Breast edema following conserving surgery and radiotherapy. Eur J Lymphology 2014;25(70):1-5

Article *in* European Journal of Lymphology and Related Problems · June 2014

Karin Johansson
Lund University

Tapani Lahtinen
Kuopio University Hospital

THE EUROPEAN JOURNAL OF lymphology and related problems
VOLUME 25 • No. 70 • 2014

BREAST EDEMA FOLLOWING BREAST CONSERVING SURGERY AND RADIOTHERAPY

KARIN JOHANSSON [1], TAPANI LATHINEN [2], THOMAS BJÖRK-ERIKSSON [3]

[1] Inst of Health Science, Lund University, Sweden
[2] Cancer Center, Kuopio University Hospital, Finland
[3] Department of Oncology, Skåne University Hospital and Lund University, Sweden

ABSTRACT

Introduction: Breast edema following cancer treatment is very rarely documented.

The aim of this study was to investigate tissue water content in skin and upper subcutis in women treated for breast cancer with breast conserving surgery and radiotherapy (RT) to the breast and compare the changes with the healthy breast.

Material and methods: One hundred eighteen patients were measured prior to, during and 2 and 4 weeks after end of RT. Local edema in the four quadrants of both breasts was measured with MoistereMeterD (Delfin Technologies Ltd, Finland). A parameter, tissue dielectric constant (TDC), directly proportional to tissue water content to the effective depth of 2.5 mm, was calculated. Breast edema was defined as a TDC ratio exceeding 1.40 (mean + 2SD) between the irradiated and healthy breast.

Results: Difference in TDC ratio ($p < 0.001$) between the operated and healthy breast was found at each measurement time-point. The incidence of breast edema was 31.4% before start of the RT treatment, increasing during RT and was 62.6% at 4 weeks after completion of RT. The mean pre-RT TDC ratio 1.30 ± 0.29 increased during the first week of therapy to 1.43 ± 0.33 and stayed elevated through the observation period ($p < 0.001$). Pre-RT patients with scar in quadrant 4 showed higher TDC ratio ($p = 0.02$) ($n = 71$, TDC ratio 1.36 ± 0.31) than patients with no scar tissue in quadrant 4 ($n = 46$, a TDC ratio 1.20 ± 0.23).

Conclusion: The healthy breast can act as a control to provide a ratio between the breasts. Based on the evaluation of the mean TDC ratio, the incidence of breast edema was found to be high (> 30%). The TDC values illustrating edema in the operated breast were higher compared to the healthy breast at all measurement time-points, also pre-RT, suggesting a high influence of surgery on breast edema. However, axillary surgery did not seem to increase breast edema more than sentinel lymph node biopsy. It was also shown that patients with scar in the fourth quadrant are more likely to have a higher TDC ratio. The higher weekly doses in the hypofractionated RT seem to induce more edema than conventional fractionation.

Keywords: Breast cancer, breast edema, breast surgery, radiotherapy, tissue dielectric constant

INTRODUCTION

It is well-known among clinicians that breast edema may occur after breast cancer treatment, still it is often an overlooked side effect. Breast edema is very rarely documented and only in a few studies the incidence has been estimated. Rönkä et al. [1] found subcutaneous edema of the breast, measured with ultrasound one year after surgery and radiotherapy (RT) to the breast, in 70% of the patients with axillary node dissection and in 28% with sentinel node biopsy. Goffman et al. [2] found an incidence of breast edema only in about 10% of the patients in a similar material but more than 2 years after cancer treatment using clinical signs like erythema and changes similar to peau d'orange of the breast and the patients complains about swelling, heaviness, redness, and pain as criterion of breast edema. It was also argued that these symptoms are distinctly different from the minor swelling often seen during RT(2). Constantine et al. [3] clinically scored breast edema on a 10-point scale and found that 17% of the patients treated for ductal carcinoma in situ experienced breast edema during and within 90 days of RT. Nuutinen et al. [4] using dielectric technique observed that skin tissue water content in irradiated and contralateral breasts decreased during RT. These observations were associated with the radiation-associated obstruction of skin capillaries. Previously, Papp et al have noticed using the same technique with experimental burn injuries in landrace pigs that a superficial burn injury damaging skin vasculature induces edema in subcutis [5].

