part. Data on individual patient treatments that had been reported to the DBCG Secretariat from the participating centers, such as tumor and lymph node characteristics, the administration of systemic treatment, and radiation treatment data, were crosschecked for any breaches in the protocol recommendations. In case of disagreements, patient records from the specific departments were surveyed in order to correct errors.

Surgery was performed in 21 departments (one to 83 patients), whereas radiotherapy was carried out in 6 institutions. No information was available to the observer at the time of the clinical investigation concerning the extent of surgery, the type of adjuvant treatment, or the specific radiation treatment techniques employed.

The oncologist and the patient scored the cosmetic outcome independently using a 4-point ordinal scale, as defined in Table 1, with examples presented in the Fig. 1. In addition to cosmetic outcome, several subjective and objective outcome measures confined to the breast were assessed, and various patient-related or treatment-related factors that might impact on the outcome were recorded (Table 1 and Table 2). Generally, these assessments were scored on an ordinal 4-point scale as grade 0 to grade 3 (none, mild, moderate, severe) including body image as described by Sneeuw et al. (5). Breast size was categorized as A, B, C, or D. Breast retraction (asymmetry) was assessed from the displacement of the nipple, i.e., from the change in jugular-nipple distance. The desire for plastic

Table 1

Treatment and demographic factors analyzed with respect to cosmetic and functional outcome

Outcome measures (dependent variables)	Treatment factors (explanatory variables)	Patient factors (explanatory variables)
Cosmetic outcome Clinician's assessment Excellent: no asymmetry, normal contour, and no skin changes in comparison with the contra-lateral untreated breast; Good: slight asymmetry with or without slight contour or skin changes; Fair: distinct asymmetry with or without distinct contour or skin changes; Poor: considerable asymmetry with or without substantial contour or skin changes.	Target absorbed dose (Gy) Tangential photons Direct electron foeld Beam energy (MV) Boost dose (Gy) Nipple excision (yes/no) Breast scar (cm)	Age (years) Adjuvant systemic treatment (yes/no) Breast size (cup A, B, C, D) Tumor size (mm) Tumor location (upper/lower quadrants) Collagen vascular disease (yes/no)
Patient's assessment 0. Excellent 1. Good 2. Fair 3. Poor		
Objective changes Dyspigmentation* Telangiectasia 0. None 1. $<1/cm^2$ 2. 1–$4/cm^2$ 3. $>4/cm^2$		
Breast fibrosis 0. None 1. Barely palpable, increased density 2. Definite increased density and firmness 3. Very marked density, retraction or fixation		
Breast retraction (jugular-nipple distance, cm) Breast edema*		
Patient-reported changes Breast pain* Sensibility* Consumption of analgesics* Body image* Change in clothing habits (yes/no) Need for plastic surgery (yes/no)		

* 0 = none; 1 = mild; 2 = moderate; 3 = severe.

surgery, as reported by the patients themselves, and any pre-existing disease that previously had been linked to adverse reactions to radiotherapy were also recorded (see references (6, 7)). Functional outcome related to the axilla and arm is described elsewhere (8).

Early during the first interviews, it was recognized that a substantial number of patients were distressed because clothing habits were compromised as a consequence of adverse skin reactions and a change of the breast contour. For this reason, a further variable was subsequently incorporated into the questionnaire, namely patient-reported 'change in clothing habits' (n = 203).

STATISTICS

Chi-square analysis was used for univariate comparisons of frequencies and the Mann–Whitney rank sum test was applied to describe differences in ordinal variables between two groups.

Univariate and stepwise, multivariate logistic regression analyses were used to identify factors impacting on cosmetic outcome and breast functioning. For this type of analysis, cosmetic outcome was dichotomized as excellent/good or fair/poor. The explanatory covariates shown in Table 1 were generally categorized, but radiation treatment dose, breast scar length, tumor size, and age were entered in the models either with their absolute values or as categorical values. Adjuvant systemic treatment was included in the regression models as a binary variable ('no/yes') corresponding to low/high-risk groups irrespective of the specific systemic treatment (CMF/tamoxifen). Differences were described in terms of odds ratios (OR) and 95% confidence intervals (CI) were estimated. The level of concordance between subjective

