



Original Research Article

Association between cumulative radiation dose, adverse skin reactions, and changes in surface hemoglobin among women undergoing breast conserving therapy



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ABSTRACT

Introduction: Radiation therapy is crucial to effective cancer treatment. Modern treatment strategies have reduced possible skin injury, but few clinical studies have addressed the dose relationship between radiation exposure and skin reaction. This prospective clinical study analyzes skin oxygenation/perfusion in patients undergoing fractionated breast conserving therapy via hyperspectral imaging (HSI).

Methods: Forty-three women undergoing breast conserving therapy were enrolled in this study. Optically stimulated luminescent dosimeters (OSLDs) measured radiation exposure in four sites: treatment breast, lumpectomy scar, medial tattoo and the control breast. The oxygenation/perfusion states of these sites were prospectively imaged before and after each treatment fraction with HSI. Visual skin reactions were classified according to the RTOG system.

Results: 2753 observations were obtained and indicated a dose-response relationship between radiation exposure and oxygenated hemoglobin (OxyHb) after a 600 cGy cumulative dose threshold. There was a relatively weak association between DeoxyHb and radiation exposure. Results suggest strong correlations between changes in mean OxyHb and skin reaction as well as between radiation exposure and changes in skin reaction.

Conclusion: HSI demonstrates promise in the assessment of skin dose as well as an objective measure of skin reaction. The ability to easily identify adverse skin reactions and to modify the treatment plan may circumvent the need for detrimental treatment breaks.

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Introduction

Radiation therapy remains a critically important and valuable component for oncologic patient care. Modern equipment and refined treatment algorithms have improved normal tissue effects from treatment particularly in breast. However, the use of increased radiation dose to tumor targets and compressed radiation treatment fractionation schedules still lead to significant ischemic effects of radiation therapy on dermal circulation and

subcutaneous tissue in other parts of the body. It is still unclear whether or not there is a dose-response relationship between radiation to both skin oxygenation and adverse skin reactions. Furthermore, from a surgical perspective, since reconstruction often requires operating within irradiated tissue, better understanding the underlying changes in skin microcirculation is paramount.

Encouraging earlier clinical studies demonstrated that laser Doppler flowmetry (LDF) could be used to study acute changes in cutaneous microvasculature [1,2], but LDF is based on the capillary flow velocity and may not be reflective of physiological tissue oxygenation. Our lab has focused on hyperspectral imaging (HSI) for evaluation of skin oxygenation and perfusion after a variety of injuries. HSI derived oxygenation has been shown to correlate with transcutaneous PO₂ measurements as well as intravascular volume

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[3–5]. We have utilized a commercially produced HSI device, which provides near real-time analysis of oxygenated and deoxygenated hemoglobin (OxyHb and DeoxyHb, respectively) content in skin. In previous animal studies, we successfully demonstrated that this technology reliably detects and assesses skin changes after exposure to both ionizing and thermal radiation [6–8]. Our translational studies on the acute phase suggest that cutaneous changes in oxygenation may be dose related and that this may be a potential surrogate marker for radiation exposure [9]. Subsequent studies by other investigators have used similar spectroscopic techniques and validated dose related oxygenation changes [10,11]. However, these previous studies have all been based on single fraction exposures of radiation and therefore have limited external validity to clinical fractionated radiation schedules.

In this prospective clinical study, we utilize fractionated dose therapy in breast cancer patients undergoing breast conserving therapy (BCT) radiation as a model for radiation exposure. By measuring their received dose at the skin level and assessing their skin oxygenation at those sites using our previous HSI methodology, we evaluate any correlation between dose and skin oxygenation level in the acute treatment phase. We designed this study around breast cancer patients since their standardized treatment maps provide consistent sites for comparison. Based on our previous studies, we hypothesize that breast skin OxyHb level will rise during the period of irradiation.

Methods

Under IRB approved protocol, all patients ($n=43$) were recruited from the Radiation Oncology Clinic at the University Campus of UMass Memorial Healthcare Center. Women aged 18–85 who were planning on having breast radiation as part of breast conserving therapy (i.e. lumpectomy plus radiation) and were able to provide informed consent were invited to participate in the study. However, patients with previous breast irradiation in situations where radiation therapy prescription doses may be altered (excluding boost dosage), inflammatory skin diseases (e.g. psoriasis, eczema) over the breast area to be irradiated, and collagen vascular disease and/or other systemic vasculitides were excluded from the study. Additionally, patients who were unable to sit or lie down comfortably for 20 s for image acquisition were excluded.