Wide differences in the incidence of breast edema are most likely due to the method and phase where the edema has been evaluated. Breast edema may also consist of several edemas of different origin. Radiation-induced edema during RT and at 3-6 months post-RT during delayed acute reaction originating mostly from failure to microvasculature may be impossible to distinguish from lymphedema resulting in damage to lymphatic vessels. Therefore, in the following we use the term breast edema to describe edema which may have different origin.

Recently, a new device, MoistereMeterD, with a technique based on electromagnetic waves measuring tissue water content, has been introduced showing potential to measure breast edema [6]. Since the MoistereMeterD enables the measurement of different quadrants of the breast, the technique may lead to improvement in conservative treatment of breast edema. In the present investigation we examined tissue water content in skin and upper subcutis in women treated for breast cancer with breast conserving surgery and RT to the breast, prior to, during and 2 and 4 weeks after RT treatment and compared to changes with healthy breast.

MATERIALS AND METHODS

Patients

Two hundred sixty breast cancer patients treated with breast conserving surgery and sentinel lymph node biopsy (SNLB) or axillary lymph node dissection (ALND) and RT to the breast at the

Department of Oncology at Skåne University Hospital, Sweden, were included in the study.
Patients with preoperative chemotherapy, recurrent cancer, concurrent diseases that may interfere with measurement of lymphedema and difficulties in participating in the study, for example dementia, were excluded.

Measurements

Local tissue water was measured with the TDC technique (MoistureMeterD, Delfin Technologies Ltd, Finland). The device transmits a very high frequency electromagnetic (EM) wave of 300 MHz into an open-ended coaxial probe in contact with the skin. A major part of the EM energy is absorbed by tissue water while the rest is reflected back to the coaxial line and an electrical parameter, tissue dielectric constant (TDC), directly proportional to tissue water content in skin and upper subcutis, is calculated[7]. With the TDC technique local tissue water of both breasts was measured to the effective depth of 2.5 mm. The effective depth illustrates the depth where the EM field has attenuated to 37% of the value at the skin surface.The TDC scale ranges from 1 to 78 based on the percentage of fluid of the measurement site where the TDC value 1 illustrates that the object has no water and 78 that object has 100% of water.
Body Mass Index as calculated by the individual's body weight divided by the square of their height expressed in kg/m^2.

Design

Measurements of local tissue water with the TDC technique were made within a week before start of RT and at the end of each week with RT treatment (lasting for 3 or 5 weeks) and 2 and 4 weeks post-RT.

Procedure

Adjuvant chemotherapy was in general given to patients with axillary node metastasis, in 6 cycles within three weeks starting approximately four weeks after surgery. For these patients RT was started after completion of chemotherapy and for patients without chemotherapy RT started approximately eight weeks after surgery. Prescribed dose of radiotherapy was 42.5 Gy in 16 fractions during 22 days (later called the hypofractionated three weeks schedule) to patients ≥ 40 years without node metastasis[8]. Patients younger than 40 years received conventional fractionation up to 50 Gy in 25 fractions during 5 weeks and one patient an additional boost of 16 Gy in 8 fractions to the pre-operative tumor volume with adequate margins for microscopic disease, movements, set-up uncertainties and beam specificities. All patients with more than 2 node metastasis, a T3 or Grade 3 tumor received 50 Gy in 25 fractions during 5 weeks.
To determine the normal variation of the TDC values, both breasts in fifteen healthy women (57.1 ± 4.7 years, BMI 24.2 ± 2.9 kg/m^2) were measured. The TDC threshold ratio for breast edema was defined as a value that equals or exceeds the mean TDC ratio of these 15 healthy right and left breasts plus 2SD. Based on the measurements the TDC threshold ratio ≥ 1.40 was then determined. In practice, a TDC ratio 1.40 illustrates that the tissue water in the affected breast skin and upper subcutis is 40% higher than that in the contralateral side.
Affected and contralateral breast TDC values were measured with the patient in a supine position. The probe was placed in the middle of each quadrant of the breast with the edge of the probe 10 mm from the areola. Three repeated measurements were made in each quadrant. The mean TDC value for the total breast (4 quadrants) was then calculated. However, quadrant(s) with scar tissue were excluded. To eliminate individual differences in tissue water content the TDC ratio between the affected and healthy breast for each patient was calculated.
Height was measured at the first visit and body weight at each measurement occasion to calculate changes of body mass index (BMI) during the follow-up period.

