Long-term outcome with interstitial brachytherapy boost in the treatment of women with early-stage breast cancer

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Breast conserving surgery followed by adjuvant radiotherapy and eventually by systemic treatment represent the current trend in therapy of the early-stage breast carcinoma. Local control and the final cosmetic effect are important factors in breast conserving therapeutic approaches.

We evaluated 215 patients who underwent breast conserving surgery (BCS) followed by adjuvant radiotherapy (RT) in our institute between October 1996 and February 2004. External beam radiotherapy (EBRT) was performed using a Cobalt-60 or linear accelerator (LINAC), the boost was administered via high dose rate interstitial brachytherapy (HDR BRT) employing the Gammamed afterloading system.

Patient survival was evaluated using the Kaplan-Meier method (disease-free survival – DFS, overall survival – OS). Late radiotherapy effects were evaluated using the LENT scales. The cosmetic effect (CE) was rated on a 4-grade scale by the patient and a committee; the Breast Retraction Assessment (BRA) was used to objectively assess the extent of the breast deformation and areolar deviation.

The median follow-up in our group of patients was 70 months (from 20 to 136 months). Local control of the disease after 5 years was achieved in 98.5% of the patients, DFS was 88.7%, the distant disease-free survival (DDFS) was 89.9% and the overall 5-year survival was 91,8%. Medium vs. heavy fibrosis were recorded in 31.2% vs. 4.2% of the patients, medium vs. heavy teleangiectasia in 11.2% vs. 14.0% of the patients, and medium vs. heavy pigmentations in 6.5% vs. 3.3% of the patients, respectively. In all other cases none or minimal late radiotherapy effects occurred. The total CE was significantly influenced by the extent of the surgery (smaller deformations following tumorectomy < 65 cm^3), by the type and orientation of the surgical incision (better results with discontinuous scars then with radial continuous scars), by the depth of the applied HDR BRT needles, by the rate of intermediate and severe postradiation late effects, plus by the value of the objective BRA parameters.

Our data show that the HDR interstitial brachytherapy boost offers both excellent local control and favorable cosmetic effect to the patient, as long as the indications are followed closely. This therapeutic approach is suitable for treatment of tumors localized deeper than 2.8 cm under the surface and in patients with voluminous breasts.

Breast conserving surgery followed by adjuvant radiotherapy and eventually by systemic treatment represent the current trend in therapy of the early-stage breast carcinoma. Local control and the final cosmetic effect are important factors in breast conserving therapeutic approaches.

Adjuvant radiotherapy (RT) represents an important part of breast preserving treatment because reduces the risk of local recurrence (LR) from 43% in patients without adjuvant RT to 10% in patients with adjuvant RT. Standard adjuvant radiotherapy consists of irradiation of the whole breast with doses of 45 – 50 Gy, necessary to eliminate potential microscopic foci of multicentric breast carcinoma [1–3].

Role of the Boost Dose to the Tumor Bed. Since 60-80% of recurring tumors appear at the site of the original tumor or close to this localization, the whole breast irradiation is supplemented by an additional dose to the tumor bed and its margins (irradiation boost) [4–9]. Such boost can be applied either

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via external beam radiotherapy (EBRT) with the use of electrons or via interstitial brachytherapy (BRT). Even though the utilization of these methods is selective, they are not in direct competition, as each technique has its own specific indications. The localization of the tumor bed within the breast, the distance of the tumor bed from the skin surface, the size of the breast and the extent of the boost target volume represent some of the decisive factors for selection of the appropriate method [10–11].

The benefits of the interstitial brachytherapy include a higher irradiation dose applied over a short period of time directly to the tumor bed, higher biological effectivity of the irradiation, lower irradiation exposure to the skin of the breast especially in correctly indicated cases (e.g. deep located tumor bed), more precise localization of the tumor bed, shorter irradiation duration and the possibility of an outpatient setting resulting in higher patient comfort. Moreover, interstitial brachytherapy use is often connected with better local control, which benefits especially patients with accumulation of multiple risk factors for local recurrence of the disease [12–14].

Therefore, it is crucial to carefully define the high risk patient group, which would take advantage of the dose accumulation. Lower age, positive or close margins, lymph-node positivity, extensive intraductal component more than 25% (EIC), multicentric carcinoma, diffuse microcalcifications, and contralateral ductal carcinoma in situ (DCIS) are the principal factors in estimation of the local recurrence risk. The influence of other prognostic factors is still being discussed in the literature with various levels of controversy [5, 6, 9, 15, 16].

Target Volume Definition and Tumor Bed Localization. The most important moment in a interstitial boost application is the definition of the adequate clinical target volume (CTV). The CTV usually comprises the tumor bed with a safety margin of 1 through 2 cm [17]. Placement of 4 – 6 x-ray contrast metal clips into the tumor bed during surgery appears to be the most reliable tool for CTV localization. Localization of the clips assisted by CT or MRI scans represents a more precise variation of this approach [18, 19]. In addition, the titanium clips affect neither the quality of the diagnostic CT or MRI scans or the dose distribution of the radiotherapy [5, 6, 8].

Late Effects of the Interstitial Boost. While the higher radiotherapy doses correlate with better local control, they are also linked to a higher percentage of negative cosmetic effects (telangiectasia and pigmentation of the skin, retraction and fibrosis of the glands) in some studies [17, 20–22]. However, aside from irradiation dose the late effects also depend on the extent of the CTV and the distance of the top row of needles from the skin of the treated breast [5, 6, 17, 23–26].

