

LYMPH CIRCULATION IN THE BREAST AFTER RADIOTHERAPY AND BREAST CONSERVATION

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ABSTRACT

The aim of this study was to investigate the breast lymph circulation and skin blood circulation after radiotherapy and breast conservation. In 23 patients who had undergone lumpectomy for breast cancer (mean age 58 years, range 44-75) and 12 patients with lumpectomy for benign lesions (mean age 51 years, range 33-72), lymph circulation in the breast was measured by ^{99m}Tc-nanocolloid clearance and skin circulation by Laser Doppler Fluxmetry (LDF). Measurements were made 2-5 years after radiotherapy (50 Gy) in the former group and at a corresponding time in the latter. The lymph circulation was measured 2 cm above and medial or lateral to the areolar border in the quadrant not operated on for carcinoma. Skin circulation was measured at corresponding sites. The lymph circulation expressed as the ratio of ^{99m}Tc-nanocolloid clearance in the operated irradiated to that in the non-operated (radiation 2-4 Gy) breast was 2.33 (2.66) (median, interquartile range) (p value 0.01) and the skin circulation ratio over the corresponding area was 0.92 (0.21). Corresponding ratios in the non-radiotherapy group were 2.07 (1.96) (p value 0.03) and 1.04 (0.18) respectively. Compared with the control breast (i.e., the non-operated non-irradiated breast), there was a 4-fold increase in lymph flow in the operated, irradiated breast, a

2.5-fold increase in the contralateral non-operated (2-4 Gy) breast and a 1.5-fold increase in the operated non-irradiated breast. Radiotherapy after breast conservation surgery leads to increased long-term changes in basal lymph circulation and smaller increases in lymph flow in the contralateral breast receiving 2-4 Gy and after surgery. If maximal lymph transport capacity is unchanged, edema may be more likely in this circumstance of reduced lymphatic transport reserve.

Keywords: breast cancer, lymph circulation, radiotherapy, breast conservation, lymphoscintigraphy, Laser Doppler Fluxmetry, skin blood flow

Adjuvant radiotherapy after breast conservation surgery (lumpectomy or when only a part of the breast has been removed), effectively reduces the incidence of local recurrence, but has no definite effect on survival (1). The most common side effects of breast radiotherapy are cardiac complications (2), pneumonitis (3,4), brachial plexus neuropathy (5), an increased incidence of lymphedema, particularly if the axilla has also been irradiated (6,7), and cosmetic changes (8-10). However, it is not certain how irradiation of a breast after conservative surgery influences the possibility of breast reconstruction after mastectomy in cases of local recurrence, or of reduction mammoplasty in patients with large breasts who later in life

want them smaller. We know that an irradiated breast shrinks and becomes firmer. That process is highly dependent on the amount of radiotherapy given and which type. 50 Gy given as 2 Gy a day as tangential photon beams with the intention to treat the whole breast glandular tissue minimally influences the cosmetic outcome but higher doses will (11). Electron beam is usually given to the thoracic wall after mastectomy and makes the tissue very firm and especially the great pectoral muscle. If a mastectomy is needed due to a local breast cancer recurrence after breast conservative treatment followed by tangential beam radiotherapy, the pectoralis major muscle often is soft which makes it possible to use a tissue expander implant (11). In other cases, healthy, non-irradiated tissue should be transferred to the area. It is not known, for example, whether the lymph circulation or the blood circulation in the breast is altered in long-term after radiotherapy, an issue that is important in the event of a need for further surgery.

The present study was therefore undertaken to quantitatively assess the lymph circulation and skin circulation two to five years after radiotherapy following lumpectomy and also in a group of patients who had undergone lumpectomy alone without radiotherapy. Two established methods were used, namely ^{99m}Tc -nanocolloid clearance, which measures the lymph circulation, and Laser Doppler Fluxmetry (LDF), which measures the skin circulation down to a depth of 1-2 mm (12). We also measured skin and room temperature during the measurement period.

