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TWO-YEAR FOLLOW-UP OF TEMPORAL CHANGES OF BREAST EDEMA AFTER BREAST CANCER TREATMENT WITH SURGERY AND RADIATION EVALUATED BY TISSUE DIELECTRIC CONSTANT (TDC)

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ABSTRACT

Background: Breast edema is reported as a common complaint after breast conserving surgery and radiotherapy (RT). Measurements of local water in skin and upper subcutis with tissue dielectric constant (TDC) technique have the potential to detect breast edema in patients after breast cancer treatment.

Objective: The purpose of the present study was to examine development of edema in breast, axilla and upper arm in women treated with breast conserving surgery and RT during a 2-year follow-up.

Method: Sixty-five patients have been included and measured at 10 time-points (before RT, three time-points during RT, 2 and 4 weeks after RT and then 3, 6, 12 and 24 months after RT). Breast edema was measured by tissue water content in skin and upper subcutis at both sides with MoistureMeterD. TDC, directly proportional to tissue water content to the effective depth of 2.5 mm, was evaluated. Definition of breast edema was determined as a TDC ratio ≥ 1.40 between the treated and healthy breast.

Results: The TDC measurements demonstrated breast edema already before RT. The mean TDC ratios at three weeks of RT and at 3 and 6 months post-RT were exceeding the edema threshold limit (i.e. TDC ratio ≥1.40). The largest proportions of patients exceeding the edema threshold limit were found at three and six month post-RT (63%) and the smallest proportions at two years post-RT (28%). Concerning axillary dissection or sentinel node biopsy, no statistically significant differences were found between the groups at any of the 10 different measurement time-points.

Conclusion: Cancer treatment related edema in the breast is very frequent at three to six months after RT but decreases at one to two years after RT. Differences in the surgical procedure are unlikely to change the incidence of breast edema during a two-year follow-up period.

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

INTRODUCTION

Breast edema is reported as a common complaint after breast conserving surgery and radiotherapy (RT) with a prevalence varying between 0 and 90% [(1)]. Breast edema is usually assessed by using clinical signs such as erythema, orange peel syndrome, and the patient's complaints of a feeling of swelling, tension, heaviness and pain [(2)] which are often found in patients with manifest breast edema. However, post-treatment changes may be diffuse depending on the extent of surgery and radiation treatment fields. Besides, these symptoms are not eventually observed in the mild breast edema [(3)].
Although mammography is primarily used for the detection of breast cancer, breast edema may be depicted on mammogram due to increased density of the breast tissue and skin thickening [(4)]. However, this method is associated with an additional radiation exposure to a very sensitive breast tissue and a non-radiation alternative is of a great value. Ultrasound was used before for this purpose and the diagnosis of breast edema was based on

measurement of dilated lymphatic channels underneath the skin and fatty parenchyma [5]. Even if this modality is significantly better than clinical assessment of breast edema at the end of RT [6], it is not the case before and during RT.
Another technique that could provide useful information for characterization of breast edema in breast cancer treated patients is TDC. The major advantages of this method are lack of radiation exposure, easy and repeated quantitative measurements of local tissue water content [7].
The aim of the present study was to investigate the temporal pattern of tissue water content in skin and upper subcutis until 2 years post-RT in women treated for breast cancer with breast conserving surgery and RT to the breast.

MATERIALS AND METHODS

Patients

Sixty-five 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 this study. Previously, Johansson et al. (2014) recruited 118 patients but finally 65 patients to whom all measurements were performed, were included in this study. The following inclusion criteria were utilized for patient selection: female, over 18 years of age, unilateral breast cancer, undergoing breast conserving surgery, RT and SNLB or ALND. The exclusion criteria were patients with preoperative chemotherapy, breast tumor recurrence, diseases that may complicate the measurement of edema such as dementia.

Measurements

TDC (Tissue Dielectric Constant): The TDC values were measured on aff ected and contralateral sides using the 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 [8]. With this technique local tissue water was measured to the effective depth of 2.5 mm.
TDC measurements were performed at both sites in the breast and the upper arm with the patient in a supine position, and in the axilla with the patient in a frontal position, arms along the body. Three repeated measurements were made at each measurement point and averaged.

Breast: Each quadrant of the breast was measured with the probe placed in the middle of each quadrant with the edge of the probe 10 mm from the areola (Fig. 1). The quadrant measurements for each breast were average (with exclusion of quadrant(s) with scar tissue) (2).

