Risk Factors of Cosmetic Outcome in Early Breast Cancer Patients After Breast Conserving Therapy

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Abstract: *Aim*: In early breast cancer treated with breast conserving therapy (BCT) the cosmetic effect is an important element of the final outcome. The aim of the study was to evaluate the cosmetic effect of 187 out of 203 consecutive patients with stage 0, I and II breast cancer treated conservatively and to identify the negative factors influencing cosmesis.

Material and Methods: From the entire group of 203 consecutive breast cancer patients with stage 0, I, and II treated with BCT at one oncological institution between 1994-1999, 187 women underwent cosmetic evaluation. The time of observation was 48-103 months, (median 74 months). Cosmesis was assessed qualitatively (subjectively) by the medical panel and patients themselves and quantitatively (objectively) by the medical panel, using measurements and comparing the treated breast with untreated. The relationship between cosmesis and the factors related to the disease and its management (breast size, localization of the tumour, clinical *vs* preclinical status, type of surgery, radiotherapy to the lymph nodes, breast boost type, adjuvant chemotherapy) was analyzed. Statistical analysis was performed using a logistic regression model. Marginal homogeneity test and Cohen kappa was calculated in order to assess the uniformity of opinion between doctors and patients.

Results: According to the medical panel the cosmetic results were assessed as excellent in 59.5% of cases, as good in 34%, as fair in 6.5% of cases with no bad cosmetic results. In the opinion of the patients 67% of cases were assessed as excellent, 23.5% as good, 7.5% as fair and 2% as bad. Statistical analysis based on marginal homogeneity test and Cohen-Kappa did not confirm any concordance between the opinions of both patients and therapists. The two factors found to limit the chance of achieving the excellent cosmetic effect were: quadrantectomy ($p = 0.007$) and brachytherapy boost ($p = 0.004$). All the other factors analyzed: the size of the breast, the localization of the tumor, a non-palpable lesion and adjuvant treatment- did not influence the cosmetic outcome ($p>0.1$).

Conclusions: BCT performed according to the guidelines applied at the Cancer Centre in Warsaw Poland provides satisfactory (excellent or good) cosmetic effect in large majority of patients (93%). A discrepancy between the cosmetic effects as evaluated qualitatively by the patients and by the medical panel was observed. The two factors limiting the chance of achieving an excellent cosmetic effect were quadrantectomy and HDR Ir192 brachytherapy boost.

Keywords: Breast conserving, cosmetic effect, risk factors.

INTRODUCTION

Breast conserving therapy is a generally accepted and effective method of treatment, which has also been confirmed by clinical trials. Despite its main goal, which is local control of the disease, a satisfactory cosmetic effect is also an important issue for conservatively treated patients. The aesthetic effect observed on the treated side is of great importance to a number of patients. The risk factors, which may affect the cosmetic effect following breast conserving therapy, may be dependent on: (1) the patient (e.g. the size of the breasts), (2) breast cancer presentation (e.g. stage and localization of the tumor) and (3) the treatment method (e.g. the surgical technique, the radiation therapy technique, and concomitant chemotherapy) [1-3]. The final appearance of the treated breast depends upon the volume of tissue excised, the size of the scars, the total radiation dose, the dose per fraction and the dose to the tumor bed (boost), the type of dose boost delivered, the homogeneity of the dose within the treated breast, and on simultaneously given adjuvant chemotherapy [1-3].

A majority of papers devoted to the cosmetic evaluation after breast conserving therapy apply two methods of assessment: qualitative and quantitative. In the qualitative method, introduced in 1979 by Harris, there exist 4 categories of the final cosmetic effect: excellent, good, fair, and poor [4]. The qualitative evaluation is performed by a medical panel and, independently, by the patients themselves. The quantitative evaluation, originally proposed by van Limbergen in 1988 and accepted by the EORTC Radiotherapy Cooperative Group, depends on measurements of the retraction and the distortion of the breast [3]. Measurements

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may be performed directly on the patient or may base on digital photographs [3, 5-7]. Other features, such as fibrosis, teleangiectasiae, and breast oedema are assessesd independently, based upon a 3-point classification of the late effects after radiotherapy. The quantitative evaluation is more objective than the qualitative one and excludes discrepancies observed in the course of qualitative assessment [3, 8, 9].

