Evaluation of cosmesis after hypo fractionated, norm fractionated and intraoperative breast radiotherapy: A photographic evaluation study of patients from prospective trials; KOSIMA, TARGIT-A and TARGIT-E

Tarek Ellethy[1,2 *], Grit Welzel[1], Elena Sperk[1], Christian Neumaier[1], Benjamin Tuschy[3], Sebastian Berlit[3], Svetlana Hetjens[4], Michael Ehmann[1], Marc Sütterlin[3], Frederik Wenz[1], Mostafa E Abdel-Wanis[2], Dalia Osama[2], Samir Shehata[5], Yasser Abo-Madyan[1]

[1]Department of Radiation Oncology, Universitätsmedizin Mannheim, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany

[2]Department of Radiotherapy and Nuclear Medicine, South Egypt Cancer Institute, Assiut University, Assiut, Egypt

[3]Department of Obstetrics and Gynaecology, Universitätsmedizin Mannheim, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany

[4]Department of Medical Statistics and Biomathematics, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany Clinical

[5]Department of Oncology and Nuclear Medicine, Faculty of Medicine, Assiut University, Assiut, Egypt

*****Corresponding author E-mail: dr.t84egypt@yahoo.com

Abstract

Purpose: Photographic documentation of breast changes after breast radiotherapy (RT) is a helpful tool to both subjectively and objectively evaluate cosmesis. This study aimed to evaluate cosmesis in breast cancer patients after receiving hypo fractionated whole breast RT (HF-WBRT), norm fractionated (NF-WBRT), intraoperative RT (IORT) or combined WBRT/IORT within prospective studies.

Methods: After excluding files with missing or inadequate photos from three prospective clinical trials (KOSIMA, TARGIT-A & TARGIT-E) 205 patients were included in subjective analysis while 185 patients were included in the objective analysis 2 years after RT respectively. Subjective evaluation was done using the Harvard scale. Objective evaluation was done by assessing percentage breast retraction. Based on the treatment received, patients were divided into 5 groups: 1.HF-WBRT 40.05Gy/2.67Gy±Boost, 2.NF-WBRT 50Gy/2Gy±Boost, 3.NF-WBRT 56Gy/2Gy, 4.IORT 20Gy, 5.IORT 20Gy +WBRT 46Gy/2Gy.

Results: Subjectively, the rate of acceptable cosmesis was 84% while objectively it was around 56%. At 2 years, there was neither a subjective ($p=0.55$) nor objective ($p=0.88$) significant difference in cosmesis between the 5 treatment groups. Regarding possible factors affecting cosmesis at 2 years, there were no differences concerning age, smoking, body mass index, chemotherapy, hormone therapy or type of axillary surgery. Significantly better cosmesis was observed in patients with tumor location in the upper outer quadrant ($p<0.001$) and with percentage of excised to total breast volume <10% ($p<0.0294$).

Conclusions: After two years of follow-up, adjuvant radiotherapy caused only minor cosmetic deterioration based on subjective assessment of photographic documentation. The influence of the treatment method was minimal. Hypo fractionated WBRT and IORT as a single treatment or as a boost were cosmetically similar to norm fractionated WBRT. Tumor location and excised breast volume were the only factors significantly affecting cosmetic outcome.

Introduction

Adjuvant breast radiotherapy (RT) is an integral part of breast conservation therapy. Norm fractionated (NF) whole breast radiotherapy (WBRT) has been the most widely practiced treatment standard. Safety and efficacy achieved through WBRT are still used as a base for comparison with newer standards and techniques (1).

In the past two decades, various radiotherapy options were clinically tested as alternatives including WBRT with different fractionation schedules and partial breast irradiation (PBI) (2). Hypo fractionated (HF) WBRT schedules were proven safe in multiple randomized clinical trials with satisfactory cosmetic and oncological outcomes when compared to NF-WBRT (3, 4).

For patients with early stage breast cancer PBI has been tested as an alternative approach using several modalities including brachytherapy, external beam irradiation

(EBRT) and intraoperative RT (IORT) aiming to shorten RT duration and reduce the irradiated breast volume. Studies testing these different techniques showed promising oncological outcome in patients with low-risk profile. That encouraged different radiation oncology societies to acknowledge PBI as a treatment option for properly selected patients (5-7) but still recommended its use within clinical trials.

