

Long-term cosmetic changes after breast-conserving treatment of patients with stage I–II breast cancer and included in the EORTC ‘boost versus no boost’ trial

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Background: In breast cancer treated with breast-conserving radiotherapy, the influence of the boost dose on cosmetic outcome after long-term follow-up is unknown.

Patients and methods: We included 348 patients participating in the EORTC ‘boost versus no boost’ mega trial with a minimum follow-up of 6 years. Digitalised pictures were analysed using specific software, enabling quantification of seven relative asymmetry features associated with different aspects of fibrosis.

Results: After 3 years, we noted a statistically significantly poorer outcome for the boost patients for six features compared with those of the no boost patients. Up to 9 years of follow-up, results continued to worsen in the same magnitude for the both patient groups. We noted the following determinants for poorer outcome: (i) boost treatment, (ii) larger excision volumes, (iii) younger age, (iv) tumours located in the central lower quadrants of the breast and (v) a boost dose administered with photons.

Conclusions: A boost dose worsens the change in breast appearance in the first 3 years. Moreover, the development of fibrosis associated with whole-breast irradiation, as estimated with the relative asymmetry features, is an ongoing process until (at least) 9 years after irradiation.

Key words: boost, breast cancer, breast-conserving therapy, cosmetic results, radiotherapy

Introduction

Breast-conserving therapy (BCT) in early-stage breast cancer results in a survival equivalent to that of mastectomy [1–7]. BCT is, therefore, considered standard treatment of stage I–II breast cancer. Optimal cosmetic outcome is considered to be of great importance. In the EORTC phase-III ‘boost versus no boost’ trial, the impact of a boost dose of 16 Gy was evaluated specifically with respect to the ipsilateral breast tumour-free survival, overall survival and cosmesis. According to the results of this trial, the administration of a boost dose results in an improved ipsilateral breast tumour-free survival and similar overall survival [8, 9]. Specifically with respect to cosmetic outcome, the additional dose of 16 Gy appeared to negatively affect cosmetic outcome after a mean follow-up period of 3 years [10–12]. After 3 years of follow-up, no further information is available. We, therefore, decided to evaluate

cosmetic changes after a minimum follow-up period of 6 years. Various methods of scoring cosmetic outcome have been used in the past. In 1979, Harris et al. [13] introduced a subjective overall cosmetic score (excellent, good, fair and poor) that would later become the standard. However, the relevance of this type of evaluation is limited. The high dependency on the experience of observers, the poor reproducibility and the time-consuming character of this method are all major drawbacks. Pezner et al. [14] introduced in 1985 an objective assessment of cosmetic result after breast surgery: breast retraction assessment (BRA). With this procedure, Limbergen [15], Noguchi [16], Krishnan [17] and Al-Ghazal [18] combined subjective scores with objective measurements thus creating an overall cosmetic score. Lacking a sufficiently reliable approach, Cardoso et al. [19, 20, 21] developed a software programme combining various measurements of both breasts with objective scores of skin colour and scar appearance, resulting in a consistent overall cosmetic score. This approach encouraged us to perform a long-term analysis on cosmetic changes in women treated with BCT for early-stage

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breast cancer in the framework of the boost versus no boost trial.

methods and materials

design of the EORTC phase-III boost versus no boost trial

From May 1989 to June 1996, 5569 early-stage breast cancer patients were entered in the trial. Patients with clinically T1-2, N0-1, M0 invasive breast cancer were treated with lumpectomy and axillary dissection, followed by whole-breast irradiation (WBI) with tangential fields to 50 Gy, with a dose per fraction of 2 Gy during 5 weeks. Patients with a microscopically complete tumour excision were randomised between no further treatment and a boost (15 Gy in case of interstitial boost and 16 Gy in case of an external boost). The first set of pictures was made postoperatively just before the start of radiotherapy and thereafter during follow-up every 3 years. Three colour pictures of the breasts were taken each time: two frontal views, one with arms along the body and one with arms lifted upwards and one profile view taken from the treated side with arms lifted upwards.

patient population

For the purposes of this analysis, the frontal view pictures with arms down of patients randomised in Tilburg and Utrecht were collected. As such, the analyses could be based on a homogeneously treated group of patients. We excluded patients with an interstitial boost (eight patients in the boost and one in the no boost group). Subsequently, we selected patients whose pictures were available for a minimum period of 6 years follow-up. Furthermore, cases were censored after the occurrence of local recurrences, distant metastases, secondary primary breast cancers or death.

