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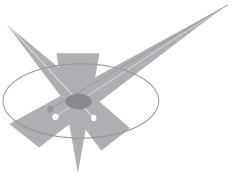

Original Paper

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Does interstitial HDR brachytherapy for breast cancer increase soft tissue fibrosis?

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Summary

Aim To analyze the physical parameters of interstitial HDR brachytherapy and their influence on the risk of soft tissue fibrosis.

Materials/Methods A retrospective analysis of 54 breast cancer patients treated between 1994–1999 in the Brachytherapy Department of the Oncological Centre in Bydgoszcz was performed. Minimum follow up period was 41 months and the maximum was 89 months. The mean follow up period was 65 months. Owing to statiscally significant differences between the groups, when compared to a normal distribution, the U Mann-Whitney non-parametrical test was used as the method for comparison.

Results Out of the nine parameters analysed, three were found to be associated with increased risk of fibrosis occurrence. Reference volumes V100, V150 and V200 showed statistically significant differences ($p<0.05$).

Conclusions In breast conserving therapy a number of parameters influence the results of treatment. Our own studies have shown that among the risk factors responsible for fibrosis are: reference volume V100 (the volume of tissue surrounded by 100% isodose), V150 (volume of tissue surrounded by 150% isodose) and V200 (volume of tissue surrounded by 200% isodose).

Key words **breast cancer • HDR brachytherapy • soft tissue fibrosis**

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Background

Breast cancer is the most commonly occurring malignant tumour among women. In the early stages, breast conservation therapy (BCT) is used. A routine procedure may involve lumpectomy and whole breast radiotherapy with external beams and tumour bed boost. Such treatment allows to active of results similar to those of amputation.

In order to increase the dose around the tumour bed, external beams or interstitial HDR brachytherapy are used. This treatment is based on local recurrence data showing that the highest recurrence risk is in the area of earlier lumpectomy [1–3]. Experience from studies in selected institutions, and from controlled clinical studies, suggests that by increasing the dose to the post-tumour area it is possible to decrease the risk of recurrence [4,5].

The method used is determined mainly by the original localisation of the cancer and the therapeutic options available at the institute.

In multi-disciplinary treatment, a number of parameters influence the cosmetic effects. The major factors are: tumour size, volume of the removed tissue, total dose, fraction dose of irradiation and the dose rate.

Aim

The aim of this study was to analyse physical parameters of interstitial HDR brachytherapy and their influence on the risk of soft tissue fibrosis in the irradiated breast.

Materials and Methods

A retrospective analysis of 54 breast cancer patients treated in the Brachytherapy Department at the Oncological Centre of Bydgoszcz between July 1994 and December 1999 was performed. The minimum follow up period was 41 months, maximum follow up was 89 months, and the mean follow up period was 65 months. All patients had undergone lumpectomy and axillary clearance. In all cases but 6, an invasive ductal carcinoma was found. In one case, medullary carcinoma was detected. In three cases, lobular invasive carcinoma was diagnosed. Additionally, two cases of DCIS were detected.

In each case, conventional radiotherapy with opposing tangential fields was applied to the whole breast. The total dose was from 50 to 50.4 Gy with dose fractions from 1.8 to 2.0 Gy. Up to 14 days after radiotherapy, interstitial brachytherapy to the area after lumpectomy was applied, in order to increase the local dose.

Insertion of the needles was carried out under short-term anaesthesia. Hospitalisation lasted 24 hours.

The needles were introduced using coordinating plates, which ensured a constant geometrical pattern. According to the Paris system, the needles were placed in parallel positions and thus created triangular patterns [6]. The distances between the needles was fixed at 16 mm. Double-plane implants were most frequently used, with an average of 6 needles (min 3, max 18).

The dose range of interstitial brachytherapy used was from 5 to 20 Gy and was specified according to the Paris system [6]. In all cases, the reference isodose was estimated as 85% of the dose value at base points marked in the central plane of the implant. Treatment was by isotope Ir-192, HDR method (high dose rate), with source activity from 10 to 5 Ci.

The area for irradiation was determined on the basis of pre-surgical mammography, ultrasound examination, clinical examination, the surgeon's report, the pathologist's report and, in some cases, post-surgical mammography. The boost area comprised the maximum tumour dimension specified in the pathologist's report and a margin from 1 to 3 cm, which depended on the microscopic margin and histological nature of the tumour [7].

The treatment was well tolerated by all patients and no early complications were observed.

An observation period followed. The first follow-up examinations took place after 4 weeks and thereafter, every 3–6 months. Annual follow up examinations started 5 years after completion of therapy. Cosmetic effects were evaluated by 2 doctors independently. Presence or absence of fibrosis, compared to the healthy breast, was evaluated.

Statistical analysis was carried out using the program STATISTICA 6.0. For all parameters, the correlation of patients' sample data was compared with normal distributions using the Kołmogorow-Smirnow test, with Lileforse's correction. In most

cases statistically significant differences were found. Therefore, for inter-group comparison of independent samples, the U Mann – Whitney test was used. In all tests, the probability's border value was estimated at $p<0.05$.

Results

Physical parameters of interstitial brachytherapy were analysed. Patients were divided into groups 1 and 2. The first group included patients with fibrosis detected around the treated breast. The second group included patients without fibrosis. The influence of the following parameters was analysed in both groups: number of needles, number of planes, active length, total dose, V100 (the volume of the tissues surrounded by 100% isodose), V150 (the volume of the tissues surrounded by 150% isodose), V200 (the volume of the tissues surrounded by 200% isodose), QI quality index and UI uniformity index.