Evaluation of toxicity and long term cosmetic outcome of these newer techniques is a matter of ongoing investigation. Several studies reported that these modalities were safe with minimal toxicity, acceptable cosmetic outcome and quality of life (8-16). However, other investigators have found that accelerated PBI was associated with increased rates of unacceptable cosmetic results and higher late radiation toxicity compared with conventional WBRT (17, 18). Such inconsistencies are mostly due to interactions between irradiated breast volume (19), dose per fraction and total dose (20). Higher dose per fraction and/or total dose to a large volume increase the risk of side effects. This requires further evaluation of different PBI techniques and dose schedules.

The aim of this study is to shed more light on possible differences in breast cosmetic outcome and determine factors affecting cosmesis in patients treated using five different standardized methods within prospective studies in a single specialized center.

Materials and Methods

The photographic evaluation was part of the initial design of the 3 prospective clinical trials; KOSIMA (ARO2010-3, NCT01403779), TARGIT-A (NCT00983684) and TARGIT-E (NCT01299987). Photos and clinical data of the patients participated in these trials were used to assess patient and treatment related factors that may affect the cosmetic outcome. Patients were classified into five groups according to radiotherapy technique, treatment dose and fractionation schedule:

Group 1: patients received HF-WBRT of 40 Gy / 15 fractions ± Boost of 16 Gy / 8 fractions.

Group 2: patients received NF-WBRT of 50 Gy / 25 fractions ± Boost of 16 Gy / 8 fractions.

Group 3: patients received NF-WBRT of 56 Gy / 28 fractions without boost.

Group 4: patients received IORT with low kV x-rays to the tumor bed, with a single dose of 20 Gy at the applicator surface.

Group 5: patients received IORT with low kV x-rays to the tumor bed, with a single dose of 20 Gy at the applicator surface + NF-WBRT of 46 Gy / 23 fractions.

All patients were treated in a single university radiation oncology center. WBRT was performed with a linear accelerator and IORT with the INTRABEAM® System. All data including medical history, diagnosis, pathology and treatment reports were evaluated with a focus on the potential influencing factors that may affect cosmesis after 2 years of RT. These factors were divided into 3 categories: 1) Patient-related factors (age, smoking, BMI); 2) Tumor-related factors (tumor size, site); and 3) Treatment-related factors (percentage of excised to total breast volume, type of axillary surgery, chemotherapy, hormone therapy, radiation treatment technique, use of EBRT boost).

Cosmetic assessment

Cosmesis was evaluated using digital photographs that were taken after 2 years of radiotherapy under standardized photographic conditions for all patients in three positions: 1) A frontal view with the arms on the waist; 2) A frontal with the arms above the head; and 3) A side view with the arms above the head. In each photo, the patient's neck, chest and upper abdomen were included. Photos that were not acquired according to these standards were excluded. Other exclusion criteria included patients that underwent mastectomy in course of their follow-up due to recurrences and patients who developed contralateral breast cancer.

Subjective evaluation was done by a panel composed of 9 observers of different backgrounds. Team-1 included 4 expert radiation oncologists, Team-2 included 2 expert breast-surgeons and Team-3 included 3 non-medical observers. All observers were blinded to the type of treatment received by the patients. Cosmetic assessment was done according to the standard Harvard scale (Fig 1) (21).

Fig 1. Subjective evaluation according to the Harvard scale

Objective evaluation was done through assessing breast retraction which reflects the symmetry and position of the nipple. Breast retraction assessment (BRA) was measured according to the method described by Pezner by calculating the difference in distance from the sternal notch to the nipple in both breasts. To overcome the differences in patients' breast size we used the percentage BRA (pBRA) instead of BRA as it is less dependent on the absolute size of the breast and measures the retraction as a percentage rather than a distance (22). Patients with a pBRA score ≤6 were considered to have excellent cosmesis, >6 to <8 good, fair and poor with scores ≥ 8 (23).

Manual measurements to calculate pBRA were performed by one person, who neither participated in the treatment of patients nor in subjective evaluation. In our trial, patients with excellent-good cosmetic results are considered to have acceptable cosmesis and patients with fair-poor cosmetic results are considered to have unacceptable cosmesis.

Since the objective evaluation requires the photos to be taken under strict standardized conditions, 20 patients were excluded due to incorrect patient positioning or shooting angle. Fig 2 shows the number of patients included in this analysis.

Fig 2. Patient stratification

Compliance with ethical standards

The photographic evaluation was part of the initial design of the 3 prospective clinical trials; KOSIMA (ARO2010-3, NCT01403779), TARGIT-A (NCT00983684) and TARGIT-E (NCT01299987). All patients provided a written informed consent. All procedures performed were approved by the ethical committee of the Mannheim faculty of Medicine, Heidelberg University.