The characteristics of patient and tumour variables of the EORTC trial population and those of the study population are given in Table S1 (available as supplementary data in *Annals of Oncology* online). The distribution of these variables between the overall population and study population as well as between no boost and boost cases did not differ significantly. Minor differences between the populations were noted: in the study population, patients with re-excisions were present more frequently. The same yielded for patients with pN1-3 disease in the boost group.

cosmetic evaluation

BCCT. core software programme. The 131 hard-copy pictures were taken with a digital 3.2-megapixel photo camera. The items used for the cosmetic evaluation were determined by the BCCT.core software system developed by Cardoso et al. [20–22] (Figure 1 and Figure 2).

With this software programme, various parameters are extracted from the patient's pictures. The following seven dimensionless asymmetry features were used in our study:

pBRA, the relative breast retraction assessment. This quantifies the relative difference in nipple position between both breasts and reflects the degree of breast retraction.

pLBC, the relative lower breast contour. This quantifies the relative difference between levels of lower breast contour.

pUNR, the relative upward nipple retraction. This quantifies the relative difference between nipple levels.

pBCE, the relative breast compliance evaluation. This quantifies the relative difference between the left and right nipple to inframammary fold distance.

pBCD, the relative breast contour difference. This quantifies the relative difference between the lengths of left and right breast contours.

pBAD, the relative breast area difference. This quantifies the relative difference between areas of left and right breasts.

pBOD, the relative breast overlap difference. This quantifies the non-overlapping area of the two breasts after flipping one of them along a vertical line and making coincident both points of junction with thorax (Figure 1).

For more detailed description of the BCCT.core software programme, we refer to <http://medicalresearch.inescporto.pt/breastresearch/BCCT.core.html>.

statistical methods

The distribution of various patient and tumour characteristics of the 348 study patients was compared with that of the boost versus no boost trial population. For each cosmetic measurement, time (in years) from randomisation was calculated. The following four time periods were created: 0, 3, 6 and 9 years after randomisation. The exact definition of these four time periods were chosen as follows: 0 = between date of randomisation till start irradiation, 1 = between 2 and 4.5 years, 2 = between 4.5 and 7.5 years and 3 = between 7.5 and 10.5 years after randomisation.

In the boost versus no boost trial, the tumour locations were grouped in 18 locations (left and right together) [11]. For the purposes of our study (with a significant lower number of cases), we had to regroup these 18 locations. We combined the medial and upper quadrant and the central and under quadrant resulting in a rather equally distribution of numbers of patients in each group.

Differences of the seven indices (pBRA, pLBC, pUNR, pBCE, pBCD, pBAD, pBOD) for breast asymmetry between boost and no boost at baseline were tested using Student's *t*-test. Analysis of the development over time of these indices was carried out using linear mixed models, with the three post-irradiation time groups, treatment (randomisation) and their interaction as fixed effects and patient as random effect. The overall treatment effect thus represents the difference between the randomisation arms excluding baseline. Figures were created to show the descriptive means and 95% confidence intervals at each time group for both randomisation arms. To check if the natural ageing process of the untreated breast had changed the contour and volume difference between the treated and the

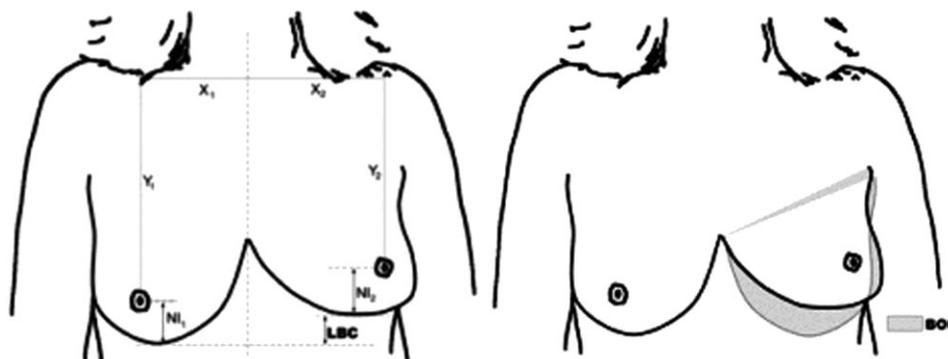


Figure 1. Schematic illustration of the measurement tools.