PATIENTS AND METHODS

In 23 patients (mean age 58 years; range 44-75), the lymph and skin circulation were assessed 2-5 years after irradiation of the breast following lumpectomy for breast cancer. The patients were given local radiation postoperatively to the affected breast only, with tangential photon beams, in a dose of 50 Gy given as 2 Gy fractions

five days a week. The energy used was 4-6 MV and the skin dose at a depth of 0.2 cm was 65% of the total dose, and at a depth of 0.5 cm 78%. No booster dose was given. None of the patients developed any persistent redness of the skin. The non-operated, non-irradiated contralateral breast received a total dose of 2-4 Gy, measured at the skin level by a diode. In 12 patients with benign lesions (mean age 51 years, range 33-72), a lumpectomy was performed but no irradiation was given. In both groups the subcutaneous lymph circulation was assessed by ^{99m}Tc -nanocolloid clearance and the skin circulation by LDF. The room temperature, and the skin temperature on the measured areas, were also recorded before and after the measurement of ^{99m}Tc -nanocolloid clearance. The study was approved by the Ethics Committee of the Karolinska Institute at Huddinge University Hospital.

Experimental Set Up

The patients were allowed to rest for 20 minutes and all measurements were performed with the patients in supine position.

Firstly the room temperature, then the skin temperature over the areas to have the injections in both breasts at the corresponding areas were measured. Then the skin blood circulation in the same area was measured followed by the injection of ^{99m}Tc -nanocolloid in the two breasts for lymph circulation. Sixty minutes later, the room temperature, skin temperature, and skin circulation were again measured.

Measurement of Lymph Circulation

Local lymph drainage was expressed as the removal rate of the radiotracer, ^{99m}Tc -nanocolloid. A gammacamera (Axis, Picker International, Inc., Highland Heights, Ohio, USA) was placed over the breasts and acquisition was started simultaneously with the subcutaneous injection of two depots of ^{99m}Tc -nanocolloid 1.0 ml each (1 MBq)

injected 2 cm above and 2 cm medial or lateral to the border of the areola in the quadrant not previously operated on for carcinoma. The elimination of ^{99m}Tc -nanocolloid was followed dynamically with 1 frame per 20 second for 60 minutes. All data were stored and analyzed on a Hermes system (Nuclear Diagnostics AB, Stockholm, Sweden). Regions of interest (ROI) were drawn around the injection areas and one region to represent the background. Background subtracted curves were generated for each region and corrected for the physical decay of ^{99m}Tc (half-life=6.0h). The elimination of tracer from the injection area was assumed to be monoexponential. Thus, one monoexponential function ($N=N_0e^{-kt}$) was fitted to each elimination curve using least squares methods. In this function N and N_0 represent counts in the curve at time t and at the time of injection, respectively. The rate constant, k (1/h), is related to the half-time, $T_{1/2}$ (h), of the elimination curve through the relation $T_{1/2} = \ln 2/k$ (13,14).

Measurement of the Skin Circulation

The skin circulation was measured by Laser Doppler Fluxmetry on an area over the site of the subcutaneous injection. The LDF value was obtained as a mean of five measuring points within a circular area with a diameter of 1 cm.

A Laser Doppler fluxmeter with a differential detection system (Periflux ® Pf 1 c. 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 (V), is proportional to the number of blood cells multiplied by their mean velocity within the scattering volume. In our experiment we used a system with a 4 kHz filter, a time

constant of 1.5 seconds and gain x 10. The Pf 108 probe was used, with a specially made adapter with a concave indentation for the nipple to stabilize its pressure on, and movements over, the tissue. The probe was held in the hand.

Room Temperature and Skin Temperature

The room temperature and the skin temperature were measured by the same equipment (Minitemp. FS. MT Food Safety, Raytek, Berlin, Germany). The tip of the instrument was held 2 cm from the skin surface.

Statistical Analysis

As the distribution of the different values showed some skewness, all data are expressed as median (interquartile range). Statistical hypotheses were tested as ratios within the different groups by a two-tailed Wilcoxon matched-pairs rank sum test and Wilcoxon rank sum test between the median values of the groups and corrected for multiple comparisons by the Bonferroni method (15). Probabilities of less than 0.05 were accepted as significant.

RESULTS

When the results were compared to those in the control breast (the non-operated contralateral breast in the patients treated with lumpectomy without irradiation with a ^{99m}Tc -nanocolloid half-time elimination of 2063 minutes), the following ratios were observed: There was a 1.5 times higher lymph flow determined as clearance of ^{99m}Tc -nanocolloid in the operated breasts in the non-irradiation group ($p < 0.001$) (Wilcoxon paired rank sum test), a 2.6 times higher lymph flow in the non-treated contralateral breast, receiving 2-4 Gy, in the group given irradiation to the operated breast ($p < 0.001$) (Wilcoxon rank sum test), and a 4 times higher lymph flow in the operated, irradiated