Statistical consideration

Categorical group differences were examined using the Chi-square test or Fisher's exact test as appropriate. To describe the agreement between objective and subjective methods after 2 years of RT, McNemar's test and Cohen's kappa statistic were calculated. A kappa statistics of 0 was considered to demonstrate no agreement, 0 - 0.20 poor agreement, 0.21 - 0.40 fair agreement, 0.41 - 0.60 moderate agreement, 0.61 - 0.80 good agreement and 0.81 to 1.00 very good agreement (24).

Estimating the inter-observer variability for the three teams of observers was done using Cochran's Q test with overall kappa coefficient of Fleiss. Univariate and multivariable binary logistic regression was used to investigate the association of patient, tumor and treatment-related factors with the cosmetic outcome based on the subjective evaluation at 2 years.

All statistical calculations were done with the SAS software, release 9.3 (SAS Institute Inc., Cary, NC, USA). Statistical significance has been assumed for p values less than 0.05.

Results

After 2 years of radiotherapy, 205 and 185 patients were included in the subjective and objective analysis respectively (Fig 2). There was no significant difference between the 5 treatment groups in relation to patient characteristics except for T-stage (p=0.0001) and N-stage (p=0.0331). This is due to inherent differences in the patient selection criteria of the three used clinical trials. Further details about the patient and tumor characteristics are shown in Table 1.

Evaluation of cosmetic outcome

Overall subjective evaluation of the 5 treatment groups revealed 83.9% acceptable and 16.1% unacceptable cosmesis with no significant difference between the 5 treatment groups (p=0.55) (Fig 3A). Objective evaluation revealed 55.7% acceptable and 44.3% unacceptable cosmesis. Regarding the cosmetic outcome of each radiation treatment group, no significant difference was observed (p=0.88) (Fig 3B).

Fig 3. Overall cosmetic outcome.

Graph (A) represents subjective evaluation using the Harvard scale while graph (B) represents objective evaluation using percentage Breast Retraction Assessment (pBRA). WBRT: whole breast radiotherapy. IORT: Intraoperative radiotherapy. HF: Hypo fractionated. NF: Norm fractionated.

Factors affecting cosmetic outcome

Univariate and multivariate analysis of factors that may affect the cosmetic outcome after 2 years of RT showed no relationship between cosmesis and age, BMI, current smoking status, previous smoking status, chemotherapy, hormone therapy or type of axillary surgery. The T- and N-stage were not further analyzed as factors that might affect cosmesis since the excised breast volume and type of axillary surgery were considered more representable and influencing on cosmesis. Only tumor location and percentage of excised to total breast volume significantly affected the results in both univariate and multivariate analysis. With 92.5% acceptable cosmesis, the upper-outer tumor site was an independent factor for significantly better cosmesis compared to other tumor sites especially the retromammary site where the

acceptable results reached only 50%. The other independent factor was the percentage of excised to total breast volume. When exceeding 10%, acceptable results dropped from 88.2% to 76%. Further details are given in Table 2.
A multivariate regression model with Receiver-operating characteristic curve (ROC) was created to predict the influence of many factors (age, BMI, current smoking status, previous smoking status, chemotherapy, hormone therapy, type of axillary surgery, percentage of excised breast volume, tumor location and method of radiotherapy) on overall cosmetic outcome after 2 years. EBRT boost was not included because patients with NF-WBRT 56Gy, IORT 20Gy, and combined IORT/WBRT 20Gy/46Gy received no EBRT boost. The AUC was 0.77 (0.69; 0.85) indicating fair predictive power of the model.

Regarding the EBRT boost, univariate analysis was calculated for patients treated with HF-WBRT (40 Gy) and NF-WBRT (50 Gy) who received 16 Gy EBRT boost versus those who did not. From the 55 patients who received the boost, 80% had acceptable and 20% unacceptable cosmetic results versus 81% and 19% respectively in those who did not (p=0.85).

Validation of evaluation methods

The inter-observer agreement of the cosmetic outcome among the three observer teams was moderate with overall kappa coefficient of 0.41. There was good agreement between the individual team result and the overall result (Team 1: Kappa=0.72; Team 2: Kappa=0.78; Team 3: Kappa=0.63). Fair agreement was observed between the results of subjective evaluation of the individual teams and pBRA (Team 1: Kappa=0.32; Team 2: Kappa=0.12; Team 3: Kappa=0.29). Agreement between subjective and objective methods was poor in which Kappa was 0.20 in which 51.9% of the patients were rated acceptable in both subjective and objective evaluations, 11.3% were rated unacceptable in both, 32.9% were rated acceptable subjectively but unacceptable objectively and 3.9% were rated unacceptable subjectively but acceptable objectively. In Table 3, patients with similar outcome according to subjective and objective evaluations (either both acceptable or both unacceptable) were grouped together and tested against factors affecting cosmesis.