Figure 1 - Each quadrant of the breast was measured with the probe placed in the middle of each quadrant with the edge of the probe 10 mm from the areola.

Axilla: The axillary measurement site was defined at a spot 5 cm below (caudal) from a line drawn between the highest point of the fold between arm and body, and the lateral scapula edge (Fig. 2). The arm measurement was performed in the medial upper arm, 5 cm proximal to the anticubital fossa.

To eliminate individual differences in tissue water content the TDC ratio between the affected and healthy side for each patient was calculated. The TDC threshold ratio for breast edema was defined from the previous study [(2)] as a TDC ratio equal to or greater than 1.40.

BMI (Body Mass Index): At the baseline, the height of the patients was measured and body weight was measured at each measurement occasion to calculate changes of BMI during the follow-up period. BMI was expressed in kg/m^2.

Design and procedure

TDC measurements were made within a week before start of RT, at the end of each week of RT, at two and four weeks after RT, and at three, six, twelve and twenty-four months after RT.

Statistical analysis

TDC values showed a normal distributed and therefore independent t-test was used for comparison between TDC values in the operated and healthy breast/axilla/arm at each time-point. Since TDC ratios at each time-point showed a significantly non-normal distribution ($p < 0.01$), tests for significance of overall TDC ratio changes were done using nonparametric tests: Friedman ANOVA test was used to reject or accept the null hypothesis (i.e. there are no differences between the breast TDC ratios in all time points). Afterwards Wilcoxon matched pairs test was used in order to find in which time-point the breast TDC ratio was significantly higher than other time-points. Man Whitney U-test was used in subgroup analysis i.e. how the distribution of the TDC ratios in the ALND and SLNB groups looks. Fisher's exact test was used to find eventual differences between proportions in these subgroups. Repeated measures ANOVA was used to test the equality of BMI means. All statistical tests were done using SPSS version 22. A value $p < 0.05$ was chosen as significance level.

RESULTS

Patients

Characteristic features of the patients are summarizes in Table 1. The majority (84.6%) of the patients had lumpectomy with SLNB and the rest (15.4%) had lumpectomy with ALND. The majority (84.6%) also received hypo-fractionated radiotherapy to breast up to 42.5 Gy and 13.8% received conventional fractionation up to 50.0 Gy, and one patient (1.6%) was given a dose up to 66.0 Gy. Before RT, 73.3% of the patients were overweight or obese with no significant change during the follow-up period.

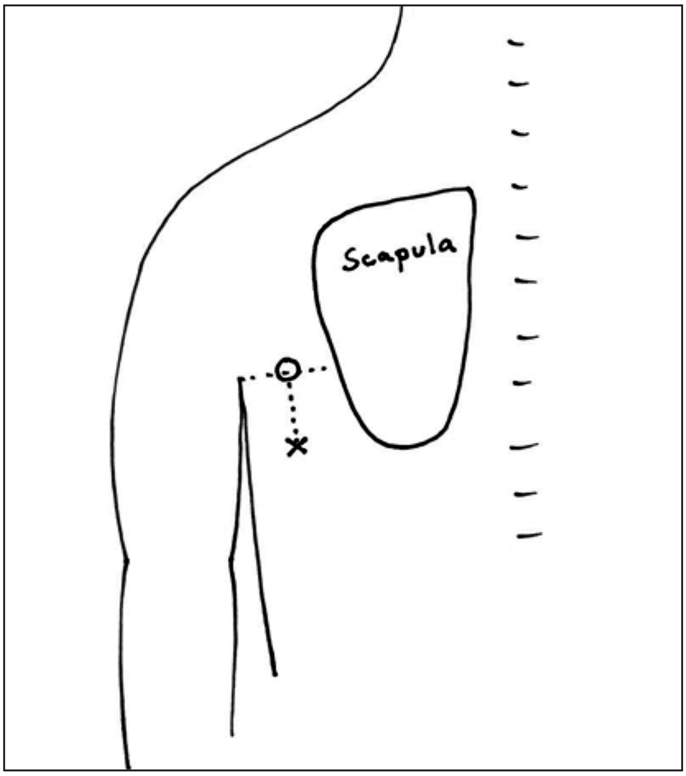

Figure 2 - The axillary measurement site was defined at a spot 5 cm below (caudal) from a line drawn between the highest point of the fold between arm and body, and the lateral scapula edge.

