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Evaluation of skin toxicity

Evaluation of acute skin toxicity in breast radiotherapy with a new quantitative approach

Amparo González Sanchis [a,*], Luis Brualla González [b], Jose Luis Sánchez Carazo [c], Jose Carlos Gordo Partearroyo [a], Altea Esteve Martínez [c], Aurora Vicedo González [b], Jose Luis López Torrecilla [a]

[a] Department of Radiation Oncology, ERESA; [b] Department of Radiophysics, ERESA; and [c] Department of Dermatology, Hospital General Universitario de Valencia (CHGUV), Spain

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ABSTRACT

Background and purpose: Current criteria to evaluate acute radiodermatitis are highly subjective so quantification of physiological parameters is needed. We describe a non-invasive method of assessing skin microcirculation in breast cancer patients treated with hypofractionated radiotherapy and correlate them with the CTCAE scale.

Methods: Prospective study of 63 patients where blood flow was measured with real-time laser Doppler flowmetry (LDF) at baseline, weekly, and 3-months post-radiotherapy. Skin toxicity was assessed with the microcirculation index (MCI), a novel index based on blood flow parameters obtained via LDF.

Results: MCI was positively correlated ($R = 0.647$; $p < 0.001$) with the dose. Changes in MCI from baseline to the end of radiotherapy and at 3-months post-radiotherapy were significant ($p < 0.001$). All CTCAE groups experienced a significant increase in MCI values from baseline to end of radiotherapy ($p < 0.001$ for CTCAE grades 0 and 1; and $p = 0.028$ for the grade 2 group). Significant differences in MCI values were observed among CTCAE groups at the end of radiotherapy ($p = 0.016$).

Conclusions: LDF is an accurate and objective measure of changes in blood flow. The comparison with the CTCAE shows the limitations of this subjective way of classifying patients. LDF is the first step for future studies of radiodermatitis treatments and prevention.

Radiodermatitis is a common adverse effect of breast irradiation that impacts on the patient's quality of life and is correlated with long term cosmesis [1].

Irradiation promotes changes in numerous physiological parameters, including a rise in skin pH, decreased skin hydration [2,3], and increases in cutaneous blood flow and pigmentation [4–6]. The physical manifestations of radiodermatitis range from mild erythema to moist desquamation and, in severe cases, necrosis [7,8].

Traditionally, acute radiodermatitis has been evaluated and classified with visual rating scales, primarily the CTCAE (Common Terminology Criteria for Adverse Events) and the Radiation Therapy Oncology Group (RTOG) scales [9–11]. However, the inherent subjectivity [5,6] of these scales, which do not quantify physiological skin parameters [12], is an important drawback. Consequently, numerous alternative methods have been developed to quantify changes in these physiological parameters to provide a more precise and objective measure of skin toxicity, such as dielectric, electrochemical, reflectance spectrophotometry/colorimetry and laser Doppler flowmetry (LDF) methods [2–4,12–20]. However, although some of these instruments have made inroads as complementary tools to assess skin toxicity [12], none has yet succeeded in replacing the CTCAE or RTOG scales.

In 2014, our group reported results from a study [21] in which we used a LDF probe to measure cutaneous blood flow. Although we found the LDF probe to be a good method of objectively assessing acute radiodermatitis, the probe is only able to measure blood flow in a very small volume (1 mm^3), which limits its accuracy and sensitivity [12,21]. Since publication of our original study, the emergence of more advanced LDF equipment has increased the reliability and accuracy of blood flow measurements.

In the present study, we describe a newly developed quantitative method, based on an advanced LDF blood flow monitor, to assess changes in skin microcirculation in breast cancer patients undergoing radiotherapy (RT). Secondarily, we also correlate these microcirculatory changes with the CTCAE skin toxicity clinical grading scale.

* Corresponding author at: Department of Radiation Oncology, Hospital General Universitario de Valencia, Avenida Tres Cruces, N° 2, 46014 Valencia, Spain.
E-mail address: agonzalez@eresa.com (A. González Sanchis).

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Material and methods

Patients

This was a prospective cohort study carried out at a university hospital in Valencia (Spain) with patients referred for treatment of early-stage unilateral breast cancer during the year 2014. All patients who met departmental criteria for breast-conserving surgery (BCS) followed by accelerated hypofractionated intensity-modulated radiotherapy (IMRT) were consecutively included in the study. None of the included patients underwent locoregional lymph node irradiation.

Exclusion criteria were as follows: prior radiotherapy to the breast; previous or simultaneous chemotherapy; oral corticosteroid treatment; and connective tissue disorders (scleroderma or lupus erythematosus). This study was approved by the hospital ethics board and conducted according to the Declaration of Helsinki criteria. Informed consent was obtained from all patients prior to participation.