Discussion

Over the past two decades there has been an increase in the use of hypo fractionated treatments and IORT for which the cosmetic results compared to norm fractionated schedules is still an interesting area of research. A direct comparison of the five different treatment methods has, to the best of our knowledge, never been previously done. Although this study is not randomized, all analyzed cases were treated at the same center under similar standardized conditions within prospective controlled trials which provides a sufficient base for comparison.
While self-assessment reflects patient satisfaction, it is affected by many factors like the patient's quality of life, the psychological adaptation to cosmetic changes and arm edema (25, 26). An observer based subjective assessment is relatively independent but less reflective of patient satisfaction. The use of patients' photographs has also the advantage of bringing low cost and high efficiency to evaluation process but has the disadvantage of missing subtle skin changes and fibrosis. Few reports observed how physicians tended to rate cosmesis less favorably than patients (27). In this trial we focused on using the standardized Harvard scale and a panel of observers with different medical and non-medical backgrounds aiming to represent a broad range of opinions.

Objective methods are not observer or patient dependent and hence more reproducible. Various tools are available for objective photographic evaluation of breast cosmesis including manual and software assisted methods. In our study we evaluated cosmesis according to Pezner, which is a widely used method that provides a simple but effective comparison of breast geometric asymmetries (28, 29).

Although the agreement between the subjective and objective analysis was statistically poor with a difference close to 30%, both methods failed to show a statistically significant difference between the five treatment methods (Fig 3). Further analysis of the patient cohorts with non-agreement versus those with agreement in both methods (Table 3) did not reveal a significantly obvious causing factor. One explanation for this lack of agreement is that each method assesses a different aspect of cosmesis.

In this trial the overall acceptable cosmesis based on photographic evaluation reached 83.9% at 2 years. Garsa et al. reported 94% acceptable results by the treating physicians after 2 years of RT (28). Extending the follow-up over 5 years may yield a larger difference in breast appearance as the process of fibrosis associated with RT may continue till (at least) 9 years after RT (30). Whelan et al. reported 5% deterioration of cosmesis after 5 years and 13% after 10 years for patients treated with NF- and HF-WBRT (3).

The START trials reported equivalent local control with similar breast and skin side effects when

comparing NF-WBRT to most of the tested HF-WBRT schedules (significantly worse side effects were observed only in the 39 Gy arm) (4). The Ontario trial has similarly shown equivalent oncological (local tumor control) as well as cosmetic outcome between NF- and HF-WBRT after 10 years of follow-up. Acceptable cosmetic results were reported to be 71.3% and 69.8% for women who received NF-WBRT and HF-WBRT respectively (3). In our analysis, there was no significant cosmetic difference between patients who received WBRT with NF or HF schedules after 2 years.

On the contrary, the RAPID trial reported worse cosmesis after PBI using three-dimensional conformal EBRT compared to NF- or HF-WBRT. Postoperatively, the proportions of patients with unacceptable cosmesis were 18.9% and 17.0% for PBI and WBRT respectively (p=0.25), at 3 years 29.0% vs. 16.5% (p<0.001) and at 5 years 32.8% vs. 13.4% (p<0.001) (18). Another PBI multicenter clinical trial using Mammosite balloon based brachytherapy reported minor cosmetic deterioration over time. Delivering 34 Gy over 10 fractions, acceptable cosmesis was 93.4% and 90.8% at 3 and 6 years respectively (31).

Not surprisingly given the very small volume irradiated, IORT yields cosmetic outcome superior to whole breast RT. A trial by Corica et al. investigated cosmetic outcome for single dose IORT with low kV x-rays versus WBRT (a subset from TARGIT-A trial). Patients who were treated with IORT had similar self-reported cosmetic results compared to patients treated with WBRT with 79% and 80% acceptable results after 2 years respectively. At 5 years, the difference increased in favor of IORT with acceptable cosmetic outcome being 90% compared to 68.4% for WBRT (p=0.042) (32). The long term cosmetic outcome was evaluated in the Salzburg Experience (median follow-up 45 months) for 403 patients after electron IORT boost of 10 Gy. Assessment was done by the treating physicians using photo-documentation as well as self-reporting by the patients. The patients' self-assessments and physicians' evaluation yielded around 93% and 64% acceptable results respectively. The authors concluded that electron IORT boost of 10 Gy is associated with excellent cosmetic results (33). In our trial, the 2 year cosmetic outcome of single modality TARGIT IORT, IORT as a boost (IORT/WBRT) and different WBRT schedules was not significantly different (p=0.55). However after longer follow-up, a significant cosmetic outcome different may be observed.