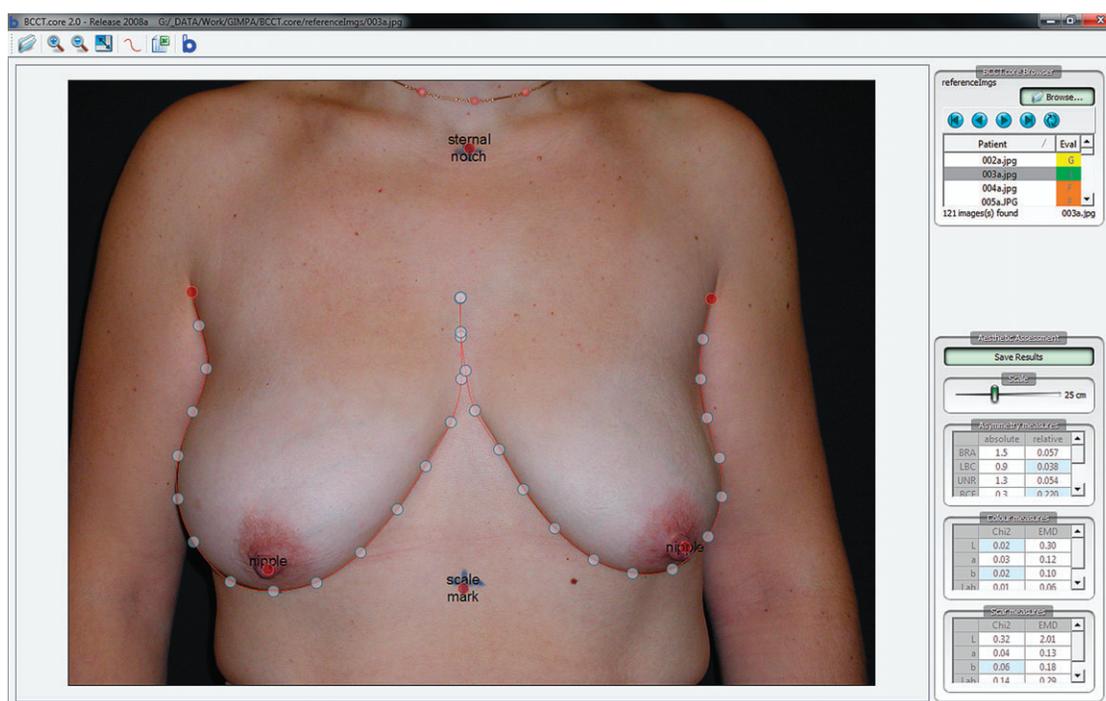


Figure 2. Illustration of the use of the measurements tools in a specific case.

untreated breast, a mixed model analysis was used for Y (the distance of the nipple to a point on the level of the sternal notch). In order to study which patient, tumour and treatment influenced the development with time on pBRA, pLBC and pBOD, a linear mixed model analysis was carried out, with the categorical time variable replaced by a continuous one (years from randomisation). In univariate and multivariate analyses, the covariate and their interaction with time were initially considered together and interaction of the covariate with time was removed from the model when not significant. Variables trend significant in univariate analysis ($P < 0.10$) were selected for multivariate analysis. Multivariate analyses proceeded with these selected variables using forward selection. A P value of <0.05 was considered statistically significant. To check the results of the BCCT.core software programme and to compare our results to the results of the entire patient population of the boost versus no boost trial, we compared these 14 curves to the curves of development of moderate fibrosis in the breasts and global cosmetic result (these items were scored in the boost versus no boost trial). Time till fibrosis was analysed with Kaplan–Meier survival curves and was tested with the log-rank test.

