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LYMPHATIC DRAINAGE IN THE BREAST BEFORE AND UP TO FIVE YEARS AFTER A REDUCTION MAMMAPLASTY

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ABSTRACT

The aim of this study was to investigate lymph circulation before and after breast reduction mammaplasty in different parts of the breast and with two different carriers of the radiopharmaceutical. Nine patients with breast hypertrophy planned for bilateral breast reduction mammaplasty were prospectively included in the study. The breast operation procedure was decided on intraoperatively. The regional lymph circulation in the breast was measured preoperatively by Technetium (^{99m}Tc) clearance in 4 different locations in each breast 1, 2 and 3 hours after injection. The procedure was repeated at one month and in six of the nine women also five years postoperatively with injection sites chosen to correspond to the preoperative location of that breast pedicle. Two different types of carriers of the radiopharmaceutical were tested, dextran in the right and nanocoll in the left breast. Dextran had a much more rapid clearance than nanocoll. There was no significant regional difference in lymph drainage up to five years after the mammaplasty, independent of dextran or nanocoll as being the carrier of the radiopharmaceutical.

Keywords: lymphatic drainage, lymphoscintigraphy, lymphatic imaging, radiopharmaceutical, breast hypertrophy, reduction mammaplasty

Lymphedema after breast cancer surgery and axillary lymph node dissection is relatively common at 6-30% (1) and in combination with irradiation, the risk increases even further (2). Sentinel lymph node biopsy is an accurate predictor of axillary lymph node status in patients with early breast cancer (3,4) and is associated with a significantly lower risk of arm morbidity compared to axillary lymph node dissection including arm lymphedema (1). Anatomical mapping studies have shown how lymph nodes and lymph vessels are organized but not much is known about lymph flow dynamics and how it is affected after previous breast surgery. Often reconstructive surgery is performed on the contralateral breast after breast cancer surgery to achieve symmetry. The risk of developing a contralateral breast cancer persists for at least 20 years after treatment for early-stage breast cancer and the annual risk is approximately 0.75% per year (5). Reduction mammaplasty implies that breast glandular tissue and skin is removed and the nipple areola complex is raised to a new position by use of different kind of pedicles. Theoretically, the lymph circulation in the

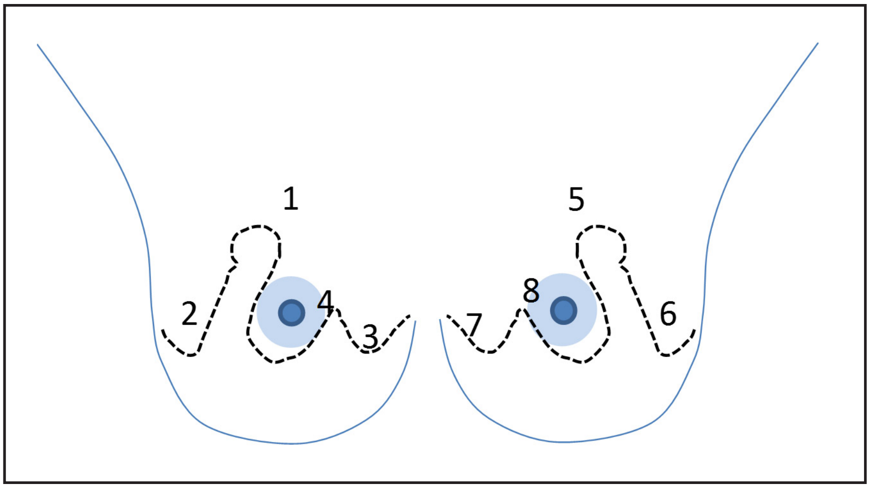

Fig. 1. Preoperatively chosen regions in the breasts for administration of the radiopharmaceutical. Regions 1-4 in the right breast received dextran-linked radiopharmaceutical and regions 5-8 in the left breast received nanocoll-linked radiopharmaceutical.

breast might be altered, possibly influencing both spread of tumor cells and reliability of the sentinel lymph node biopsy technique for staging of axillary lymph nodes. Disruption of breast lymphatics might modify drainage pathways, and performance of a sentinel lymph node biopsy after a previous excisional biopsy is still controversial (4,6-8). The aim of the present study was to investigate lymphatic drainage from different regions of reduction mammaplasty operated breasts, particularly focusing on drainage from the pedicle inside the breast. A secondary aim was to test two different types of carriers of the radiopharmaceutical.