Clinical information including patient age, BMI, smoking status, significant past medical history, and history of chemotherapy were recorded. All patients were enrolled and consented to the study either by their radiation oncologist or the study coordinator.

Radiation measurement

Breast irradiation for breast conserving therapy involved two opposing X-ray beams from a megavoltage medical linear accelerator. Radiation dose measurements at the skin surface were assessed by use of optically stimulated luminescent dosimeters (OSLD). Calibrated OSLDs were placed on each patient's chest in four areas during the initial treatment fraction. Three measured areas were in the irradiated field: middle of treatment breast (TB), lumpectomy scar site (SCAR), and medial tattoo (MT). TB and SCAR sites were selected since they were always within the irradiated field. MT was chosen as a readily identifiable site in each patient that could demonstrate a dose gradient as it is offset from the target site. One OSLD was placed on the nipple of the untreated breast as control (CONTROL). (Fig. 1) All subsequent fractions were assumed to have the same skin dose, unless a boost was noted. In this case, an additional OSLD was placed and measured that session's additional doses. Each OSLD was developed and read 24 h

after radiation exposure. Cumulative dose measurements were calculated for each treatment site as number of treatment fractions times OSLD measurement, with additions accounting for any boost.

Hyperspectral imaging

Our group has previously established the use of monitoring of irradiated skin using HSI [8,9]. A commercial FDA-approved hyperspectral device (OxyVu-2™ (Hypermed, Inc., Waltham, MA)) was used to obtain images at each OSLD measurement site (TB, SCAR, MT and CONTROL) at baseline before therapy as well as before and after each treatment fraction. The OxyVu-2™ analyzes the skin content of oxygenated and deoxygenated hgb at a depth of 2 mm, which corresponds anatomically to the subdermal plexus. The system was calibrated to a reference card for all acquisitions, and pixel reflectance was determined relative to this standard reflectance. A target dot was used to correct for motion artifact from respiratory effort. Patients were asked to position themselves prone on stretcher during the imaging. Spatial maps of tissue oxygenation were then generated using the device's proprietary algorithms. The general optical properties of this device have been previously described [12]. A narrow band-pass, liquid-crystal tunable filter (LCTF-10-20, CRI, Inc. Hopkinton, Massachusetts) was used to vary the wavelength of light passed on to a digital imaging detector (Guppy F-146B, Allied Vision Technologies, Stadtroda, Germany) to provide many images at 15 select wavelengths between 500 and 660 nm. Broadband light-emitting diodes were used to illuminate the sample (LUXEON, Philips Lumiled, Inc. San Jose, California). Twenty-second scans of tissue samples were obtained at approximately a 17-inch focal distance. Color images were created from the scans to demonstrate tissue oxygenation spatially. The spatial resolution of the OxyHb and DeoxyHb images was 60 μm .

Skin reaction assessment

At each HSI acquisition, a concurrent digital photograph was obtained of each measured site. These photographs were graded by two independent technicians using the RTOG skin toxicity scale on a categorical scale of 0 through 4 (0 = no reaction, 1 = slight erythema, 2 = bright erythema or patchy desquamation, 3 = confluent desquamation, or 4 = ulceration) [13]. The average grading score between the two technicians was used for analysis. Due to a computer hard drive failure there were 10 women with lost data for at least one skin reading; in this case the single technician's reading was used in lieu of a mean.

Statistical methods

We examined the unadjusted dose-OxyHb association by computing mean change in OxyHb in each successive cumulative dose interval, in 200 cGy dose increments. We computed the linear slope as cumulative dose increased (adjusted for woman), to help assess the general shape of association, and to identify at what cumulative dose the association becomes detectable.

We used a mixed model, in which individual woman was treated as a random effect, to examine the association between cumulative radiation dose and change from baseline OxyHb or DeoxyHb at skin surface. Cumulative radiation dose was the cumulative sum of each day's dose, including any boost doses. Changes in hemoglobin were differences between measurements immediately after a daily dose, and baseline hemoglobin before treatment, where each woman had a different baseline at each location (TB, SCAR, MT, and CONTROL, where CONTROL received minimal or insignificant radiation).

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