TABLE 1
Lymph Circulation Measured by ^{99m}Tc -Nanocolloid Clearance and Skin Circulation Measured by Laser Doppler Fluxmetry in 23 Operated Irradiated (50 Gy) Breasts and the Contralateral Non-Operated Breasts (Radiation Dose 2-4 Gy) and Also in 12 Operated Non-Irradiated Breasts and the Contralateral Non-Operated Breasts. Data Are Expressed as Median (Interquartile Range). The P Values are Given for Comparison of Paired - Differences Within Each Patient.

	n	^{99m}Tc -nanocolloid Half-life (min)	Inverse ratio to the control breast (i.e., the non-operated non-irradiated)	Laser Doppler Fluxmetry (V)
Breast cancer:	23			
Operated, irradiated breast (50 Gy)		554 (438)	4.0	6.6 (2.4)
Non-operated breast (radiation dose 2-4 Gy)		796 (1218)	2.6	7.4 (2.6)
Ratio operated: non-operated side		2.33 (2.66)		0.92 (0.21)
p value		0.01		0.03
Benign lesions:	12			
Operated, non-irradiated breast		1310 (834)	1.5	8.7 (3.4)
Non-operated, non-irradiated		2063 (1824)	1.0	8.6 (2.8)
Ratio operated: non-operated side		2.07 (1.96)		1.04 (0.18)
p value		0.03		0.94

breasts ($p < 0.001$) (Wilcoxon rank sum test). Of this latter 4-fold increase, 1.5 was due to surgery and 2.5 to radiation (*Table 1*). LDF showed that there was no difference in skin blood circulation in the area over the subcutaneous injection site between the treated and the opposite, untreated breast in either group (*Table 1*). The room temperature was slightly (but significantly) higher (by 0.2°C) after than before ^{99m}Tc -nanocolloid clearance (*Table 2*). The skin temperature was significantly increased in the operated, irradiated breast by 1.5°C , and in the opposite breast (radiation 2-4 Gy) by 0.9°C . The skin blood circulation, measured by LDF, did not increase either in the operated, irradiated breast or in the non-operated breast (radiation 2-4 Gy) (*Table 2*).

In the group of patients who underwent lumpectomy alone without irradiation there was no increase in skin temperature or in skin circulation either in the operated breast or in the contralateral, non-operated breast after ^{99m}Tc -nanocolloid clearance (*Table 3*).

DISCUSSION

Our results show that there is a change in subcutaneous lymph circulation both after surgery and after radiotherapy measured as the half-time elimination of ^{99m}Tc -nanocolloid. Compared to the control breast (non-operated, non-irradiated breasts), the basal lymph circulation had increased 1.5-fold in operated breasts at least two to five years after lumpectomy. When radiotherapy had

TABLE 2
Skin Temperature and Skin Circulation (Laser Doppler Fluxmetry) in the Operated and Non-operated Breasts of the 23 Patients with Breast Cancer, Before and after ^{99m}Tc-Nanocolloid Clearance. Room Temperature Is Also Given. Data Are Expressed as Median (Interquartile Range)

	Before ^{99m} Tc nanocolloid clearance	After ^{99m} Tc nanocolloid clearance	p value
Room temperature (°C)	24.8 (1.2)	25 (1.5)	0.02
Skin temperature, operated, irradiated side (°C)	31.8 (1.5)	33.3 (0.9)	0.001
Skin temperature, non-operated side (radiation dose 2-4 Gy) (°C)	32.1 (1.5)	33.0 (1.5)	0.003
Laser Doppler, operated, irradiated side (V)	6.6 (2.4)	7.4 (3.3)	0.16
Laser Doppler (V), non-operated side, (radiation dose 2-4 Gy)	7.4 (2.6)	7.2 (2.9)	0.78

TABLE 3
Skin Temperature and Skin Circulation (Laser Doppler Fluxmetry) in the Operated and Non-Operated Breasts of the 12 Patients with Benign Lesions Before and After ^{99m}Tc- Nanocolloid Clearance. Room Temperature Is Also Given. Data Are Expressed as Median (Interquartile Range)

