Influence of Radiation Therapy on Skin Circulation in the Breast after Breast Conservative Surgery

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Acta Oncologica Vol. 36, No. 7, pp. 715–718, 1997

It is not known whether the skin circulation is altered in the long term by radiotherapy following breast conservative surgery. The skin circulation in the breast was therefore measured in 24 breast cancer patients (mean age 57 years; range 40–76), one year after radiotherapy (50 Gy) following lumpectomy. None of the patients showed any persistent redness of the skin. The skin circulation was measured using laser Doppler fluxmetry (LDF) and fluorescein flowmetry within three areas: 2 cm above the border of the areola (position 1), within the nipple–areola complex (position 2) and 2 cm below the border of the areola (position 3). It was found that when measured with LDF, the skin circulation expressed as the ratio of operated irradiated to non-operated non-irradiated breast was 0.99 in position 1, 1.07 in position 2 and 0.91 in position 3; and when measured by fluorescein flowmetry, 1.00 in position 1, 1.08 in position 2 and 1.00 in position 3. The results indicate that radiotherapy following breast conservative surgery does not lead to long-term changes in basal skin circulation in the breast.

Received 10 February 1997
Accepted 28 August 1997

Adjuvant radiotherapy after breast conservative treatment for breast cancer very effectively reduces the frequency of local recurrences, but has no definite effect on the overall 10-year survival (1). However, the irradiation has some long-term side effects such as induced pneumonitis (2, 3) an increased frequency of lymphoedema, especially if the axilla has also been irradiated (4, 5), cardiac complications (6), brachial plexus neuropathy (7) and cosmetic changes (8–10). It is known that radiation therapy applied to breasts that have been reconstructed with a prosthesis increases the frequency of capsular contracture and thereby worsens the cosmetic results (11). However, there are uncertainties about how an irradiated breast is influenced with respect to the possibilities of a breast reconstruction after salvage mastectomy for a local recurrence following lumpectomy, or of a reduction mammaplasty in patients with large breasts. It is not known whether the skin circulation in the breast is altered in the long term after radiotherapy, a question which is of importance in the event of the necessity of further surgery. The present study was therefore undertaken to evaluate the influence of irradiation on the skin circulation after breast conservative treatment, using two established methods: laser Doppler fluxmetry (LDF), which measures the circulation down to a skin depth of 1–2 mm (12), and fluorescein flowmetry, which mimics the transport of small solutes to a depth of 0.6 mm in the skin (13).

MATERIAL AND METHODS

In 24 patients, (mean age 57 years; range 40–76), the skin circulation was examined one year after irradiation of the breast following lumpectomy for breast cancer. The patients were given local radiation therapy postoperatively to the affected breast only, with tangential photon beams, of 50 Gy given as 2 Gy fractions 5 days a week. The energy used was 4–6 MV and the skin dose at a depth of 0.2 cm was 65% and at a depth of 0.5 cm 78% of the total dose. No boost dose was given. None of the patients showed any persistent redness of the skin. The skin circulation was assessed by two methods, LDF and fluorescein flowmetry. The study was approved by the Ethics Committee of the Karolinska Institute at Huddinge University Hospital.

Skin circulation measurement

The skin circulation was measured using laser Doppler fluxmetry (see below) in three different areas, both in the operated irradiated and in the contralateral, intact, non-irradiated breast. The first area, position 1, was 2 cm above the upper border of the nipple–areola complex. The second area, position 2, was within the nipple–areola complex, and the third one, position 3, was 2 cm below the lower border of the complex. The LDF value was obtained as a mean of five measuring points within a circular area with a diameter of 1 cm.

 ISSN 0284-186X

Fluorescein flowmetry (see below) was carried out 5 min after the LDF measurements in all cases; 7 mg sodium fluorescein/kg body weight was given intravenously as a bolus injection and the skin circulation was measured over a period of 5 min. Fluorescence was estimated from the film negatives within an area corresponding to that of the laser Doppler measurements. These areas correspond to a circular area with a natural size diameter of 1 cm.

Calculation of skin circulation with laser Doppler fluxmetry

A laser Doppler fluxmeter with a differential detection system (Periflux ® Pf 1c, Perimed AB, Järfälla, Sweden) was used for the measurements. The operating principle of LDF is that monochromatic laser light broadens spectrally when scattered by moving objects such as blood cells, whereas light beams scattered in static structures alone remain unchanged in frequency. The flowmeter output signal, measured in volts, is proportional to the number of blood cells multiplied by their average velocity within the scattering volume. In our experiment we used a system with a 4 kHz filter, a time constant of 1.5 s and gain × 10. The results are expressed in volts. The Pf 108 probe with a specially made adapter with a concave indentation for the nipple was used in order to stabilize its pressure on and movements over the tissue. The probe was held manually.