Radiotherapy

All patients underwent virtual computed tomography (CT) simulation with a breast board immobilization system. CT images were acquired at 3-mm intervals from the level of the mandible through the lung bases. Target volumes and the risk organs were delineated in accordance with the recommendations of ICRU Reports 50 and 62 [22,23]. The clinical target volume (CTV) was defined as the whole treatment breast. The planning target volume (PTV) was obtained by applying a 7-mm margin around the CTV to account for treatment setup variations and respiratory motion.

In all cases, treatment consisted of 40 Gy delivered with IMRT (6 MV) in 15 fractions of 2.67 Gy, administered daily, 5 days per week for 3 weeks [24]. The Pinnacle Treatment Planning System (v. 9.4, Philips) was used. Plan acceptance required 95% of the PTV volume be covered by 95% of the prescribed dose and that <1% of the volume receive 106% of the dose. Daily positioning verification was performed with the AlignRT image-guided system (VisionRT Ltd., London, England).

Laser Doppler flowmetry

Skin toxicity was assessed with the MoorLDI2-IR LDF (Moor Instruments, Devon, UK) a non-invasive method, which provides a real-time measure of cutaneous microcirculation using a skin-penetrating infrared laser beam (785 nm). The source-to-surface distance was set at 50 cm to obtain the largest possible image size (256×256 matrix) over an area measuring 13.5×13.5 cm^2. The selected distance allows an easy positioning of the patient, a wide scanning area and a high resolution. To assure that the LDF equipment was functioning properly, we verified calibration on a weekly basis.

Blood flow was measured prior to radiotherapy (baseline), weekly during radiotherapy (after treatment sessions 5, 10, and 15), and at 3 months post-radiotherapy. Because blood flow measurements are affected by changes in body temperature and by the patient's activity level, we corrected for these changes by measuring blood flow in both the treated and untreated (contralateral) breasts at the same time, thus obtaining two sets of measures (treated breast and control breast) in each patient at the same location. We measured the surface skin of the upper internal quadrant of the breast, with the areola included in the lower corner of the image (right side for left breast, left side for right breast). The Laser Doppler measurement was carried out in the Radiation Oncology Department with the patient lying on her back in a static position. The total required time was 10 min, 5 min each breast acquisition.

Acute radiation-induced skin reactions were graded using the CTCAE scoring criteria [10], ranging from grade 0 (no visible reaction) to grade 4 (life-threatening consequences, urgent intervention required). All patients were assessed independently by an experienced dermatologist and by a radiation oncologist, both blinded to the LDF measurements. Following these individual assessments, a joint meeting between the two specialists was held to reach a consensus CTCAE score.

LDF systems measure blood flow phenomena. However, given the multidirectional blood flow in capillaries and connecting small blood vessels and the dependence of measurements on the skin type and properties, it is not generally appropriate to use absolute flow units (e.g., ml/min/100 g tissue); instead, measurements are expressed as perfusion units (PU), arbitrary units derived from the measure obtained by scanning a sample pattern containing polystyrene spheres, whose movement responds to a thermal pattern (Brownian movement). Therefore, each image pixel value describes perfusion measured in a small skin volume and expressed in PUs. For both the ipsilateral and contralateral breasts, we obtained a median value calculated from all the pixels contained in the image.

To facilitate comparison, we developed an index—the microcirculation index (MCI)—to characterize variation in the distribution of blood perfusion in the measured area. The MCI was defined as the relative variation in median PU values in the treated breast in relation to median PU values in the contralateral breast. The MCI thus quantifies the response of the treated skin to radiotherapy, calculated according to the following formula:

$$\mathrm{MCI} = (\mathrm{Mi} - \mathrm{Mc})/\mathrm{Mc}$$

where Mi and Mc are the median perfusion values for the ipsilateral and contralateral breasts, respectively.

Statistical analysis

The MCI data are presented as medians with interquartile ranges. Patient reported symptoms are described as frequencies and percentages. MCI values obtained before RT, at the end of RT, and after RT were compared using the Friedman test. For each CTCAE group, pre- and post-RT MCI values were compared using the Wilcoxon signed-rank test. The Kruskal–Wallis test was used to compare the MCI values among the various CTCAE groups. Correlation between radiotherapy doses and MCI values before and during the three-week course of radiotherapy was determined with Spearman's correlation test. P values of <0.05 were considered statistically significant.

Results

Patients

A total of 63 women were enrolled in this prospective study. Table 1 shows the clinical and demographic characteristics of the

Table 1
Clinical characteristics of patients.

Clinical feature or variable		Number of cases (%)
Median age (range)		63 years (39–89)
Breast cancer stage	0	16 (26%)
	IA	32 (50%)
	IB	8 (13%)
	II	7 (11%)
Tumor location	Right breast	26 (41%)
	Left breast	37 (59%)
Phototype	II	9 (14%)
	III	47(75%)
	IV	7 (11%)
Diabetes mellitus		9 (14%)
Hypertension		28 (44%)
Hormone therapy		56 (88%)