A recent study in France reported significantly better cosmetic outcomes for early breast cancer patients treated with IORT only than with IORT+WBRT (p<0,001). Evaluation of cosmesis was done after 36 months by patients self-evaluation as well as by two radiation oncologists, on a 1–10 scale. Although cosmetic results were excellent in the IORT group and still good in the combined IORT+WBRT group but the study concluded that cosmetic results of IORT remained good and in range with those reported in the literature in patients treated with WBRT and boost, which is consistent with our conclusion. It should be noted that, in our study, the IORT arm is underrepresented due to low number of patients suitable for evaluation. Increasing the number of patients in this arm may add to the power of the study (34).

Age has been controversially reported upon as a contributing factor. Ozmen et al. reported 88.7% acceptable results after mean follow-up time of 37.9 months. The mean age for patients with acceptable results was 57.6 years and for unacceptable results was 58.1 years (p=0.78) (35). This concurs with our as well as other studies (32). On the contrary, lower cosmetic scores with increasing age which is associated with increased fibro-fatty tissue and the subsequent fibrosis was also reported (36, 37). Other patient related factors like BMI, menopausal status and race and their impact on cosmetic outcome were discussed by many investigators (3, 36). Physicians' assessment of cosmesis revealed a significantly increased risk of unacceptable cosmesis with BMI ≥25, tumor size >2 cm and large breast size > cup-C (29). In our analysis, patient related factors like BMI, current smoking and previous smoking status did not affect cosmesis after 2 years of RT.

Most authors agree that surgical factors appear to be a bigger driver of the cosmetic outcome. Multiple excisions, large volume of excision, Tumor's size relative to the breast size and type of breast surgery are influencing factors that are associated with lower cosmetic results (35, 37-39). In our study we chose the percentage of the excised volume as the dominant factor that represents many surgical factors at the same time. It gives an idea about the tumor size relative to the breast size and/or excised volume relative to the total breast volume also about type of breast surgery. As reported, large excision volume which may be associated with large tumor relative to breast size, multiple excisions or extensive excision is associated with lower cosmetic results. Cochrane et al. reported better cosmetic outcome and patient satisfaction when the percentage of the excised volume was <10% of the whole breast (40). In our clinical trial, regardless of the type of radiotherapy, univariate and multivariate analysis revealed

significantly better cosmetic outcome with less than 10% excision of total breast volume.

Regarding the location of the tumor, better cosmetic outcome and patient's satisfaction was reported with tumors located in the outer half compared to those in the inner half of the breast which was associated with greater nipple deviation (40). However Charfare et al. reported that tumor location was not a significant factor affecting cosmesis (47/77 and 8/18 patients had acceptable results in outer and inner breast half respectively, p=0.39) (38). In our study, univariate and multivariate analysis revealed that location of the tumor is significantly affecting cosmesis. Better cosmetic results were observed in upper-outer quadrant tumors and worst results in the retromammary region.

After two years follow-up adjuvant chemotherapy and hormone therapy were found to have no significant effect on cosmetic outcome, which agrees with some reports (29, 38). On the contrary, Garsa et al. reported that chemotherapy was strongly but not significantly associated with worse cosmetic outcome after 3 years follow-up with odds ratio (OR, 5.03; p=0.053) (28). Ozmen et al. reported 14% cosmetic deterioration in patients who received chemotherapy ($p<0.05$) after mean follow-up of 37.9 months (35), which is consistent with other clinical reports (37, 41). Another investigation reported that cosmetic deterioration increased from 9% to 13% with the addition of chemotherapy (p=0.04) while tamoxifen did not affect the cosmetic outcome (42).

This analysis is an attempt to provide a current and updated overview of cosmetic outcome using modern breast cancer treatment methods. The comparison of five differently treated patient groups in the same medical center, at the same period, in similar treatment conditions was revealing in terms of safety and feasibility of all examined methods which in turn may help to adjust these methods to individual cases without compromising oncological results. With longer follow-up differences between the treatment groups could possibly be revealed which is a motivator for further update of the data. The IORT group although relatively underrepresented it still provides important aspect that is generally lacking in the literature.

Conclusions

After two years of follow-up, adjuvant radiotherapy caused only minor cosmetic deterioration based on subjective assessment of photographic documentation. The influence of the treatment method was minimal. Hypo fractionated WBRT and IORT were cosmetically similar to norm fractionated WBRT. Tumor location and excised breast volume were the only factors significantly affecting cosmetic outcome.