results

study population characteristics

The total number of randomised patients in the boost versus no boost trial accrued from Tilburg and Utrecht was 1.435 patients (Tilburg 826, Utrecht 609). We, ultimately, received pictures suitable for our study of 348 patients. Breast cancer-related reasons for missing cases were cases with recurrent disease in the ipsilateral breast ($n = 154$), distant metastases ($n = 245$) and secondary primary breast cancers ($n = 107$), who died due to breast cancer ($n = 59$). The remaining two reasons for missing cases were an inadequate follow-up as well as a too short follow-up period (<6 years). The distribution of tumour location is shown in Figure 3. We grouped the tumour

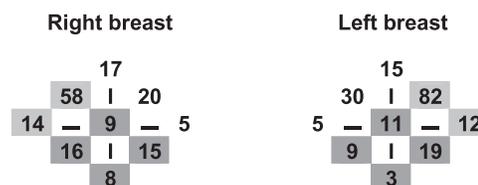


Figure 3. The location of the primary tumour in the breast is represented by total numbers in each corresponding quadrant of the breast. Grey indicates the different categories: white, medial-up; light grey, lateral; dark grey, central-under.

locations into three separate categories: (i) lateral, the lateral and lateral upper quadrant (166 patients, 47.7%); (ii) medial-up, the upper, medial upper and medial quadrant (92 patients, 26.4%); (iii) central-lower, the medial lower, lower, lateral lower quadrant and central part of the breast (90 patients, 25.9%). In our study population, treatment characteristics (Table S2, available as supplementary data in *Annals of Oncology* online). Between the no boost and boost group did not differ significantly. Of all 348 patients, 169 were randomised in the ‘no boost’ arm of the trial and 179 in the ‘boost’ arm. All patients underwent axillary dissection; the major part of which was carried out discontinuously with the tumour excision. The tumour excision volume was on average 100–200 cm³, (range: 50–300 cm³). In most cases, the dose distribution was homogeneous and was in line with the guidelines of the International Commission on Radiation Units report 50 [23]. The median boost dose was 16 Gy, given in eight fractions of 2 Gy. In the majority of the cases, the boost dose was given with electrons (74.9% versus 20.1% photons). Of all boost target volumes, 30.7% were 100–150 cm³, 18.4% were <100 cm³ and 50.9% were >150 cm³. A total of 47 patients

received adjuvant chemotherapy. A larger number of patients in the boost group received adjuvant chemotherapy than in the no boost group (18.5 versus 8.3%). For 34 (9.8%) of these patients, chemotherapy started after radiotherapy. Tamoxifen was administered in 55 patients, 15.6% in boost group, 16.0% in the no boost group. In most of these patients, tamoxifen started before the radiotherapy (81.8%). In the EORTC boost versus no boost trial, complications in the breast and axilla were scored after surgery and before the start of radiotherapy (Table S3, available as supplementary data in *Annals of Oncology* online). There were no significant differences in number and type of complications between the no boost and boost group (31.0% versus 35.2%), respectively.

the seven dimensionless asymmetry features

With the BCCT.core software programme, we extracted from the patients' pictures seven dimensionless features for breast fibrosis. For each feature, we noted no significant difference of the start level of the curve ($t = 0$, before start radiotherapy) between the boost and the no boost group. After 3 years follow-up, a significant difference was observed for six out of seven indices (not for pBCE). After 3 years, however, it appeared that the difference between the slopes of the boost cases versus the no boost cases had disappeared. This phenomenon was observed until 9 years of follow-up and the degree of fibrosis was worse for the patients randomised to receive a boost dose (Figure 4).

