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Abstract. Optical mammography is a functional imaging technique that uses near-infrared light to produce three-dimensional breast images of tissue oxygen saturation and hemoglobin concentration. It has been used to monitor the response to neoadjuvant chemotherapy in breast cancer patients. We present the first results on monitoring tumor response to hormone therapy using optical mammography. We present three case studies from postmenopausal women treated with neoadjuvant hormone therapy for locally advanced breast cancer. The women were scanned before starting treatment, once during treatment, and then before surgery. Changes in physiological and optical properties within the tumor and in the rest of the breast were evaluated. At the time of surgery, two patients partially responded to treatment and one did not respond. The patients that partially responded on ultrasound revealed a corresponding recovery to normal in the hemoglobin concentration images, whereas the nonresponder indicated an increase in hemoglobin concentration in the tumor compared to her pretreatment images. These case studies suggest that optical imaging of the breast during neoadjuvant hormone treatment can provide potentially valuable information, and that physiological changes within the tumor can be seen in response to treatment. [DOI: 10.1117/1.JBO.18.5.056012]

Keywords: optical mammography; diffuse optical tomography; response to therapy.

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1 Introduction

1.1 *Background*

Clinical studies on diffuse optical imaging (DOI) and diffuse optical spectroscopy (DOS) of breast disease have been appearing in the literature over the last 20 years.[1–5] The total hemoglobin concentration ([HbT]) of malignant tumors is about three times that for healthy breast tissue (65 ± 34 versus 21 ± 6 μM).[6] There is no reported significant difference in tissue oxygen saturation ($SatO_2$) ($66\% \pm 24\%$ versus $67\% \pm 6\%$).[6] However, not all tumors develop chronic hypoxia, and differences between the tumor and the background tissue may be lost when all tumors are averaged together, as reduced $SatO_2$ is seen in some breast tumors.[7–9]

1.2 *Primary Medical Endocrine Therapy*

Primary medical therapy describes chemotherapy and hormone therapy administered presurgically. It was introduced in the 1970s to shrink inoperable breast tumors in an attempt to make them operable by mastectomy or breast-conserving surgery.[10] Although primary medical therapy does not increase overall survival, it does increase the likelihood of successful breast-conserving surgery.[11–13]

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Recently, neoadjuvant hormone therapy has become a popular treatment option for women with estrogen receptor–positive (ER^+) tumors, especially in women who may not tolerate the toxic effects of chemotherapy.[14] More than 75% of breast tumors have an overproliferation of ERs.[15] When estrogen binds to the ERs, pathways that enhance cell proliferation are activated.[16] Letrozole (trade name Femara) is commonly used to treat postmenopausal women with ER^+ tumors, by blocking estrogen production. This reduces cell proliferation, slows or stops tumor growth, and causes tumor shrinkage.[17]

1.3 *Optical Imaging of Treatment Response*

Reports on the use of DOS and DOI to assess response to primary medical therapy have been appearing in the literature since 2004.[18] Significant papers have been published by the Beckman Laser Institute at University of California Irvine,[18] the Biomedical Optics group at Dartmouth College,[19,20] the University of Connecticut,[21,22] Massachusetts General Hospital Optical Imaging Lab,[23] the University of Toronto,[24] and the University of Pennsylvania Biomedical Optics Group,[25,26] among others. Several reviews of the topic have also been published.[27,28] All published papers to date have been on patients treated with neoadjuvant chemotherapy, with no publications examining the response to hormone therapy. In this paper, we present the results of repeat optical scans performed on patients undergoing neoadjuvant hormone therapy for locally advanced breast cancer. We anticipated that optical imaging of the response to hormone therapy would reveal a slower response time than chemotherapy (where optical changes have been seen

days after the start of treatment[28]), as the median response time to letrozole treatment on MRI is around 9 weeks.[29] Classic chemotherapy drugs act on the DNA of all rapidly dividing cells, not just cancer cells. Hormone therapy will only cause a response in cells that have a particular receptor (in this case estrogen).[30] Estrogen also plays a role in the regulation of vascular endothelial growth factor and new blood vessel growth, so blocking its action will have a direct effect on the vasculature of the tumor. Therefore, any changes seen in [HbT] are likely to be caused by the treatment.[31]

2 Method

2.1 *Patients*

Suitable patients were identified from among women attending Guy's and St Thomas' NHS Foundation Trust and the Lewisham Hospital NHS Trust (UK). Three women with ER^+ tumors to be treated with neoadjuvant letrozole gave informed consent to take part in this study. Primary hormone therapy is generally offered to postmenopausal women if the tumor is expected to respond to the treatment or if they are too ill to tolerate chemotherapy.[32] The women presented here were three of 27 women who had been recruited for a larger project.