The aim of the study was to evaluate the late cosmetic effect observed in 187 out of 203 consecutive patients over a mean follow-up time of 74 months, and to analyze the influence of different factors upon the excellent cosmetic outcome.

MATERIAL AND METHODS

Breast conserving therapy (BCT) has been performed at the Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology in Warsaw, Poland since 1994. Our particular group of 203 consecutive early breast cancer patients had been treated with BCT between November 1994 and June1999. From a total of 203 patients, 187 underwent cosmetic evaluation after a median time of observation 74 months (range 48-103 months). The remaining16 patients had been excluded from the analysis for various reasons: 11 due to local failure and/ or distant metastases,1 due to non cancer specific death, 1 due to contralateral breast cancer, and 3 patients due to refusal to undergo cosmetic assessment. The clinical characteristics of the patients have been presented in Table **1**. Median age was 51 years (range: 24-76 years). There were 60% (112/187) premenopausal and 40% (75/187) postmenopausal patients. In 71 patients (38%) the disease was diagnosed at a pre-clinical stage, in 116 (62%), it was clinically apparent on diagnosis. In 14 patients (7.5%), quadrantectomy and in 173, patients (92.5%) tumorectomy was performed. In all patients, clear surgical margin was achieved (although in 29 patients reexcision was necessary due to an initially positive surgical margin). All patients underwent full axillary lymph node dissection (all III levels of the axillary fossa). The median number of lymph nodes excised was 16. In all patients, radiation therapy of the breast was performed. Patients were positioned supinely on a breast board with both arms raised overhead. 3D CT planning of the breast was used. Patients were treated with two tangential fields with either gamma-rays from a cobalt unit or with 4-6 MV photon X-rays. Whole breast radiotherapy was delivered as 50 Gy in 25 fractions over 5 weeks to the ICRU 50 reference point in the centre of the breast. The maximal and the minimal doses followed ICRU 50 recommendations [10]. Radiotherapy to the tumor bed was applied in all patients with invasive cancer (175 cases), by using electrons (104 patients) or Ir-192 HDR brachytherapy with (71 patients). Twelve patients with ductal carcinoma in situ did not received additional dose to the tumour bed. The boost to the tumor bed was delivered with electrons using 2 Gy per fraction prescribed to the 90% isodose line to a 10 Gy total dose to all the patients. In 12 patients, radiotherapy to the regional nodal fields was given. In 51 (27%) cases, adjuvant chemotherapy was performed. Patients received either 6 courses according to the CMF (cyclophosphamide, methotrexate, and fluorouracil) schedule (47) or 4 courses of epirubicine followed by 4 courses of CMF (4). In 60 patients tamoxifen was administered as adjuvant endocrine therapy was ordered and in 15 of them it was commenced after chemotherapy. The different methods of primary treatment have been presented in Table **2**.

Table 1. Clinical Characteristics of 187 Patients

Clinical Features	No. pts.	Percentage
No. pts	187	100
Age < = 40 years	82	44
>40 years	105	56
Premenopausal	112	60
Postmenopausal	75	40
Type of cancer:		
Nonpalpable	71	38
Clinically evident	116	62
pT0	12	6
pT1	145	78
pT2	30	16
pN0	155	83
pN1	23	17
Histological type:		
Ductal carcinoma	115	61
Lobular carcinoma	36	19
Other	36	19
Microscopical margin in mm:		
1-2	36	19.5
3-5	47	25
>5	94	50
no data	10	5.5
Size of breasts:		
Small	18	10
Medium	94	50
Large	53	28
Very large	22	12
Breast cancer		
Left side	90	48
Right side	97	52
Tumour site within the breast (quadrant)		
Upper external	127	68
Lower external	20	11
Upper internal	18	10
Lower internal	10	5
Spence's tail	12	6

In 187 cases, the qualitative (subjective) and quantitative (objective) cosmetic effect were evaluated according to the suggestions of Harris and van Limbergen, based upon comparing the healthy and the treated breast [3, 4].