Table 1 - Patient Characteristics (n = 65)

Age (mean± SD)	61.2 ± 8.1 years
BMI (mean± SD)	27.3 ± 4.4 kg/m^2
Tumor size *(mean± SD)	14.3 ± 7.3 mm
Affected site n (%)	
Left	28 (43.1%)
Right	37 (56.9%)
Chemotherapy n (%)	
Yes	10 (15.4%)
No	55 (84.6%)
Surgery type n (%)	
Lumpectomy + SLNB	55 (84.6%)
Lumpectomy +ALND	10 (15.4%)
Total dose of radiotherapy n (%)	
42.5 Gy	55 (84.6%)
50 Gy	9 (13.8%)
66 Gy**	1 (1.6%)

(*) With multifocal tumors in 4 patients the size of each tumor were added up to a total sum.

(**) One patient had an extra boost of 16 Gy to the operation area.

Temporal changes of TDC

Breast

At all measurement time-points there was a significantly higher TDC value in the treated breast compared with the healthy breast (Table 2).

Figure 3 shows the mean breast TDC ratios between treated and contralateral sites at 10 different measurement occasions. There were significant differences between these mean TDC ratios ($p < 0.001$). The mean TDC ratios were indicative for edema (TDC ≥ 1.40) during the third week of radiotherapy and also at three (1.56 ± 0.04) and six months (1.50 ± 0.03) post-RT. The mean TDC ratio was 1.27 ± 0.03 at base-line, and 1.23 ± 0.03 at two years after RT treatment. The highest ratios were 1.56 ± 0.04 and 1.50 ± 0.03 which were seen at three respective six months after the treatment.

There were no differences between the mean TDC ratios during RT treatment, shortly (at two and four weeks after RT) and at one year after the treatment. Significant differences were found between the mean TDC ratios before RT and other time-points ($p \leq 0.02$), between the mean TDC ratios at three and six months after RT and other time-points ($p \leq 0.001$), and between the mean TDC ratios at two years after RT and other time-points ($p \leq 0.02$).

The proportions of patients exceeding the edema threshold limit (TDC ratios ≥ 1.40) at the 10 different time-points were 29%, 42%, 40%, 43%, 39%, 40%, 63%, 63%, 39% and 28%.
The largest proportion of patients with TDC ratios were found at three and six months post-RT and the smallest proportions at two years post-RT.

Axilla and arm

TDC measurement at axilla and arm were following: at baseline, the average TDC values were 22.4 ± 4.6 and 22.1 ± 3.8 for the operated and healthy arm sites, and 30.1 ± 4.7 and 29.1 ± 4.5 for the operated and healthy axillary sites. No statistical significant changes between treated and non-treated side were detected across the 2 years follow-up.

Temporal changes in TDC between different patient groups

The breast TDC ratios in patients in the SLNB or ALND group were not statistically different at each measurement time-point showing no difference in increase of edema in the breasts in these subgroups of the patients. Differences between proportions were neither found in the subgroups of patients having edema indicating or non-edema indicating breast TDC ratios. At three months after RT there was a tendency towards a difference in edema indicating or non-edema indicating breast TDC ratios across these subgroups ($p = 0.08$, Table 3).
There were no significant differences between these subgroups concerning TDC values on both axilla and arm at each time-point.
b) No significant differences were found concerning breast/ axilla/ arm TDC ratio between patients given hypo-fractionated or standard fractionated radiotherapy.

BMI

Before RT, 49,2% of the patients had overweight (BMI>25 kg/ m^2) and 24,1% were obese (BMI>30 kg/ m^2), with no significant change during the follow-up period.

Table 2 - Comparison between TDC values (mean ± SD) in the treated and healthy breast at 10 different time-points

Time-point	Operated breast	Healthy breast	p-value*
Before start of RT	34.8 ± 8.5	27.5 ± 5.0	$1.9 * 10^{-8}$
After first week of RT	37.9 ± 9.1	27.9 ± 4.8	$1.2 * 10^{-12}$
After second week of RT	38.1 ± 8.7	28.4 ± 6.4	$5.4 * 10^{-11}$
After third week of RT	38.9 ± 9.4	28.0 ± 4.4	$5.0 * 10^{-11}$
Two weeks after RT	38.0 ± 9.1	28.8 ± 5.1	$8.3 * 10^{-11}$
Four weeks after RT	38.5 ± 8.5	28.8 ± 4.6	$3.4 * 10^{-13}$
Three months after RT	44.4 ± 8.6	28.6 ± 3.8	$<1.0 * 10^{-18}$
Six months after RT	42.6 ± 7.5	28.7 ± 4.0	$<1.0 * 10^{-18}$
One year after RT	37.0 ± 7.8	27.6 ± 3.5	$5.8 * 10^{-15}$
Two years after RT	32.8 ± 6.2	26.8 ± 3.4	$3.1 * 10^{-10}$

(*) A value $p < 0.05$ was chosen as significance level.