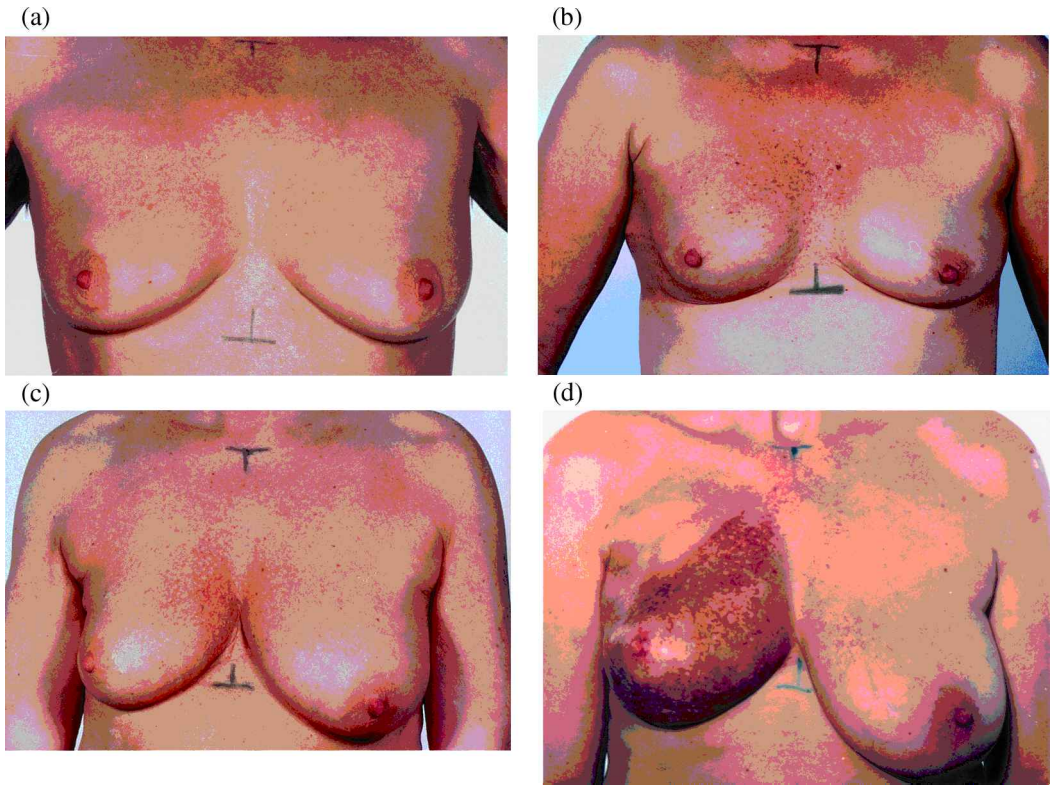

Fig. 1. Examples of clinical scores using a 4-point ordinal scale. Scores were obtained from an assessment of breast shape as well as skin changes. Skin marks were used for subsequent breast retraction measurements. a) excellent cosmetic result (score = 0), b) good cosmetic result (score = 1) with slight asymmetry and slight telangiectasia, c) fair outcome (score = 2) with distinct asymmetry, grade 2 telangiectasia, and grade 2 breast fibrosis, d) poor outcome (score = 3) with considerable breast retraction ≥ 10%, severe breast fibrosis, telangiectasia and dyspigmentation.

and objective scoring was described using Cohen's kappa. A two-sided p-value of less than 0.05 was considered significant.

RESULTS

Demographic data

Patient characteristics are listed in Table 2. The patients received a median target absorbed dose of 50.0 Gy (5th percentile to 95th percentile: 46.5–52.0 Gy) with either tangential photons (160 patients) or electrons (106 patients). Boost doses to the tumor bed were given to 213 patients (80%), 203 of them with electrons.

Cosmetic outcome—general results

The cosmetic scores and breast morbidity scores are shown in Table 3. After a median follow-up time of 6.6 years, the cosmetic outcome was reported as excellent/good by 73% of the patients (195 out of 266) compared with 47% (125 out of 266) as assessed by the oncologist ($p < 0.001$). When the individual scores between the patients and the observer were compared, a significant but low level of concordance was found ($\kappa = 0.18$, $p < 0.001$) (Table 4).

Cosmetic outcome—relation to treatment technique

To identify the treatment characteristics or patient factors that affected cosmetic outcome, and whether complication patterns were confined to a specific treatment, univariate and multivariate analyses were done using the explanatory variables listed in Table 1.

Univariate analysis showed that treatment with tangential photons was superior to a direct electron field, i.e., 78% of the patients reported an excellent/good outcome after photon treatment compared with 66% of patients receiving electrons ($p = 0.04$). The corresponding observations by the clinician showed 55% excellent/good cosmetic scores vs. 35% in favor of photons ($p = 0.002$).

Treatment with a direct anterior electron field also caused significantly more grade 2 and grade 3 late reactions compared to treatment with tangential photons, i.e., grade ≥ 2 dyspigmentation occurred in 32% vs. 9% ($p < 0.001$), grade ≥ 2 telangiectasia in 42% vs. 3% ($p < 0.001$), and grade ≥ 2 breast fibrosis in 29% vs. 18% ($p < 0.05$) (Table 3).