Table 2. Methods of Primary Treatment of 187 Patients

Methods of Treatment	No. pts.	Percentage
BCS +RT	91	49
BCS+ RT+ CT	36	19
BCT+RT+HTH	45	24
BCT+RT+CT+HTH	15	8
Radiotherapy:		
Only breast	175	94
Breast + regional lymph nodes	12	6
Boost type:		
Electrons	104	56
Brachytherapy HDR Ir –192	71	38
No boost	12	6
Type of chemotherapy:		
CMF	47	25
4x CMF + 4x EPIRUBICIN	4	2

Legend: BCS-breast conserving surgery, RT-radiotherapy, CT-chemotherapy, HTH-endocrine therapy, CMF-cyclophosphamide + methotrexate + fluorouracil.

The quantitative evaluation was performed only by the medical panel consisting of the same three persons in all cases: radiotherapist (AN), surgeon (MN), and physiotherapist (HT). The quantitative evaluation of the level of retraction and distortion of the breast was performed with the aid of the following measurements: (1) the difference in the level of nipples, (2) the difference in the level of the submammary folds, (3) the difference of the distances between the jugular incision of the sternum and the nipples, (4) the difference of the distances between the middle of the clavicle and the nipple, (5) the difference of the distances between the mid-sternal line and the nipples. The measurements were performed directly on the patients. Additionally the degree of fibrosis, pigmentation, teleangiectasiae, breast oedema, tissue loss, and scar retraction were also assessed using a three point scale (from 1-minimal to 3-intense changes) according to EORTC/ RTOG score. The volume of both the breasts and upper limbs were also measured.

The qualitative analysis was performed by the medical panel and, independently, by the patients. The results of the evaluation were presented according to a ten point scoring system proposed by Harris [4], where 9-10 points stand for an excellent effect - no apparent signs of treatment (no skin changes, no deformity, no difference in size between two breasts), 7-8 points stand for a good effect, a slight difference could be discerned in the treated breast when compared to the healthy breast; no skin changes, just a noticeable difference in size between the two breast or skin changes with no difference in size between two breasts, 5-6 points stand for a fair effect-obvious treatment effects, significant difference in the appearance between the two breast and 1-4 points stand for a poor effect – a highly evident difference between the two breast and severe malformation of the treated breast.

STATISTICAL ANALYSIS

The uniformity between patient's and doctors' rating of qualitative (subjective) cosmesis was assessed by the marginal homogeneity test and Cohen-Kappa. The qualitative outcome for different levels of quantitative measurements was compared using the Mann Whitney test [11]. The influence of factors related to the disease itself and the treatment performed in patients with excellent cosmetic results was analyzed using a univariate model and a logistic regression model. The different analyzed factors were: the size of the breast (small, average, large *vs* very large), the quadrant of the breast involved, stage of breast cancer at presentation (clinically apparent *vs* subclinical form), type of surgery within the breast (tumorectomy *vs* quadrantectomy), the type of boost to the tumour bed (electron external beam therapy *vs* HDR Ir192 brachytherapy), radiotherapy to the lymph node areas, adjuvant chemotherapy (yes *vs* no). A logistic regression model was used with a stepwise selection procedure in order to identify factors significant at the level of 0.05. Excellent cosmetic scores were used in all statistical analyzes unless otherwise specified.

RESULTS

Qualitative Evaluation

According to the evaluation of the medical team, the cosmetic effect was excellent in 111 cases (59.5%), good in 64 cases (34%), and fair in 12 cases (6.5%). We observed no cases of poor cosmesis. According to patient the evaluation the effect was excellent in 125 cases (67%), good in 44 cases (23.5%), fair in 14 cases (7.5%), and poor in 4 cases (2%). The qualitative analysis results have been presented in Table **3**. The statistical analysis (Marginal homogeneity test $p = 0.015$, Cohen-Kappa concordance = 0.46) did not confirm the concordance of the evaluations as pronounced by the medical panel and by the patients.

