

The influence of patient, tumor and treatment factors on the cosmetic results after breast-conserving therapy in the EORTC ‘boost vs. no boost’ trial

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Abstract

Purpose: To analyze the influence of different patient, tumor, and treatment parameters on the cosmetic outcome after breast-conserving therapy at 3-year follow-up. A subjective and an objective cosmetic scoring method was used and the results of both methods were compared.

Patients and methods: In EORTC trial 22881/10882, 5569 early-stage breast cancer patients were treated with tumorectomy and axillary dissection, followed by tangential fields irradiation of the breast to a dose of 50 Gy in 5 weeks, at 2 Gy per fraction. A total of 5318 patients, having a microscopically complete tumorectomy, were randomized between no further treatment and a boost of 16 Gy to the primary tumor bed. The cosmetic result at 3-year follow-up was assessed by a panel for 731 patients, and by digitizer measurements, measuring the displacement of the nipple, for 1141 patients. Univariate and multivariate analyses were used to evaluate the correlation between various patient, tumor, and treatment factors and cosmesis.

Results: The factors associated with a worsened cosmesis according to the panel evaluation were: an inferior tumor location, a large excision volume, the presence of postoperative breast complications, and the radiotherapy boost. According to the digitizer measurements, a central/superior tumor location, a large excision volume, an increased pathological tumor size, an increased radiation dose inhomogeneity, and an increased bra cup size resulted in an increased asymmetry in nipple position. It appeared that the evaluation of the nipple position (whether by panel or by digitizer) is only moderately representative of the overall cosmetic outcome.

Conclusion: To achieve a good cosmesis, it is necessary to excise the tumor with a limited margin, to avoid postoperative complications, to assess the need for a boost in the individual patient, and to give the radiation dose as homogeneously as possible. As far as the method of evaluation is concerned, the panel evaluation is the most appropriate method for giving an overall impression of the cosmetic result after breast-conserving therapy (BCT). The use of the digitizer is recommended for comparing the cosmetic outcome of two different approaches to BCT or for analyzing cosmetic changes over time. © 2000 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Breast cancer; Breast-conserving therapy; Cosmetic result; Prognostic factor analysis

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1. Introduction

Since a good cosmetic result is a very important reason for the breast-conserving approach to early-stage breast cancer, it is important to know how to assess this cosmetic result as well as which factors influence this cosmetic outcome. Many studies have analyzed the cosmetic outcome after breast-conserving therapy (BCT). The cosmetic result was evaluated by physicians as excellent or good in 57–88% of patients, with a median follow-up ranging from 2 to 5 years [1,5,6,8,17,18,20–22,27,31]. Most studies which considered the influence of different patient, tumor and treatment parameters on cosmetic outcome, analyzed patients treated over a period of time during which the approach to BCT changed substantially (1960–1985) [1,2,5–7,9,10,17,21,22,25,26] and only relatively few studies performed a multivariate prognostic factor analysis for cosmetic outcome [3,7,11,18,20,26].

The cosmetic outcome after BCT and, more specifically, the influence of the radiotherapy boost on the cosmetic result, was one of the endpoints of the European Organization for Research and Treatment of Cancer (EORTC) ‘boost vs. no boost’ trial 22881/10882. From 1989 to 1996, more than 5000 patients with early-stage breast cancer were treated with BCT according to this trial protocol. A qualitative panel evaluation as well as a quantitative assessment of the cosmetic result were performed. In a previous study it was shown that the quantitative assessment, using a digitizer, was more accurate than the panel evaluation in terms of intra- and interobserver variability [29]. Digitizer measurements can be performed by one person, are easy to carry out and are relatively quick; this is in contrast to the multiple panel members having to go through the time-consuming process of assessing hundreds of photographs. With this comparison in mind, the question whether it is possible to use only digitizer measurements for comparing the cosmetic result of two different approaches to BCT, is an obvious one. However, before this question can be answered, it has to be established whether both methods are able to identify the same treatment parameters influencing cosmesis. In other words, do they measure the same aspects of cosmesis (can they be considered as interchangeable), or do they measure different aspects of the cosmetic result and be considered as supplementary? To be able to answer this question, a prognostic factor analysis has been performed.

We decided to analyze not only the influence of treatment parameters on cosmesis (to answer the question concerning the optimal cosmetic evaluation method), but to include patient and tumor factors as well. This analysis was performed on the cosmetic result at 3-year follow-up. The purpose of this analysis is to identify the parameters that have the largest impact on the cosmetic outcome following a contemporary approach to BCT. Furthermore, the results of this analysis, based on the quantitative and qualitative assessment of the cosmetic result, will be compared in order to determine whether these methods are interchangeable.

2. Patients and methods

2.1. Trial design

From 1989 to 1996, 5569 patients with T1-2 N0-1 M0 invasive breast cancer were entered in the EORTC ‘boost vs. no boost’ trial. Patients were treated with tumorectomy, axillary dissection and tangential fields irradiation of the whole breast of 50 Gy, with a dose per fraction of 2 Gy, in 5 weeks. Patients with a microscopically complete tumor excision were randomized between no further treatment and a boost of 15 or 16 Gy (15 Gy in case of an interstitial boost and 16 Gy in case of an external boost). Patients with a microscopically incomplete excision were randomized between a boost of 10 Gy and a boost of 25 or 26 Gy (25 Gy in case of an interstitial boost and 26 Gy in case of an external boost). A more detailed description of the trial design, eligibility criteria, characteristics of the patients and tumors, surgical and radiation techniques used, has previously been published [29,30].