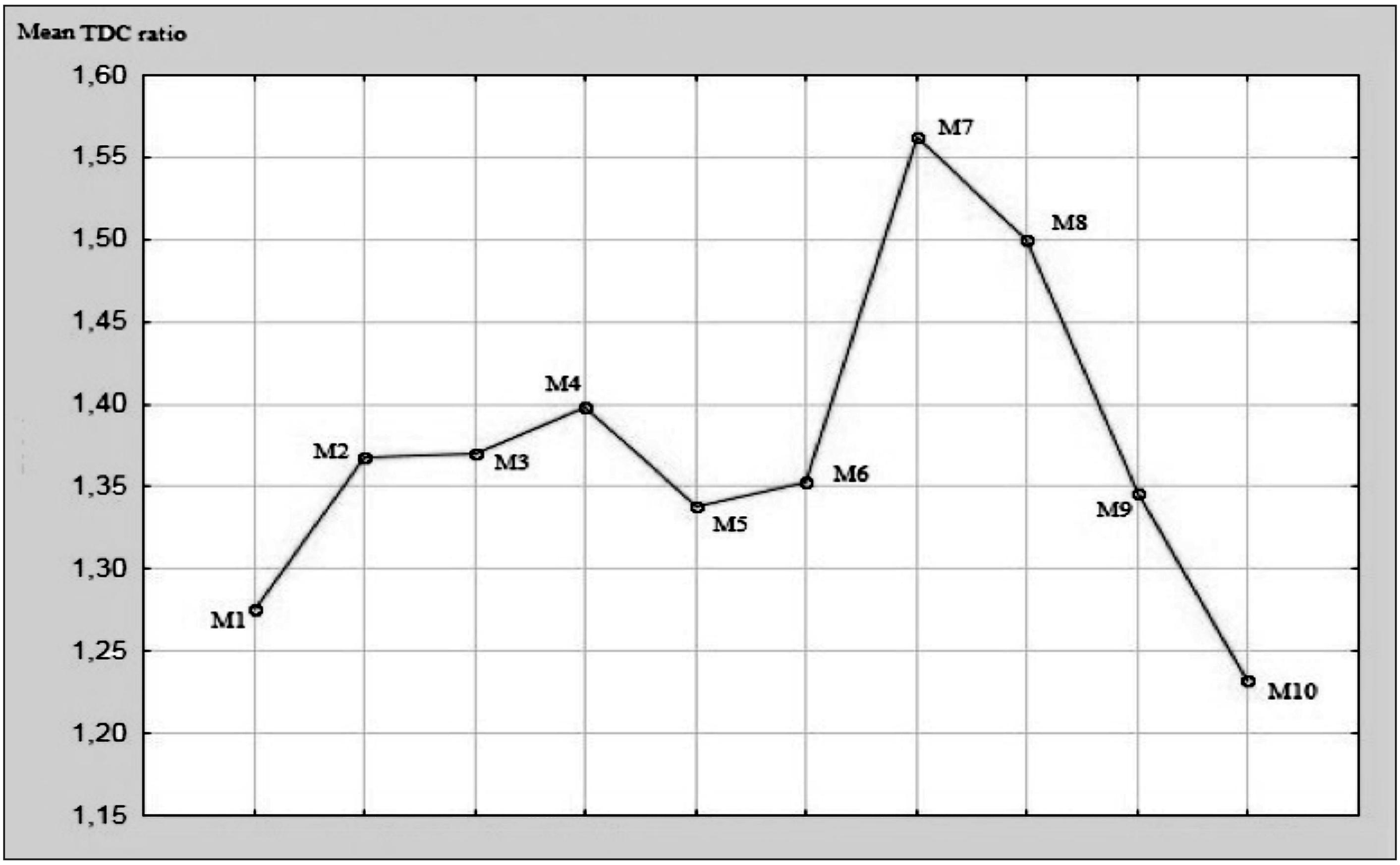

Figure 3 - Graphical comparison between mean breast TDC ratios at 10 different time-points Note: M1=at start of RT, M2, M3, M4=time-points during RT, M5 and M6=two respective four weeks after RT M7, M8, M9 and M10=three months, six months, one year respective two years after RT.