Calculation of skin circulation with fluorescein flowmetry

The technique of fluorescein flowmetry has been described in detail elsewhere (13) and is therefore only summarized here. The skin circulation, or rather the transcapillary exchange of sodium fluorescein in the skin, is expressed as a fluorescence index, which is the ratio between the fluorescence obtained during the first circulatory passage of sodium fluorescein and the rise time defined as the time interval between the occurrence of 10% and 90% of the maximum fluorescence. The maximum fluorescence reflects the fraction of cardiac output distributed to the tissue according to Sapirstein's indicator fractionation principle (14). The rise time indicates the time taken for 80% of the bolus to disperse, and the use of this factor thus eliminates the uncertainty about when the first and the last part of the bolus become trapped in the tissue. Rise time is an expression of blood velocity. It has been shown to correlate both with the mean transversal time of the bolus proper ($r = 0.96$) and the mean transit time of the system ($r = 0.74$) (13). Rise time is inversely proportional to cardiac output, but is also influenced by peripheral resistance. Since the amount of sodium fluorescein administered is known, groups of subjects can be compared.

Photographic equipment and techniques used in the evaluation of the images

A Nikon F 501 (yellow Barrier filter: Scott glass GG 495 or Kodak gelatine Wratten filter 15) with a Paffrath & Kremper ringflash (blue excitation filter: Kodak gelatine filter Wratten 47 A) was used. The camera was fed by a specially built fast-repetitive generator. An objective lens was used (Micronikor 105:4.0). Black and white film (AGFA SCOPIX 1c 3B) was used for imaging. Images of the skin at a size scale of 1:5 were used for numerical evaluation of the fluorescence intensity by measurement of the optical density of negative film with a manual densitometer (Macbeth TD 501). Circular areas of the images, 2 mm in diameter, were analyzed. Values were expressed in density units, with the background density from the tissue fluorescence subtracted.

Statistical analysis

Analysis of variance showed a fairly normal distribution of values in all positions on both breasts as measured with LDF but considerable skewedness as measured with fluorescein flowmetry. All data are therefore expressed as medians and interquartile ranges. Statistical hypotheses were tested by a two-tailed Wilcoxon matched-pairs signed ranks test and 'corroborated' by a multiple comparison test as described by Bonferroni/Dunn, where the two dependent factors were side, with two levels (treated and untreated breast), and position, with three levels. A p-value of less than 0.05 was accepted as significant.

RESULTS

There was no significant difference in skin circulation between the treated and the contralateral, untreated breasts in any of the three positions as measured by either LDF or fluorescein flowmetry (Table 1, ratio of operated to non-operated breasts).

LDF showed that the circulation in the nipple–areola complex (position 2) was about 2–3 times higher than that in positions 1 ($p < 0.0001$) and 3 ($p < 0.0001$) in both the irradiated and the contralateral breast. There was no difference in skin circulation between positions 1 and 3 in either the treated or contralateral breast. Fluorescein flowmetry showed no differences in skin circulation between the different positions in either the treated or the contralateral untreated breast. (Table 1)

DISCUSSION

We found no reduction in basal skin circulation in the treated breast compared with the contralateral breast at least one year after treatment with lumpectomy and radiotherapy. The intention with radiotherapy is to focus on the glandular tissues while affecting the breast skin as little as possible. Irradiation after conservative surgery of the breast usually causes a strong inflammatory reaction of the skin, which gradually declines within one year. There were no visible abnormalities of the breast skin in any of the patients. We find it most unlikely that the skin circulation will be significantly reduced after the first year as a result

Table 1

Skin circulation in three different areas of the breast, 2 cm above the nipple–areola complex (position 1), within the complex (position 2) and 2 cm below the complex (position 3), measured by laser Doppler fluxmetry or by fluorescein flowmetry in the operated, irradiated breast and the non-operated, non-irradiated breast. The values are median values, with interquartile ranges in parentheses

