Radiation-induced morbidity evaluated by high-frequency ultrasound

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To the Editor,

Radiotherapy (RT) is an important part of curative treatment for early breast cancer. A focus on the radiation-induced morbidity after RT in breast cancer survivors is justified by the large number of women treated for breast cancer and a long expected life span after RT.

Radiation-induced morbidity following anti-cancer treatment is routinely registered clinically, using scoring systems such as RTOG, LENT-SOMA or CTC-AE. Clinical scoring systems can be subject to inter-individual differences of interpretation [1]. Therefore, objective measures of different endpoints may be useful tools. Ultrasound (US) of the skin may provide a means of objectification. High-frequency ultrasound (HFUS) is a subtype of US that allows visualization of smaller areas of the body with a high resolution.

Previous work has tested the use of US/HFUS in the assessment of radiation-induced morbidity in patients treated for breast cancer with RT. Study designs have correlated HFUS/US findings with single [2] or combined [3] morbidity endpoints, tested for predictive value of edema development [4] or simply stated if there was a difference between irradiated and non-irradiated breasts [5, 6].

In a pilot-study, we tested a HFUS device in a cohort of patients treated with RT for early breast cancer. The thickness of the dermal layer in the skin was measured and correlated to grade of induration and edema, hypothesizing that these will affect dermis thickness.

Patients, materials and methods

Patients were recruited from the Danish Breast Cancer Group protocols: DBCG-HYPO and DBCG-PBI (ClinicalTrials.gov ID: NCT00909818 and NCT00892814) and comprised 15 women
treated curatively for early breast cancer in 2009 – 2013 with lumpectomy and RT 40 or 50 Gy +/- systemic therapy. The cohort represents a highly selected subgroup, characterized by having developed edema and/or induration. Morbidity follow-up was done at baseline and yearly. Edema and induration were scored according to DBCG guidelines, following the LENT-SOMA Scale [7]. Due to few grade 2 edema, this was dichotomized into grade 0 or 1-2.

The HFUS device investigated was the 20 MHz DermaScan® C from Cortex Technology ApS, Denmark. It recognizes structures above 60 µm, corresponding to tissue microstructures sized like collagenous fibres. More deeply laying structures cannot be visualized, therefore the subcutaneous tissue was not evaluated. Scanning was performed 3 cm from the areola in all four quadrants in both irradiated and contralateral breast. Dermis thickness was registered by Bscans. The epidermal layer was not included in dermis thickness. All HFUS scans were performed by a single observer. Each patient served as her own control based on data from the two breasts, that were analyzed using a two-tailed paired t-test. In a multiple regression analysis, we tested the impact of edema and induration on dermis thickness difference between irradiated and contralateral breast. Statistics were done using Stata-13 [StataCorp TX, USA].

**Results and discussion**

Patient characteristics were: Median age 66 years (range 44 - 75). Median follow-up time 3.0 years (range 1.0 - 4.6). Median breast volume 715 ml (range 177 - 1627). The distribution of clinical induration and edema was: Nine patients were without edema, induration distribution was: grade 0: n=1, grade 1: n=3, grade 2: n=5. Six patients were with edema, induration distribution was: grade 0: n=0, grade 1: n=1, grade 2: n=5.
The mean dermis thickness of the untreated contralateral breast was 1.26 mm (95% CI: 1.08 - 1.44) and of the irradiated breast 2.22 mm (95% CI: 1.78 - 2.66), Table 1 shows distribution in quadrants. The mean difference in dermis thickness between irradiated and non-irradiated breast was 0.96 mm (95% CI: 0.50 - 1.42, p=0.0003) and distributed in quadrants as follows: Lower lateral 1.50 mm (95% CI: 0.80 - 2.21, p=0.0004). Lower medial 1.19 mm (95% CI: 0.57 - 1.80, p=0.0007). Upper lateral 0.38 mm (95% CI: 0.14 - 0.62, p=0.004). Upper medial 0.77 mm (95% CI: 0.16 - 1.38, p=0.02).

In patients without clinical edema, the mean difference in dermis thickness for grade 1 induration was 0.35 mm (95% CI: -0.48 - 1.18, p=0.29). For grade 2 induration it was 0.71 mm (95% CI: 0.02 - 1.40, p=0.05). In patients with clinical edema, only one patient had grade 1 induration (mean dermis thickness difference 1.34 mm). In patients with clinical edema and grade 2 induration, mean difference in dermis thickness was 1.61 mm (95% CI: 0.41 - 2.82, p=0.02).

The difference in dermis thickness between breasts was tested in a multiple regression analysis, including induration and edema as independent variables. By method of backwards elimination, induration was excluded as it did not contribute to the model. The remaining simple linear regression of edema’s effect on dermis thickness difference between breasts was statistically significant adding 1.01 mm (95% CI: 0.21 - 1.82, p=0.018, R^2=0.36) to dermis thickness when present versus not present.