Patients and Methods

The goal of this retrospective study was evaluation of individual parameters of survival in our group of patients (local tumor control-LTC, disease-free survival-DFS, overall survival-OS), late effects of radiotherapy and cosmetic effect (CE) in early breast carcinoma patients.

We evaluated 215 patients between October 1996 and February 2004 who underwent breast conserving surgery (BCS) followed by adjuvant radiotherapy (RT) of the whole breast with a 48 – 50 Gy dose in 25 fractions, supplemented by irradiation of the lymphatic region when indicated in our institute. External beam radiotherapy (EBRT) was performed using a Cobalt-60 or linear accelerator (LINAC), the boost was administered via high dose rate interstitial brachytherapy (HDR BRT) employing the Gammamed afterloading system. This type of boost was employed in cases where the primary tumor was located at least 2 cm deep under the skin surface. Median follow-up was 70 months (range 20 – 136 months). The median age of the patients was 54 years (range 31 – 80 years). The patient group comprised women post-surgery classification pT0-2, pN0-1, M0. Characteristics of the patient group in regard to the primary tumor are summarized in Table 1.

The surgical treatment was reclassified as tumorectomy (<65 cm^3), wide excision (65-345 cm^3), and quadrantectomy (>345 cm^3). All women with invasive carcinoma underwent an axillary lymph node dissection but in patients with DCIS the axillary dissection was not necessary [27].

The safety margin status and the incision technique – in continuity or discontinuity – were evaluated. Adjuvant chemotherapy was indicated in 37.7% of cases, adjuvant hormonotherapy in 70.2% of cases, respectively. No systemic treatment was applied in 12.1% of cases. The treatment characteristics are presented in Table 2.

Description of the Interstitial Application Technique. The interstitial boost was applied using the hollow steel needle probes technique. The planning treatment volume (PTV) equaled the clinical target volume (CTV) and was designed considering the size of the tumor bed plus a 10 mm safety margin. Median PTV was 45 cm^3 (range 4 cm^3-140 cm^3). The Amedis mammary template was used for precise implant geometry, while interstitial applications were performed on the Gammamed automatic high-dose-rate afterloading. In a majority of cases (67.0%) the boost was performed prior to EBRT in local or general anesthesia. The target volume of the boost was determined based on surgery protocol, pre-surgery and post-surgery mammography (MG), plus on clip localization using a C-shoulder.

The Gammadot planning system was employed for interstitial brachytherapy designing, with the stereometric reconstruction based on the use of semi-orthogonal images and a planning bridge. Minimal anti-tumor dose was specified at 5 mm from the source. Minimal distance of the specified dose from the skin surface was set at 5 mm in 14.9%, and at 10 mm from the skin surface in 85.1% of cases, respectively.

Methodology

For cosmetic effect evaluation a comprehensive methodology was introduced, which considers both quantitative and

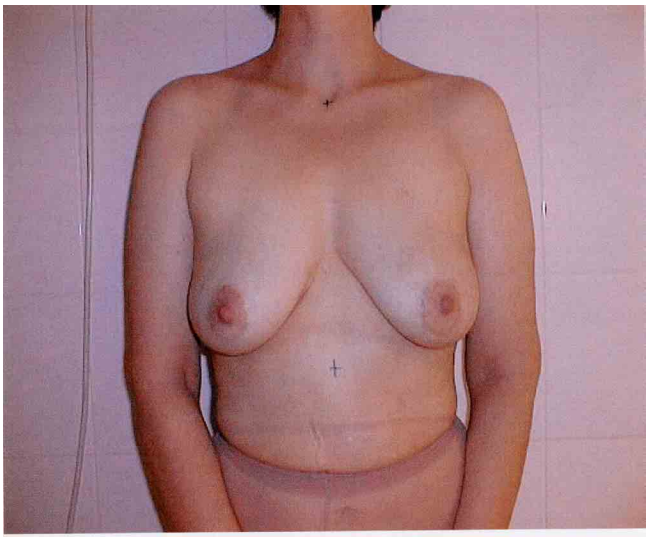
Table 1. Basic characteristics of examined patients and their tumor (N=215)

		Mean (Range) or %
Age (years)		55.0 (31.0 – 80.0)
Categorized age		
	up to 40 years	4,7
	41 – 50 years	28,8
	50 – 55 years	23,7
	more than 55 years	42,8
pT		
	0	7,0
	1	61,4
	2	31,6
pN		
	0	67,9
	1	22,3
	Missing	9,8
Number of positive lymph nodes		
	0	67,9
	1 – 3	18,6
	> 3	3,7
	Missing	9,8
Stage		
	0	7,0
	1	50,7
	2	42,3
Histology		
	DCIS	7,0
	Invasive ductal	78,6
	Invasive lobular	11,6
	Other	2,8
Grade		
	1	32,6
	2	31,2
	3	33,5
	Missing	2,8
HER2		
	Negative	54,9
	Positive	7,4
	Missing	37,7
PCNA or Ki67		
	+	40,0
	++	22,8
	+++	24,2
	Missing	13,0
EIC		
	< 25%	71,6
	? 25%	23,7
	Missing	4,7
LVI		
	No	59,5
	Yes	35,8
	Missing	4,7
Hormonal status		
	ER- PgR-	25,1
	ER+ PgR+	67,4
	Missing	7,4