		Laser Doppler flowmetry (volts) Position			Fluorescein flowmetry (Δ density units × 10^{-2}/S) Position		
	n	1	2	3	1	2	3
Operated, irradiated breast	24	7.3 (5.6)	25.0 (18.4)	8.3 (5.0)	0.11 (0.12)	0.16 (0.15)	0.13 (0.09)
p value		< 0.0001			0.18		
p value			0.76			0.49	
p value			< 0.0001			0.52	
Non-operated breast	24	7.3 (4.3)	21.4 (18.4)	8.6 (4.4)	0.15 (0.10)	0.16 (0.14)	0.18 (0.17)
p value		< 0.0001			0.71		
p value			0.53			0.09	
p value			< 0.0001			0.06	
Ratio op/non-op.		0.99 (0.48)	1.07 (0.64)	0.91 (0.53)	1.00 (0.37)	1.08 (0.70)	1.00 (0.22)
p value		0.93	0.56	0.65	0.78	0.15	0.37

of radiotherapy. It can therefore be concluded that, with respect to the skin circulation, there is nothing to prohibit the same type of surgery in an irradiated breast as that in a non-irradiated one. However, we have not examined the subcutaneous blood flow or evaluated its importance for successful reconstructive surgery of the breast, nor have we studied the subcutaneous and breast glandular blood flow in reduction mammaplasty. It must also be emphasized that we have only measured the skin circulation under basal conditions. It is possible that the ability to react to different kinds of provocation, e.g. traumatic hyperemia or a healing process, might be altered by radiation therapy. However, in a recent study of 28 women who had received postoperative, unilateral irradiation for breast cancer at least one year before, Evans et al. (15) found no statistically significant difference in vessel diameter or peak systolic velocity when using sonographic evaluation of the internal mammary artery and comparing the irradiated artery with that on the non-irradiated side.

The laser Doppler fluxmetry technique is very sensitive to artifacts caused by movements of the probe and its pressure on the tissue. We have sought to overcome this disadvantage by using a probe with a specially made adapter with a diameter of 3 cm and with a concave indentation for the nipple. By using this adapter and by applying it very gently to the tissue, we obtain a stable laser Doppler signal.

With laser Doppler fluxmetry, but not with fluorescein flowmetry, a two to three times higher skin circulation was found in the nipple–areola complex compared with the areas 2 cm above and below the border of the areola. These results are in concordance with earlier findings of a twice as high skin circulation in the nipple–areola complex compared with the surrounding areas, as measured by laser Doppler fluxmetry, and a 20% higher skin circulation below the complex compared with that above it, in both an intact breast and after subcutaneous mastectomy (16). There are several explanations for this discrepancy between the methods. First, laser Doppler fluxmetry differs from fluorescein flowmetry by measuring a deeper circulation. How deep is a matter of controversy; 1–2 mm in the skin (12), but even down to 6 mm in the gastrointestinal tract has been suggested (17). The blood flow velocity is much higher in the arterioles than in the capillaries, which means that the blood flow in the arterioles exerts much more influence on the laser Doppler signals than that in the capillaries, despite a larger capillary network. Secondly, it is likely that there is a true difference in circulation values between different layers of the skin, as has in fact been shown, for example, after subcutaneous mastectomy, and especially after subcutaneous reduction mammaplasty, when the circulation to the nipple–areola complex is based on a wide vertical pedicle. In cases of epidermal necrosis of the nipple–areola complex after this operation, fluorescein flowmetry showed no skin circulation in the complex, whereas with laser Doppler fluxmetry signals were recorded (18). Another explanation for the absence of an increased fluorescence index in the nipple–areola complex is that the skin over the nipple is more strongly pigmented, and it is known that the skin of black people exhibits only half the fluorescence of that of the white population (19).

There is no single clinical method whereby capillary blood flow is readily measured quantitatively in the skin. The combination of laser Doppler fluxmetry and fluorescein flowmetry would seem appropriate, since laser Doppler fluxmetry continuously measures the flux of erythrocytes within a small area and fluorescein flowmetry measures the transcapillary exchange of a small solute (sodium fluorescein, molecular weight 376) within a large area and thus reveals whether the circulation is homogeneous or not.

In conclusion, there seem to be no long-term differences in skin circulation between breasts treated by lumpectomy

and radiotherapy with a total dose at 50 Gy and the contralateral, non-operated, non-irradiated breasts, which suggests that further surgery in an irradiated breast does not need to be restricted compared with that in a non-irradiated breast, with the reservation that the importance of the circulation in the subcutaneous and breast glandular tissues has not yet been evaluated.

ACKNOWLEDGEMENTS

This research was supported by the Serafimer Hospital Foundation. The authors gratefully acknowledge the technical assistance of J. Holm.

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