Conflict of Interest

T.Ellethy, G.Welzel, A.Sperk, C.Neumaier, B.Tuschy, S.Berlit, S.Hetjens, D.Osama, S.Shehata, M.Abdelwanis and M.Sütterlin have nothing to disclose. M.Ehmann reports personal fees from Elekta AB Stockholm, during the conduct of the study. F.Wenz reports grants, personal fees and non-financial support from Elekta and Carl Zeiss Meditec, during the conduct of the study; grants and non-financial support from IBA, outside the submitted work. Y.Abo-Madyan reports personal fees from Carl Zeiss Meditec, during the conduct of the study.

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Table 1. Patient characteristics

		HF-WBRT 40Gy± 16Gy	NF-WBRT 50Gy ±16Gy	NF-WBRT 56Gy	IORT 20Gy	IORT/ WBRT 20Gy/46 Gy	Total N. (%)	p-value
Number of Patients		50	64	39	18	34	205	
Age	Mean ± SD	67.8±6.4	68.5±6.2	65.3±8.2	69.9±7.6	65.4±8.8	67.3±7.3	0.60[d]
	< 70	34 (68%)	38 (59.4%)	26 (66.7%)	9 (50%)	23(67.6%)	130 (63.4%)	
	≥ 70	16 (32%)	26 (40.6%)	13 (33.3%)	9 (50%)	11 (32.4%)	75 (36.6%)	
BMI	Normal	19 (38%)	30 (46.8)	18(46.2%)	4 (22.2%)	13 (38.2%)	84 (41%)	0.28[d]
	Overweight	22 (44%)	17 (26.6%)	12(30.8%)	11 (61%)	12 (35.3%)	74 (36.1%)	
	Obese	9 (18%)	17 (26.6%)	9 (23%)	3 (16.7)	9 (26.5%)	47 (22.9%)	
Site	Upper outer	31 (62%)	38 (59.3%)	25 (64.1%)	16 (88.8%)	23 (67.7%)	133 (64.9%)	0.33[e]
	Upper inner	9 (18%)	8 (12.5%)	5 (12.8%)	1 (5.6%)	2 (5.8%)	25 (12.2%)	
	Lower outer	6 (12%)	4 (6.3%)	2 (5.1%)	1 (5.6%)	5 (14.8%)	18 (8.8%)	
	Lower inner	3 (6%)	10 (15.6%)	6 (15.4%)	0 (0%)	4 (11.7%)	23 (11.2%)	
	Retromammary	1 (2%)	4 (6.3%)	1 (2.6%)	0 (0%)	0 (0%)	6 (2.9%)	
Current Smoking	No	45 (90%)	54 (84.4%)	31(79.5%)	14 (77.8%)	27 (79.4%)	171 (83.5%)	0.24[e]
	Yes	3 (6%)	6 (9.4%)	7 (17.9%)	0 (0%)	5 (14.7%)	21 (10.2%)	
	Unknown	2 (4%)	4 (6.3%)	1 (2.6%)	4 (22.2%)	2 (5.9%)	13 (6.3%)	
Previous Smoking	No	32 (64%)	37 (57.8%)	22(56.4%)	12 (66.7%)	17 (50%)	120 (58.5%)	0.27[d]
	Yes	16 (32%)	23 (35.9%)	16 (41%)	2 (1.1%)	15 (44.1%)	72 (35.1%)	
	Unknown	2 (4%)	4 (6.3%)	1 (2.6%)	4 (22.2%)	2 (5.9%)	13 (6.4%)	
T-Staging	pT1a	4 (8%)	3 (4.69%)	2 (5.1%)	0 (0%)	0 (0%)	9 (4.4%)	0.00001[e]
	pT1b	3 (6%)	15 (23.4%)	12 (30.8%)	7 (38.9%)	4 (11.8%)	41 (20%)	