the degree of fibrosis

We evaluated which patient, tumour or treatment-related factors were associated with an increased degree of fibrosis. Therefore, the following 12 variables were analysed: age, menopausal status, tumour location, T-stage, excision volume, complication, maximum dose with the WBI, WBI modality (Co-60 versus accelerator), treatment with a boost (or not), boost modality (electrons versus photons), boost volume and the use of adjuvant tamoxifen. The majority of these variables was also evaluated in Vrieling's study on cosmetic results of the boost versus no boost trial [10]. The impact of these factors was checked on the pBRA (nipple and breast retraction), pLBC ('lifting' of the breast) and pBOD (contour and volume changes). We concluded that pBRA, pLBC and pBOD are the three most relevant variables representing various aspects of breast fibrosis. These analyses showed that breast and nipple retractions were both significantly associated with a larger excision volume ($P < 0.001$), giving a boost treatment ($P = 0.002$) and giving a boost with photons instead of electrons ($P = 0.018$). Young age ($P = 0.038$), large excision volumes ($P = 0.030$) and giving a boost treatment ($P = 0.030$) all were significantly associated with lifting of the breast. There was a negative effect on volume and contour changes of the treated breast associated with young age ($P < 0.001$), tumours located in the central-under quadrant ($P < 0.001$), large excision volumes ($P < 0.001$) and giving a boost treatment ($P = 0.004$) (Table 1). Finally, we determined the subjective scores (no-, slightly-, moderate- and severe fibrosis) of our cases, as registered by the physicians participating in the boost versus no boost trial. We found that for none of the patients the presence of 'severe fibrosis' was registered. Three patients

(1.8%) in the no boost, and 28 patients (15.6%) in the boost arm developed moderate fibrosis ($P < 0.001$) after 6 years.

the natural ageing process of the untreated breast

We checked if the relative difference between the treated and untreated breast was increased by the natural ageing process of the untreated breast (loss of elasticity, more pending of the breast and increase of the downwards inclination of the nipple). We created a curve of the change in time of the distance of the nipple to a point on the level of the sternal notch (Y) of the untreated breast (Figure 5). There was no significant increase of this value in time. This implies that the natural ageing process does not have a significant influence on the relative difference between the treated and untreated breast, at least up to 6 years of follow-up.

discussion

the degree of fibrosis

In our series, we confirmed the association between applying a boost dose and the degree of fibrosis [11]. We also found that the degree of (objectively assessed) fibrosis of the irradiated breast increased with time. After 3 years, the process of fibrosis still continued. Between the slopes of the boost versus the no boost curves, however, no differences were noted anymore. The fact that the difference in pace of the development of fibrosis is pronounced in the first 3 years and is most pronounced in the boost group, can be interpreted as proof that giving a boost results in more formation of scar tissue (also called fatty tissue necrosis or fibrosis). The development of fibrosis after 3 years in the boost and no boost arm develops at the same pace and suggests that WBI has also long-term effect on breast tissue.

multivariate analyses

After multivariate analysis on the slopes of pBRA, pLBC and pBAD, we noticed that a boost of 16 Gy was one of the strongest variables predicting a higher degree of fibrosis. Other variables that turned out to be of significance were: a larger excision volume (for pBRA, pLBC and pBOD), a boost with photons instead of electrons (pBRA), young age (pLBC, pBOD) and tumours in the central lower quadrant of the breast (pBOD).

Vrieling et al. [10] reported that the prognostic factors for poorer cosmetic outcome included the following as well: giving a boost, larger excision volumes and tumours located in the central upper quadrant of the breast. They also found large excision volumes were associated with worsening of the cosmetic outcome. A higher maximum dose in the central plane also turned out to be of significance in their study. In our study, with a more limited number of cases and analysing the relevance of fibrosis, we were unable to confirm these associations [23, 24].

Collette et al. [25] developed a model predicting the risk of moderate to severe (clinically assessed) fibrosis in time on 3624 patients participating in the boost versus no boost trial. They found that the risk of fibrosis increased with higher maximum WBI doses. In the boost arm, the risk on fibrosis further