Statistics

Paired sample t-test was used for the study group to detect differences at different time-points. Independent sample t-test was used for comparison between groups. No imputation was used for missing data. A level of significance was set at 0.05 and two tailed p-values are reported. All statistical analyses were performed using IBM SPSS Statistics 21.

RESULTS

Patients

Of the two hundred sixty patients recruited to the study 138 patients declined to participate and four patients dropped out after the pre-RT measurement. Finally, 118 patients were included (Table 1).

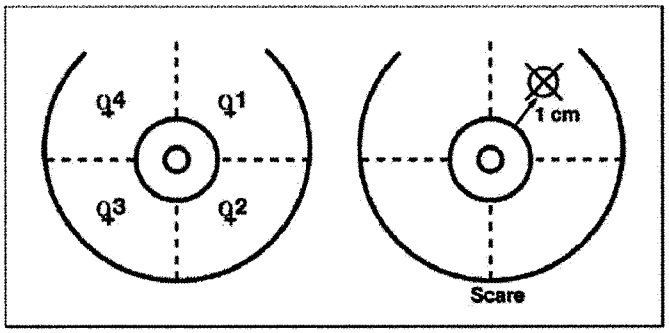
Table 1 - Characteristics of the breast cancer treated patients (n = 118) taking part in the study.

Age (years)*	61.3 ± 8.4
Affected site, left/right, n (%)	57(48.3) / 61 (51.7)
Sentinel node/Axillary dissection, n (%)	96 (81.4) / 22 (18.6)
Tumor size (mm)[α]	14.7 ± 7.2
Scar in quadrant, n (%)	
No 1/2/3/4	8 (6.8) / 5 (4.2) / 11 (9.3) / 20 (16.9)
1+2/2+3/3+4/1+4	1 (0.8) / 4 (3.4) / 6 (5.1) / 44 (37.3)
1+2+4/1+3+4/2+3+4	1 (0.8) / 1 (0.8) / 1 (0.8)
0,[β]	16 (13.6)
Radiotherapy	
Total dose 42.5 Gy/50 Gy/66 Gy, n (%)	96 (81.4) / 21 (17.8) / 1 (0.8)
Chemotherapy, yes/no, n (%)	16 (13.6) / 102 (86.4)
BMI (kg/m^2)*	27.0 ± 4.4

(α) With multifocal tumors in 15 patients the size of each tumor were added up to a total sum.
(β) Surgery considered to be performed in 0 quadrants are illustrated in Figure 1.
(*) Mean ± 1SD.

The majority (81.4%) of the patients had surgery with SLNB and related hypofractionated radiotherapy to breast up to 42.5 Gy. The rest (18.6%) had ALND and RT to breast and axilla to 50.0 Gy. Scar tissue in the breast was most frequent (36%) in quadrants 1 and 4 followed by quadrant 4 (17%) only (Table 1). A scar that did not interfere with any quadrant was frequent (14%) (Figure 1).

Figure 1 - The 4 quadrants of the breasts were marked before the TDC probe was placed in the middle of each quadrant of the breast with the edge of the probe 10 mm from the areola.



BMI was 27.0 ± 4.4 at start and 27.3 ± 5.3 kg/m^2 at end of the study with no significant change.
In order to determine that the healthy group was representative for the study group a matching was made. At start of the study the women in the study group and healthy group of fifteen women were similar by age (57.6 vs 57.1 years) and BMI (24.2 vs 24.2 kg/m^2). The mean TDC values (30.0 vs 29.6) in the healthy breast of the study group and corresponding breast in the healthy group, also indicated no difference between the groups.

TDC values

In the study group there was a higher TDC value in the operated breast compared to the non-operated breast at all measurement occasions ($p < 0.001$) (Table 2). The TDC value increased during the first week of RT in the operated breast and stayed elevated throughout the observation period ($p < 0.001$). An increased TDC value was also found in the healthy breast at 4 weeks post-RT ($p < 0.05$) (Table 2).