The target-absorbed dose to the breast was not an important factor for an adverse cosmetic outcome over the range of doses applied here, irrespective of whether clinician scores ($p = 0.74$) or patient assessments were used ($p = 0.27$),

Table 2

Patient and treatment characteristics of 266 women undergoing BCT

	All patients n = 266	Photons n = 160	Electrons n = 106
Age[a] (median, range)	50 (24–70)	51 (30–69)	48 (24–70)
Menopausal status			
Premenopausal	170 (65%)	97 (61%)	73 (69%)
Postmenopausal	96 (35%)	63 (39%)	33 (31%)
Nodes removed (median, range)	7 (0–22)	6 (0–21)	9 (0–22)
Node-positive	85 (32%)	48 (30%)	35 (33%)
Tumor size (median, mm)	15 (1-80)		
>2 cm	50/254 (20%)	34/157 (22%)	16/97 (16%)
Adjuvant therapy			
None	172 (65%)	109 (68%)	63 (59%)
CMF	67 (25%)	33 (21%)	34 (32%)
Tamoxifen	27 (10%)	18 (11%)	9 (9%)
Absorbed dose, breast (Gy) (5th to 95th percentile)	50.0 (46.5–52.0)	50.0 (47.0–50.0)	50.0 (46.3–54.0)
Boost	213 (80%)	127 (79%)	86 (81%)
Boost dose (Gy) (5th to 95th percentile)	9.2 (0.0–24.0)	9.8 (0.0–20.0)	8.3 (0.0–14.0)
Axillary radiation treatment	121 (46%)	61 (38%)	60 (57%)
Follow-up (median years, range)	6.6 (3.5–10.5)	6.8 (3.5–10.4)	6.3 (3.8–10.5)

Abbreviations: BCT = breast-conserving treatment; CMF = cyclophosphamide, methotrexate, 5-FU.
[a] Years at the time of treatment.

nor did boost treatment have any significant effect on cosmesis. Patients receiving electron treatment were analyzed with respect to the fractionation schedule, 4 vs. 5 fractions per week, but no effect of dose per fraction could be discerned.

Patients receiving adjuvant systemic treatment had poorer cosmetic results compared with those who had no systemic treatment ($p = 0.004$). No variables other than electron radiotherapy and systemic treament were found to impact on cosmesis in the univariate analyses, but breast size (larger breasts), tumor size (larger tumors) and age (younger age) were of borderline significance for a fair/poor cosmetic outcome in relation to both observer and patient assessments. Therefore, these covariates were also entered in the multivariate models.

Radiation treatment per se did not influence breast retraction, but breast size, tumor location in the upper quadrants as well as tumor size were all significantly associated with the development of breast retraction on univariate logistic regression, i.e., patients with larger breasts ($p = 0.0009$) and larger tumors ($p = 0.04$) tended to have more breast retraction.

Breast edema of any grade was observed in only six patients (2%).

Cosmetic outcome—observer scores and multivariate analysis

On multivariate analysis, treatment with a direct electron field and also adjuvant systemic treatment emerged as independent predictive factors of a fair/poor cosmetic result as scored by the clinician, OR = 2.15 (CI 1.25–3.70, $p = 0.006$) and OR = 2.13, (CI 1.22–3.71, $p = 0.008$), respectively. Since adjuvant treatment might be considered a surrogate variable for high-risk patients, of whom 96% had received regional lymph node irradiation, systemic therapy was omitted from the model in a second step. In this model, cosmetic outcome was still significantly associated with electron radiotherapy, OR = 2.3 (CI 1.4–4.1, $p = 0.002$), as was breast size, OR = 1.33 (CI 1.00–1.81, $p = 0.05$) while age (younger) and tumor size (larger) almost reached statistical levels of significance, $p = 0.09$ and $p = 0.06$, respectively.

Since treatment with single-field electrons is generally characterized by some decree of dose inhomogeneity compared with tangential photon treatment, cosmetic outcome was evaluated in a separate multivariate analysis of the 160 patients who were treated tangentially. This also showed a significant effect of increasing breast size on adverse cosmetic outcome, OR 1.73 (CI 1.17–2.56, $p = 0.006$).

Cosmetic outcome—patient assessments

On examining the patients' ratings of cosmetic outcome, systemic therapy was still found to be a significant explanatory factor of an unfavorable outcome on multivariate analysis OR = 2.0 (CI 1.1–3.7, $p = 0.02$) while the OR associated with a direct electron field was 1.6 (0.90–3.0, $p = 0.11$). In this model, age at the time of treatment was found to be an independent predictor of a poorer cosmetic outcome, OR = 0.97 (CI 0.93–1.00, $p = 0.04$), that is, younger women tended to be more dissatisfied with the cosmetic results than older women.

