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BRIEF COMMUNICATION

Diffuse optical tomography breast imaging measurements are modifiable with pre-surgical targeted and endocrine therapies among women with early stage breast cancer

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Abstract

Purpose Diffuse optical tomography breast imaging system (DOTBIS) non-invasively measures tissue concentration of hemoglobin, which is a potential biomarker of short-term response to neoadjuvant chemotherapy. We evaluated whether DOTBIS-derived measurements are modifiable with targeted therapies, including AKT inhibition and endocrine therapy.

Methods We conducted a proof of principle study in seven postmenopausal women with stage I-III breast cancer who were enrolled in pre-surgical studies of the AKT inhibitor MK-2206 ($n=4$) or the aromatase inhibitors exemestane ($n=2$) and letrozole ($n=1$). We performed DOTBIS at baseline (before initiation of therapy) and post-therapy in the affected breast (tumor volume) and contralateral, unaffected breast, and measured tissue concentrations (in μM) of total hemoglobin (ctTHb), oxyhemoglobin (ctO_2Hb), and deoxyhemoglobin (ctHHb), as well as water fraction (%).

Results We found consistent decreases in DOTBIS-measured hemoglobin concentrations in tumor volume, with median percent changes for ctTHb, ctHHb, ctO_2Hb, and water fraction for the entire cohort of − 27.1% (interquartile range [IQR] 37.5%), − 49.8% (IQR 29.3%), − 33.5% (IQR 47.4%), and − 3.6% (IQR 10.6%), respectively. In the contralateral breast, median percent changes for ctTHb, ctHHb, ctO_2Hb, and water fraction were + 1.8% (IQR 26.7%), − 8.6% (IQR 29.3%), + 6.2% (IQR 29.5%), and + 1.9% (IQR 30.7%), respectively.

Conclusion We demonstrated that DOTBIS-derived measurements are modifiable with pre-surgical AKT inhibition and endocrine therapy, supporting further investigation of DOTBIS as a potential imaging assessment of response to neoadjuvant targeted therapies in early stage breast cancer.

Keywords Diffuse optical tomography · Neoadjuvant therapy · Early stage breast cancer · Endocrine therapy · AKT inhibition

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Introduction

Neoadjuvant chemotherapy (NACT) is increasingly used in early stage breast cancer given the potential for less morbid breast surgery [1–3], the ability to assess tumor response to therapy, and compelling evidence that pathologic complete response (pCR) associates with improved long-term clinical outcomes [4]. Current methods to assess response to neoadjuvant therapy, including physical exam and standard breast imaging techniques, lack sensitivity [5, 6],are costly [7], or use intravenous contrast (*i.e.,* gadolinium-based MRI contrast agent) and/or ionizing radiation [8]. There is therefore an unmet need for a sensitive, non-invasive, non-ionizing method to assess response to neoadjuvant therapies in breast cancer, which could inform treatment decisions and optimize patient outcomes.

Diffuse optical tomography breast imaging system (DOTBIS) is a novel three-dimensional imaging modality that quantitatively measures near-infrared light absorption and scattering in tissues to determine tissue concentrations of oxyhemoglobin (ctO_2Hb), deoxyhemoglobin (ctHHb), water, and fat, thereby providing information on tissue vascularity and distinguishing malignant from normal breast tissue [9–12]. DOTBIS has been investigated as a method to assess early response to NACT in breast cancer, and studies have shown that two-week decreases in ctO_2Hb and ctHHb concentrations are significantly different between patients who do and do not achieve pCR after completion of NACT [13, 14]. However, DOTBIS has not yet been evaluated as a potential imaging assessment of response to neoadjuvant endocrine or targeted therapies in breast cancer, which are increasingly utilized in clinical trials and practice.

In this proof of principle study, we performed DOTBIS imaging among women with early stage breast cancer who were enrolled in a pre-surgical study with either the AKT inhibitor MK-2206 or an aromatase inhibitor, with the goal of assessing whether DOTBIS-derived measurements are modifiable with these therapies.