In Table 1, medium values and standard deviations for the analysed parameters in both groups are presented. Statistically significant differences were found in case of three parameters. These parameters were reference volumes V100, value ($p=0.0236$), V150 ($p=0.0221$) and V200 ($p=0.0311$).

Discussion

Soft tissue fibrosis is a common side effect of radiotherapy. The risk of its occurrence may be determined from the total dose used [8,9]. Bentzen et al, described this in the case of patients after mastectomy and irradiated on the sides of the chest [10]. The study found that a 50% risk of fibrosis occurrence is associated with a dose of 47.5 Gy given in 22 fractions. On the other hand, the studies carried out by Borger et al., showed that in case of breast conserving treatment, when radiotherapy is combined with interstitial brachytherapy, a 50% risk of fibrosis occurrence is associated with a dose of 72 Gy. These significant discrepancies are mainly due to application of various surgical methods and therefore, as a result, varying blood-vessel changes within the irradiated field. Blood-vessel changes are one of the factors known to increase the risk of soft tissue fibrosis. Another factor, one we know little about, is the difference in the radiosensitivities of the skin and the glandular or fatty tissue of the breast. Furthermore, this factor may be of high diversity.

Polgar and Moreno [11,12] described the relationship between irradiation dose and fibrosis occurrence in cases of interstitial high dose rate brachytherapy. Similar studies of patients with limited area irradiation after lumpectomy were described by Lawenda et al. [13].

Our own studies showed that reference volumes V100, V150 and V200 influence the risk of fibrosis occurrence. The V100 parameter is mainly determined by the tumour size and the extent of soft tissue removal. The correlation between the amount of tissue lost in surgery and the risk of fibrosis occurrence has been the subject of numerous studies [15–17]. The V150 and V200 parameters are its derivatives, but depend mainly on implant quality. Using different numbers of catheters, planes and by carrying out geometrical optimisation we influenced the above-mentioned parameters, thereby decreasing the probability of fibrosis occurrence. Our studies did not show, as we had expected, any statistically significant influence from the number of tracks and implant planes used. This is an inversely proportional relationship and was described by the authors of studies carried out at the Oncological Centre in Warsaw (A. Kulik, personal message) and is logically justified.

Another issue is the time of fibrosis occurrence and the period of follow up. In this study, to evaluate the effects of fibrosis, a minimal period of 3 years after the end of brachytherapy, was taken into consideration. Apparently, the risk is highest within the first 3 years after radiotherapy, however, following years of follow up also show slightly increased risk, a change which disappears entirely in the ninth year of the follow up period [14].

The studies carried out, were aimed at analysing various physical aspects and their influence on the risk of fibrosis occurrence. Therefore, a number of other clinical treatment factors which may have an influence on fibrosis occurrence, were not taken into consideration. Among these are: the range and type of surgery, chemotherapy or photon energy used in teleradiotherapy.

Conclusions

To summarise, a number of factors have an influence on the final cosmetic effect and on fibrosis risk in breast conserving therapy. One of the greatest factors is the quality of brachytherapy used. It should be based on multi-plane implants with suitable distance between the source and skin placement (min. 5 mm) and high dose area re-

Table 1. Medium values and standard deviation for interstitial brachytherapy parameters.

	Fibrosis			Without fibrosis			p test U Mann-Whitney
	medium	±	SD	medium	±	SD	
	mediana			mediana			
	–95%	÷	+95%	–95%	÷	+95%	
	n=21			n=33			
Number of needles	6.71	±	3.35	5.61	±	3.26	0.0918
	6.00			5.00			
	5.19	÷	8.24	4.45	÷	6.76	
Active length (cm)	6.00	±	2.55	5.17	±	2.39	0.2175
	5.50			4.00			
	4.84	÷	7.16	4.32	÷	6.01	
Number of planes	1.38	±	0.50	1.30	±	0.59	0.4778
	1.00			1.00			
	1.15	÷	1.61	1.10	÷	1.51	
V100 (cm^3)	72.70	±	52.47	56.03	±	68.44	0.0236
	59.90			38.00			
	48.81	÷	96.58	31.76	÷	80.30	
V150 (cm^3)	17.74	±	8.27	13.65	±	9.74	0.0220
	14.80			11.05			
	13.97	÷	21.51	10.19	÷	17.10	
V200 (cm^3)	7.83	±	2.94	6.21	±	3.44	0.0310
	7.30			5.40			
	6.49	÷	9.17	4.99	÷	7.43	
QI	1.98	±	0.72	1.77	±	0.65	0.2487
	1.64			1.50			
	1.65	÷	2.31	1.54	÷	2.00	
UI	1.68	±	0.31	1.59	±	0.27	0.3076
	1.65			1.50			
	1.54	÷	1.82	1.49	÷	1.68	
Total dose (Gy)	10.10	±	3.02	9.23	±	2.01	0.3943
	10.00			10.00			
	8.72	÷	11.47	8.51	÷	9.94	

duction (V150 and V200) in the target. Another important step would be to determine the target on the basis of magnetic resonance or ultrasound examination which would make clinical brachytherapy's introduction more possible and its application more standard than currently.

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