Table 3

Relationship between treatment factors and observer scores and patient reports regarding cosmetic outcome and breast morbidity after BTC

Observed changes	All, n = 266 n (%)	Photons (%)	Electrons (%)	Dose (Gy)		Boost		Systemic adjuvant treatment	
				<50 (%)	≥50 (%)	No (%)	Yes (%)	No	Yes
Dyspigmentation									
0. None	158 (60)	**123 (77)**	**35 (33)**	35 (52)	123 (62)	28 (52)	130 (62)	**118 (69)**	**40 (43)**
1. Mild	58 (22)	**21 (13)**	**37 (35)**	13 (19)	45 (23)	14 (26)	44 (21)	**29 (17)**	**29 (31)**
2. Moderate	45 (17)	**15 (9)**	**30 (28)**	19 (28)	26 (13)	12 (22)	33 (16)	**24 (14)**	**21 (23)**
3. Severe	4 (1)	**0 (0)**	**4 (4)**	1 (1)	3 (2)	0 (0)	4 (2)	**1 (1)**	**3 (3)**
Telangiectasia									
0. None	160 (62)	**138 (86)**	**22 (21)**	36 (53)	124 (63)	30 (56)	130 (61)	**115 (67)**	**45 (48)**
1. <1/cm^2	57 (21)	**17 (11)**	**40 (38)**	17 (25)	40 (20)	13 (24)	44 (21)	**34 (20)**	**23 (25)**
2. 1–4/cm^2	22 (8)	**4 (2)**	**18 (17)**	5 (7)	17 (9)	3 (6)	19 (9)	**11 (6)**	**11 (12)**
3. > 4/cm^2	27 (10)	**1 (1)**	**26 (24)**	10 (15)	17 (9)	8 (15)	19 (9)	**12 (7)**	**15 (16)**
Breast fibrosis									
0. None	130 (49)	**92 (58)**	**38 (36)**	32 (47)	98 (50)	31 (57)	99 (47)	**100 (58)**	**30 (32)**
1. Mild	76 (29)	**39 (24)**	**37 (35)**	17 (25)	59 (30)	10 (19)	66 (31)	**48 (28)**	**28 (30)**
2. Moderate	43 (16)	**24 (15)**	**19 (18)**	13 (19)	30 (15)	7 (13)	36 (17)	**19 (11)**	**24 (26)**
3. Severe	17 (6)	**5 (3)**	**12 (11)**	6 (9)	11 (6)	6 (11)	11 (5)	**5 (3)**	**12 (13)**
Breast edema									
No	258 (98)	154 (98)	104 (98)	68 (100)	190 (97)	52 (98)	206 (98)	168 (99)	90 (96)
Yes	6 (2)	4 (2)	2 (2)	0 (0)	6 (3)	1 (2)	5 (2)	2 (1)	4 (4)
Breast retraction (jugular-nipple distance)									
< 10%	157 (63)	90 (60)	67 (67)	36 (55)	121 (65)	31 (62)	126 (63)	109 (67)	48 (55)
≥ 10%	94 (37)	61 (40)	33 (33)	29 (45)	65 (35)	19 (38)	75 (37)	54 (33)	40 (45)
Cosmetic outcome									
Clinician's assessment									
0. Excellent	29 (11)	**23 (14)**	**6 (6)**	9 (13)	20 (10)	10 (18)	19 (9)	**23 (13)**	**6 (6)**
1. Good	96 (36)	**65 (41)**	**31 (29)**	22 (32)	74 (37)	16 (30)	80 (38)	**69 (40)**	**27 (29)**
2. Fair	93 (35)	**54 (34)**	**39 (37)**	22 (32)	71 (36)	20 (37)	73 (34)	**55 (32)**	**38 (40)**
3. Poor	48 (18)	**18 (11)**	**30 (28)**	15 (22)	33 (17)	8 (15)	40 (19)	**25 (15)**	**23 (25)**
Patient's assessment									
0. Excellent	99 (37)	**72 (45)**	**27 (25)**	26 (38)	73 (37)	19 (35)	80 (38)	**69 (40)**	**30 (32)**
1. Good	96 (36)	**53 (33)**	**43 (41)**	18 (27)	78 (39)	18 (33)	78 (37)	**66 (38)**	**30 (32)**
2. Fair	51 (19)	**25 (16)**	**26 (25)**	16 (24)	35 (18)	15 (28)	36 (17)	**32 (19)**	**19 (20)**
3. Poor	20 (8)	**10 (6)**	**10 (9)**	8 (12)	12 (6)	2 (4)	18 (8)	**5 (3)**	**15 (16)**