2.2. Cosmetic assessment

Since the surgical excision of invasive disease was microscopically complete for 95% of patients, the cosmetic outcome was evaluated only for patients randomized to receive either no boost or a boost of 15 or 16 Gy. The cosmetic result was evaluated based on photographs taken postoperatively (before the start of radiotherapy) and after 3 years of follow-up. For this prognostic factor analysis the cosmetic evaluation at 3-year follow-up was used. The cosmetic result was assessed by a panel consisting of five persons (see Acknowledgments) as well as by digitizer measurements performed by one person (see Acknowledgments), measuring the difference in nipple position between both breasts. A more detailed description of the cosmetic assessment used in this trial as well as the reliability of both methods used have been described elsewhere [29,30].

The panel scored 731 patients, 367 no boost and 364 boost patients. These patients were not randomly selected, but were the first patients evaluable at both time points (postoperative and after 3-year follow-up). The items scored by the panel were global result, appearance of the surgical scar, breast size, breast shape, nipple position, and shape of areola. In scoring these items the treated breast was compared with the untreated breast, using a 4-point scale: excellent (0) if there was no difference between both breasts; good (1) if there was only a slight difference; fair (2) when a more marked difference was present; and poor (3) in case of a disturbing difference [10]. The scores given for each patient by the different reviewers have been combined in a single average. The bra cup size of the untreated breast was estimated by the panel. It appeared that the reviewers did not use the same standards for scoring the different bra cup sizes A, B, C or D. A general size for the breast was obtained by averaging the five evaluations,

Table 1
Patient, tumor and treatment characteristics of patients scored by the digitizer at 3-year follow-up ($n = 1141$)^a

Characteristic	Pt digitized, <i>n</i> (%)	Characteristic	Pt digitized, <i>n</i> (%)	Characteristic	Pt digitized, <i>n</i> (%)
Age (years)		Radiation quality WBI		Volume of external boost (cm ³)	
≤ 40	84 (7)	Cobalt-60	153 (13)	≤ 100	85 (16)
41–50	288 (25)	X-ray	976 (86)	101–150	130 (24)
51–60	386 (34)	Combination	12 (1)	151–200	99 (18)
> 60	383 (34)	Dose WBI in isocenter (Gy)		201–250	74 (14)
Tumor location		≤ 49.5	34 (3)	251–300	53 (10)
Lateral	570 (50)	49.5–50.5	1079 (95)	> 300	97 (18)
Central/superior	163 (14)	> 50.5	28 (2)	Unknown	2 (0)
Medial	199 (18)	Energy used at WBI (for X-ray) (MV)		Timespan surgery and start RT (days)	
Inferior	209 (18)	≤ 4	68 (7)	≤ 28	103 (9)
Tumor side		5–6	572 (58)	29–35	255 (22)
Left	574 (50)	7–8	153 (16)	36–42	330 (29)
Right	567 (50)	> 8	162 (16)	43–49	213 (19)
T palpation (mm)		Unknown	33 (3)	50–55	114 (10)
Non-palpable	265 (23)	Maximum dose central plane (Gy)		> 55	126 (11)
≤ 10	138 (12)	≤ 51	349 (31)	Axillary irradiation	
11–20	349 (31)	52–53	523 (46)	Yes	60 (5)
> 20	226 (20)	54–55	208 (18)	No	1081 (95)
Unknown	163 (14)	> 55	58 (5)	IMC irradiation	
T mammography (mm)		Unknown	3 (0)	Yes	141 (12)
≤ 10	229 (20)	Maximum dose tumor plane (Gy)		No	1000 (88)
11–20	471 (41)	≤ 51	257 (23)	Chemotherapy	
> 20	239 (21)	52–53	490 (43)	Yes	107 (9)
Unknown	202 (18)	54–55	255 (22)	No	1034 (91)
T clinical		> 55	71 (6)	Tamoxifen	
T1	617 (54)	Unknown	68 (6)	Pre-menopausal	
T2	524 (46)	Maximum dose border plane (Gy)		Yes	416 (37)
T pathology (mm)		≤ 51	213 (19)	No	175 (15)
≤ 10	271 (24)	52–53	445 (39)	Overall treatment duration (days)	
11–15	374 (33)	54–55	273 (24)	≤ -3	155 (14)
16–20	272 (24)	> 55	80 (7)	-2, -1	185 (16)
> 20	207 (18)	Unknown	130 (11)	0	119 (10)
Unknown	17 (1)	Boost treatment		1,2	336 (30)
N clinical		No boost	541 (47)	3,4	175 (15)
N0	1012 (89)	Boost	600 (53)	> 4	111 (10)
N1-2	76 (7)	Boost modality		Unknown	60 (5)
Unknown	53 (4)	Electron	376 (63)	Overall total dose (Gy)	
Type of axillary dissection		Cobalt-60	49 (8)	≤ -3	51 (5)
Discontinuous	984 (86)	X-ray	114 (19)	-2, -1	214 (19)
En bloc	151 (13)	Interstitial	60 (10)	0	389 (34)
Unknown	6 (1)	Unknown	1 (0)	1,2	347 (30)
Reexcision		Energy electron boost (MeV)		> 2	78 (7)
Yes	304 (27)	≤ 6	16 (4)	Unknown	62 (5)
No	837 (73)	7–9	104 (28)	Bra cup size (panel patients only)	

Table 1 (continued)

Characteristic	Pt digitized, n (%)	Characteristic	Pt digitized, n (%)	Characteristic	Pt digitized, n (%)
Volume of excision (cm ³)					
≤ 50	150 (13)	10–12	133 (35)	A	33 (5)
51–100	197 (17)	13–15	77 (21)	B	176 (27)
101–200	296 (26)	> 15	31 (8)	C	298 (46)
201–300	139 (12)	Unknown	15 (4)	D	140 (22)
> 300	122 (11)	Energy X-ray boost (MV)		Type of surgical scar (panel patients only)	
Unknown	237 (21)	≤ 5	28 (25)	Concentric	403 (62)
Postoperative breast complications		6–7	34 (30)	Radial	114 (18)
Present	150 (13)	> 8	47 (41)	En bloc	78 (12)
Absent	990 (87)	Unknown	5 (4)	Not evaluable	52 (8)
Unknown	1 (0)	Maximum dose per boost fraction (Gy)			
Postoperative axilla complications		≤ 2	481 (90)		
Present	181 (16)	> 2	40 (7)		
Absent	959 (84)	Unknown	15 (3)		
Unknown	1 (0)				