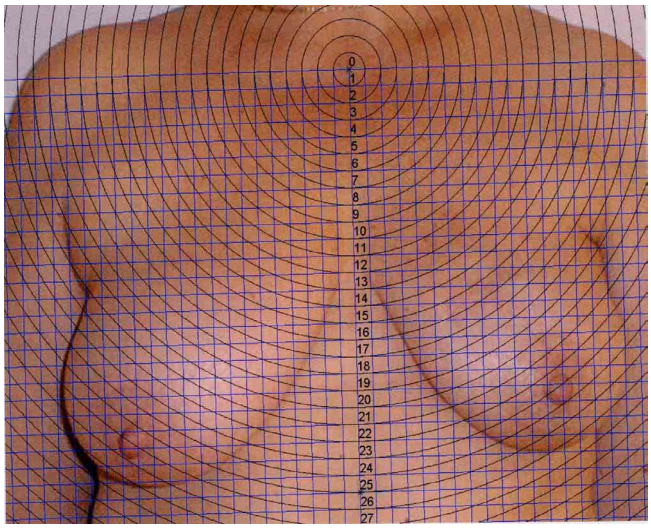
Table 2 Basic description of treatment parameters with potential influence on cosmetic effect. Frequency tables were used to obtain these values. (N=215)

		%
Length of follow-up		
	Less than 3 years	52,1
	More than 3 years	44,2
	Missing	3,7
Extent of operation		
	< 65 cm3	14,4
	65 – 345 cm3	60,5
	> 345 cm3	20,5
	Missing	4,7
Scar orientation		
	Radial continuous scar	47,0
	Other type discontinuous scar	49,8
	Missing	3,3
Margin status		
	0 mm	21,9
	< 2 mm	12,6
	2 – 5 mm	18,6
	5 -10 mm	20,5
	> 10 mm	12,1
	Missing	14,4
TRT target volume		
	mamma	88,4
	mamma + LN	11,6
Sequence of treatment		
	BRT-TRT or TRT-BRT-TRT	75,8
	TRT-BRT	23,7
	Missing	0,5
HDR dose (Gy)		
	8	4,2
	9	84,7
	10	8,8
	12	2,3
Irradiated tissue volume		
	<36 cm3	31,2
	36-65 cm3	51,6
	>65 cm3	17,2
Depth of needles		
	0	14,9
	1	85,1
Axilla dissection		
	No	8,4
	Yes	90,7
	Missing	0,9
Chemotherapy		
	No	62,3
	Yes	37,7
Hormonal therapy		
	No	29,8
	Yes	70,2

Frequency tables, mean, as well as the range of observed values were used for basic description of considered parameters.



Picture 1



Picture 2

qualitative aspects, and represents a substantial part of the result evaluation in our patient group.

The evaluation was performed based on objective and subjective parameters as presented and recommended by the EORTC Breast Cancer Group in the "Manual for Clinical Research in Breast Cancer" from the year 2000 [27].

Digital photography was used for objective evaluation of the cosmetic effect from the quantitative and qualitative point of view. Easy archiving, plus the opportunity to compare various phases of the treatment and potential changes of the cosmetic effect in time all belong to the advantages of this approach.

The Breast Retraction Assessment (BRA) was employed for objective CE evaluation, i.e. the difference between the distances from incisura jugularis to the nipple, as measured on both the healthy and the involved breast, reflecting the scale of breast deformation and craniolateral retraction of the areola.

The images clearly showed marks drawn on the patient's skin prior to photographing. One mark was drawn in incisura jugularis, the other in the median line 25 cm lower. These two points served for calibration of the measurements and for eventual corrections in vertical direction. All patients were measured with a solid ruler for control of the measurement error evaluation.

The following distances were evaluated on the patients body

vertical axis: distance A from the projection of incisura jugularis to the nipple

horizontal axis: distance M from the median line to the nipple

The differences A' vs. A characterize the retraction of the nipple and the lower breast outline in the vertical direction, while M' vs. M determine the asymmetry in the medio-lateral direction. The aforementioned parameters serve for calculation of the slant distance from the incisura jugularis to the nipple, called BRA:

$$BRA = \sqrt{(A' - A)^2 + (M' - M)^2}$$ (Picture 1).

The programming language Matlab was used to create an application, allowing for digital camera data transfer with a subsequent parameter evaluation via a projected grid, resulting in objective evaluation of the BRA parameter. (Picture 2).

At the same time the late post-radiation changes were evaluated based on the Late Effects on Normal Tissue (LENT) scores in accordance with the WHO recommendation, where the final cosmetic effects are influenced by fibrosis, telangiectasia, and pigmentation. Each feature was ranked in one of four grades. Fibrosis: gr. 0-no palpable induration, gr.1-mild palpable, gr.2-evident, gr.3-heavy induration, retraction and fixation of the hypodermis. Telangiectasia: gr.0-no telangiectasia, gr.1-telangiectasia on a surface <1 cm^2, gr.2- on a surface of 1 – 4 cm^2, gr.3-on a surface >4 cm^2. Pigmentation: gr.0-no pigmentation, gr.1-mild, gr.2-mediate, gr.3-heavy pigmentation. The subjective evaluation of the cosmetic effect was performed by the patients themselves and by an independent committee comprised of a physician, a nurse, and a photographer. The evaluation was again performed using a 4 grade scale: 1 = excellent, 2 = very good, 3 = good or acceptable, 4 = unacceptable.