	Age (years)		Breast size		Tumor location		T-size	
	≤ 50 (%)	> 50 (%)	A/B (%)	C/D (%)	Upper quadrants	Inferior quadrants	< 2 cm (%)	≥ 2 cm (%)
Dyspigmentation								
0. None	**64 (48)**	**94 (72)**	46 (61)	112 (59)	111 (57)	42 (67)	95 (57)	62 (72)
1. Mild	**39 (29)**	**19 (15)**	18 (24)	40 (21)	43 (22)	14 (22)	43 (26)	10 (12)
2. Moderate	**28 (21)**	**17 (13)**	11 (15)	34 (18)	40 (20)	5 (8)	27 (16)	12 (14)
3. Severe	**3 (2)**	**1 (1)**	0(0)	4 (2)	2 (1)	2 (3)	2 (1)	2 (29)
Telangiectasia								
0. None	73 (54)	87 (66)	51 (68)	109 (57)	112 (57)	43 (68)	95 (57)	62 (71)
1. <1/cm^2	34 (25)	23 (18)	12 (16)	45 (24)	44 (22)	13 (21)	43 (26)	11 (13)
2. 1–4/cm^2	12 (9)	10 (8)	7 (9)	15 (8)	19 (10)	3 (5)	13 (8)	6 (7)
3. > 4/cm^2	16 (12)	11 (8)	5 (7)	22 (11)	22 (11)	4 (6)	16 (10)	8 (9)
Breast fibrosis								
0. None	66 (49)	64 (49)	**48 (64)**	**82 (43)**	92 (47)	34 (54)	87 (52)	39 (45)
1. Mild	44 (33)	32 (24)	**18 (24)**	**58 (30)**	54 (27)	21 (33)	47 (28)	27 (31)
2. Moderate	19 (14)	24 (18)	**9 (12)**	**34 (18)**	37 (19)	5 (8)	25 (15)	14 (16)
3. Severe	6 (4)	11 (8)	**0 (0)**	**17 (9)**	14 (7)	3 (5)	8 (5)	7 (8)

Table 3 (Continued)

	Age (years)		Breast size		Tumor location		T-size	
	≤ 50 (%)	> 50 (%)	A/B (%)	C/D (%)	Upper quadrants	Inferior quadrants	< 2 cm (%)	≥ 2 cm (%)
Breast edema								
No	131 (97)	127 (98)	74 (99)	184 (97)	191 (97)	61 (98)	162 (98)	84 (97)
Yes	4 (3)	2 (2)	1 (1)	5 (3)	5 (3)	1 (2)	3 (2)	3 (3)
Breast retraction (jugular-nipple distance)								
< 10%	82 (63)	75 (62)	**53 (75)**	**104 (58)**	**105 (56)**	**47 (84)**	100 (64)	50 (60)
≥ 10%	48 (37)	46 (38)	**18 (25)**	**76 (42)**	**84 (44)**	**9 (16)**	56 (36)	34 (40)
Cosmetic outcome								
Clinician's assessment								
0. Excellent	13 (10)	16 (12)	10 (13)	19 (10)	23 (12)	5 (8)	16 (10)	11 (13)
1. Good	49 (36)	47 (36)	30 (40)	66 (34)	70 (36)	22 (35)	63 (38)	29 (33)
2. Fair	50 (37)	43 (33)	21 (28)	72 (38)	67 (34)	26 (41)	65 (39)	27 (31)
3. Poor	23 (17)	25 (19)	14 (19)	34 (19)	37 (19)	10 (16)	23 (14)	20 (23)
Patient's assessment								
0. Excellent	46 (34)	53 (41)	26 (35)	73 (38)	68 (34)	29 (46)	59 (35)	37 (43)
1. Good	48 (36)	48 (37)	26 (35)	70 (37)	76 (39)	17 (27)	67 (40)	26 (30)
2. Fair	31 (23)	20 (15)	17 (23)	34 (18)	35 (18)	16 (25)	32 (20)	14 (16)
3. Poor	10 (7)	10 (8)	6 (8)	14 (7)	18 (9)	1 (2)	8 (5)	10 (12)

Bold figures indicate significant differences on χ^2 or Mann–Whitney U tests.

To test whether the assessment criteria laid down in the clinician's objective scoring system of cosmetic outcome (skin reactions, retraction, etc.) also formed the basis for the patients' judgements, univariate analyses were performed to describe the relation between physical breast changes and an unfavorable outcome as expressed by the patients (Table 5). This showed that women reporting a less satisfactory cosmetic result had significantly more breast fibrosis, skin telangiectasia, dyspigmentation and breast retraction, and thus a good agreement was found between patient evaluations and the breast reactions that were used as objective scoring criteria by the clinician.

Other patient-perceived outcome measures

Constant or frequent breast pain occurred in 35 patients (13%). Half of them (n = 18) had no additional pain from the axilla, shoulder, or arm, and therefore these patients could be evaluated for a consequential use of analgesics because of breast pain. Only one patient required analgesics and then just occasionally. In the whole study group, less than 2% used analgesics on a regular basis for any pain. On looking at the treatment and patients' characteristics in Table 1, a multivariate analysis failed to discern any specific factor that was responsible for the occurrence of breast pain. Reduced breast sensibility and breast paresthesia of any degree were reported in 15% and 3%, respectively.