^a Pt, patients; N, number of patients; T, tumor size; N clinical, clinical nodal status; WBI, whole-breast irradiation; RT, radiotherapy; IMC, internal mammary chain.

where size A was scored as value 1, B as 2, C as 3 and D as 4. For the overall population the type of axillary dissection was known (discontinuous or en bloc), but the specific type of tumorectomy scar (concentric, radial or en bloc) was evaluated by the reviewers. The outcome was defined as the type of scar obtaining the greatest consensus among the raters: if at least three of the five reviewers agreed on one type of scar, it was considered the overall type of scar. If no consensus was attained for a picture then the type of scar was scored as not evaluable. These two variables, bra cup size and specific type of tumorectomy scar, were known only for the panel patients.

Follow-up pictures were available for 1141 patients and these pictures were scored by the digitizer (546 no boost and 595 boost patients). A description of the patient, tumor and treatment characteristics of the digitizer population as well as the categorization of the different characteristics are given in Table 1. The digitizer measurements were used to calculate the breast retraction assessment (BRA) values. In this analysis the relative BRA (or percentage BRA, pBRA), defined as the BRA/reference length $\times 100$, has been used instead of the absolute BRA for technical reasons [29]. Both measurements assess the lack of symmetry between the nipple positions (Fig. 1). The measurements were performed using a digitizer of a radiotherapy treatment planning system.

In both groups an axillary dissection was performed in more than 99% of patients and the number of fractions of the whole breast irradiation (WBI) was 25 in more than 98% of patients, therefore, these items were not considered any further in this analysis. Since only a very small number of patients received an interstitial boost, it was not possible to assess the influence of the dose rate and of the interstitial boost volume. The volume of the surgical resection was calculated by multiplying the three dimensions of the pathology specimen. If a reexcision was performed, the volumes of the originally excised and reexcised specimen were calculated separately and subsequently added. For

21% of patients the excision volume was unknown. Postoperative breast complications were defined as hematoma or infection of the breast, postoperative axilla complications were defined as seroma or infection of the axilla. The time-span between surgery and start of radiotherapy was defined as the period between the day of tumorectomy or reexcision and the first day of the whole breast irradiation. The administration of tamoxifen was known for postmenopausal patients. The different treatment arms were associated with a different radiotherapy treatment duration and a different total dose to the tumor bed. To analyze the influence of variations in treatment duration and total dose to the tumor bed for the overall population, the median duration and dose in both study arms were considered as standard and patients were categorized according to variation in duration and dose around the standard (see Table 1).

2.3. Statistical methods

2.3.1. Panel scoring

The patient, tumor and treatment characteristics were all recoded as either binary variables or as categorical variables. The continuous variables were all transformed into equally spaced ordinal categories. When the sample size in some categories was small compared with the overall sample size (roughly $< 10\%$) adjacent categories were added together. An ordinal variable was first tested as a nominal variable and the hypothesis of linearity of the effect of the variable was tested. If there was no significant evidence of the hypothesis being violated, the variable was then considered as an ordinal variable. Otherwise, adjacent categories with similar odds ratios were added together and for the various remaining categories separate odds ratios were used. Linearity was assumed only for the variables overall treatment duration and overall total dose. The cosmetic scores were dichotomized into ‘excellent/good’ and ‘fair/poor’ outcomes. Univariate and multivariate logistic regression models [4] were used to assess the relationship between patient, tumor and treatment characteristics and the cosmetic result. A backward selection procedure was applied and all variables significant at the 0.05 level in the univariate analysis were entered in the first step of the multivariate model selection procedure. Factors related to the boost were not considered for the multivariate model unless the boost itself was a significant factor according to the multivariate model. The effect of the different characteristics was expressed in terms of odds ratios (OR). The OR represents the relative increase ($OR > 1$) or relative decrease ($OR < 1$) in the probability of having an excellent/good result when the value of a certain variable is changed. The final models are presented at an 0.01 significance level.

2.3.2. Digitizer scoring

To obtain a Gaussian distribution, the values of the pBRA were log-transformed for all analyses. As a consequence,

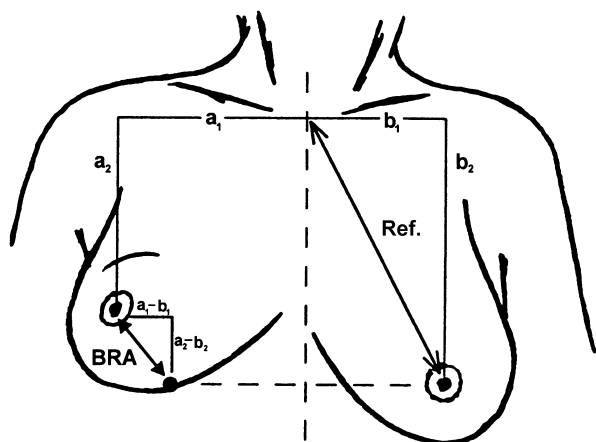


Fig. 1. Illustration of the BRA measurements. $BRA = \sqrt{((a_1 - b_1)^2 + (a_2 - b_2)^2)}$; reference length (ref.) = $\sqrt{(b_1^2 + b_2^2)}$; %BRA = (BRA/reference length) $\times 100$.

the average pBRA values reported here are the geometric means. Analysis of variance (ANOVA) and linear regression models [13] were used to assess the effect of patient, tumor and treatment parameters on the log(pBRA). This resulted in a multiplicative factor model on pBRA. When this multiplicative factor (or ratio) of a certain change in variable is <1 , the effect of this change is a decrease in pBRA (less asymmetry between the nipple positions, an improvement in cosmetic outcome); when the ratio is >1 , the effect increases pBRA, indicating a worsened cosmetic outcome. Again, a backward selection procedure was applied and variables significant at the 0.05 level in the univariate analyses were entered in the first step of the multivariate model. Factors related to the boost were not considered for the multivariate model unless the boost itself was a significant factor according to the multivariate model. Statistical significance in the multivariate model was reached at an 0.01 level.