Table 3. The Qualitative (Subjective) Evaluation of the Cosmetic Effect After Breast Conserving Treatment of Breast Cancer (Opinions of the Medical Panel and Patients)

Effect Evaluation	Medical Panel	Patients	p-Value
Excellent (10-9 points)	111 (59.5%)	125 (67%)	
Good (8-7 points)	64 (34 %)	44 (23.5%)	
Fair (6-5 points)	12 (6.5%)	14 (7.5%)	
Poor (4-1 points)	0	4 (2%)	P = 0.015

Quantitative Evaluation

The statistical analysis has revealed, that all measurements regarded as elements of the quantitative evaluation statistically significantly correlated with the subjective evaluation as performed by the medical panel. In patients with excellent cosmetic outcome, the differences in all measurements between the treated and the untreated breast were statistically significantly lower, than in patients with worse cosmetic outcome (Mann Whitney test, $p = 0.0001$ for all measurements).

Factors Worsening Cosmesis

The results of the univariate analysis are presented in Table **4**. Quadrantectomy ($p = 0.004$), brachytherapy ($p = 0.01$), and chemotherapy ($p = 0.02$) were the factors decreasing the chance of excellent cosmetic result.

Table 4. Univariate Analysis of Factors Affecting the Cosmesis After Breast Conserving Treatment in 187 Patients

Factor	Number of Patients	No. of Patients with Excellent Cosmetic Effect (Percent)	No. of Patients with a Less Than Perfect Effect (Percent)	p Value
pT stage:				
0, I	157	97 (62)	60 (38)	
II	30	15 (50)	15 (50)	p=0.23
Type of cancer:				
Nonpalpable	71	47 (66)	24 (34)	
Clinically evident	116	64 (55)	52 (45)	p=0.14
Size of breasts:				
small & medium &large	165	96 (58)	69 (42)	
vs very large	22	14 (68)	7 (32)	p=0.46
Quadrant involved:				
Upper external				
and Spence' s tail	139	86 (62)	53 (38)	
Lower external	20	10 (50)	10 (50)	
Upper internal	18	10 (56)	8 (44)	
Lower internal	10	5 (50)	5 (50)	p=0.67
Surgical method:				
Tumorectomy	173	108 (62)	65 (38)	
Quadrantectomy	14	3 (21)	11 (79)	0=0.0004
Regional lymph node irradiation:				
Yes	12	6 (50)	6 (50)	
No	175	105 (60)	68 (40)	p=0.55
Boost to the tumour bed:				
Electrons	104	68 (65)	36 (35)	
Ir-192	71	33 (46)	38 (54)	p=0.01
No	12			
Chemotherapy:				
Yes	51	23 (45)	28 (55)	
No	136	88 (65)	48 (35)	p=0.02

A multivariate model of logistic regression has revealed a significant, negative influence of quadrantectomy (p = 0.007, OR = 0.15, 95% CI = [0.04,0.6]) and brachytherapy (p = 0.004, OR = 0.38, 95% CI = [0.2,0.73]) on achieving an excellent cosmetic effect. Patients treated with quadrant-ectomy had a worse cosmetic effect than those treated with tumorectomy. Similarly, patients who had received a boost dose using brachytherapy HDR Ir-192 presented with a worse final cosmetic effect than those treated by electrons. None of the other factors such as age (p = 0.29), size of the breast (p = 0.65), localization of the tumour (p = 0.46), the diameter of the tumour (p = 0.62), clinical *vs* preclinical stage (p = 0.45), radiotherapy to the lymph node areas (p = 0.78), chemotherapy (p = 0.14) did not have a significant effect on overall cosmetic results. Results of a multivariate model are presented in Table **5**.

Table 5. The Only Independent Factors Affecting the Excellent Cosmetic Results in Multivariate Analysis

Factor	OR [95% C.I.]	P Value
Surgical treatment: tumorectomy *vs* quadrantectomy	**0.15 [0.04, 0.6]**	**0.007**
Boost to tumour bed: brachytherapy vs electrons	**0.38 [0.2, 0.73]**	**0.004**

DISCUSSION

Qualitative and Quantitative Assessment

In a majority of published studies, the percentage of excellent and good cosmetic results of the qualitative evaluation ranges between 70 and 90 percent [12-20]. About 55-65% of the patients has excellent, 25-35% - good, 5-10% - fair and <5%-poor cosmetic effect [1, 2, 12, 21-24]. This concurs with our results. We had found 59.5% of excellent, 34 % of good and 6.5% cases of poor effect. We did not observe patients with bad cosmesis after a median time of observation of 74 months.