Before the interview, 6% of the women had undergone reconstructive surgery for either breast asymmetry, breast retraction, or skin reactions. This was more common in women who reported only a fair/poor response ($p < 0.0001$). Another 15% of all women wished to undergo reconstructive surgery or had serious thoughts about it, also significantly more in the group with a fair/poor self-assessment score.

Twenty-one women (8%) expressed a negative change in body image after treatment and obviously a higher proportion of these women reported a fair/poor cosmetic outcome compared with the excellent/good outcome group ($p < 0.0001$). However, none of the independent variables described above which impacted on cosmetic outcome (electrons, systemic treatment, breast size, and age) was found to affect body image, as assessed by multivariate regression analysis. In a further investigative analysis we looked at morbidity patterns of the breast for any associations with body image. From this analysis, breast retraction (OR 6.3 (CI 2.0–20), $p = 0.002$), skin telangiectasia (OR 1.65 (CI 1.04–2.6), $p = 0.03$), and tumors confined to inferior quadrants (OR 6.8 (CI 2.0 – 23), $p = 0.002$) were found to be associated with body perception.

Table 4

Concordance between patient and observer scores of cosmetic outcome after breast-conserving treatment. Only a modest agreement was found ($\kappa = 0.18$, $p < 0.001$)

Clinician	Patient self-assessment				
	Excellent	Good	Fair	Poor	Total
Excellent	25	4	0	0	29
Good	43	39	14	0	96
Fair	26	40	23	4	93
Poor	5	13	14	16	48
Total	99	96	51	20	266

Table 5

Relationship between breast changes and cosmetic outcome as scored by the patients and the clinician. Univariate analysis

Observed breast changes	Cosmetic outcome					
	Patient assessments			Clinician's assessments		
	0/1 (%)	2/3 (%)	p-values	0/1 (%)	2/3 (%)	p-values
Dyspigmentation			0.05			<0.001
0. None	124 (64)	34 (49)		91 (73)	67 (48)	
1. Mild	39 (20)	19 (27)		20 (16)	38 (27)	
2. Moderate	30 (15)	15 (21)		14 (11)	31 (22)	
3. Severe	2 (1)	2 (3)		0 (0)	4 (3)	
Telangiectasia			0.02			<0.001
0. None	126 (65)	34 (48)		93 (74)	67 (48)	
1. $<1/cm^2$	41 (21)	16 (22)		25 (20)	32 (23)	
2. $1–4/cm^2$	12 (6)	10 (14)		6 (5)	16 (11)	
3. $>4/cm^2$	16 (8)	11 (16)		1 (1)	26 (18)	
Breast fibrosis			0.03			<0.001
0. None	102 (53)	28 (39)		77 (62)	53 (38)	
1. Mild	57 (29)	19 (27)		33 (26)	43 (30)	
2. Moderate	26 (13)	17 (24)		13 (10)	30 (21)	
3. Severe	10 (5)	7 (10)		2 (2)	15 (11)	
Breast edema			0.41			0.78
No	190 (98)	68 (96)		122 (98)	136 (98)	
Yes	3 (2)	3 (4)		31 (2)	3 (2)	
Breast retraction			0.01			<0.001
< 10%	124 (67)	33 (49)		96 (78)	61 (48)	
≥ 10%	60 (33)	34 (51)		27 (22)	67 (52)	
Nipple excision			0.99			0.009
No	185 (95)	68 (96)		124 (99)	129 (91)	
Yes	10 (5)	3 (4)		1 (1)	12 (9)	
Tumor in			0.88			0.65
Upper quadrants	144 (76)	53 (76)		93 (78)	104 (74)	
Inferior quadrants	46 (24)	17 (24)		27 (22)	36 (26)	
Scar (continuous variable, cm)			0.61			0.84

Twenty-one percent of the women felt that a change in clothing habits was needed because of obvious skin changes and breast retraction, and again, a significantly higher proportion of these women were found in the fair/poor group ($p < 0.0001$). In this respect, tattoo marks were also noted as unsightly.

DISCUSSION

Study population

The objective of the present investigation was to characterize the impact of combined surgery and radiation treatment as well as host factors on the cosmetic outcome and breast morbidity after breast-conserving therapy. The data describe the results from a national randomized trial as opposed to a single-institution report. The data were collected from 21 surgical departments and 6 radiotherapy centers throughout Denmark. More than three-quarters of the recurrence-free patients on the DBCG-82TM trial participated in this follow-up study. Since more than 95% of women with newly diagnosed breast cancer in Denmark are registered in the DBCG treatment protocols or follow-up programs (9), we believe that the results presented here are representative of the treatment quality that can be expected in a large geographical region.