Breast edema incidence and TDC ratio

Due to the individual variation of TDC values in the healthy group (ranging from 19.8 to 39.4) the absolute TDC value is not useful to determine the incidence of breast edema. Therefore, a TDC ratio between the right and left breasts was calculated. Despite minor increase of TDC values in the non-operated breast at 4 weeks post RT (Table 2) the TDC ratio was determined as a ratio between operated and non-operated breast at each time-point. Accordingly, there was a significant difference in TDC ratio ($p < 0.001$) between the operated and healthy breast at each measurement time-point. The incidence of breast edema was 31.4% before start of the RT treatment, increasing during RT and was 62.6% at 4 weeks after completion of RT. The mean pre-RT TDC ratio increased during the first week of radiotherapy to 1.43 and stayed elevated through the observation period ($p < 0.001$) (Table 3). Although the mean TDC ratio was lower in the sentinel node biopsy group than in the axillary node dissection group during the whole observation period the difference was not significant. Therefore, the groups are not stratified for surgery and the data presented in Table 3 include all patients.

Comparison between the SLNB and the ALND groups

Although the ALND group had a higher TDC ratio (n = 24, 1.36 ± 0.25) than the SLNB group (n = 95, 1.29±0.30) before RT the difference was not significant.
When comparing patients with scar tissue in quadrat 4 (n = 71, TDC ratio 1.36 ± 0.31) to patients with no scar tissue in quadrant 4 (n = 46, a TDC ratio 1.20 ± 0.23) a significant difference between the groups was found before RT ($p = 0.02$).

Comparison between conventional and hypofractionated RT

For patients receiving conventional fractionation to 50 Gy (n = 22) the measurements were made also at 4 and 5 weeks during radiotherapy (Table 4). The TDC ratio of the hypofractionated group (n = 96) was higher at all time points compared with pre-RT ($p < 0.001$) but in the group of conventional fractionation only at the end of the five week schedule ($p < 0.01$). The difference between the groups was significant only at end of the third week ($p = 0.01$), i.e. at the end of the three weeks schedule (Table 4).

Table 2 - TDC values (mean ± 1SD) in the healthy and operated breast prior to and during radiotherapy treatment and 2 and 4 weeks after RT.

	n	Healthy	Operated
Pre RT	118	27.8 ± 4.8	36.0 ± 9.5 *
End of 1st week of RT	112	27.7 ± 4.7	39.2 ± 9.9 */**
End of 2nd week of RT	112	27.8 ± 5.0	39.1 ± 9.8 */**
End of 3rd week of RT	111	27.5 ± 4.5	39.1 ± 9.8 */**
2 weeks after RT	99	28.3 ± 4.4	39.1 ± 9.9 */**
4 weeks after RT	101	28.3 ± 4.2 ***	39.8 ± 9.0 */**

(*) Significant ($p < 0.001$) increase in compared to healthy breast.
(**) Significant ($p < 0.001$) increase compared to pre RT for operated breast.
(***) Significant ($p < 0.01$) increase compared to pre RT for healthy breast.

Table 3 - Incidence of edema (TDC ratio ≥ 1.4 between the breasts), TDC ratio mean±SD values and range in the breast prior to and during radiotherapy treatment and 2 and 4 weeks after.

	n	Edema n (%)	TDC ratio mean±SD	range
Pre RT	118	37 (31.4)	1.30±0.29	0.91-2.13
End of 1st week RT	112	53 (47.3)	1.43±0.33*	0.88-2.28
End of 2nd week RT	112	53 (47.3)	1.44±0.35*	0.77-2.37
End of 3rd week RT	111	51 (45.9)	1.44±0.37*	0.75-2.50
2 weeks after RT	98	45 (45.9)	1.44±0.36*	0.74-2.39
4 weeks after RT	101	53 (62.6)	1.47±0.35*	0.79-2.47

(*) Significant (p = 0.001) increase compared to pre RT.

Table 4 - Comparison of TDC ratios (mean ± 1SD) of the breasts between patients treated with breast conserving surgery with adjuvant radiotherapy to 42.5 Gy in 3 weeks or 50.0 Gy in 5 weeks.