Since the bra cup size and the type of surgical scar were available only for patients evaluated by the panel, the effect of these factors on pBRA could be assessed only for the subset of panel patients. Digitizer measurements were available for 647 of the 731 patients, therefore, this subgroup of 647 patients was used for the analysis of these two variables (in 84 patients the photographs could not be used for digitizer scoring, as the suprasternal notch, needed as a reference point, was omitted from the picture). The univariate analysis was performed by means of ANOVA I models. The variables bra cup size and type of surgical scar were then introduced in the multivariate prognostic factor model and the backwards selection procedure was continued until all variables were significant at the 0.01 level.

3. Results

3.1. Patient population

A detailed description of the panel population and a comparison of this group with the rest of the population have been given previously [30]. There appeared to be small imbalances in the distribution of these characteristics between the 1141 digitizer patients and the patients not evaluated by digitizer at 3 years. Significant differences are described in Table 2. The digitizer patients were less frequently irradiated with cobalt-60 and the dose in the isocenter was less frequently greater than 50.5 Gy. The digitizer patients received less often IMC irradiation as well as chemotherapy, although the overall proportion of patients receiving concomitant chemotherapy was 4% in both groups. The maximum dose in the central and border plane was more often ≤ 51 Gy in the digitizer patients, while less frequently unknown. These factors may result in a better outcome in the patients with digitizer measurements available compared with the outcome in the entire population.

3.2. Panel scoring (n = 731)

The cosmetic result at 3 years in the no-boost group was excellent in 42%, good in 44%, fair in 13% and poor in 1% of patients, compared with 33, 38, 26 and 3% in the boost group, respectively.

3.2.1. Global score

The univariate analysis showed that the probability of an excellent/good global cosmetic outcome after 3 years of follow-up was decreased by increasing age, an inferior tumor location, a large tumor size (assessed by palpation, mammography and pathology, as well as clinical tumor stage), an increased surgical excision volume, the presence of breast or axilla complications, the radiation boost, an

Table 2
Patient, tumor and treatment characteristics of the digitizer population^a

Variable	Pt digitized, n = 1141 (n (%))	Pt not digitized, n = 4157 (n (%))	P-value
Radiation quality WBI			
Cobalt-60	153 (13)	1281 (31)	<0.001
X-ray	976 (86)	2785 (67)	
Combination	12 (1)	53 (1)	
Unknown	0 (0)	38 (1)	
Dose WBI in isocenter (Gy)			
≤ 49.5	34 (3)	107 (2)	<0.001
49.5–50.5	1079 (95)	3654 (88)	
> 50.5	28 (2)	359 (9)	
Unknown	0 (0)	37 (1)	
Maximum dose central plane (Gy)			
≤ 51	349 (31)	999 (24)	<0.001
52–53	523 (46)	1804 (43)	
54–55	208 (18)	742 (18)	
> 55	58 (5)	219 (5)	
Unknown	3 (0)	393 (10)	
Maximum dose border plane (Gy)			
≤ 51	213 (19)	608 (15)	<0.001
52–53	445 (39)	1360 (33)	
54–55	273 (24)	987 (24)	
> 55	80 (7)	347 (8)	
Unknown	130 (11)	855 (20)	
IMC irradiation			
Yes	141 (12)	946 (23)	<0.001
No	1000 (88)	3173 (76)	
Unknown	0 (0)	38 (1)	
Chemotherapy			
Yes	107 (9)	540 (13)	<0.001
No	1034 (91)	3578 (86)	
Unknown	0 (0)	39 (1)	

^a Pt, patients; N, number of patients; WBI, whole-breast irradiation; IMC, internal mammary chain.

Table 3
Univariate model for the different cosmetic items scored by the panel (variables significant at 0.05 are displayed)

Variable	Coding	Global score		Surgical scar		Breast size		Breast shape		Nipple position		Shape areola	
		OR (95% CI) ^a	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Age (years)	≤40 ^b vs. >40	0.29 (0.10–0.66)	0.009					0.36 (0.12–0.83)	0.03				
	≤60 ^b vs. >60			0.62 (0.42–0.93)	0.02					0.58 (0.42–0.80)	<0.001		
Tumor location	≤40 ^b vs. 41–60 vs. >60					0.31 (0.20–0.49)	<0.001	0.20 (0.13–0.31)	<0.001			0.24 (0.13–0.46)	<0.001
	Inferior vs. other ^b	0.30 (0.20–0.46)	<0.001	0.24 (0.16–0.38)	<0.001	0.39 (0.16–1.02)	0.04					0.19 (0.07–0.61)	<0.001
T palpation (mm) ^c	Central vs. other ^b							0.80 (0.66–0.96)	0.02				
	Non-palp. ^b vs. ≤10 vs. 11–20 vs. >20	0.83 (0.69–0.99)	0.04										
T mammography (mm)	≤20 ^b vs. >20			0.58 (0.36–0.95)	0.03					0.64 (0.47–0.86)	0.003		
	≤10 ^b vs. 11–20 vs. >20	0.63 (0.47–0.84)	0.002									0.35 (0.19–0.67)	0.001
T clinical	T1 ^b vs. T2	0.56 (0.39–0.79)	0.001					0.66 (0.45–0.96)	0.03	0.60 (0.41–0.86)	0.006	0.43 (0.23–0.77)	0.006
	≤10 ^b vs. 11–15 vs. 16–20 vs. >20	0.78 (0.66–0.91)	0.003					0.83 (0.69–0.99)	0.03				
Excision volume (cm ³)	≤20 ^b vs. >20			0.53 (0.34–0.83)	0.005					0.62 (0.41–0.95)	0.03	0.47 (0.26–0.89)	0.02
	≤50 ^b vs. >50	0.28 (0.12–0.55)	<0.001					0.24 (0.09–0.53)	0.001				
Breast compl. ^d	≤50 ^b vs. 51–200 vs. >200			0.68 (0.47–0.96)	0.03	0.49 (0.34–0.69)	<0.001			0.52 (0.37–0.71)	<0.001	0.40 (0.24–0.67)	<0.001
	Present vs. absent ^b	0.42 (0.27–0.67)	<0.001	0.42 (0.25–0.71)	<0.001	0.50 (0.31–0.84)	0.007	0.49 (0.30–0.80)	0.004	0.37 (0.23–0.60)	<0.001	0.45 (0.23–0.94)	0.02
Axilla compl.	Present vs. absent ^b	0.58 (0.37–0.92)	0.02							0.60 (0.38–0.97)	0.03		
	≤8 ^b vs. >8			2.40 (1.19–5.53)	0.02								
Energy used at WBI ^e (MV)	≤4 ^b vs. 5–8 vs. >8									1.65 (1.07–2.60)	0.03		
	No boost ^b vs. boost	0.41 (0.28–0.59)	<0.001	0.37 (0.24–0.58)	<0.001	0.42 (0.27–0.62)	<0.001	0.38 (0.25–0.56)	<0.001	0.55 (0.38–0.80)	0.002	0.39 (0.20–0.71)	0.003
Max. dose per boost fraction (Gy)	≤2 ^b vs. >2									0.35 (0.17–0.76)	0.007		