Statistical Methodology

For basic description of continuous parameters the mean, median, and the range of observed values were used, for description of categorized parameters the frequency tables were employed. Construction of survival curves was based on the Kaplan-Meier methodology [28], differences in survival between single categories of analyzed parameters were evaluated

via a log-rank test. The relative risk estimates along with 95% confidence intervals plus the statistical significance of relationship between disease-free survival and considered risk factors were obtained via Cox proportional-hazards model [29]. Maximum Likelihood test for contingency tables [30] and Fisher's exact test [31] were used for the evaluation of association of treatment parameters to late effects and for the subjective cosmetic effect judged both by the patients themselves and by the independent committee. Relationships of treatment parameters to objective BRA cosmetic indices as well as the relationship between objective BRA cosmetic indices and subjective CE were appraised via the Mann-Whitney nonparametric test [32]. The a=0.05 was used as the critical level of statistical significance for all analyses. The analyses were performed using Statistica for Windows 7.1. (StatSoft Inc., 2005) and SPSS 12.0.1 (SPSS Inc., 2003) software.

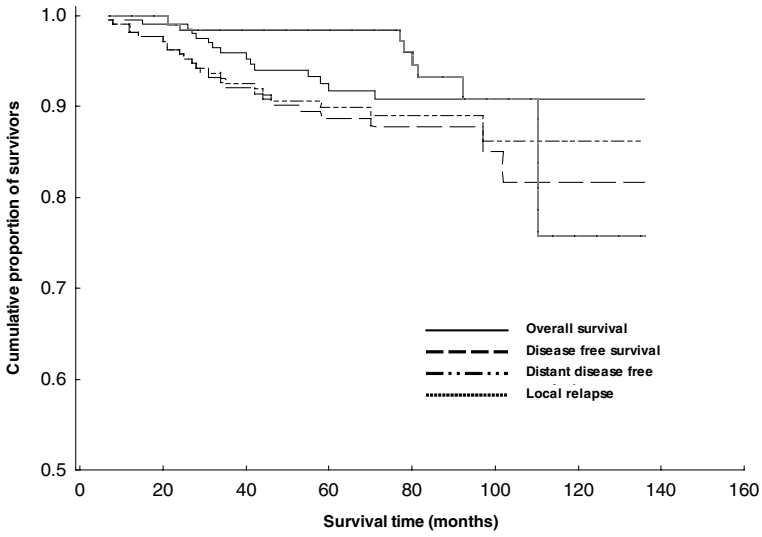


Figure 1 Survival profile of the whole cohort of patients, i.e. overall survival, disease-free survival, distant disease-free survival and time to local relapse. Survival analysis is based on the Kaplan-Meier methodology.

Results

Survival Evaluation in Relation to Selected Risk Parameters. Until August 2005 (the time of study evaluation) 200 patients were alive (93,0%), out of which 188 patients were disease-free (87.4%). Twelve patients were alive with symptoms of the disease (LR in 6 patients, distant dissemination in 6 patients). Fifteen women passed away (7.0%), 12 with proven distant dissemination and 3 with a combination of local recurrence and distant metastases. The median follow-up reached 34 months in the deceased patients (range 11 – 71 months). The five-year survival rates are presented in Figure 1 and Table 3.

The analysis showed a significant correlation between occurrence of local relapse and subsequent dissemination of the disease (Fischer's exact test, $p \leq 0.05$)(Table 4). Due to the small number of patients with local recurrence it was difficult to evaluate the influence of individual parameters on local relapse incidence in our group of patients. Therefore, we evaluated the DFS in regard of known patient-related risk factors, tumor characteristics, and treatment performed. Significantly worse therapeutic outcome was observed in clinical stage II disease when compared with stage I ($p = 0.010$), in patients with positive axillary lymph-nodes vs. negative lymph-nodes ($p < 0.001$), in patients with more than 3 positive lymph-nodes vs. 3 or less positive lymph-nodes ($p < 0.001$), in patients with lymphangiovascular invasion ($p < 0.001$), and in cases of the removed tumor safety margin smaller than 2 mm ($p = 0.014$) (Figure 2). Considering the significant correlation between local relapse and subsequent distant dissemination occurrence, it is recommendable to indicate a repeated resection of the afflicted breast in case of positive or close (under 2 mm) safety margins following initial surgery.

Evaluation of Cosmetic Effect in Relation to Selected Risk Parameters. The cosmetic effect was not assessed in 10 women (4.7%) due to death prior to the scheduled evaluation. Complete CE evaluation using all aforementioned parameters (breast retraction assessment – BRA, late effect assessment – LE, verbal cosmetic effect assessment – VCE) was performed in 128 patients (59.9%). The remaining 77 patients (35.8%) refused photographic documentation, yet agreed with late effect evaluation within the regular follow-up, including verbal cosmetic effect assessment in 74 cases.

Radiotherapy late effects were represented in our group of patients as follows. Medium or heavy fibrosis (gr. 2 and 3) occurred in 31.2% and 4.1% of cases, respectively. Medium or heavy telangiectasia was present in 11.2% and 14% of women, respectively. Medium or heavy pigmentation was observed in 6.5% and 3.3% of women, respectively. In the remaining cases the radiotherapy late effects were minimal or non-present.