	RT 42,5 Gy		RT 50,0 Gy		RT 42,5 Gy/50,0 Gy
	n	mean±SD	n	mean±SD	p-value
Pre RT	96	1.32 ± 0.29	22	1.23 ± 0.28	= 0.232
End of 1st week RT	91	1.45 ± 0.29*	22	1.31 ± 0.30	= 0.067
End of 2nd week RT	91	1.44 ± 0.33*	22	1.31 ± 0.33	= 0.088
End of 3rd week RT	91	1.47 ± 0.32*	20	1.26 ± 0.31	= 0.011**
End of 4th week RT	–	–	21	1.29 ± 0.31	
End of 5th week RT	–	–	20	1.34 ± 0.30**	
2 weeks after RT	80	1.41 ± 0.32*	18	1.29 ± 0.33	= 0.780
4 weeks after RT	83	1.43 ± 0.31*	19	1.30 ± 0.23	= 0.101

(*) Significant (p < 0.001) increase compared to pre RT.
(**) Significant (p < 0.01) increase compared to pre RT.
(***) Significant difference in comparison between 42.5 Gy and 50 Gy treatment schedule.

DISCUSSION

The incidence of breast edema cannot be assessed based on the results in this study since the reference measurements were not performed before the breast operation. However, matching of the study group with the healthy group indicates that the TDC values of the contralateral healthy breast in the study group did not differ from those of a healthy population. The healthy breast in the study group could thus act as control to provide a reference ratio between the breasts. Similar assumption is made when arms of healthy and operated side are compared with breast cancer treatment related arm lymphedema [9, 10].

The slight increase of the TDC values found in the healthy breast in the study group 4 weeks post-RT may be explained by the fact that the lymph collaterals between the breasts have opened up. Normally there is an anatomical lymphatic midline in the thoracic part of the body where lymph transportation is directed into the axilla of each side [11]. However, the midline is richly provided with collaterals between the two sides. When the irradiated side can no longer be emptied sufficiently through the normal passage, lymph fluid will instead find new pathways through the collaterals into the healthy side.

A significantly higher mean TDC value was found in the operated breast compared to the healthy breast at all measurement occasions and also pre-RT. Also the incidence of breast edema, based on the evaluation of the mean TDC ratio, was found to be high (> 30%). The duration between breast surgery and start of radiotherapy treatment was rather short, about 8 weeks with almost all patients. Therefore, the high incidence of breast edema may be explained by a post-surgery wound healing including an inflammatory process. However, 16 patients (14%) had chemotherapy delaying the start of radiotherapy with 4 to 5 months. Still, the chemotherapy group had an equally high TDC value before RT (1.27 ± 0.28). Although the patients receiving chemotherapy had a much longer period of recovery after surgery than the non-chemotherapy group, the finding suggest that the surgery has a more extensive and long-lasting influence on the drainage of edema from the breast.

The influence of surgery on the edema/lymphedema drainage from the breast becomes even clearer when looking at the fact that patients having surgery to the 4th quadrant also had significant higher TDC values than those with no surgery to quadrant 4. The influence of scar tissue in the breast seems to be even more important for edema formation than axillary dissection as we noticed that seven patients (6%) that had the TDC ratio >1.80 (indicating 80% edema compared with contralateral healthy breast) all were found among patients with SLNB surgery. In this group the most frequent quadrant with scare tissue was quadrant 4.

Quadrant 4 is the quadrant situated closest to the axilla and through this quadrant runs most of the lymph drainage from the breast (except for quadrant 1) [12]. Thus lymph nodes from this region as well as the scar tissue cause more edema than injury to other parts of the breast.
During 3 weeks of RT a significant increase (11.4%) of TDC ratio was found in the hypofractionated group receiving 42.5 Gy ($p < 0.001$). However, respective increase was 8.9% until the fifth week in patients with conventional fractionation up to 50 Gy. Although the difference is small the higher weekly doses in the hypofractionated RT seem to induce more edema, most likely due to the inflammatory process related to RT[13, 14]. This finding is in contrast with the UK START trial where standard fractionation induced more edema than hypofractionated RT[15]. The reason for the difference may be related to the assessment of edema which in the START trial was clinical evaluation of the whole breast while in the present investigation our quantitative approach was based on superficial edema measurements. Also timing of the edema evaluation may influence the results since the START trail provide results from a 10-year follow-up.