The study was approved by the University College London (UCL) Research Ethics Committee and Guy's Hospital Research and Development Department. Patients were offered a modest honorarium for taking part, and transport costs were reimbursed.

2.2 *Imaging Protocol*

The UCL time-resolved optical imaging system[33] is used to transmit light to and from the patient breast via a liquid-coupled patient interface.[9,34] The patient lies prone with her breast pendant in the liquid-coupled patient interface. The system is described in detail elsewhere,[33] but in summary, picosecond laser pulses at 780 and 815 nm are transmitted to the breast via 31 optical fibers. Photons transmitted through the breast are collected by optical fiber bundles coupled to microchannel-plate photomultiplier tubes that produce an electronic pulse for each detected photon. A histogram of photon arrival times, known as a temporal point spread function (TPSF), is generated for each source-detector combination by timing electronics (Becker & Hickl, Berlin, Germany). Images are reconstructed using the intensity and mean flight-time data types extracted from the TPSFs.[34]

Patients underwent three optical imaging sessions. The first scan was before the start of treatment. A second scan was performed halfway through treatment, and the third scan on completion of treatment, before surgery. Each scan took 3 min, and both breasts were scanned.

2.3 *Image Reconstruction and Analysis*

Three-dimensional (3-D) images of scatter (μ_S') and absorption (μ_a) coefficients were reconstructed using the time-resolved optical absorption and scattering tomography reconstruction package developed at UCL.[9,35] We assume that the optical absorption represented in the absorption images is due to three components: oxyhemoglobin (HbO_2), deoxyhemoglobin (Hb), and a background component with the same absorption coefficient at both wavelengths (assumed to be due to lipid, water, proteins, and other absorbers).[36] The background component was assumed to contribute 70% of the total absorption, based on previous findings.[9] The combination of absorption data at two wavelengths and knowledge of the appropriate extinction coefficients are used to derive [HbT] and $SatO_2$.

A two-dimensional (2-D) coronal slice was extracted from each 3-D μ_a, μ_S', [HbT], and $SatO_2$ reconstructed image at the location where the lesion contrast was maximal. A circular tumor region of interest (ROI) was selected around the peak contrast in the 2-D image. A second ROI was manually selected as background breast tissue (excluding the tumor ROI and the coupling fluid). The mean and standard deviation (SD) of the optical and physiological values within each ROI were calculated. An equivalent breast ROI from the contralateral breast was also analyzed. The changes within the tumor and the rest of the breast were evaluated during the course of therapy.

The statistical differences between measurements, e.g., tumor and healthy breast tissue at the start of treatment, were calculated using a two-tailed t-test with $P \leq 0.001$ taken as significant. The degrees of freedom for the t-test were calculated from the number of resolution elements in the image. The spatial resolution for the optical images was taken from previous work.[36–38] The full-volume half-maximum for 3-D images was calculated from phantom studies and varies from 10 to 40 cm^3 (Ref. 36). We took 20 cm^3 as a suitable midrange estimate. From this, we calculated that the equivalent full-width half-maximum as 16 mm.[37] The number of resolution elements of the image was calculated by dividing the area of the ROI by the area of one resolution element ($=\pi.8^2$ mm^2). This gives us the number of resolution elements for the ROI (both tumor and breast regions), which was taken to be the number of degrees of freedom for the t-test. This approach has weaknesses (e.g., the FWMH varies across the image) but gives a reasonable estimate of the number of degrees of freedom. It is unreasonable to assume that every pixel in the image is an independent measurement, as each pixel is very closely related to its neighbors.[38]

3 Results

3.1 *Patient A*

Patient A is a 66-year-old woman with a grade II carcinoma in the upper outer quadrant of her right breast. The tumor size was recorded on clinical notes as 60 by 40 mm using 2-D ultrasound. Ten weeks after the start of treatment, the lesion measured 34 by 27 mm on ultrasound. On treatment completion, the lesion was 3 mm on ultrasound, indicating a partial response to treatment.