Methods

Study population

We conducted a proof of principle study among women at Columbia University Irving Medical Center (CUIMC) in New York, NY, USA with newly diagnosed, histologically confirmed, operable clinical stage I–III breast cancer. Patients were eligible if they had not received prior systemic chemotherapy or radiation therapy for their breast cancer, and if they were concurrently enrolled in a pre-surgical treatment trial at CUIMC. We ultimately enrolled patients from three treatment trials that were open at CUIMC at time of this study: (1) a pre-surgical study with the allosteric AKT inhibitor MK-2206 [ClinicalTrials.gov Identifier: NCT01319539] [15], (2) a pre-surgical study of alternative dosing of exemestane [ClinicalTrials.gov Identifier: NCT02598557] [16], and (3) a neoadjuvant study of letrozole plus ribociclib vs. placebo [ClinicalTrials.gov Identifier: NCT02712723] [17]. Patients in the trial of pre-surgical MK-2206 received two weekly oral (po) doses of MK-2206, on days -9 (± 1 day) and -2 (± 1 day) before surgery. Those enrolled in the trial of exemestane received either exemestane 25 mg po daily, three times weekly, or weekly for a total of 4 to 6 weeks before surgery, and those in the trial of letrozole ± ribociclib were randomized to letrozole 2.5 mg po plus placebo daily vs. ribociclib at two dosing schedules for a total of 22 weeks before surgery. The institutional review board at CUIMC approved the study protocol (AAAI9154). Informed consent was obtained from all patients prior to their enrollment.

Study procedure

Each participant underwent a baseline assessment including breast tumor size (mm) measurement with calipers as well as pre-treatment core needle tumor biopsy with assessment for tumor histological subtype, grade, estrogen receptor (ER), progesterone receptor (PR), HER2 expression, and Ki67 proliferation index. At initial assessment, tumor anatomic clinical stage was determined according to the American Joint Committee on Cancer (AJCC) 8th Edition, and patient age (in years), menopausal status (premenopausal, postmenopausal), and body mass index (BMI) in kg/m^2 were recorded.

All patients underwent DOTBIS of the affected breast (tumor volume) and contralateral, unaffected breast at two time points: before initiating treatment (baseline), and after completion of pre-surgical therapy. The DOT breast imaging procedure has been previously described [13, 14]. Briefly, DOTBIS measurements were made by placing each subject's breasts into a measurement head containing 96 optical fibers (32 sources and 64 detectors per breast). During the optical measurements, light from four laser diodes (wavelengths 765–905 nm, light intensity around 5 mW well below the ANSI standards) were sequentially coupled into 64 fibers that contacted the breast. Transmitted light intensities were collected by 128 detection fibers in total (64 detection fibers per breast) coupled to individual silicon photodiodes, which recorded the light intensities. The measured data were then processed by a partial differential equation (PDE)-constrained multispectral image reconstruction code [18] that employs the equation of radiative transfer as a light

propagation model. As a result, the volumetric image of ctO_2Hb, ctHHb, water, and total hemoglobin concentration (ctTHb), which is defined by Eq. 1, are generated for both breasts. Based on the assumption that changes in absorption (i.e., ctO_2Hb, ctHHb, ctTHb) would most strongly reflect tumor responsiveness to target therapies, we did not include scattering parameters in our reconstruction.

$$ctTHb = ctO_2Hb + ctHHb \quad (1)$$

Tumor volume was selected by entering radiologic information such as tumor side, clock position and distance from the nipple, and assumed as true for all the imaging time points by the automated tumor selection algorithm. Due to high vascularization and metabolic activity characteristics attributed to the tumor volume, an automated code selects the highest value in the breast quadrant previously identified from the tumor position. Next, a region-based image segmentation method selects neighboring pixels considering a mask factor of 0.9. Values for ctTHb, ctO_2Hb, and ctHHb, as well as water fraction (%) were quantified by calculating the mean concentration for the region of interest.

Outcome measures and statistical analysis

Given the small number of patients enrolled, statistical analysis was descriptive. Median age at diagnosis and BMI (in kg/m^2) were calculated for the entire cohort. Percent change in each DOTBIS-derived measurement from baseline to post-therapy was calculated for each patient, and median percent change and interquartile range (IQR) were then calculated for the patient cohort. We also calculated absolute change in Ki67 proliferation index from baseline to post-therapy among patients, when available.