The occurrence of gr. 2 or 3 fibrosis was significantly higher in women who underwent the CE effect evaluation three years or later after the treatment completion ($p = 0.031$), pointing out the fact that the late effect intensity can grow over time. On the other hand, no correlation between gr. 2 or 3 fibrosis and the irradiated tissue volume ($p = 0.318$) and the HDR BRT dose (p

Table 3 Counts of risk events for each survival end-point, supplied with estimated 5-year survival rate.

	No of events	5-yr survival (%)
Overall survival	15	91.8
Disease-free survival	24	88.7
Distant disease-free survival	21	89.9
Local relapse	9	98.5

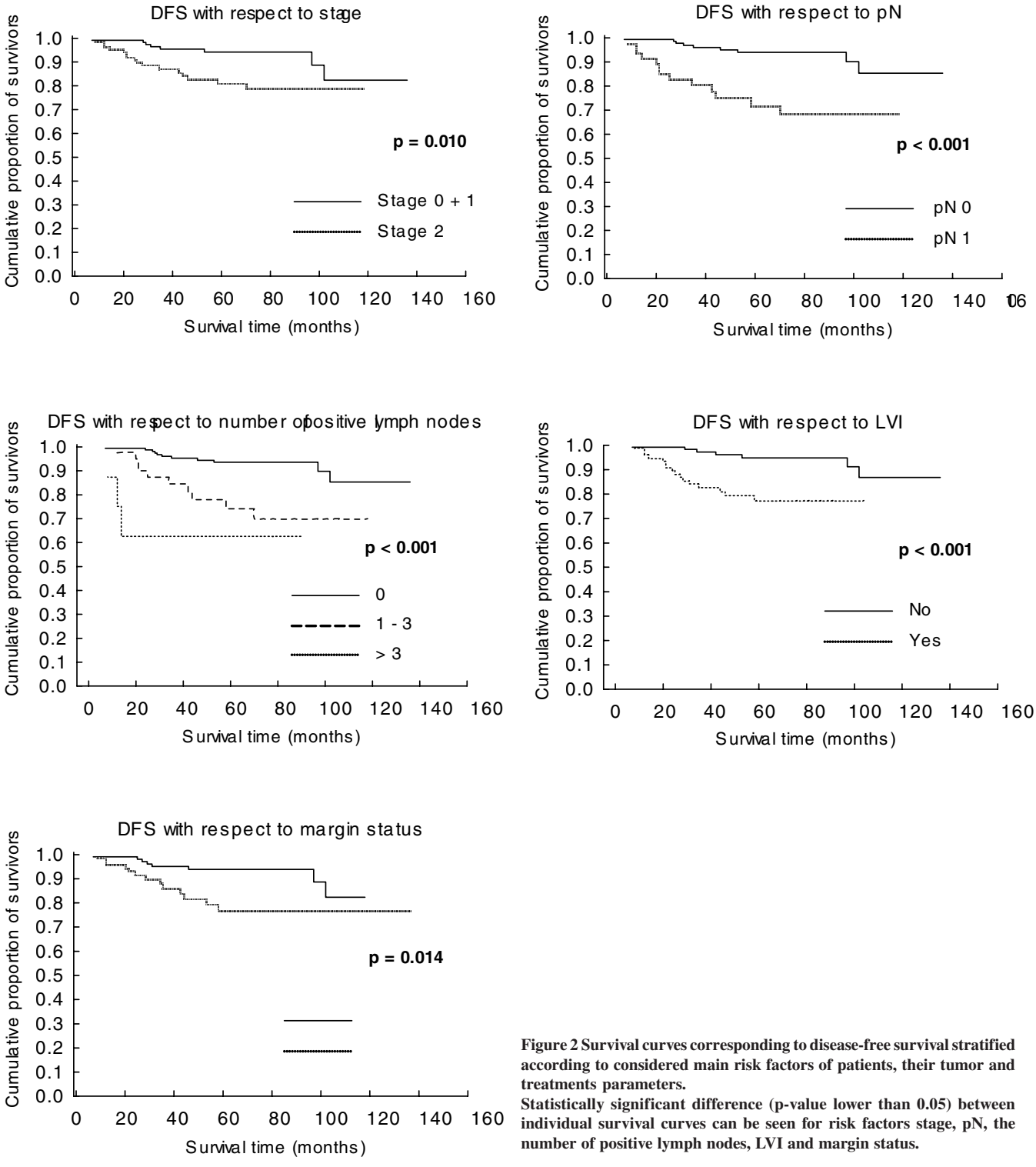


Figure 2 Survival curves corresponding to disease-free survival stratified according to considered main risk factors of patients, their tumor and treatments parameters.
Statistically significant difference (p-value lower than 0.05) between individual survival curves can be seen for risk factors stage, pN, the number of positive lymph nodes, LVI and margin status.

= 0.635) were found in our study. The occurrence of gr. 2 or 3 telangiectasia was influenced by the HDR BRT dose, showing higher incidence with doses of 10 Gy or more (p = 0.003), and with needle application less than 10 mm under the surface of the skin (p = 0.005). The intensity of telangiectasia lesions increased over time (p = 0.01). No correlation was found between gr. 2 and 3 pigmentation occurrence and the monitored treatment parameters (Table 4).