Figure 1 shows the changes in the mean [HbT] in the lesion and the background tissue over time. The tumor [HbT] was 36 ± 6 μM before treatment, and shrank to 33 ± 4 μM by week 10 and 20.7 ± 0.4 μM by week 15 of treatment. Background breast tissue [HbT] and contralateral breast tissue [HbT] remained relatively stable at 21 ± 3 μM. The lesion was hypoxic at the beginning of treatment at $64\% \pm 2\%$ $SatO_2$ versus $70\% \pm 2\%$ in the breast ($P \leq 0.001$). The lesion $SatO_2$ rose over the course of treatment to $69.4\% \pm 0.5\%$, while the background $SatO_2$ remained constant at $69\% \pm 3\%$ ($P = 0.76$).

3.2 *Patient B*

Patient B is a 64-year-old woman with a grade 1 carcinoma in the upper inner quadrant of her right breast. Before treatment, the tumor was 19 by 18 by 20 mm on MRI. The patient was operated on after 15 weeks of treatment due to lack of response

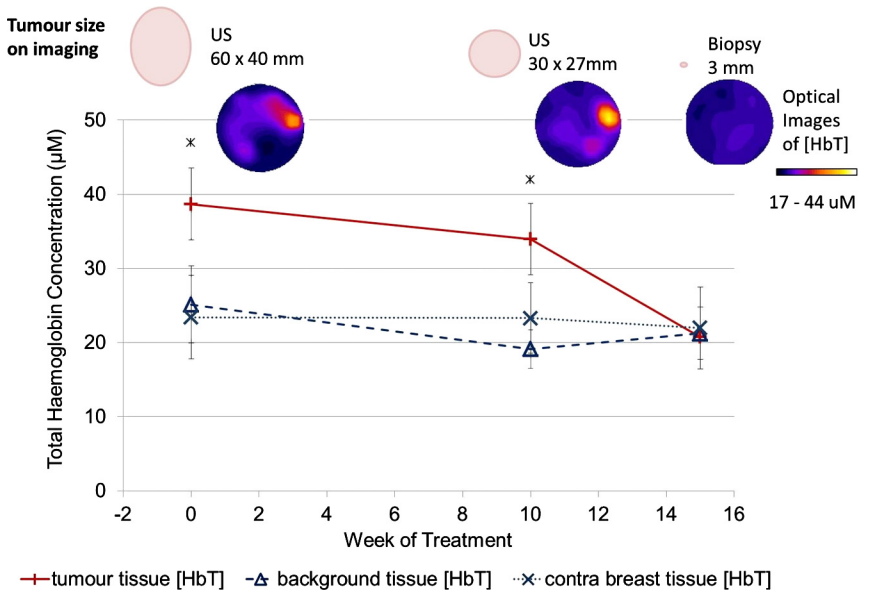

Fig. 1 Mean and standard deviation (SD) total hemoglobin concentration ([HbT]) of the tumor region of interest (ROI) (solid line), healthy background tissue in the affected breast (dashed line), and tissue of the contralateral breast (dotted line) over time in patient A. There is a significant difference between the tumor and the background tissue at week 0 ($P \leq 0.001$). The background [HbT] remains constant, while the tumor [HbT] decreases by 57% over the course of treatment to equal that of the background. At the end of treatment, there was no significant difference between the tumor and the background ($P = 0.79$). A two-dimensional (2-D) slice of the three-dimensional (3-D) [HbT] image is shown for each of the three scans. An increased region of [HbT] concentration can be seen on the right of the images from scans 1 and 2. *$P \leq 0.001$.

on ultrasound, with the tumor measuring 32 by 20 mm on ultrasound before surgery. She had an 18-mm grade 1 carcinoma removed and was classified as not having responded to treatment.

Figure 2 shows the changes in the mean [HbT] in the lesion and the background tissue over time. Before treatment, there was increased [HbT] in the region of tumor compared to the rest of the breast (30 ± 1 versus 21 ± 3 μM). There was a reduction in the tumor [HbT] at week 4 to 14.3 ± 0.5 μM, followed by a large increase in tumor [HbT] to 45 ± 3 μM compared to the breast [HbT] of 23 ± 6 μM by week 14. Background breast tissue [HbT] and contralateral breast tissue [HbT] remained stable at around 22 ± 2 μM. There the tumor was hypoxic compared to the rest of the breast at the start of