Results

Between July 2012 and May 2018, we enrolled seven women, of whom four were concurrently enrolled in the MK-2206 study, two in the exemestane study, and one in the letrozole ± ribociclib study, who was randomized to receive placebo. Baseline clinicopathologic characteristics are summarized in Table 1. All women were postmenopausal, with median age at diagnosis 67 years (range, 51–72 years) and median body mass index (BMI) 30.5 kg/m^2 (range, 24.5–36.5 kg/m^2). Six women had hormone receptor-positive, HER2-negative breast tumors, and one (Patient 2) had a triple-negative tumor.

Change in DOTBIS measurements from baseline to post-treatment in the tumor volume and contralateral breast are summarized in Table 2 and shown in box plots in Fig. 1. Median percent changes for ctTHb, ctHHb, ctO_2Hb, and

Table 1 Baseline clinicopathologic characteristics among enrolled patients ($n = 7$)

Patient ID	Therapy	Duration of therapy (weeks)	Age (years)	BMI (kg/m^2)	Baseline tumor characteristics						
					Side	Histology	Tumor grade	HR/HER2 status (+/−)	Ki67 (%)	Tumor size (mm)	Clinical stage*
1	MK-2206	1	70	34.1	Right	IDC	I	+/−	5	15	I
2		1.1	69	32.0	Right	IDC	unk	−/−	unk	30	II
3		1	51	24.5	Left	IDC	II	+/−	5	20	II
4		1	61	30.5	Right	IDC	II	+/−	10	25	II
5	Letrozole	21.9	72	25.6	Left	IDC	III	+/−	30	40	III
6	Exemestane	4.9	67	36.5	Right	IDC/ILC	III	+/−	10	8	I
7		3.7	61	28.7	Left	IDC	II	+/−	15	8	I

*American Joint Committee on Cancer (AJCC) 8th Edition anatomic stage

BMI body mass index, *HR* hormone receptor, *IDC* invasive ductal carcinoma, *ILC* invasive lobular carcinoma

Table 2 Change in DOTBIS measurements and Ki67 proliferation index from baseline to post-treatment among enrolled patients ($n = 7$)

Patient ID	Therapy	Duration of therapy (weeks)	Pre-treatment Ki67 (%)	Post-treatment Ki67 (%)	Absolute change in Ki67 (%)	Percent Change in DOTBIS Measurements from Baseline							
						Tumor volume				Contralateral breast volume			
						ctTHb (%)	ctHHb (%)	ctO_2Hb (%)	Water (%)	ctTHb (%)	ctHHb (%)	ctO_2Hb (%)	Water (%)
1	MK-2206	1	5	3	− 2	− 50.5	− 49.8	− 50.9	− 11.3	+ 1.8	− 13.1	+ 11.4	+ 20.7
2		1.1	N/A	N/A	N/A	− 15.9	− 22.1	− 11.6	+ 2.2	+ 31.1	+ 24.6	+ 36.1	+ 59.3
3		1	5	2	− 3	− 13.8	− 29.5	− 9.2	+ 3.4	+ 6.3	+ 6.7	+ 6.2	+ 1.9
4		1	10	4	− 6	− 19.3	− 52.3	+ 1.3	+ 3.6	− 8.5	− 14.3	− 4.9	− 2.0
5	letrozole	21.9	30	N/C	N/C	− 73.1	− 62.1	− 83.4	− 63.2	− 23.2	− 29.6	− 17.9	− 14.3
6	exemestane	4.9	10	10	0	− 59.8	− 57.9	− 64.5	− 4.2	− 7.4	− 8.6	− 6.6	− 20.0
7		3.7	15	30	+ 15	− 27.1	− 12.9	− 33.5	− 3.6	+ 40.3	+ 33.3	+ 45.5	+ 24.4
				Median		− 27.1	− 49.8	− 33.5	3.6	1.8	− 8.6	6.2	1.9
				Interquartile range (%)		37.5	29.3	47.4	10.6	26.7	29.3	29.5	30.7