A qualitative difference in the HFUS images in patients with edema was noted. The dermis appeared less dense, and in some cases the subcutaneous-dermal transition was indistinctly demarcated. Figure 1 illustrates an example of dermis appearance by HFUS when edema is, or is not, present. Dermal density decreased (and dermal thickness increased) especially in
the lower quadrants, where edema tends to accumulate. This was interpreted as extracellular fluid diffusion from the subcutaneous tissue into the dermis (Figure 1).

Epidermal appearance did not change with the presence of edema. A quantification of these findings was unfortunately not possible. Our study protocol did not address this issue adequately and lacked algorithms for gain- and profile settings when density changes necessitated adjustments.

Our study follows other studies that have investigated HFUS/US in radiation-induced morbidity of the skin. The first to investigate HFUS was Le Floch et al in 1998. They found mean skin thicknesses of 1.35 ± 0.26 mm (healthy breast) and 1.92 ± 0.62 mm (irradiated breast) after tumorectomy and RT for breast carcinoma [6].

Landoni et al found a mean increase in skin thickness (epidermis and dermis) between healthy and irradiated breast of 0.52 ± 0.67 mm/0.62 ± 0.74 mm at 34/42 Gy regions [2]. Measures were correlated to induration/fibrosis evaluated by CTCv3. Edema was not reported.

Wratten et al investigated epidermal thickness by HFUS, prior to, during and following RT for early breast cancer and found that HFUS predicted prolonged edema better than clinical assessment at the end of RT [4]. Induration was not reported.

Yoshida et al developed and validated the UBTAT-tool and correlated it to radiation-induced morbidity by RTOG score [3]. UBTAT measurements correlated with late toxicity grades. Skin and subcutaneous endpoints were pooled, and it is unknown if the UBTAT-tool can distinguish between these endpoints.
Zhou et al found two US measures from subcutaneous tissue in women treated with RT for early breast cancer being significantly different between irradiated and contralateral breast. Findings were not correlated to a clinical assessment of radiation-induced morbidity [5].

To our knowledge, our pilot study is the first to consider both induration and edema and has the force of gaining experience but the shortcomings of a small sample size and an inadequate protocol for data acquisition of density measures in edematous patients. We found the largest difference in dermis thickness of 1.61 mm in patients with grade 2 induration combined with edema, whereas the lowest of 0.35 mm was for patients with grade 1 induration and without edema, although the latter was not statistically significant. Regression analysis showed a significant effect of edema, increasing dermis thickness with a mean 1.01 mm when present versus not-present. The effect of induration alone remains inconclusive.

Presently, we do not see US/HFUS evaluation of the skin as a part of large-scale follow-up routines in the assessment of radiation-induced morbidity. Data from the present study and the literature confirm a measurable skin (dermis +/- epidermis) thickness difference present between irradiated and non-irradiated breast after RT, that is partly caused by edema. What we still seek is a reliable discriminative quality between radiation-induced morbidity endpoints and their grades. This would enable inter-individual and inter-institutional quality assurance and serve as an objective marker in future trials testing new regimens in treatment of radiation-induced morbidity of the skin.
**Declaration of interest**

The authors declare no conflicts of interest. The authors alone are responsible for the content and writing of the paper.
References


Figure 1. HFUS images of dermis in two patients. One with- and one without edema. Both have induration grade 2 in the irradiated breast. In the patient with edema, the dermal layer appears thickened and less dense; this is especially true in the lower quadrants to the extent where demarcation against subcutaneous tissue is blurred.
Table 1. Dermis thickness in contralateral and irradiated breast. Measures are in millimeters.

<table>
<thead>
<tr>
<th>Quadrant</th>
<th>Mean (mm) (95% CI)</th>
<th>Combined mean (95% CI)</th>
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<tr>
<td><strong>Contralateral breast</strong></td>
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<tr>
<td>Lower lateral</td>
<td>1.11 (0.96 - 1.26)</td>
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<tr>
<td>Lower medial</td>
<td>1.45 (1.18 - 1.72)</td>
<td>1.26 (1.08 - 1.44)</td>
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<tr>
<td>Upper lateral</td>
<td>1.17 (1.01 - 1.34)</td>
<td>1.26 (1.08 - 1.44)</td>
</tr>
<tr>
<td>Upper medial</td>
<td>1.31 (1.09 - 1.53)</td>
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<tr>
<td><strong>Irradiated breast</strong></td>
<td></td>
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</tr>
<tr>
<td>Lower lateral</td>
<td>2.62 (1.92 - 3.31)</td>
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</tr>
<tr>
<td>Lower medial</td>
<td>2.64 (2.06 - 3.22)</td>
<td>2.22 (1.78 - 2.66)</td>
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<tr>
<td>Upper lateral</td>
<td>1.55 (1.33 - 1.78)</td>
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