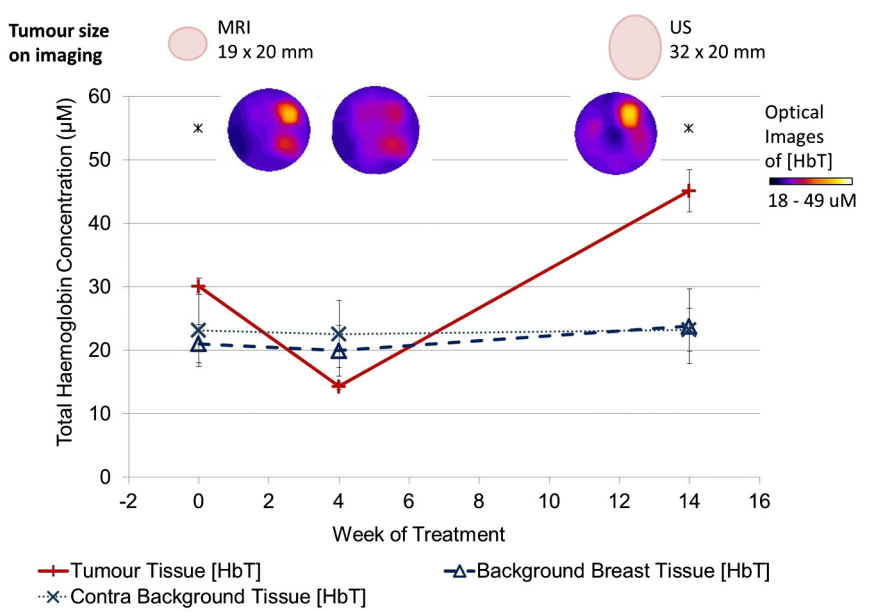

Fig. 2 Mean and SD [HbT] of the tumor ROI (solid line), healthy background tissue in the affected breast (dashed line), and tissue of the contralateral breast (dotted line) over time in patient B. There is a significant difference between the tumor and the background tissue at week 0 ($P \leq 0.001$). The background [HbT] remains constant, while the tumor [HbT] increases by 60% over the course of treatment. At the end of treatment, there was a significant difference between the tumor and the background ($P \leq 0.001$). A 2-D slice of the 3-D [HbT] image is shown for each scan. An increased region of [HbT] concentration can be seen in the upper inner quadrant. There is also an artifact seen in the first and second scans in the lower inner quadrant. *$P \leq 0.001$.

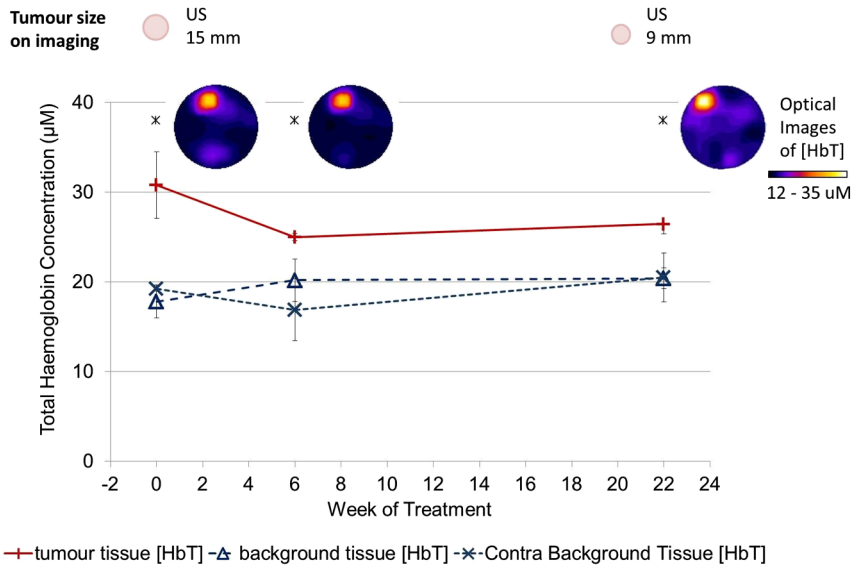

Fig. 3 Mean and SD [HbT] of the tumor ROI (solid line), healthy background tissue in the affected breast (dashed line), and tissue of the contralateral breast (dotted line) over time in patient C. There is a significant difference between the tumor and the background tissue at week 0 ($P \leq 0.001$). The background [HbT] remains constant, while the tumor [HbT] decreases by 20% by week 10 of treatment. At the end of treatment, there was a significant difference between the tumor and the background ($P \leq 0.001$). A 2-D slice of the 3-D [HbT] image is shown for each scan. An increased region of [HbT] concentration can be seen in the region of the tumor. *$P \leq 0.001$.

treatment ($62\% \pm 1\%$) versus ($69\% \pm 1\%$) ($P \leq 0.001$), which resolved by week 4 ($P = 0.5$). In the images, a region of increased [HbT] can be seen in the upper inner quadrant, in the region of the tumor in all three images. An area of artifact can also be seen in the lower inner sector of the image.