Latency and late reactions

The incidence of late breast reactions in our study was high compared with that in other studies. One evident explanation for this is the fairly long observation time in this study compared with the observation time in other clinical trials. It has previously been found that cosmetic outcome deteriorates over time (10–15). This is also in line with the data derived from a pilot study preceding the present investigation, which showed that 63 women out of 73 (86%) scored their cosmetic outcome as excellent/good within the first years of observation and that as many as 49% of these patients rated their cosmetic results one or

two grades below the initial score after another two years of observation time (data not shown).

Late-occurring, normal tissue reactions to radiotherapy, such as subcutaneous fibrosis, seem to stabilize within 4 years (16). A comparable result was found in a subset of the present study population who underwent consecutive mammographies (17). This demonstrated that skin thickness increased over the initial 6–12 months after breast-conserving therapy and did not reach a steady thickness level before 3 to 4 years after completion of treatment. The relatively long observation time in this study thus explains the low incidence of observed breast edema (2%).

It is essential to consider the follow-up time in clinical studies in order to characterize the impact of various treatment factors on long-term outcome. Variable observation times make comparisons between different studies difficult and, consequently, it is difficult to draw definitive conclusions. In the present study, the median follow-up time was 6.6 years, which indicates that a relevant observation time was employed to score treatment morbidity properly and derive firm conclusions.

Radiation treatment techniques

The high incidence of breast changes in this study could primarily be ascribed to a poor radiation technique employing electron treatment to the entire breast in a large proportion of the women. The cosmetic outcome after electron treatment was clearly inferior compared with that after tangential photon fields as seen from both the patients' and the physician's ratings, which reflected the increased degree of dyspigmentation, skin telangiectasia, and breast fibrosis after electron treatment. However, breast retraction also had a significant impact on cosmesis, but the degree of retraction was not significantly associated with electron treatment. This is explained by the fact that breast retraction is related to the surgical procedure from the volume of resected tissue. We were unable to obtain information on resected breast volumes and, alternatively, tumor size and scar length were analyzed with respect to the degree of breast retraction. This showed that tumor size, but not scar length, was significantly associated with breast retraction.

Higher doses per fraction, as used in one of the participating departments, are known to cause increased late normal tissue complications (18). Since all the patients treated with 2.2 Gy per fraction also received electron treatment, the dose-fractionation factor could not be separated as an independent effect on cosmetic outcome here.

Treatment with electrons to the whole breast was not an unusual practice in the 1980s (19), but nowadays it is considered inappropriate and this treatment was excluded from subsequent DBCG protocols when the preliminary results of this quality assurance program emerged. The reason for introducing electron treatments in breast conservation was because of concern about lung toxicity as well as to the concept of including the skin in the clinical target volume.

All the patients here were interviewed about lung diseases and lung symptoms of any kind or degree, but the prevalence of symptoms was low (data not shown) so that no further statistical analysis was considered. Only 15 patients complained of lung symptoms of any cause with no significant difference between the two treatment techniques. The risk of lung morbidity after electron treatment, especially in large-breasted patients, makes electron treatment unjustifiable in itself, and not just due to poor cosmesis.

Increasing doses of radiation and dose per fraction have been shown significantly to affect breast fibrosis and reduce excellent/good cosmetic ratings (14, 20, 21). Total dose could not be discerned as a predictive factor of poor outcome in this study. In the large EORTC 'boost vs. no boost' trial which included the cosmetic scores of 1141 breast cancer patients (22), the maximum central breast dose was only significant for the cosmetic result in one of two multivariate models which used a digitizer assessment of cosmesis, while radiation dose to the breast did not influence the global cosmetic outcome as scored by a panel of five persons. In our analyses of dose dependence, boost radiation was not significantly associated with poor results as assessed by either the patients or the clinician. This is in contrast to the results from the EORTC study, which clearly showed an adverse effect of a boost on the global cosmetic results as assessed by the five clinicians. In the same study, the excised volume, tumor size, an inferior location, and postoperative complications were also found to impact on the cosmesis, whereas systemic treatment was only of significance in the univariate analysis. This is also in contrast to the present findings.

Patients' assessments

The degree of patient satisfaction after BCT was high in our study, i.e., 73% of the patients regarded their cosmetic outcome as excellent or good after a median follow-up of 6.6 years. This figure is lower than that in other studies (14, 22–26) for reasons explained above, but by using an appropriate treatment technique with tangential photons, close to 80% of the patients in this study reported excellent/good results even after a long observation time.

Breast sequelae such as skin changes and breast retraction are obviously related to the extent of surgery and radiation techniques, and evidently also to the administration of systemic therapy, although no detailed exploration was carried out here to distinguish between cytostatic or hormone treatment in high-risk patients. Cosmesis is a much more complex endpoint than the observed physical reactions because the scoring is likely to be under the influence of the patients' expectations, psychosocial status, or body perception. However, this study showed that physical breast changes also impacted on the patients' ratings of cosmetic outcome since breast fibrosis, skin telangiectasia, dyspig-

mentation, and breast retraction were all significantly associated with a poorer outcome. Even though the EORTC study did not include patient evaluations, it was concluded that an objective evaluation is more appropriate than evaluations based on photographs.