Table 3 (continued)

Variable	Coding	Global score		Surgical scar		Breast size		Breast shape		Nipple position		Shape areola	
		OR (95% CI) ^a	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Boost volume (cm ³)	≤200 ^b vs. >200	0.47 (0.29–0.76)	0.002										
Chemotherapy	Yes vs. no ^b	0.48 (0.28–0.85)	0.009					0.38 (0.22–0.67)					
Tamoxifen	Yes vs. no ^b	0.62 (0.40–1.00)	0.04			0.45 (0.28–0.74)	0.001	0.58 (0.36–0.94)		0.02	0.52 (0.33–0.83)		0.006
Bra cup size	A/B ^b vs. C vs. D					0.76 (0.58–1.00)	0.05						
	A/B ^b vs. C/D										0.54 (0.35–0.83)		0.005
Type of surgical scar	Concentric/en bloc ^b vs. radial/n.e. ^f							0.64 (0.43–0.96)		0.03			

^a OR, odds ratio; CI, confidence interval.

^b Indicates reference level.

^c T, tumor size.

^d Compl., complications.

^e WBL, whole-breast irradiation.

^f N.E., not evaluable.

increased boost volume, as well as by giving chemotherapy or tamoxifen (Table 3).

In the first step of the multivariate analysis for the global score, all variables significant in the univariate analysis, except the boost volume, were entered. The boost volume was not immediately introduced in the multivariate selection procedure, as its effect is only relevant in the presence of a significant effect of the boost itself. It was introduced in the model at the end of the selection procedure, but was not retained in the model. The multivariate analysis retained only tumor location, volume of excision, breast complications, boost treatment and clinical tumor stage (Table 4).

3.2.2. Other cosmetic items

An overview of the univariate analyses for the other five cosmetic items scored by the panel is given in Table 3. The variables that influenced four or more cosmetic items negatively were inferior tumor location, an increased pathologi-

cal tumor size, an increased excision volume, the presence of breast complications and the boost treatment.

According to the multivariate analysis, most items scored by the panel were influenced by the following factors: inferior tumor location; an increased excision volume; the presence of breast complications; and the boost treatment (Tables 4 and 5). The final multivariate models for appearance of the surgical scar, breast size, breast shape and shape of areola were very similar. The final model for nipple position was somewhat different, since this item was not influenced by tumor location and boost treatment.

3.3. Digitizer scoring (n = 1141)

The mean pBRA at 3 years in the no-boost group was 7.55 pBRA (95% CI, 7.11–8.02), compared with 8.26 pBRA (95% CI, 7.79–8.75) in the boost group.

3.3.1. Overall population (n = 1141)

The univariate analysis selected tumor location, tumor

Table 4
Multivariate models for the different cosmetic items scored by the panel (at 0.01 significance level)

Variable	Coding	OR (95% CI) ^a	P-value
<i>Global score</i>			
Tumor location	Inferior vs. other ^b	0.21 (0.13–0.36)	<0.001
Excision volume (cm ³)	≤50 ^b vs. >50	0.29 (0.12–0.90)	0.002
Breast complications	Present vs. absent ^b	0.34 (0.19–0.61)	<0.001
Boost treatment	No boost ^b vs. boost	0.42 (0.27–0.65)	<0.001
T clinical	T1 ^b vs. T2	0.53 (0.34–0.82)	0.005
<i>Surgical scar</i>			
Tumor location	Inferior vs. other ^b	0.23 (0.12–0.37)	<0.001
Boost treatment	No boost ^b vs. boost	0.38 (0.22–0.64)	<0.001
Breast complications	Present vs. absent ^b	0.38 (0.20–0.73)	0.003
Excision volume (cm ³)	≤50 ^b vs. 51–200 vs. >200	0.59 (0.40–0.87)	0.008
<i>Breast size</i>			
Tumor location	Inferior vs. other ^b	0.28 (0.17–0.47)	<0.001
Excision volume (cm ³)	≤50 ^b vs. 51–200 vs. >200	0.43 (0.30–0.63)	<0.001
Boost treatment	No boost ^b vs. boost	0.45 (0.28–0.73)	0.001
<i>Breast shape</i>			
Tumor location	Inferior vs. other ^b	0.14 (0.09–0.24)	<0.001
Excision volume (cm ³)	≤50 ^b vs. >50	0.22 (0.09–0.54)	<0.001
Chemotherapy	No ^b vs. yes	0.33 (0.16–0.68)	0.003
Breast complications	Present vs. absent ^b	0.39 (0.21–0.74)	0.004
Boost treatment	No boost ^b vs. boost	0.40 (0.25–0.65)	<0.001
<i>Nipple position</i>			
Breast complications	Present vs. absent ^b	0.36 (0.21–0.63)	<0.001
Bra cup size	A/B ^b vs. C/D	0.49 (0.28–0.84)	0.009
Excision volume (cm ³)	≤50 ^b vs. 51–200 vs. >200	0.58 (0.42–0.82)	0.002
<i>Shape areola</i>			
Tumor location	Central vs. other ^b	0.12 (0.05–0.54)	0.003
Tumor location	Inferior vs. other ^b	0.22 (0.11–0.44)	<0.001
Excision volume (cm ³)	≤50 ^b vs. 51–200 vs. >200	0.34 (0.19–0.59)	<0.001
Boost treatment	No boost ^b vs. boost	0.38 (0.19–0.76)	0.006