Table 4 Relative frequency of late cosmetic effects (Fibrosis, Telangiectasia and Pigmentation) within the individual categories of examined treatment parameters. Relationship between examined treatment parameters and late cosmetic effects was appraised via Maximum Likelihood test for contingency tables and Fisher's exact test. It can be seen from the resulting p-values that fibrosis is significantly related to the length of follow-up, telangiectasia appears to be associated to the length of follow-up, HDR dose and depth of needles.

	Fibrosis			Telangiectasia			Pigmentation		
	None, Light N=129	Medium, Heavy N=76	p-value	< 2 cm2 N=151	> 2 cm2 N=54	p-value N=184	None, Light N=21	Medium, Heavy	p-value
Length of follow-up			**0,03**			**0**			1
< 3 years	69,64%	30,36%		93,75%	6,25%		89,29%	10,71%	
≥? 3 years	54,84%	45,16%		49,46%	50,54%		90,32%	9,68%	
HDR dose (Gy)			0,64			**0**			0,7
8 + 9	63,60%	36,40%		77,20%	22,80%		89,10%	10,90%	
10 + 12	57,10%	42,90%		42,90%	57,10%		95,20%	4,80%	
Volume of irradiated tissue			0,32			0,31			0,19
<36 cm3	69,20%	30,80%		80,00%	20,00%		89,20%	10,80%	
36-65 cm3	58,10%	41,90%		69,50%	30,50%		87,60%	12,40%	
>65 cm3	65,70%	34,30%		74,30%	25,70%		97,10%	2,90%	
Depth of needles			0,53			**0,01**			0,75
0	57,10%	42,90%		50,00%	50,00%		92,90%	7,10%	
1	63,80%	36,20%		77,40%	22,60%		89,30%	10,70%	
TRT target			0,36			0,45			0,48
mamma	61,70%	38,30%		72,70%	27,30%		90,20%	9,80%	
mamma & other	72,70%	27,30%		81,80%	18,20%		86,40%	13,60%	
Chemotherapy			0,370			1			0,81
No	60,60%	39,40%		73,50%	26,50%		90,20%	9,80%	
Yes	67,10%	32,90%		74,00%	26,00%		89,00%	11,00%	

Objective breast retraction assessment (BRA) was obtained by comparison of the healthy and the treated breast, measured directly on the patient and calculated with the help of digital photography. The value of 0 represents no cosmetic difference between both breasts, while increasing value of the coefficient shows increasing degree of treated breast deformation. BRA coefficients were significantly influenced by the extend of the surgical procedure – better results were achieved in women undergoing a tumorectomy ($p = 0.003$, $p = 0.007$) – and by the type and orientation of the scar, where continuous scars lead to higher degree of breast deformation when compared to discontinuous scars ($p = 0.031$). A significant increase of BRA values was apparent in women with HDR BRT dose of 10 Gy or higher ($p = 0.023$), and women with needle application less than 10 mm under the surface of the skin ($p = 0.005$). Moreover, the breast deformation correlated with radiotherapy late effects ($p = 0.001$ for gr. 2 or 3 fibrosis, $p = 0.014$ for gr. 2 or 3 telangiectasia). No statistical significance was observed comparing the objective breast deformation with the irradiated tissue volume during HDR BRT boost ($p = 0.774$, $p = 0.942$).

The cosmetic effect subjective evaluation using a 4 grade scale was performed in a total of 202 women. Both the patients and the committee assessed the CE as excellent, very good, good or acceptable in 92.6% of cases. The CE was deemed unacceptable only in 1.4% of cases (3 patients). The subjective CE evaluation was significantly influenced by the size of the tumor removed ($p = 0.002$ for patients, $p = 0.001$ for committee), by the type and orientation of the scar (better results with discontinuous scars, $p = 0.027$ for patients, $p = 0.001$ for committee), by the depth of the needle placement ($p = 0.023$ for patients, $p = 0.013$ for committee), and by the presence of gr. 2 or 3 fibrosis ($p = 0.033$ for patients, $p = 0.001$ for committee). Moreover, the CE evaluation correlated with the BRA values, i.e. it reflected the degree of the objective breast deformation ($p = 0.006$ for patients, $p = 0.001$ for committee). The CE evaluation by the patients was significantly influenced by the presence of gr. 2 or 3 telangiectasia ($p = 0.004$), and gr. 2 or 3 pigmentation ($p = 0.003$). The CE evaluation of the committee was significantly influenced by the axillary dissection ($p = 0.015$) and by length of the time period since the treatment completion. Patients evaluated after 3 and more years showed higher late effect incidence and, therefore, worse cosmetic effects ($p = 0.002$) (Table 5).

Discussion

All five-year survival parameters evaluated in our study (LTC = 98,5%, DFS = 88,7%, DDFS = 89,9%, OS = 91,8%)

Table 5 Relative frequency of cosmetic effect assessment within the individual categories of examined treatment parameters, late cosmetic effects and BRA indices. Relationship between considered parameters and categories of cosmetic effect assessment was evaluated via Maximum Likelihood test for contingency tables and Fisher's exact test. It can be concluded that cosmetic effect appraised by the patient itself is connected to the extent of operation, scar orientation, depth of needles and all three objective measures of cosmetic effect as well as both BRA indices. On the other hand the cosmetic effect judged by the committee is associated to the extent of operation, scar orientation, axilla dissection, depth of needles and fibrosis as the objective measure of cosmetic effect and both BRA indices.