	Before ^{99m} Tc-nanocolloid clearance	After ^{99m} Tc-nanocolloid clearance	p value
Room temperature (°C)	26.0 (1.8)	26.0 (2.0)	0.07
Skin temperature, operated side (°C)	34.0 (1.6)	34.5 (1.8)	0.19
Skin temperature, non-operated side (°C)	34.5 (1.8)	34.3 (1.2)	0.23
Laser Doppler, operated side (V)	8.7 (3.4)	9.0 (2.0)	0.31
Laser Doppler, non-operated side (V)	8.6 (2.8)	9.3 (3.4)	0.50

also been given, a further 2.5-fold increase in basal lymph circulation was seen. There was also a 2.6-fold increase in lymph transport in the breasts contralateral to the operated, irradiated breasts even though the former

received only 2-4 Gy. We chose a time period of 2-5 years after operation and radiotherapy in order to exclude any acute inflammatory reaction to irradiation. No patients had any clinical sign of edema. The skin blood

circulation measured by Laser Doppler Fluxmetry did not show any differences between the different treatments. The ^{99m}Tc -nanocolloid clearance measurement took 60 minutes and during that time the room temperature slightly increased. The clinical consequences of the up to four-fold increase in lymph circulation in an operated irradiated breast is not clear. Most patients do not have any obvious symptoms or clinical signs. Lymphedema develops when the production of lymph exceeds the transport capacity of the tissue and implies low output failure of the lymph vascular system (16). The difference between the patient's normal transport capacity and the maximum lymph flow that can be transported from the tissue without the development of lymphedema is called the lymphatic transport reserve (17). It can be exemplified as follows: theoretically, the lymph transport from the breast can increase 10 times from the normal transport capacity before lymphedema develops. In an operated irradiated breast the basal lymph flow already is increased 4 times and if the maximum lymph flow transport capacity is the same as in a non-operated, non-irradiated breast then the lymphatic transport reserve will be only 6 times. Since none of our operated, irradiated patients demonstrated any clinical sign of lymphedema, the maximal lymph transport capacity before lymphedema developed was not reached. The normal transport capacity in the breast is not known, but clearly the lymphatic transport reserve of a surgically treated irradiated breast will be reduced, a fact which might be clinically relevant in a situation when the lymph load is increased, for example as a result of the trauma of a reoperation or infection. Tengrup et al (18) studied arm morbidity after breast-conserving therapy for breast cancer, and after 5 years of follow-up they found lymphedema, defined as an increase in volume by >10%, in 12% when axillary dissection was performed to level I-II and in 17% when radiotherapy to the breast was added 50 Gy over a period of 5 weeks. The incidence of

clinically significant lymphedema as a complication following surgery for primary operable breast cancer can be reduced. Rampaul et al (19), in a questionnaire study of 1242 patients, found a lymphedema frequency of 0.04% among patients in whom low axillary sampling had been performed. The use of the sentinel node technique might in the future lead to corresponding results.

It is generally accepted that irradiated tissue heals less well than normal tissue. Fisher et al (20) reported from experiments in rats that smaller areas had survived in both delayed and non-delayed irradiated flaps than in non-irradiated flaps 8 months after radiation. In man, the gross radiation-induced changes that influence cutaneous healing in the long term are atrophy of the skin, changes in pigmentation, telangiectasia, and woody fibrosis (21). It is also well known that the frequency of capsular formation around an implant is much higher after radiotherapy in breast reconstruction (22,23). We have previously found that postoperative irradiation causes no long-term changes in the skin, subcutaneous and glandular circulation in the breast (24). A possible reason for the increase in lymph circulation might be that the lymph system is much more sensitive to inflammatory changes than the blood system and that even a low dose of 2-4 Gy given over a period of 25 days affects the lymph circulation. Another postulated mechanism underlying the increase in lymph circulation is the prolonged inflammatory reaction caused by dysfunction of irradiated fibrocytes, leading to an imbalance of collagen production and resorption as a consequence of slow loss of fibroblasts, which could result in incomplete resorption of collagen that has already been deposited by the fibroblasts before their death (25). Noticeable fibroblast disorganization has been reported, with findings of swollen, degenerating mitochondria, multiple vacuoles and dilated, irregular rough endoplasmic reticulum on electron microscopy, suggesting that permanent damage to fibroblasts or

fibroblast stem cells may have an important role in chronic radiation-induced skin ulceration (26). In 1988, Rudolph et al (27) also found retarded growth of cultured fibroblasts from human radiation wounds, again suggesting that radiation has a permanent intrinsic effect on fibroblasts, or that there is selective ablation of faster-growing fibroblast subpopulations that is not dependent on a reduction in blood supply. The amount of radiotherapy given is of crucial importance in producing these adverse effects.

In conclusion, there seems to be a long-term increase in lymph flow probably as a consequence of an inflammatory reaction in a surgically treated, irradiated breast that might lower the lymphatic transport reserve of the breast making lymphedema development more likely.

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