MATERIALS AND METHODS

Patients

Women with breast hypertrophy planned for bilateral reduction mammaplasty at Karolinska University Hospital Huddinge were prospectively included in the study between January and December 2004. The regional lymph circulation in the breasts was measured preoperatively and one month postoperatively. Six of the nine patients were also measured five years postoperatively. Scintigraphic images are missing of the syringes 1 month postoperatively for one patient and images acquisitioned 3 hours after injection preoperatively for another patient.

Breast Operation Procedures

Reduction mammaplasty implies a reduction of breast glandular tissue and skin and raising of the nipple areola complex based on different types of pedicles. The decision whether to use a medially or a vertically based pedicle was made intra-operatively when the skin over the pedicle had been deepithelialized and depended on the possibility to move the nipple-areola complex to its new position without tension in the tissues.

In the medially based pedicle, breast glandular tissue was extirpated caudally in the breast and cranially at the new location for the nipple. The pedicle was turned cranially like a U into the new location for the nipple areola complex. In the vertically based pedicle, breast tissue was removed medially and laterally from the pedicle.

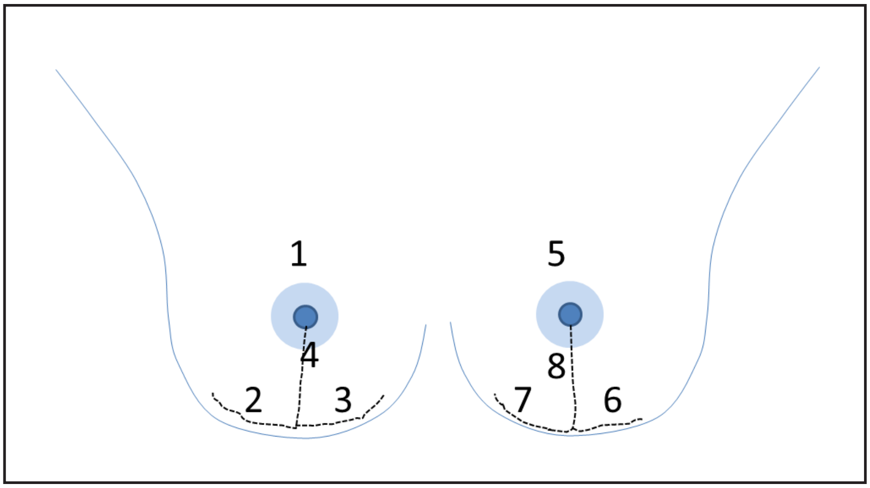

Fig. 2. Postoperatively chosen regions in the breasts for administration of the radiopharmaceutical. Regions 1-4 in the right breast received dextran-linked radiopharmaceutical and regions 5-8 in the left breast received nanocoll-linked radiopharmaceutical.

The deepithelialized pedicle was covered by the skin and subcutaneous tissue of the flaps.

Administration of Radiotracer

Preoperatively, injection site numbers 1 and 5 were chosen two cm above the planned border of the areola, injection site numbers 2 and 6 were two cm lateral to the planned vertical incision line and two cm above the submammary fold, injection site numbers 3 and 7 were two cm medial to the planned vertical incision line and two cm above the submammary fold and injection site numbers 4 and 8 were two cm from the planned postoperative lower border of the areola and two cm medial to the vertical incision line. The injections were given five mm deep into the subcutaneous fat (*Fig. 1*).

Postoperatively, injection sites were chosen to correspond to the same region that had been injected preoperatively and the injections were given at the same depth, except in the medial pedicle, which postoperatively was located deeper. In these regions (4 and 8, respectively), the injections were given two cm deep into the subcutaneous tissue of the pedicle. The medially based pedicle was postoperatively located caudally from the border of the areola as were the injection sites of the vertically based pedicle (*Fig. 2*).

Each patient was injected with 5 MBq ^{99m}Tc-dextran in 0.1 ml in each of four locations in the right breast and with 5 MBq ^{99m}Tc-nanocoll in 0.1 ml in the corresponding four locations in the left breast. The syringes were imaged with the same gamma camera as the study patients before and after each injection to assess the amount of injected activity.