N/A not available, *N/C* not calculated, only rare invasive cancer cells in surgical specimen, *ctTHb* tissue concentration of total hemoglobin, *ctHHb* tissue concentration of deoxyhemoglobin, *ctO_2Hb* tissue concentration of oxyhemoglobin, *water* water volume

water fraction in the tumor volume for the entire cohort were -27.1% (IQR 37.5%), − 49.8% (IQR 29.3%), − 33.5% (IQR 47.4%), and − 3.6% (IQR 10.6%), respectively. In the contralateral breast, the median percent changes for ctTHb, ctHHb, ctO_2Hb, and water fraction averaged over the whole breast volume were + 1.8% (IQR 26.7%), − 8.6% (IQR 29.3%), + 6.2% (29.5%), and + 1.9% (30.7%), respectively. Representative three-dimensional maps for one patient who received MK-2206 and one who received letrozole are shown in Fig. 2, with images for all patients shown in Supplemental Fig. 1

Among the four patients who received MK-2206, median percent changes for ctTHb, ctHHb, ctO_2Hb, and water fraction in the tumor volume were − 17.6% (IQR 11.7%), − 39.7% (IQR 22.8%), − 10.4% (IQR 29.5%), and 2.8% (IQR 3.8%), respectively. Patient 5, who received letrozole for a total of 21.9 weeks, had the greatest absolute change in DOTBIS measurements in both breasts, with percent change in ctTHb, ctHHb, and ctO_2Hb of − 73.1, − 62.1, and − 83.4%, respectively, in the tumor volume and − 23.2, − 29.6, and − 17.9%, respectively, in the contralateral breast. Patients 6 and 7 each received exemestane for approximately one month, and while both showed decrease in all DOTBIS parameters in the tumor volume, Patient 6 had a greater absolute decrease exceeding 50% in ctTHb, ctHHb, and ctO_2Hb. Of note, Patient 7 had the greatest absolute change in all DOTBIS parameters in the contralateral breast among the study cohort, with a 45.5% increase in ctO_2Hb.

Change in Ki67 proliferation index was able to be calculated for five patients and is summarized in Table 2. Three of the five patients, all of whom received MK-2206, had decrease in Ki67 with therapy, while the two remaining patients, both of whom received exemestane, either had no change in Ki67 (Patient 6) or an increase in Ki67 (Patient 7). Notably, Patient 5 did not have calculable post-treatment Ki67 because only rare invasive cancer cells were present in the surgical specimen.

Discussion

We demonstrated that DOTBIS-derived measurements, including ctTHb, ctHHb, and ctO_2Hb, were modifiable with the targeted anti-neoplastic interventions MK-2206 and aromatase inhibitor therapy. While there was variability in the type and duration of therapy that patients received, there was a consistent decrease in DOTBIS-measured hemoglobin concentrations in the tumor volume, as well as observed change in DOTBIS measurements in the contralateral breast.

As novel neoadjuvant therapies are increasingly used in early stage breast cancer, identifying an imaging-based biomarker of response to these therapies not only could have treatment implications, but also could be used in the clinical