^a OR, odds ratio; CI, confidence interval.

^b Indicates reference level.

Table 5
Summary of the multivariate models according to the panel score

Variable	Coding score	Global scar	Surgical size	Breast size	Breast shape	Nipple position	Shape areola
Tumor location	Inferior vs. other ^a	+ ^b	+	+	+		+
Tumor location	Central vs. other ^a						+
Boost treatment	No boost ^a vs. boost	+	+	+	+		+
Excision volume (cm ³)	≤50 ^a vs. >50	+			+		
Excision volume (cm ³)	≤50 ^a vs. 51–200 vs. >200		+	+			+
Breast complications	Present vs. absent ^a	+	+		+	+	
Bra cup size	A/B ^a vs. C/D					+	
Chemotherapy	No ^a vs. yes				+		
T clinical	T1 ^a vs. T2	+					

^a Indicates reference level.

^b +, indicates $P < 0.01$.

size (according to palpation, mammography and pathology, as well as clinical tumor stage), volume of excision, maximum dose in the central, tumor and border plane, boost treatment, maximum dose per boost fraction, and treatment with tamoxifen as significant prognostic factors for the pBRA at 3 years (Table 6).

These significant variables were entered in the first step of the multivariate analysis, except for the maximum dose per boost fraction. This variable could not be entered in a multivariate model because it concerned only a subset of patients and its relevance was conditional to a significant effect of the boost treatment parameter. The multivariate analysis retained tumor location, excision volume, pathological tumor size and maximum dose in the central plane: a central/superior tumor location, a large excision volume, an increasing pathological tumor size and a high maximum dose in the central plane were factors associated with an increased pBRA, indicating a worse cosmetic outcome (Table 7). Because the boost treatment itself was not an independent prognostic factor, the maximum dose per boost fraction was not considered relevant to the multivariate model.

3.3.2. Panel patients only ($n = 647$)

The univariate and multivariate analyses were repeated for the panel sample only, in order to evaluate the impact of the bra cup size and the type of surgical scar. The multivariate analysis identified the same factors as the analysis of the larger sample, with equal effect, although the maximum dose in the central plane was borderline significant this time.

The bra cup size and the type of surgical scar were highly significant prognostic factors for the pBRA according to the univariate analysis (Table 6). The multivariate analysis was repeated and these factors were included in the first step of the selection procedure in addition to the other univariately significant variables. Of the variables of the initial model, only the pathological tumor size remained significant. The variables tumor location, excision volume and maximum dose in the central plane dropped out of the multivariate

model and were replaced by the variables bra cup size and type of surgical scar ($P = 0.008$ and $P < 0.001$, respectively; Table 7). This should be related to the observation that the size of the breast as measured by the bra cup size is correlated to the excision volume and to the maximum dose in the central plane: the larger the bra cup size, the larger the excision volume and the higher the maximum dose in the central plane. Patients with a not-evaluable surgical scar had a better cosmetic outcome than the three other groups. This can be explained by the fact that a superiorly located tumor occurred less frequent in these patients, whereas they had more often a small excision volume. The three other groups (with a concentric, radial or en bloc excision) all had a similar cosmetic result. It is obvious that it is difficult to draw conclusions from this result, since the not-evaluable group is, of course, undefined.

Apart from the above described associations, possibly explaining the replacement in the repeated model of tumor location, excision volume and maximum dose in the central plane by bra cup size and type of surgical scar, it should also be kept in mind that the power of the test is reduced when the multivariate analysis is repeated on a sample of a smaller size. We can only reasonably assume that the bra cup size and type of surgical scar would also have been significant in the model for all patients, and that factors that dropped out of the model became non-significant due to lack of power in the panel-evaluated subgroup.

The treatment factor maximum dose to the central plane leads to the following question: did the whole plane receive an increased dose, or is the increased maximum dose in the central plane an indicator of increased dose inhomogeneity? Since the dose in the isocenter (located in the central plane) was >50.5 Gy in only 2% of the patients, and the maximum dose in the central plane was >53 Gy in 23% of patients, it can be concluded that in this study a high maximum dose in the central plane indicates for most cases increased dose inhomogeneity.

Thus, we concluded that the digitizer evaluations show that central/superior tumor location, large excision volume,

increasing pathological tumor size, increased inhomogeneity, large bra cup size and concentric, radial or en bloc type of surgical scar were all factors associated with worsened cosmetic outcome.