^{99m}Tc-Dextran

^{99m}Tc-dextran was prepared according to a standard stannous reduction method using preparations of dextran and stannous chloride. Before each study, radiotracer was obtained by adding freshly eluted ^{99m}Tc-pertechnetate. The reagent kits were prepared in 15 unit batches, dextran (Mw 64,000-76,000) in a concentration of 50 mg/ml and $Sncl_2$ $2H_20$ in a concentration of 1 mg/ml. The reagent solutions were prepared under aseptic conditions, dispensed in 1 ml portions through a 0.22 µm sterile membrane filter into 10 ml sterile vials which were stoppered and stored at -15°C until used.

Lymphoscintigraphy was performed preoperatively and twice postoperatively, after one month and five years after the breast reduction mammaplasty. Each patient was injected in the right breast with a dextran- and in the left breast with a nanocoll-labeled radiopharmaceutical on four corresponding locations in each breast defined by the breast surgeon.

Labeling

0.5 ml of stannous chloride solution (1mg/ml) was added to the vial containing 1 ml of dextran 50 mg/ml. 1ml ^{99m}Tc-pertechnetate solution with a radioactive concentration of 120 MBq/ml was added to the dextran/Sn reagent solution, which was mixed and incubated for five minutes. The solution was diluted with 3.5 ml of 0.9% NaCl to a final radioactive concentration of 20 MBq/ml.

Quality Control

The labeling efficiency was measured by thin layer chromatography using ITLC-SG strips (Pall) with acetone as mobile phase. The strips were scanned in gamma camera. R_f ^{99m}Tc-dextran=0, R_f $^{99m}TcO4^-$=100. $^{99m}TcO4^-$ was found to be less than 2% in every case.

^{99m}Tc-Nanocoll

^{99m}Tc-nanocoll (Nanocoll, GE Health-care): 1 ml ^{99m}Tc-pertechnetate solution with a radioactive concentration of 120 MBq/ml was added to the nanocoll kit. Then 5 ml of 0.9% NaCl solution was added to obtain the same final radioactive concentration as the ^{99m}Tc-dextran solution (20 MBq/ml).

Imaging Procedures

Imaging was performed with a Siemens ECAM gamma camera equipped with a low-energy, high-resolution, parallel hole-collimator. Data acquisition was performed in anterior projections with the patient supine and the gamma camera centered over the areola regions. A dynamic acquisition was started directly after injection and lasted for 30 minutes (10 frames per minute). Planar images were acquired 1 hour, 2 hours, and 3 hours after injection with an acquisition time of 10 minutes.

Evaluation of Scintigraphic Data

Regions of interest (ROI) were drawn around each of the eight injection sites (four on the left and four on the right side). Counts registered in each ROI on the scintigraphic images were converted to percentage of injected dose and corrected for physical decay of ^{99m}Tc. The elimination of radiotracer from the injection sites (wash-out) was considered a measure of lymph drainage.

The study was approved by the Regional Ethical Review Board (Dnr 410/02) and the Regional Nuclear Protection Committeé (Dnr 18/02) in 2002.

Statistical Analysis

The statistical analysis was performed with the Statistica statistical software package (Statistica 10, StatSoft Inc, Tulsa, OK, USA). The data were analyzed by nonparametric one-way-analysis of variance. *P* values less than 0.05 were considered significant.

The class 1 interclass correlation test (ICC) was used (9,10). This is a typical test to measure the agreement between two data sets with 1.0 indicating perfect agreement. According to Landis and Koch, values greater than 0.81 indicate almost perfect agreement (11).

RESULTS

Patients

Nine women planned for breast reduction mammaplasty were prospectively included during the study period. In four of

TABLE 1
Clinical Characteristics of the Patients

	Median	Range
Age (years)	41	26-64
BMI (kg/m^2)	24.7	22-30
Breast size preoperatively (ml)	900	700-1500
Average weight of resected breast tissue per breast (gram)	307.5	150-685

the women the breast surgeon intraoperatively decided on a medially based nipple areola pedicle according to the technique of Strömbeck (12). Five women received a vertically/caudally based pedicle, McKissock or Robins technique (13,14). Clinical characteristics of the patients are given in *Table 1.*

Lymph Drainage

Evaluations of the scintigraphic data were performed by one nuclear radiologist and one breast surgeon, who achieved an interclass correlation (ICC) in their measurements of at least 94.5%. The difference is not statistically significant meaning that the method is stable and independent of examiner.

Dextran, carrier of the tracer in the right breast, had a much quicker clearance (wash-out) compared to nanocoll in the left breast, especially preoperatively. Clearance of the radiotracer from all regions in the right breast (dextran) was faster preoperatively compared to postoperatively. The slowest elimination was seen five years postoperatively (p-value = 0.0017). There was no significant difference in clearance between the different regions in the right breast.