The qualitative evaluation score performed by patients and medical panel differs in a number of papers. Doctors usually rate cosmesis less favourably than patients [1, 5, 8, 25, 26]. In the recent study there was also a difference between the evaluation performed by the medical panel and the patients (Marginal homogeneity p = 0.015). In the opinion of the patients there were both more excellent and more bad results than in the opinion of doctors. Doctors more commonly reported cosmetic effect as either good or poor. It is impossible to judge which group rated cosmesis better.

Risk Factors

TNM Stage

In most studies, the diameter of the tumor has a significant influence on the cosmetic effect, because of the volume of the excised tissue. In large tumors a worse cosmetic effect is observed [4-6, 12, 13, 24, 27, 28]. Tumors greater than 2 cm in diameter negatively influenced cosmesis [12, 16, 29, 30]. Similarly, palpable tumor (as contrary to nonpalpable), negatively influenced cosmesis [22]. In our material, there were many patients with T0 and T1 which may explain our results. We did not observe worse cosmetic effects in relation to the diameter of the tumor and TNM stage because of the homogeneity of our evaluated group in an early stage of disease.

Size of the Breast

In patients with very large or pendulous breast, worse cosmetic effects have been observed [12, 22, 24, 31, 32] as a consequence of the unhomogeneity of the radiation dose in the irradiated breast. In such patients, fibrosis and teleangiectases were observed more frequently [22, 31]. However, small breasts can also affect cosmesis negatively [17]. In our material, we compared the cosmetic effects of patients with very large tumour versus other sizes. We stated that the percentage of excellent cosmetic effects did not depend on the size of the breasts in evaluated group.

Localization of the Tumour

According to some authors, tumours located in the medial, upper [16, 17, 33] and inferior quadrants [6, 29, 30] lead to worse cosmetic effects [3, 5, 6, 31, 32]. In the recent study we analyzed cosmesis depending on the localization in medial, lower and upper quadrants. We did not observe relationship between localization of the tumour and cosmetic effect.

Type of Surgery

The volume of tissue removed remains a significant determinant influencing cosmesis [6,12, 13, 17, 22, 29, 33-35]. Reexcision is associated with worse cosmesis as well [22, 36]. There is a good correlation between type of surgery and volume of tissue excised. Quadrantectomy leads to worse cosmetic effect compared to tumorectomy [4-6, 12, 13, 18, 19, 24, 27, 28], but not all authors agree with this standpoint [26]. Long scars negatively influence cosmesis [17]. We revealed lower rate of patients with excellent cosmetic effect after quadrantectomy and it was confirmed by statistical analysis (p = 0.007, OR = 0.15, 95% CI [0.04,0.6]).

Radiotherapy Technique

Oedema of the breast, hyperpigmentation, depigmentation of the nipple and papillae, teleangiectases and fibrosis are all consequences of radiation therapy [8]. Edema of the breast is observed mainly during and directly the end of radiotherapy. In 10-20% of patients, it can appear as a late reaction after 18-36 months after radiotherapy; in such cases it is moderate and reversible [8]. Teleangiectases are observed mainly in areas of high doses of radiotherapy given by electrons or in areas of skin folds. They can be observed in 30% of patients and time to their appearance is the longest out of all side effects of radiotherapy. Contrary to other side effects, the probability and intensity of teleangiectases increases in the course of follow-up [8]. The most important late effect of radiation is breast fibrosis. Contrary to other factors, which are reversible (oedema) or limited to a small area of the breast (teleangiectases), fibrosis encompasses the whole breast and is the most important factor of breast's retraction [8]. Fibrosis appears after 6-18 months and the highest intensity is observed after 3 years. Longer observations of patients did not revealed progression of the retraction of the treated breast. It is advised to perform cosmetic evaluation 3 years after primary treatment because at this point most late effects already appear. Late