	pT1c	16 (32%)	24 (37.5 %)	18 (46.2%)	10 (55.6 %)	26 (76.5%)	94 (45.9%)	
	pT2	17 (34%)	14 (21.9 %)	7 (17.9%)	1 (5.6%)	4 (11.8%)	43 (21%)	
	pT3	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)	
	pTis	9 (18%)	8 (12.5 %)	0 (0%)	0 (0%)	0 (0%)	17 (8.3%)	
N-Staging	pN0	48 (96%)	58 (90.6 %)	31 (79.5%)	17 (94.4 %)	25 (73.5%)	179 (87.3%)	0.033[e]
	pN1	2 (4%)	6 (9.4%)	7 (17.9%)	1 (5.6%)	8 (23.5%)	24 (11.7%)	
	pN2	0 (0%)	0 (0%)	1(2.6%)	0 (0%)	1 (2.9%)	2 (1%)	
Axillary surgery	AD[a]	8 (16%)	17 (26.6 %)	12(30. 8%)	2 (11.1 %)	12 (35.3%)	51 (24.9%)	0.18[d]
	SLN[b]	40 (80%)	47 (73.4 %)	27 (69.2%)	16 (89%)	22 (64.7%)	152 (74.2%)	
	No	2 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (0.9%)	
Percentage of excised volume	< 10 %	29 (58%)	33 (51.6 %)	23 (59%)	1 (5.6%)	24 (70.6%)	110 (53.7%)	0.12[d]
	≥ 10%	19 (38%)	26 (40.6 %)	16 (41%)	5 (27.7 %)	9 (26.5%)	75 (36.6%)	
	Unknown	2 (4%)	5 (7.8%)	0 (0%)	12 (66.6 %)	1 (2.9%)	20 (9.7%)	
CHT[c]	No	41 (82%)	53 (82.8 %)	31 (79.5%)	16 (88.9 %)	23 (67.6%)	164 (80%)	0.33[d]
	Yes	9 (18%)	11 (17.2 %)	8 (20.5%)	2 (11.1 %)	11 (32.4%)	41 (20%)	
Hormone therapy	No	11 (22%)	9 (14%)	2 (5.1%)	4 (22.2 %)	6 (17.6%)	32 (15.6%)	0.23[d]
	Yes	39 (78%)	55 (86%)	37 (94.9%)	14 (77.8 %)	28 (82.4%)	173 (84.4%)	

Abbreviations: [a]AD: Axillary dissection, [b]SLN: Sentinel lymph nodal dissection and [c]CHT: Chemotherapy. [d]p-value: Chi-square test, [e]p-value: Fisher's exact test.

Table 2. Factors affecting cosmetic outcome after 2 years of radiotherapy

Factors affecting cosmesis		Acceptable	Unacceptable	Total N. (%)	p-value	p-value[c]	Odds ratio 95% CI
Age	< 70	111 (84.6%)	19 (14.6%)	130 (63.4%)	0.45[a]	0.19	0.54 (0.21;1.36)
	≥ 70	61 (81.3%)	14 (18.7%)	75 (36.5%)			

BMI	Normal	70 (83.3%)	14 (16.7%)	84 (41%)	0.70[a]	0.63	0.87 (0.51;1.51)
	Overweight	64 (86.5%)	10 (13.5%)	74 (36.1%)			
	Obese	38 (80.9%)	9 (19.1%)	47 (22.9%)			
Current Smoking	No	143 (83.6%)	28 (16.4%)	171 (89%)	1.0[b]	0.89	1.12 (0.21;6.04)
	Yes	18 (85.7%)	3 (14.3%)	21 (11%)			
Previous Smoking	No	100 (83.3%)	20 (16.7%)	120 (62.5%)	0.80[a]	0.57	1.34 (0.49;3.63)
	Yes	61 (84.7%)	11 (15.3%)	72 (37.5%)			
Site	Upper-outer	123 (92.5%)	10 (7.5%)	133 (64.9%)	< 0.001[a]	0.0009	0.57 (0.4;0.79)
	Upper-inner	19 (76.0%)	6 (24.0%)	25 (12.2%)			
	Lower-outer	11 (61.1%)	7 (38.9%)	18 (8.8%)			
	Lower-inner	16 (69.6%)	7 (30.4%)	23 (11.2%)			
	Retromammary	3 (50.0%)	3 (50%)	6 (2.9%)			
Axillary surgery	Axillary dissection	43 (84.3%)	8 (15.7%)	51 (25%)	1.0[a]	0.98	0.99 (0.34;2.85)
	Sentinel node	127 (83.6%)	25 (16.4%)	152 (75%)			
Percentage of excised volume	< 10%	97 (88.2%)	13 (11.8%)	110 (59.5%)	0.029[a]	0.033	0.24 (0.07;0.89)
	≥ 10%	57 (76%)	18 (24%)	75 (40.5%)			
Hormone therapy	No	24 (75%)	8 (25.0%)	32 (15.6%)	0.14[a]	0.19	2.05 (0.7;5.99)
	Yes	148 (85.5%)	25 (14.5%)	173 (84.4%)			
Chemotherapy	No	139 (84.8%)	25 (15.2%)	164 (80%)	0.51[a]	0.24	0.51 (0.17;1.56)
	Yes	33 (80.5%)	8 (19.5%)	41 (20%)			
EBRT Boost	No	48 (81%)	11 (19%)	59 (51.8%)	0.85[a]	--[d]	--[d]
	Yes	44 (80%)	11 (20%)	55 (48.2%)			
Radiotherapy	HF-WBRT 40Gy±16Gy	41 (82%)	9 (18%)	50 (24.4%)	0.55[a]	0.56	1.1 (0.8;1.5