On the left side where nanocoll was carrier of the radiopharmaceutical, the injection site above the areola (region 5) displayed a significantly (p-value = 0.03) slower clearance of radiotracer preoperatively compared to postoperatively. However, the postoperative clearance from region 5 was not significantly slower compared to the other regions in the same breast. In the three other regions (region 6-8) in the left breast, there was no significant difference in clearance between regions or visits (*Fig. 3*)

DISCUSSION

The present study investigated regional lymph flow dynamics in nine prospectively recruited women before and after bilateral reduction mammaplasty which took place between January and December 2004. Six of the nine women were also examined in 2010, just over five years after the mammaplasty. We used two different types of carriers of the radiopharmaceutical, dextran in the right breast and nanocoll in the left breast.

In the right breast, the clearance was significantly quicker preoperatively compared to postoperatively, and the slowest clearance was observed five years postoperatively. Dextran was eliminated quicker than nanocoll, especially preoperatively. This we concluded must be due to the smaller particle size of dextran. No significant regional difference in clearance was seen in the right breast, neither pre- nor postoperatively. The particle size of dextran was small enough to allow equal lymph flow independent of breast region and amount of lymph vessel disruption and scarring. The reason why the clearance was quicker one month postoperatively compared to five years postoperatively could be due to increased lymph flow following the acute inflammatory reaction. In an earlier publication in *Lymphology*, Perbeck et al reported on long-term increase in lymph flow in the breast, 1.5-fold in a breast operated for a benign lesion, 2.5-fold in the contralateral non-operated, but indirectly irradiated breast and 4-fold in the operated, irradiated breast 2-5 years after surgery. None of these breasts demonstrated any clinical lymphedema (15).

In the left breast, elimination of nanocolloid did not differ significantly temporally