4. Discussion

The outcome of the prognostic factor analysis for the different cosmetic items according to the panel showed

Table 6
Univariate model for cosmetic outcome evaluated by the digitizer

Characteristic	Coding	Ratio (95% CI) ^a	P-value
<i>Overall population (n = 1141)</i>			
Age (years)	≤60 ^b vs. >60		0.21
Tumor location	Lateral ^b vs.	1.00	<0.001
	Central/superior	1.20 (1.06–1.35)	
	Medial	1.13 (1.01–1.27)	
	Inferior	0.86 (0.77–0.96)	
Tumor side	Right ^b vs. left		0.38
T palpation ^c (mm)	≤20 ^b vs. >20	1.21 (1.08–1.35)	<0.001
T mammography (mm)	≤10 ^b vs. 11–20 vs. >20	1.13 (1.06–1.20)	<0.001
T clinical	T1 ^b vs. T2	1.11 (1.02–1.21)	0.012
T pathology (mm)	≤10 ^b vs. 11–20 vs. >20	1.18 (1.10–1.26)	<0.001
N clinical ^d	N0, Nx ^b vs. N1-2		0.48
Type of axillary dissection	Discontinuous ^b vs. en bloc		0.83
Reexcision	Yes vs. no ^b		0.78
Volume of excision (cm ³)	≤50 ^b vs. 51–200 vs. >200	1.25 (1.16–1.34)	<0.001
Breast complications	Present vs. absent ^b		0.64
Axilla complications	Present vs. absent ^b		0.74
Radiation quality of WBI ^e	Cobalt-60 ^b vs. X-ray vs. combination		0.22
Dose WBI in isocenter (Gy)	≤49.5 ^b vs. 49.5–50.5 vs. >50.5		0.38
Energy used at WBI (for X-ray) (Gy)	≤4 ^b vs. 5–6 vs. 7–8 vs. > 8		0.97
Maximum dose central plane (Gy)	≤51 ^b vs. 52–53 vs. 54–55 vs. >55	1.10 (1.05–1.16)	<0.001
Maximum dose tumor plane (Gy)	≤51 ^b vs. 52–53 vs. 54–55 vs. >55	1.07 (1.02–1.13)	0.005
Maximum dose border plane (Gy)	≤51 ^b vs. 52–53 vs. 54–55 vs. >55	1.07 (1.02–1.13)	0.009
Boost treatment	No boost ^b vs. boost	1.09 (1.01–1.18)	0.04
Boost modality	Electron ^b vs. Cobalt-60 vs. X-ray vs. interstitial		0.11
	≤6 ^b vs. 7–9 vs. 10–12 vs. 13–15 vs. >15		0.95
Energy X-ray boost (MV)	≤5 ^b vs. 6–7 vs. >8		0.63
Maximum dose per boost fraction (Gy)	≤2 ^b vs. >2	1.34 (1.07–1.69)	0.01
Volume of external boost (cm ³)	≤100 ^b vs. 101–150 vs. 151–200 vs. 201–250 vs. 251–300 vs. >300		0.11
	≤28 ^b vs. 29–35 vs. 36–42 vs. 43–49 vs. 50–55 vs. >55		0.14
Timespan between surgery and start RT (days) ^f	50–55 vs. >55		0.14
Axillary irradiation	Yes vs. no ^b		0.08
IMC irradiation ^g	Yes vs. no ^b		0.08
Chemotherapy	Yes vs. no ^b		0.65
Tamoxifen	Yes vs. no ^b	1.18 (1.05–1.32)	0.006
Overall treatment duration (days)	≤–3 ^b vs. –2, –1 vs. 0 vs. 1, 2 vs. 3, 4 vs. >4		0.68
	≤–3 ^b vs. –2, –1 vs. 0 vs. 1, 2 vs. >2		0.30
<i>Panel patients only (n = 647)</i>			
Bra cup size	A/B ^b vs. C vs. D	1.17 (1.08–1.26)	<0.001
Type of surgical scar	Concentric ^b vs.	1.00	0.02
	Radial	0.91 (0.79–1.05)	
	En bloc	0.97 (0.82–1.15)	
	Not evaluable	0.73 (0.59–0.89)	

^a CI, confidence interval.

^b Indicates reference level.

^c T, tumor size.

^d N clinical, clinical nodal status.

^e WBI, whole-breast irradiation.

^f RT, radiotherapy.

^g IMC, internal mammary chain.

that the nipple position was influenced somewhat differently than the other items scored. The nipple position was not influenced by an inferior tumor location or by the boost treatment, whereas all other items were. However, the nipple position was influenced by the bra cup size, whereas all other items were not. The result of the digitizer evaluation is rather similar to the outcome of the panel evaluation of the nipple position: both evaluations concluded that a large excision volume and an increased bra cup size influence cosmesis negatively, while the cosmetic outcome is not influenced by an inferior tumor location or the boost treatment. Thus, the digitizer evaluation corresponds with the panel evaluation of the nipple position. However, looking at the panel evaluation of all items, it must be concluded that evaluation of the nipple position (whether by panel or by digitizer) is only moderately representative of the overall cosmetic outcome.

The tumor location led to a clear discrepancy in the outcome of both methods: the panel evaluation indicated that an inferior tumor location was associated with a worsened cosmesis, whereas according to the digitizer a central/superior tumor location resulted in an impaired cosmetic outcome. The digitizer measures the nipple position and does not take into account the deformation of the inferior breast contour. Therefore, it can be expected that an inferior tumor location does not influence the digitizer measurements as much as a superior location does. This is a limitation of the digitizer scoring that is not shared by the panel, since the panel evaluates the overall cosmetic result. Other studies also concluded that an inferior tumor location increases the probability of a fair or poor cosmetic result [11,20,26]. Specific treatment approaches can minimize the detrimental effect of an inferior tumor location on cosmesis. Nos et al. [14] suggested associating lumpectomy with a bilateral remodeling mammoplasty for breast carcinomas located in the inferior quadrant, in order to avoid residual deformities. Fifty patients with a lower quadrant tumor were

treated in their series, with a median follow-up of 48 months. The cosmetic outcome at 1 year was very good in 31% and good in 37% of patients. In our study, 59% of the patients with an inferior tumor location had an excellent/good result at 3 years. Since the cosmetic outcome in the study of Nos et al. was scored using a 5-point scale (very good, good, fair, moderate and poor), the results are not directly comparable and the follow-up for the cosmetic evaluation is still short, but the first results of their approach are promising.