3.3 *Patient C*

Patient C is a 73-year-old woman with a grade 1 carcinoma in the upper inner quadrant of her left breast. Before treatment, the tumor was recorded on clinical notes as measuring 15 mm on mammography and ultrasound. At the time of surgery, a 10-mm tumor (on pathology) was removed, and the patient was classified as having a partial response to treatment.

Figure 3 shows the changes in the mean [HbT] in the lesion and the background tissue over time. There was a significant difference between the tumor and background [HbT] throughout the study ($P \leq 0.001$). The tumor [HbT] was 30 ± 4 μM before treatment, falling to 25.2 ± 0.4 μM by week 6 and remaining constant at 26 ± 1 μM by week 22 of treatment. Background breast tissue [HbT] and contralateral breast tissue [HbT] remained stable at 19 ± 2 μM. The tumor showed a significant increase in tissue $SatO_2$ at the beginning of treatment of $74\% \pm 2\%$ compared to $69\% \pm 1\%$ in the rest of the breast ($P \leq 0.001$). At the end of treatment, there was no longer a significant difference between tumor $SatO_2$ and that of the rest of the breast $64\% \pm 1\%$ ($P = 0.84$).

4 Discussion

We have imaged three women being treated with hormone therapy for locally advanced breast cancer, with the longest study taking place over 20 weeks. All three women were imaged three times, resulting in nine useable data sets. All three patients showed changes in both optical and physiological properties compared to the rest of the breast in the region of the tumor (location confirmed by MRI, ultrasound, or mammography) in their baseline optical scans. For every patient, the physiological results from their final optical images strongly correlated with the clinical assessment of response to treatment.

When the background [HbT] levels are compared to published data for postmenopausal women, the average values are slightly higher, with all three women having a background [HbT] between 19 and 22 μM compared to the published bulk average values $\sim$14 μM.[6] The observed maximum [HbT] for tumors at the start of treatment ranged from 30 to 38 μM, which is at the lower end of the range in the literature (average [HbT] $= 65 \pm 34$ μM).[6] All three patients had lower histological grade tumors, which may be the reason for the lower tumor [HbT] compared to the previously published values. It has been shown that greater microvessel density is linked to more aggressive disease in breast cancer.[39]

For patient A, the [HbT] in the region of the tumor returned to baseline at the end of treatment. On ultrasound, she was classified as a partial responder to treatment, and at surgery, only 3 mm of tumor tissue was removed. A decrease in tumor [HbT] was observed in the optical images at 10 weeks into treatment.

Patient B was operated on early in her proposed treatment plan due to a lack of response to therapy, and a similar lack of response was seen on her optical scan conducted at 15 weeks of treatment. However, there was a decrease in tumor [HbT] seen 4 weeks into therapy. This dip in [HbT] (and in absorption at both wavelengths) followed by an increase suggests that optically measured early changes in the tumor region following treatment may not always correlate with final outcome, as has been shown in patients treated with chemotherapy.[40,41] An area of artifact was also seen in this image, and care was taken not to include this region in the image analysis, to avoid introducing errors to the calculated values.

One possible reason for this decrease and then increase in tumor [HbT] may be the clonal nature of malignant tumors. When a tumor has reached a size that can be detected on x-ray imaging, the original cancer cell has already undergone numerous cell divisions and reached a mass of 10^8 cells.[42]

In this mass, there will be cells that are resistant to treatment, or a certain form of treatment (such as a particular chemotherapy drug), owing to genetic mutations.[43] The initial phase of treatment will kill the cells that are not resistant to treatment, leading to an initial decrease in tumor mass, followed by an increase as the treatment-resistant cells continue to proliferate.

Patient C had a partial response to treatment as classified by ultrasound. A similar decrease in tumor [HbT] was observed in the optical images and physiological data acquired 6 weeks after the start of treatment.

In conclusion, we present three case studies on monitoring patients treated with neoadjuvant letrozole for locally advanced breast cancer with 3-D optical mammography. This is the first paper published on monitoring tumor response to endocrine therapy using optical tomography. Optical imaging results during treatment have shown a strong correlation with treatment outcome. Optical mammography is a promising technique for monitoring the response to hormone therapy and may provide valuable physiological information that could be used as an early predictor of nonresponders and potentially have applications in drug development.

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