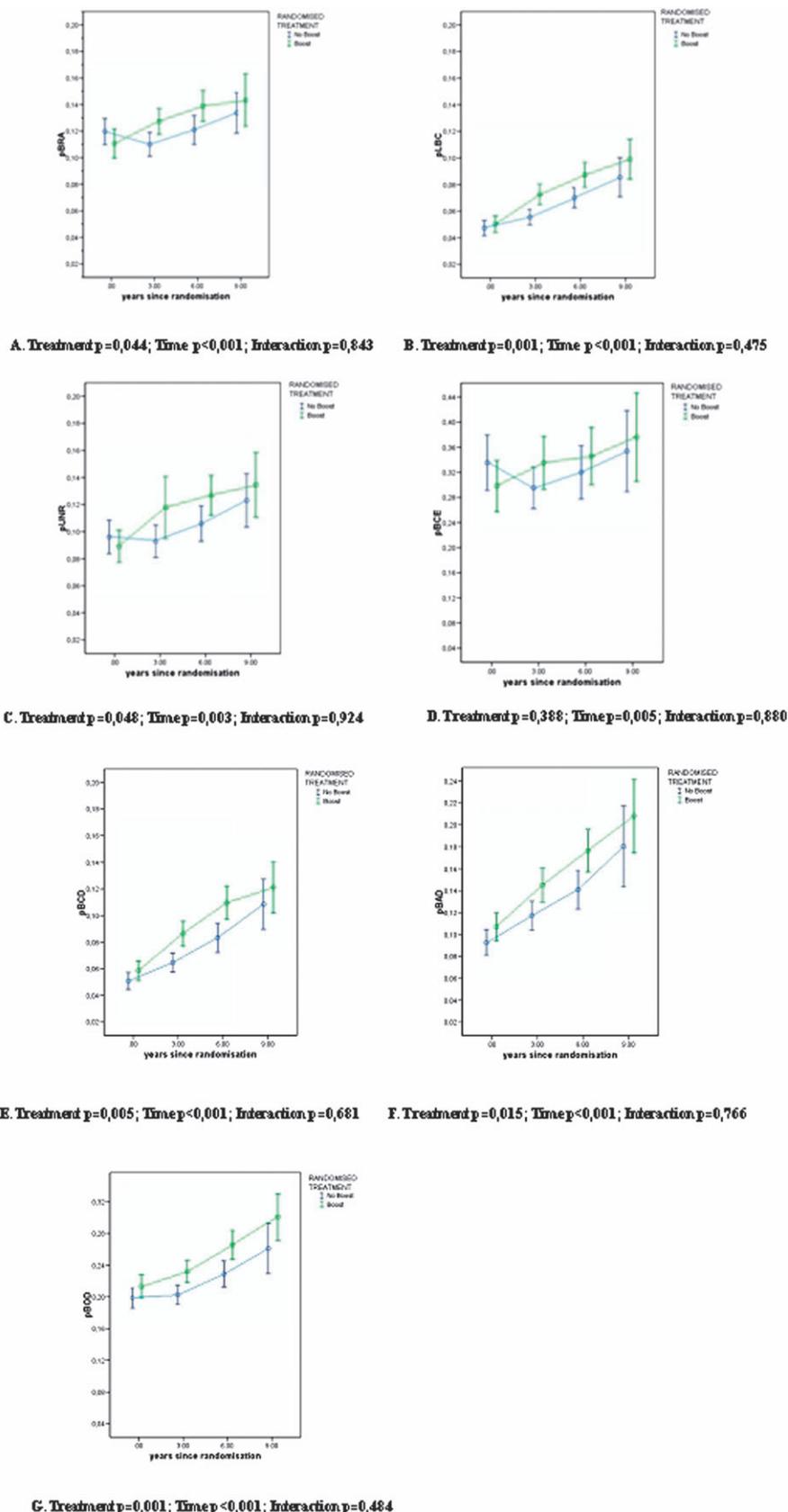


Figure 4. Curves of the seven dimensionless asymmetry features with time. (A) pBRA (relative difference in breast retraction assessment), (B) pLBC (relative difference in lower breast contour), (C) pUNR (relative difference in upward nipple retraction), (D) pBCE (relative difference in breast compliance evaluation), (E) pBCD (relative breast contour difference), (F) pBAD (relative breast area difference) and (G) pBOD (relative breast overlap difference).