It is obvious that a cosmetic result that is fair or poor due to disturbing skin changes, such as telangiectasia, cannot reliably be assessed by the digitizer [27]. However, the outcome of the panel evaluation showed that only very few patients had visible skin changes at 3-year follow-up. Therefore, this limitation of the digitizer was not considered a major disadvantage in this cosmetic evaluation. Concerning the conclusions related to the influence of the bra cup size, the following should be kept in mind: the bra cup size, together with type of surgical scar, was evaluated by the panel based on the photographs. It was not assessed by the treating physician itself. This might result in a discrepancy between the actual bra cup size and the estimated bra cup size.

The results of the prognostic factor analyses according to both methods showed that the following treatment factors had a large negative impact on cosmesis: a large excision volume, the giving of a boost, increased inhomogeneity, and the presence of postoperative breast complications.

A large excision volume has been recognized in many studies as impairing the cosmetic outcome [5,8–10,15,19,22–24,28,31]. This questions whether it is possible to excise the tumor with a smaller volume of surrounding breast tissue, without increasing the proportion of incomplete excisions. The tumor is often located eccentrically in the excision volume, suggesting that it should be possible to excise a smaller volume without decreasing the minimal

Table 7

Multivariate model for cosmetic outcome evaluated by the digitizer (at 0.01 significance level)

Variable	Coding	Ratio (95% CI) ^a	P-value
<i>Overall population (n = 1141)</i>			
Tumor location	Central/superior vs. other ^b	1.21 (1.06–1.37)	0.001
Excision volume (cm ³)	≤50 ^b vs. 51–200 vs. >200	1.19 (1.11–1.28)	<0.001
T pathology (mm) ^c	≤10 ^b vs. 11–20 vs. >20	1.14 (1.06–1.23)	<0.001
Max. dose central plane (Gy)	≤51 ^b vs. 52–53 vs. 54–55 vs. >55	1.10 (1.04–1.16)	0.002
<i>Panel patients (n = 647)</i>			
Type of surgical scar	Radial vs. concentric ^b	0.93 (0.08–1.07)	0.008
	En bloc vs. concentric ^b	0.94 (0.80–1.11)	
	Not evaluable vs. concentric ^b	0.71 (0.58–0.86)	
Bra cup size	A/B ^b vs. C vs. D	1.17 (1.10–1.26)	<0.001
T pathology (mm)	≤10 ^b vs. 11–20 vs. >20	1.16 (1.09–1.25)	<0.001

^a CI, confidence interval.^b Indicates reference level.^c T, tumor size.

tumor-free margin. Two sources of uncertainty may cause unnecessary wide excision: radiological inaccuracy and surgical inaccuracy. The first inaccuracy relates to the discrepancy that exists between the perceived tumor boundary using preoperative diagnostic images and the true tumor boundary. The advised excision boundary is generally based on the perceived tumor boundary to which is added a safety margin. The second inaccuracy relates to the discrepancy between the advised excision boundary and the true excision boundary. In order to minimize both uncertainties, research is being done to improve preoperative estimation of the tumor boundaries, as well as to develop strategies for image-guided surgery.

The panel associated the boost with a worsened cosmetic result, while the digitizer associated an increased inhomogeneity with a worsened cosmetic outcome. No explanation could be found for the fact that, although both methods identified a parameter associated with an increased radiation dose, they identified a different one. In the univariate analysis for the panel assessment inhomogeneity was not significant, whereas in the univariate analysis for the digitizer assessment the boost was only borderline significant. An increased inhomogeneity was associated with a worsened cosmetic result by other studies as well [20,22,31]. Moody et al. showed a clear association between breast size and dose inhomogeneity. Their advice is to use multi-level planning, incorporating lung corrections and customized 3D compensators, to minimize the breast inhomogeneity [12]. Concerning the radiotherapy boost, some studies concluded that it had a negative effect on cosmesis [8,31], whereas other studies concluded that the boost had no effect on cosmesis [16,22].

Only a few studies analyzed the effect of postoperative breast complications on cosmesis. Three studies included either postoperative hematoma or postoperative infection of the breast in the analysis [11,16,31]. In only one study postoperative infection was univariately related to a worsened cosmetic result [11]. In the present study it appeared that the presence of postoperative hematoma or infection is a very important factor impairing the cosmesis according to the panel evaluation.

In conclusion, the evaluation of the nipple position is only moderately representative of the overall cosmetic outcome as assessed by the panel. Therefore, if the aim of a future study is to give an overall impression of the cosmetic result after BCT, the panel evaluation is the most appropriate method. It gives a better translation of the overall cosmetic result, since it incorporates also the inferior part of the breast in its evaluation. The prognostic factor analysis for the global score identified all factors that had a major impact on the other items scored by the panel, so it can be concluded that using the global score alone is sufficient for the identification of the parameters that influence cosmesis negatively. If the aim of a future study is to compare the cosmetic outcome of two different approaches to BCT or to analyze the cosmetic changes over time, the use of digitizer

evaluation is recommended, as it is a more reproducible method and less time-consuming. Since it is difficult to compare the outcome of different panel reviews, this is not the method to use for these kind of studies. However, if one of the approaches to BCT is known to be associated with disturbing skin reactions, then the panel evaluation should be used in addition to the digitizer measurements. Furthermore, the outcome of the prognostic factor analysis for the cosmetic outcome after BCT showed that in order to achieve as good a cosmesis as possible, it is necessary to excise the tumor with a limited margin, to avoid postoperative infection and hematoma, to assess the need for a boost in the individual patient, and to give the dose of the WBI as homogeneously as possible.

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