	Cosmetic effect – patient			Cosmetic effect – committee		
	Very good or Good N=146	Acceptable or Unacceptable N=56	p-value	Very good or Good N=156	Acceptable or Unacceptable N=46	p-value
Categorized age			0,998			0,351
Age < 50 years	71,93%	28,07%		82,46%	17,54%	
Age > 50 years	72,41%	27,59%		75,17%	24,83%	
Length of follow-up			0,117			**0,002**
Less than 3 years	76,79%	23,21%		85,71%	14,29%	
More than 3 years	66,67%	33,33%		66,67%	33,33%	
Extent of operation			**0,002**			**0,001**
< 65 cm3	93,33%	6,67%		100,00%	0,00%	
65 – 345 cm3	73,77%	26,23%		81,15%	18,85%	
> 345 cm3	55,00%	45,00%		57,50%	42,50%	
Scar orientation			**0,027**			**0,001**
Radial	64,21%	35,79%		63,16%	36,84%	
Other	79,05%	20,95%		89,52%	10,48%	
Axilla dissection			0,162			**0,015**
No	88,20%	11,80%		100,00%	0,00%	
Yes	70,80%	29,20%		75,10%	24,90%	
HDR dose (Gy)			0,304			0,098
8 + 9	73,50%	26,50%		79,00%	21,00%	
10 + 12	61,90%	38,10%		61,90%	38,10%	
Volume of irradiated tissue			0,142			0,525
<36 cm3	70,80%	29,20%		72,30%	27,70%	
36-65 cm3	68,90%	31,10%		79,60%	20,40%	
>65 cm3	85,30%	14,70%		79,40%	20,60%	
Depth of needles			**0,023**			**0,013**
0	53,60%	46,40%		57,10%	42,90%	
1	75,30%	24,70%		80,50%	19,50%	
TRT target			0,600			0,782
mamma	71,40%	28,60%		77,50%	22,50%	
mamma & other	80,00%	20,00%		75,00%	25,00%	
Chemotherapy			0,515		0,862	
No	73,80%	26,20%		77,70%	22,30%	
Yes	69,40%	30,60%		76,40%	23,60%	
Fibrosis			**0,033**			**0,001**
None and Light	77,50%	22,50%		89,10%	10,90%	
Medium and Heavy	63,00%	37,00%		56,20%	43,80%	
Telangiectasia			**0,004**			0,056
< 2 cm2	78,00%	22,00%		80,70%	19,30%	
> 2 cm2	55,80%	44,20%		67,30%	32,70%	
Pigmentation			**0,003**			0,270
None and Light	75,70%	24,30%		78,50%	21,50%	
Medium and Heavy	42,90%	57,10%		66,70%	33,30%	
BRA – patient						
Median (Range)	2.4 (0.0 – 11.6)	3.2 (0.0 – 10.5)	**0,006**	2.5 (0.0 – 7.0)	4.5 (1.1 – 11.6)	**0,001**
BRA – photo						
Median (Range)	2.5 (0.0 – 12.0)	3.7 (0.0 – 9.2)	**0,004**	2.5 (0.0 – 7.6)	4.5 (0.0 – 12.0)	**0,001**

show excellent results comparable with previously published data. Previously published data states that 60- 80% of local relapses following BCS occur in the quadrant where the primary tumor was localized [3, 5, 33]. Hence, increasing the radiation dose to the afflicted quadrant should significantly reduce the likelihood of local recurrence of the disease.

Age: Majority of authors states worse local control in young and premenopausal patients [9, 15, 34]. In our group of patients age did not show a statistically significant influence on local recurrence rate ($p = 0.559$).

Primary tumor size: Most studies consider this factor insignificant [5,9]. A similar observation was made in our study as well.

EIC: An extensive intraductal component surpassing 25% is being linked to a higher rate of residuum detection in tissue surrounding the primary tumor site, which negatively affects the local control rate in women following BCS [35, 36]. The impact of this parameter bordered statistical significance in our study ($p = 0.054$).

Grading. The value of grading as a prognostic factor of local recurrence remains controversial. In our study the comparison of G3 or G2 vs. G1 type tumor failed to show a statistically significant impact on DFS ($p = 0.162$ and $p = 0.157$, respectively) [5, 15, 16].

LVI: Numerous authors consider the lymphangiovascular invasion a risk factor of locoregional recurrence in patients after BCS [9, 22]. In our study LVI was detected in 35.8% of cases and was linked significantly to a shorter DFS ($p = 0.001$) [5, 15, 16].

Extent of the surgical procedure. The influence of the surgery extent is described as significant for DSF in a number of studies [15, 16]. In our group we did not record significant differences between the group of patients treated with tumorectomy, wide excision vs. the group undergoing quadrantectomy with zero failure rate ($p = 0.976$)

Margin status: Positivity of the specimen margins is accepted as a significant factor affecting the local recurrence rate following BCS with adjuvant radiotherapy [16, 37]. Positivity or closeness of the margins (34,5%) significantly affected the recurrence rate in our group of patients as well ($p = 0.015$).