Table 3 - Proportion of patients with TDC ratios indicative for breast edema (TDC ≥ 1.40) and without significant breast edema (TDC < 1.40)

Patient group / Time-point	TDC ratio ≥1.40		TDC ratio <1.40		Two-tailed p-value*
	SLNB	ALND	SLNB	ALND	
Before start of RT	15 (23.1%)	4 (6.2%)	40 (61.5%)	6 (9.2%)	46
After first week of RT	23 (35.4%)	4 (6.2%)	32 (49.2%)	6 (9.2%)	100
After second week of RT	23 (35.4%)	3 (4.6%)	32 (49.2%)	7 (10.8%)	73
After third week of RT	24 (36.9%)	4 (6.2%)	31 (47.7%)	6 (9.2%)	100
Two weeks after RT	22 (33.8%)	3 (4.6%)	33 (50.8%)	7 (10.8%)	73
Four weeks after RT	23 (35.4%)	3 (4.6%)	32 (49.2%)	7 (10.8%)	73
Three months after RT	32 (50.0%)	9 (14.1%)	22 (34.4%)	1 (1.5%)	8
Six months after RT	33 (50.8%)	8 (12.5%)	22 (33.8%)	2 (3.1%)	30
One year after RT	20 (30.8%)	5 (7.7%)	35 (53.8%)	5 (7.7%)	49
Two years after RT	14 (21.5%)	4 (6.2%)	41 (63.1%)	6 (9.2%)	44

(*) The comparisons were done with using Fisher's exact test.

DISCUSSION

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, in order to provide information about development of edema, during the two years post-treatment.

Results demonstrated that absolute TDC values in the treated breasts were significantly greater than in the healthy breasts at all measurement time points.

The results further showed that the mean TDC ratio increased slightly during the radiation treatment but gradually diminished over the course of the next four weeks.

The TDC ratio increased again reaching the greatest value at three months after radiation treatment. The mean TDC ratio decreased again after this time-point, reaching the lowest value at two years. The temporal pattern showed that at 24 months post-RT, 28% of patients demonstrated a breast TDC ratio equal or greater than the 1.40 edema threshold limit.

The high incidence of breast edema at two years after the treatment, and also the nonlinear and wavy pattern of TDC ratio (Figure 1) during this follow-up period could reflect occurrence of edema of different origin. For example a radiation induced edema occurring several weeks (2-4 weeks) after completion of RT with an induction of inflammatory markers which may change the vascular permeability of breast tissue, and breast edema becomes a reality [(9)]. In opposite to another delayed radiation reaction at 3 to 6 months post-RT caused by the killing of vascular endothelial cells blocking the vessel lumen and resulting in plasma leakage to extravascular space.

Differences in surgical procedure impact the incidence of arm lymphedema. According to McLaughlin et al. [(10)] and Mansel et al. [(11)] the incidence at one year was 13% and 19%, for patients undergoing ALND compared to 5% and 3% for patients with SLNB, respectively. Moreover, the incidence of ipsilateral arm edema is clearly associated with both the extent of axillary surgery and radiation therapy [(12)].

In the present study, comparison of the breast, axillary or arm TDC ratios or the proportions of patients with increased breast TDC ratios for the different groups of patients showed no significant differences between these groups at any measurement occasions (Table 3). This might be due to a small number of patients with ALNB and small number of patients with higher radiation dose.

Despite the insignificant changes in body weight during two year follow-up period, the TDC ratio between treated and healthy breast changed significantly after the radiation treatment. Therefore, BMI cannot be confirmed as a factor affecting the TDC ratios between affected and contralateral side. This finding is in agreement with previous results from breast cancer related arm lymphedema [(13,14)].

CONCLUSION

Many patients have breast edema following breast cancer therapy. Based on the present findings, 29% had this complication already before radiation treatment. A very frequent transient edema occurs at three to six months followed by decrease of the incidence of edema after one and two years. Although the number of observations was small, differences in the surgical procedure in SLNB and ALND are unlikely to change the incidence of breast edema or lymphedema in axilla and upper arm during a two-year follow-up period.

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