effects, those that appear years after, don't affect final cosmesis [8, 14, 16]. In most studies the total dose to the breast over 65-70 Gy and dose per fraction over 2.5Gy causes a worse cosmetic effect [2, 3, 6, 12, 20, 22, 24]. The cosmetic effect of patients who had received total dose of 50 Gy in 25 fractions was comparable to those treated only by surgery only [7]. A high dose to the tumour bed (over 16Gy) is a factor escalating the risk of fibrosis and teleangiectases and negatively affects the overall cosmetic effect [20, 22, 29, 32, 37-39]. It remains a controversial issue whether the risk of late effects after radiotherapy depends on the boost type (electrons *vs* brachytherapy). There is no evidence in the literature to prove that one type of boost is better, than the other [12, 22, 27, 40]. Some authors have achieved better cosmetic results with brachytherapy [28, 36] while the others using electrons [13]. No differences were observed in the cosmetic outcome between intraoperative brachytherapy (implants during the tumor excision) and delayed brachytherapy boost [41]. Irradiation to lymph node areas negatively affects cosmetic effect [4, 6, 22, 31, 32, 37].

In our material, all patients received a total dose to the breast of 50Gy in 25 fractions with a boost dose 10Gy in a majority of cases (except for patients with DCIS). It is postulated that these doses do not significantly affect the final cosmesis. We did observe a small group of patients irradiated to the lymph node areas, so it is difficult to assess the influence of irradiation on the overall cosmetic effect. In our material, brachytherapy boost did influence the cosmetic effect. Patients who were administered HDR brachytherapy to the tumour bed presented with a significantly worse cosmetic effect, than those treated by electrons ($p = 0.004$, OR = 0.38, 95% CI = [0.2,0.73]). This conclusion calls for a careful analysis as in the Cancer Centre in Warsaw we have introduced brachytherapy into the breast conserving therapy protocol in 1994 and therefore, the patients, which we are hereby presenting are, in fact, a pioneer group. The first group of patients, treated between 1994 and1997 was prospectively evaluated by team of brachytherapists, and as a result of observation (relatively high percentage of fibrosis and teleangiectasia) the protocol of the brachytherapy boost was corrected (isodose 100% obtained the tumour bed with 1 cm margin) and the technique has thus improved. As a consequence, we did not observe late effects in patients treated interstitially after 1997. Our data confirm the notion, that the cosmetic effect after brachytherapy depends on the applied technique.

Adjuvant Treatment

Clinical data about the influence of concomitant chemotherapy and radiotherapy on the cosmetic outcome are controversial. In most studies, cosmesis was assessed after CMF (cyclophosphamide, methotrexate, fluorouracil). According to some authors, chemotherapy applied concomitantly with radiotherapy negatively affects cosmesis [23, 30, 42, 43]. According to others, concomitant chemotherapy does not influence the appearance of the breast [12, 44]. Taylor *et al*. [12] have shown that concomitant chemotherapy with radiotherapy impaired an excellent cosmetic outcome, but the administration of sequential chemotherapy did not appear to diminish excellent cosmetic outcomes [12]. Markiewicz *et al*. compared 214 patients receiving chemotherapy with 612 patients without adjuvant therapy [45]. In their study, after 3 years of follow-up, the use of chemotherapy had an adverse effect on the cosmetic outcome when compared to the no chemotherapy, but after 5 years of follow-up the cosmesis did not differ between the groups. The cosmetic effect was the same in patients who had been receiving CMF versus programs with doxorubicin CAF [45]. In majority of studies, hormonal therapy with tamoxifen as adjuvant treatment did not have an adverse effect on cosmesis or complications [12, 45-47].

Although, the result of our univariate analysis may have suggested, that chemotherapy was one of the factors negatively influencing the likelihood of an excellent cosmetic result, this has not been confirmed by the multivariate model ($p>0.1$).

CONCLUSIONS

1. Breast conserving therapy in patients with breast cancer performed in the Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology Warsaw, Poland allows to achieve an excellent and good (satisfactory) cosmetic effect in a majority of cases (93%).
2. The results of the qualitative cosmetic evaluation vary between the patients and the physicians. Patient satisfaction with cosmesis is determined not only by surgery and radiotherapy, but also by factors unrelated to the appearance of the breast.
3. Quadrantectomy and HDR brachytherapy were the factors decreasing the chance of excellent cosmetic result.

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