Invasive lobular carcinoma. The ILC histopathological type is considered a relative contraindication of BCS, since it is often connected with multifocality and diffuse propagation. However, long-term results from the 1990s state comparable results in both lobular and ductal carcinoma following adequately performed surgery and adjuvant radiotherapy [5]. The percentage of lobular carcinoma reached only 11.6% in our study, without significant differences based on histopathological type of the tumor ($p = 0.490$).

Boost type. The role of boost type in local control rate remains to be clarified. Our experience shows excellent local control and better CE of the interstitial HDR BRT boost over the electron boost, as long as the indications for interstitial application are fully observed. The indications include localization of the primary tumor deeper than 2.8 mm from the skin surface and placement of the top row of needles at least 10 mm from the skin surface [12-14].

Irradiated tissue volume during HDR BRT boost. Analyzing the volumes of tissue irradiated via HDR BRT in our study we determined a range from 4 through 140 cm^3 with an average of 45 cm^3, which corresponds with volumes deemed insufficient by some authors. In spite of this fact the local recurrence rate in our group of patients was very low. One possible explanation is a higher average volume of tissue extirpated during surgery, reaching 168 cm^3 in our study vs. the published average excised tissue volume of 80 cm^3 *(5,13).*

The interstitial boost dose. In several publications the local recurrence rate is linked to the irradiation dose [5, 38]. Most publications mention a 10 Gy dose for HDR and 15 through 26 Gy for LDR BRT. The most frequently applied dose in the reference isodose was 9 Gy (range 8 – 12 Gy) in our study. We did not record significant correlation between the boost dose and local recurrence rate.

The influence of local recurrence on distant dissemination. In accordance with published data, our study showed a significant correlation between local relapse frequency and distant dissemination occurrence ($p = 0.046$). It remains to be clarified, whether the biological characteristics or rather just insufficient control of the disease are responsible for this fact [5].

Late effects. Incidence of gr. 1 or 2 late effects according to the LENT scale in our group of patients was comparable or slightly higher than previously published [39]. However, the fibrosis and pigmentation evaluations represent a very subjective method of assessment. Therefore, it is difficult to distinguish whether our results were truly worse, or whether our evaluation of these late effects was simply more strict. Grade 3 late effects were very rare and their quantity in our study was comparable with previously published data.

Cosmetic effect (CE). The CE in our study was assessed as excellent or very good in 69.7% of cases by the patients, and in 72.6% of cases by the independent committee, which correlates with data in the literature [20, 39, 40]. Poor cosmetic effects evaluated by both the patients and the committee were in significant relation to the extent of the surgical procedure ($p = 0.002$, and $p = 0.001$, respectively), to the type and orientation scar ($p = 0.027$, $p = 0.001$), and to the needle placement lower then 10 mm of depth from the skin surface ($p = 0.023$, $p = 0.013$). Poor CE evaluated by both the patients and the committee also significantly correlated with occurrence of mediate or heavy fibrosis ($p = 0.033$, $p = 0.001$). The subjective CE evaluation significantly correlated with the objective BRA parameters in the $p = 0.001$ through $p = 0.006$ range, which supports validity of the data obtained via both the measurement and the digital photography method. Chemotherapy application in our study did not correlate with aggravation of radiotherapy late effects ($p = 0.370$ for fibrosis, $p = 0.998$ for telangiectasia, $p = 0.813$ for pigmentation), with objective BRA parameters ($p = 0.918$ and $p = 0.510$), or

with subjective CE evaluation by the patients (p = 0.515) or the committee (p = 0.862).

In conclusion, the importance of radiotherapy for local tumor control is well known. The 5-year survival rates in our study correspond to the above-standard results previously published in women treated with breast conserving surgery followed by adjuvant radiotherapy, eventually with survival rates in patients treated with modified mastectomy without subsequent radiotherapy.

Increase of radiation dose to the tumor bed via a boost in women with early stage breast carcinoma after BCS demonstrably reduce the local recurrence rate. A consensus is for the radiotherapy boost to be used in women under the age of 50, patients with insufficient or positive margins at surgery, and in patients with the presence of extensive intraductal component ≥25% (EIC) or the ductal carcinoma in situ (DCIS). Our analyses exposed the presence of lymphangiovascular invasion (LVI) as another significant risk factor.

Interstitial HDR BRT boost via a single 9 – 10 Gy dose can be considered simple, safe and effective type of RT boost. It is very well tolerated, shows excellent local control and very good cosmetic effects with acceptable late toxicity. The retrospective evaluation of survival outcome and cosmetic effects demonstrates, that further radicalization of the surgical procedure (assuming the minimal 2 mm safety margin is obtained), increase of the HDR interstitial boost dose over 10 Gy, or further extension of the irradiated tissue volume within the HDR boost (provided the minimal 10 mm safety margin is kept) do not lead to improvement of the therapeutic effect. On the contrary they may lead to increase of radiotherapy late effects, higher rate of breast deformation and impairment of the overall cosmetic effect, which would reflect negatively in the quality of life of the treated women.

Since higher radiobiological effect and more precise localization of the tumor bed lead to improved local control, this type of boost is beneficial especially in case of deep located tumor bed, in patients with voluminous breasts and in patients with accumulation of the risk factors. The possible outpatient setting, shorter treatment duration and higher comfort represent undeniable advantages to the patient as well.

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