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Table 1. The results of the univariate and multivariate analyses for pBRA, pLBC and pBOD

Factor	pBRA		pLBC		pBOD	
	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate
Age	n.s.	n.s.	$P = 0.01$	$P = 0.038$	$P = 0.001$	$P < 0.001$
Menopause	n.s.	n.s.	$P = 0.013$	n.s.	n.s.	n.s.
Tumour location	$P = 0.017$	n.s.	n.s.	n.s.	$P = 0.003$	$P < 0.001$
pT-stage	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Excision volume	$P < 0.001$	$P < 0.001$	$P = 0.002$	$P = 0.030$	$P = 0.003$	$P < 0.001$
Complications	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Maximum WBI dose	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
WBI energy	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Boost treatment	$P < 0.001$	$P = 0.002$	$P < 0.001$	$P = 0.030$	$P < 0.001$	$P = 0.004$
Boost modality	$P = 0.045$	$P = 0.016$	$P = 0.009$	n.s.	n.s.	n.s.
Boost volume	n.s.	n.s.	$P < 0.001$	n.s.	$P = 0.002$	n.s.
Tamoxifen	$P = 0.044$	n.s.	$P = 0.071$	n.s.	n.s.	n.s.

n.s., not significant; pBRA, the relative breast retraction assessment; pBOD, the relative breast overlap difference; pLBC, the relative lower breast contour; WBI, whole-breast irradiation.

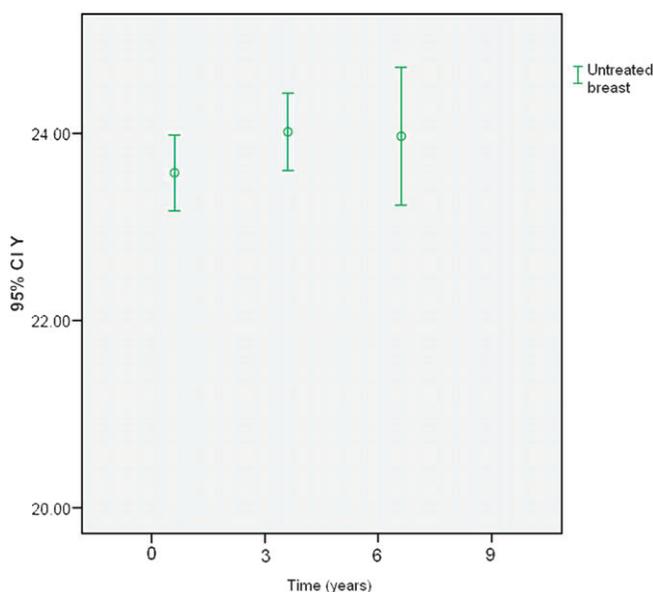


Figure 5. The natural ageing process of the untreated breast Y (distance of the nipple to a point on the level of the sternal notch), $n = 348$.

increased if patients received tamoxifen, in the presence of postoperative breast oedema or haematoma and when the boost was given with photons, Co-60 or brachytherapy and higher electron energies. In our study, a photon boost also turned out to be of significance. This latter might be explained by the fact that boost volumes using photons instead of electrons were on average twice as large [26].

The effect of chemotherapy or tamoxifen, as described in other studies [27–35], was not found to be of significance in our analysis. Other factors being prognostic for fibrosis in Collette's model were postoperative haematoma and oedema. This was in line with the reports of others [10, 36]. We were not able to confirm these findings. We noted that young age was an independent factor for having poorer results for pLBC and pBOD, thus more lifting and more contour and volume

changes of the treated breast. The independent effect of age on cosmesis has been described in earlier publications [28, 37–40] and cannot be explained completely by larger tumours or larger excision volumes, more re-excisions or more systemic treatments. This age factor is nowadays of importance, because younger women have a higher probability of local recurrence after BCT [8, 9, 41, 42]. Apart from objective scores, subjective scores, specifically dealing with the cosmetic result as determined both by physicians and patients, are of great importance. The cosmetic result is of great importance for body image, emotional reactions, sexuality and quality of life [43–49]. In the EORTC boost versus no boost trial, no quality of life data were obtained. Hence, it was not possible in our study to compare the objectively derived fibrosis scores with the quality of life scores.

conclusions

Specifically, in the first 3 years after treatment, the boost dose worsens the change in breast appearance. After 3 years, the process of fibrosis still continued. Between the slopes of the boost curves and the no boost curves, however, no differences were noted anymore. Finally, we found that the method estimating the degree of fibrosis with the use of the dimensionless asymmetry features has the advantages of being objective, time efficient and reproducible.

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disclosure

The authors declare no conflicts of interest.

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