Breast size has been described to impact significantly on cosmetic outcome after BCT. Large breasts were shown adversely to affect cosmesis (22, 27, 28) mainly due to large dose inhomogeneities and this was also found in the present study in two multivariate models, one including patient assessments, and one model assessing exclusively those patients receiving tangential radiation treatment.

Psychosocial factors

The psychosocial morbidity after treatment of breast cancer has been described in several prospective studies from the 1980s and early 1990s, but observation times have been short (12–36 months) (13, 24, 29–33). These reports show a fairly high incidence of emotional distress after both mastectomy and BCT and in general no obvious advantage has been noted to be associated with breast-preserving procedures compared with mastectomy, with the exception of body image and clothing. This has been confirmed in a study with a somewhat longer follow-up (34), but recent data from a larger study have shown that patient satisfaction regarding cosmetic outcome and psychosocial aspects were higher following BCT (35, 36).

Our data showed that cosmetic outcome has a small but significant impact on body image several years after treatment. Eight percent of the patients experienced a negative change in body image, significantly more women with adverse cosmetic outcomes.

Body perception was found to be significantly associated with breast retraction, skin telangiectasia, and tumors confined to inferior quadrants, which is in agreement with the findings by others (5). Young age was clearly associated with a poorer cosmetic outcome, a fact that might be related to psychosocial rather than strictly biological factors. Since patients' satisfaction with cosmetic outcome and body perception might also be influenced by acceptance, quantitative measurements of breast asymmetry have been introduced to assess the quality of BCT (37–39). We introduced 'change in clothing' to get around the fact that acceptance may affect self-evaluation. This is a functional or behavioral effect variable, which takes into consideration a combination of contour and skin changes of the breast and reflects to what extent the individual woman had changed her clothing habits over time as a consequence of the side effects. Women with unfavorable results needed a change in clothing style more frequently than women with a satisfactory result and they had higher demands for reconstructive breast surgery as well. Thus, our data lend support to results from other studies that the behavior of the women regarding reconstructive surgery, clothing habits, and body perception was significantly related to cosmetic outcome after BCT (5, 24) and that this in turn was affected by specific treatments and breast changes after combined surgery and radiotherapy.

The prevalence of breast pain was low. Only 13% complained of frequent or constant pain, and mild analgesics were required in only 1 out of 18 patients who had breast pain. No individual factor emerged as an independently predictor for the occurrence of breast pain. The low prevalence of breast pain might be related to the fairly long follow-up period in the present study group and to the fact that breast pain, as well as some other late effects, tends to improve over time (40). Only 15% and 3% of patients had any impaired sensibility or paresthesia of the breast, which is clearly less than the incidence of phantom pain and non-painful phantom sensations (around 30%) that has been reported elsewhere from 5-year follow-ups after mastectomy (41).

Considerations about assessments of cosmetic outcome

As already mentioned, the patients generally reported a more favorable cosmetic result compared with that of the clinician. We found a significant but weak concordance between the scores by the patients and those by the oncologist. This follows other reports on cosmetic outcome after BCT, which have demonstrated a high agreement between observers but a low concordance between the patient self-assessments and the evaluations done by doctors or husbands (42, 43).

A considerable problem in the international literature dealing with cosmetic outcome after breast conservation is the lack of a precise description of the clinical endpoints, whether conclusions have been drawn from patient or observer evaluations. This is of course a minor problem when cosmetic ratings are high, with only small variations in success scores, but the degree of concordance between patients and observers is rarely specified. This weakens the conclusions of the studies, and a clarification is warranted on whether patient or observer evaluations were entered into the statistical models.

Since the ultimate goal of BCT is to satisfy and fulfill the patients' expectations, we performed statistical analyses on objective as well as subjective ratings of cosmesis. This ultimately showed that radiation treatment techniques and systemic adjuvant therapy had a detrimental effect on the final treatment results, irrespective of the applied clinical endpoint. Because patients' self-assessments now have been documented to relate to physical side effects after BCT, it is concluded that valuable information can be obtained from the patients' own ratings and that subjective perceptions and observations as reported by breast cancer patients are relevant for the identification of treatment factors that impact on normal tissue reactions.

CONCLUSION

The patients' satisfaction with BCT in this multicenter trial was high despite a high frequency of observed breast changes primarily related to treatment with electrons, resected breast volume, and the administration of adjuvant systemic therapy. The prevalence of breast morbidity, as reported by the patients themselves, was low. The present investigation underscores the importance of quality assurance programs in daily clinical practice that continuously must give due attention to the occurrence of treatment sequelae and psychosocial functioning in breast cancer patients in order to improve treatment results in breast conservation.

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