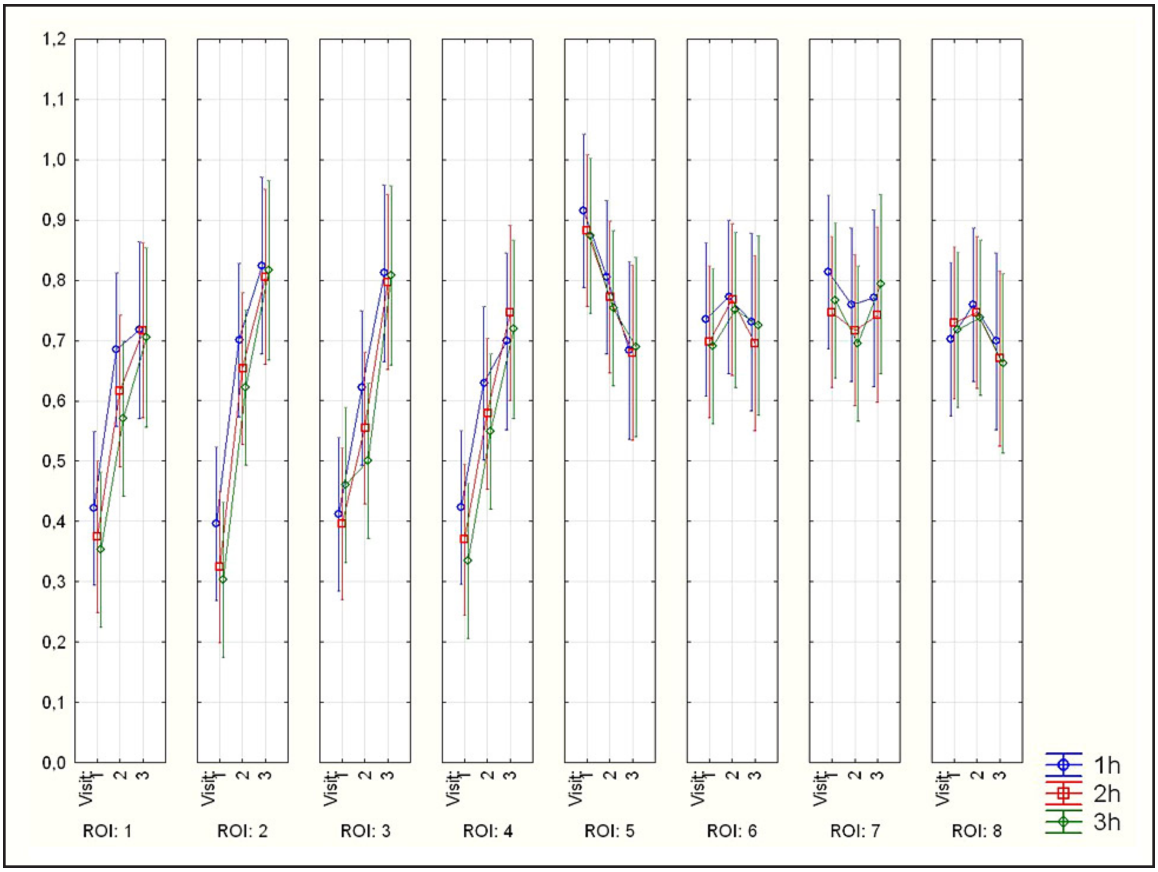

Fig. 3. Clearance of the radiopharmaceutical from different regions of interest (ROI) in the right and left breast. ROI 1-4: Right breast (dextran-linked radiopharmaceutical) and ROI 5-8: Left breast (nanocoll-linked radiopharmaceutical). Visit 1= preoperatively; Visit 2= one month postoperatively; Visit 3= five years postoperatively. The y-axis depicts counts registered in each region 1 (blue), 2 (red) and 3 (green) hours after injection. The counts were converted to percentage of injected dose and corrected for physical decay of ^{99m}Tc.

or between regions except for region 5 above the nipple areola complex where the elimination unexpectedly was significantly slower preoperatively compared to postoperatively. The authors have no reasonable explanation for this finding.

As mentioned above, the behavior of the carrier is dependent on the particle size. In the localization of sentinel lymph nodes, smaller particles travel more quickly and reach more lymph nodes, thereby offering lower false-negative rates (8) with the risk of only a fraction of the radiotracer being retained in the first lymph node. On the contrary, large particles are trapped in the interstitium and can be retained for a long time at the injection site (16). In Europe, nanocolloid with a particle size of <16 nm and 95% linked to ^{99m}Technetium, is the most frequently used radiopharmaceutical for lymphoscintigraphy (17). A particle size ranging from 100 to 200 nm is considered ideal for retention in the sentinel lymph node (16). The relatively larger particle size of nanocoll was retained equally pre- as post-operatively except for in region 5. Images acquired 3 hours, in comparison with 1 hour after injection, did not change the clearance significantly.

Limitations with this study are that only nine women were included and that different kinds of reduction mammaplasty techniques were used. The type of pedicle to be used was decided upon intraoperatively. The purpose was to move the nipple areola complex to its new position without tension. Four patients had a medially based pedicle, but five had a vertically or caudally based pedicle in which the preoperative injection sites in position 4 and 8 were not the same as the postoperative sites. The preoperative injection site should theoretically have been at the six o´clock position and two centimeters below the areola border. However, these were preoperative measuring areas and the likelihood that there should be a difference between these areas below and medially from the nipple areola complex is very low, which is also supported by our results showing no regional difference in clearance of the radiopharmaceutical postoperatively. According to Mostbeck et al and also Partsch et al, assessment of abnormal lymphatic drainage cannot be done only by measuring clearance rates of the radiotracer but should also include a standardized stress test, assessment of both prefascial and subfascial lymph transport as well as quantification of storage rates over the regional lymph nodes (18,19). In this study, our aim was to evaluate regional differences in lymph circulation from different parts of the breast before and after a reduction mammaplasty. Measurement of axillary or regional lymph nodal storage of the radiopharmaceutical was not performed. The reason for this is that this information would not have added any knowledge about regional lymph flow differences, instead it would have been a measure of the total lymph clearance from the breast.

The strengths of this study are that six of the women were examined as long as five years postoperatively and that the results add information about lymph flow dynamics after breast surgery and how it is affected regionally and temporally. If these results, which suggest that the regional lymph clearance is not affected significantly after prior breast surgery, can be reproduced in larger studies, a sentinel lymph node biopsy after earlier breast surgery should be considered feasible.

CONCLUSIONS

This study showed that the lymph drainage from different areas and pedicles in the breast after a reduction mammaplasty is not altered significantly regionally, measured as the elimination of ^{99m}Tc-nanocoll or ^{99m}Tc-dextran up to five years postoperatively. The two different carriers of the radiopharmaceutical demonstrate different lymph drainage timing with elimination of ^{99m}Tc-dextran occurring much faster due to its smaller particle size.

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