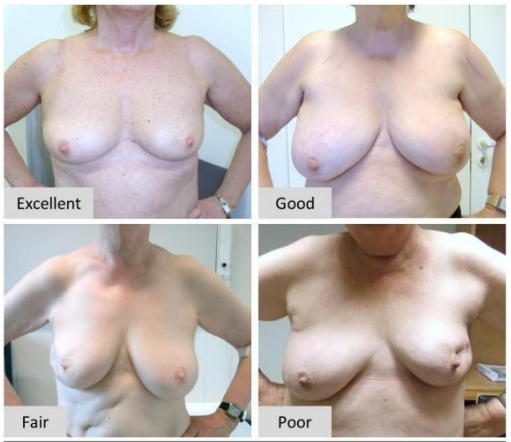
group	NF-WBRT 50Gy±16Gy	51 (79.7%)	13 (20.3%)	64 (31.2%)	)
	NF-WBRT 56Gy	36 (92.3%)	3 (7.7%)	39 (19%)	
	IORT 20Gy	15 (83.3%)	3 (16.7%)	18 (8.8%)	
	IORT/WBRT 20Gy/46Gy	29 (85.3%)	5 (14.7%)	34 (16.6%)	

[a]p-value: Univariate analysis, Chi-square test, [b]p-value: Univariate analysis, Fisher's exact test, [c]p-value: Multivariate analysis, logistic regression. [d]EBRT Boost was not included in the multivariate analysis and odds ratio as the patients of only two treatment groups received EBRT boost.

Table 3: Estimation of agreement between subjective and objective methods regarding factors affecting cosmetic outcome

Factors affecting cosmetic outcome		Non-agreement [a]	Agreement [b]	p-value [c]
Age	< 70	50 (73.5%)	71 (60.7%)	0.07
	≥ 70	18 (26.5%)	46 (39.3%)	7
BMI	Normal	25 (36.8%)	49 (41.9%)	0.76
	Overweight	26 (38.2%)	43 (36.8%)	
	Obese	17 (25.0%)	25 (21.4%)	
Current Smoking	No	58 (92.1%)	99 (88.4%)	0.44
	Yes	5 (7.9%)	13 (11.6%)	
Previous Smoking	No	43 (68.3%)	67 (59.8%)	0.27
	Yes	20 (31.7%)	45 (40.2%)	
Site	Upper-outer	41 (60.3%)	78 (66.7%)	0.07
	Upper-inner	13 (19.1%)	11 (9.4%)	6
	Lower-outer	8 (11.8%)	7 (6.0%)	
	Lower-inner	4 (5.9%)	18 (15.4%)	
	Retromammary	2 (2.9%)	3 (2.6%)	
Axillary surgery	Axillary dissection	15 (22.1%)	30 (26.1%)	0.54
	Sentinel node	53 (77.9%)	85 (73.9%)	
Percentage of excised volume	< 10%	37 (61.7%)	61 (57.5%)	0.60
	≥ 10%	23 (38.3%)	45 (42.5%)	
Hormone therapy	No	8 (11.8%)	19 (16.2%)	0.41
	Yes	60 (88.2%)	98 (83.8%)	
Chemotherapy	No	56 (82.4%)	94 (80.3%)	0.74
	Yes	12 (17.6%)	23 (19.7%)	
EBRT Boost	No	43 (63.2%)	89 (76.1%)	0.06
	Yes	25 (36.8%)	28 (23.9%)	3
Radiotherapy group	HF-WBRT 40Gy±16Gy	15 (22.1%)	33 (28.2%)	0.58
	NF-WBRT 50Gy±16Gy	21 (30.9%)	38 (32.5%)	
	NF-WBRT 56Gy	13 (19.1%)	20 (17.1%)	
	IORT 20Gy	5 (7.4%)	10 (8.5%)	
	IORT/WBRT 20Gy/46Gy	14 (20.6%)	16 (13.7%)	

[a]Non-agreement between subjective and objective results. [a]greement between subjective and objective results. [c]p-value: Univariate analysis, Chi-square test.



Harvard Scale			
Excellent	Treated breast nearly identical to untreated breast	0	acceptable
Good	Treated breast slightly different from untreated	1	
Fair	Treated breast clearly different from untreated but not seriously distorted	2	unacceptable
Poor	Treated breast seriously distorted	3