CONCLUSION

The healthy breast can act as control to provide a reference TDC ratio between the breasts. Based on the evaluation of the mean TDC ratio, the incidence of breast edema was found to be high (> 30%). The TDC values in the operated breast were higher compared to the healthy breast at all measurement time-points, also pre-RT, suggesting a high effect of surgery on breast edema. However, axillary surgery did not seem to increase breast edema more than sentinel lymph node biopsy. It was also shown that patients with scare in the fourth quadrant are more likely to have higher TDC ratio, i.e. edema of the breast. The higher weekly doses in the hypofractionated RT seem to induce more edema than the conventionally fractionated RT.

ACKNOWLEDGEMENT

This study was supported by research grants from the Swedish Cancer Foundation and was made possible by the women who generously gave up their time to participate.

REFERENCES

1. Rönkä R.H., Pamilo MS, von Smitten KA, Leidenius MH: *Breast lymphedema after breast conserving treatment.* Acta Oncol., 2004; 43: 551-557.
2. Goffman T.E., Laronga C., Wilson L., Elkins D.: *Lymphedema of the arm and breast in irradiated breast cancer patients: risk in an era of dramatically changing axillary surgery.* Breast J., 2004; 10: 405-11.
3. Constantine C., Parhar P., Lymberis S., Fenton-Kerimian M., et al.: *Feasibility of accelerated whole-breast radiation in the treatment of patients with ductal carcinoma in situ of the breast.* Clinical Breast Cancer, 2008; 8(3): 269-274.
4. Nuutinen J., Lahtinen T., Turunen M., Alanen E., et al.: *A dielectric technique for measuring early and late reactions in irradiated human skin.* Radiother Oncol.,1998; 47: 249-54.
5. Papp A., Lahtinen T., Härmä M., Nuutinen J., et al.: *Dielectric measurement in experimental burns: a new tool for burn depth determination?* Plast. Reconstr. Surg., 2006; 117: 889-98.
6. Johansson K., Lahtinen T., Björk-Eriksson T.: *Breast edema following breast conserving surgery and radiotherapy: Preliminary results.* Proc. 24th Congress of ISL, September 16-20, 2013, Rome, Italy.
7. Nuutinen J., Ikäheimo R., Lahtinen T.: *Validation of a new dielectric device to assess changes of tissue water in skin and subcutaneous fat.* Physiol. Meas., 2004; 25(2): 447-54.
8. Whelan T., MacKenzie R., Julian J., Levine M., et al.: *Randomized trial of breast irradiation schedules after lumpectomy for women with lymph node-negative breast cancer.* J. Natl. Cancer Inst., 2002; 94: 1143-50.
9. Bernas M., Witte M., Witte C., Belch D., et al.: *Limb volume measurements in lymphedema issues and standards.* Lymphology (Suppl) 1996; 29: 199-202.
10. Mayrovitz H.N., Weingrad D., Davey S.: *Local tissue water in at-risk and contralateral forearms of women with and without breast cancer treatment-related lymphedema.* Lymphat. Res. Biol., 2009; 7(3): 153-8.
11. Mayrovitz H.N., Brown-Cross D., Mayrovitz B., Humble-Golla A.: *Lymphedema: Role of truncal clearance as a therapy component.* Home Health Care Management & Practice 2009; 21(5): 325-37.
12. Suami H., Wei-Ren P., Bruce Mann G., Taylor G.I.: *The lymphatic anatomy of the breast and its implications for sentinel lymph node biopsy: A human cadaver study.* Ann. Surg. Oncol., 2008; 15(3): 863-71.
13. Gillette E.L., Mahler P.A., Powers B.E., Gillette S.M., et al.: *Late radiation injury to muscle and peripheral nerves.* Int. J. Radiat. Oncol. Biol. Phys., 1995; 31: 1309-18.
14. Denham J.W., Hauer-Jensen M.: *The radiotherapeutic injury – a complex 'wound'.* Radiother. Oncol., 2002; 63(2): 129-45.
15. Haviland J.S., Owen J.R., Dewar J.A., Agrawal R.K., et al.: *The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials.* The Lancet Oncology, 2013; 14(11), 1086-94.