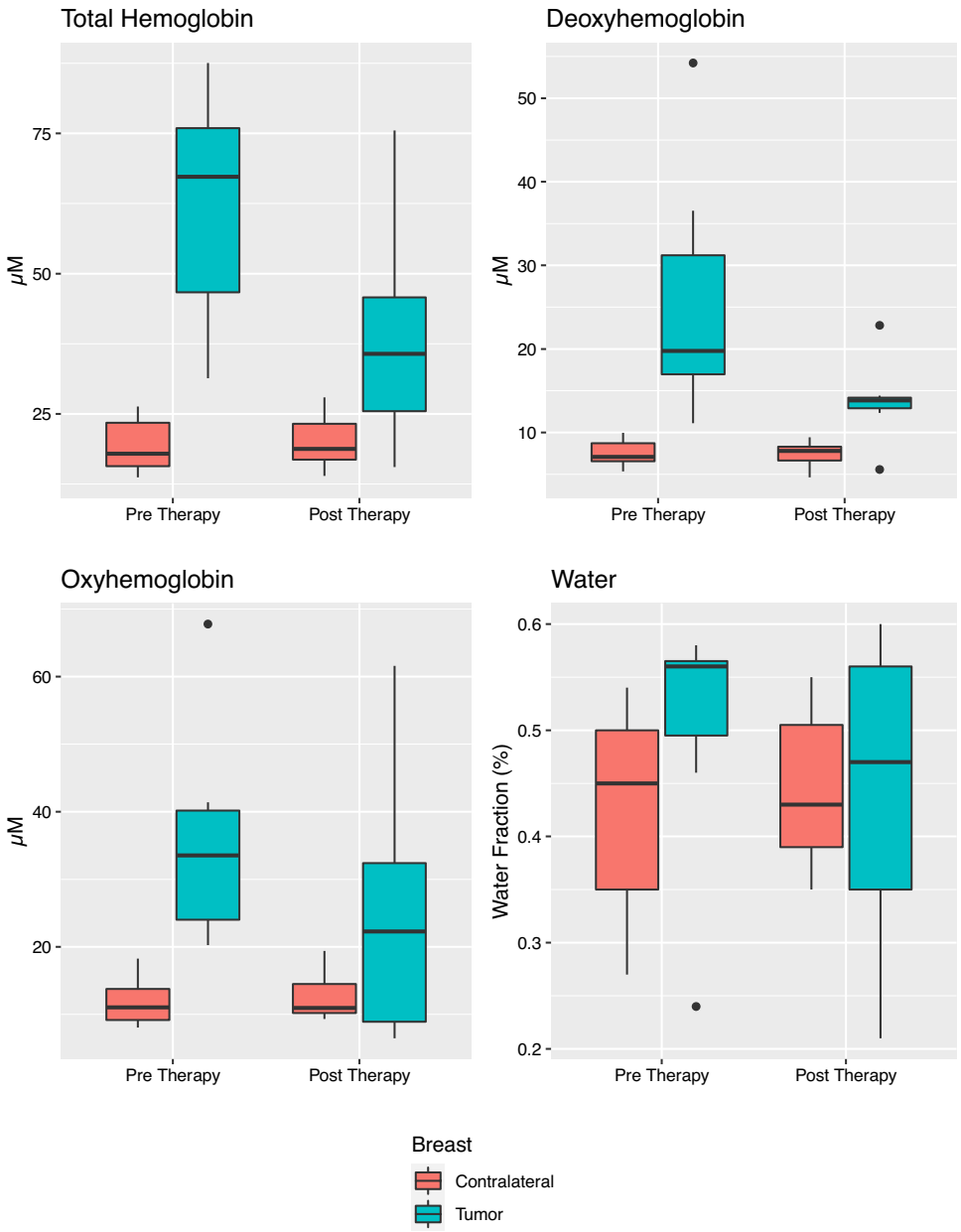

Fig. 1 Box plots of pre- and post-therapy DOTBIS measurements in tumor volume and contralateral breast among enrolled patients ($n = 7$)

trial setting as a predictor of pathologic response. Our current proof of principle study could not assess for statistical correlation between changes in DOTBIS measurements and pathologic response given the relatively short interventions in the pre-surgical trials, as well as our small patient cohort with heterogeneity in type and duration of therapy. However, our finding that DOTBIS measurements in breast tumors were modifiable with pre-surgical targeted and endocrine therapies, including after only one week of therapy, is in agreement with our previous studies demonstrating that short-interval change in DOTBIS measurements with standard NACT and correlated with pathologic response [13, 14]. Future prospective studies are therefore warranted to further investigate DOTBIS's ability to predict pathologic response among women who receive novel breast cancer therapies. In addition, given that the rate of pCR is expected to be less than 10% among women with hormone receptor-positive, HER2-negative breast cancer [19], future studies should evaluate for correlation between change in DOTBIS measurements and change in Ki67, a validated prognostic marker among women receiving neoadjuvant therapy, including endocrine therapies [20, 21].

In addition, our DOTBIS system uniquely images both the affected and unaffected breasts simultaneously, allowing for the evaluation of changes in DOTBIS measurements in the contralateral breast with neoadjuvant therapies. We previously observed that DOTBIS-measured ctO_2Hb in the contralateral breast among women

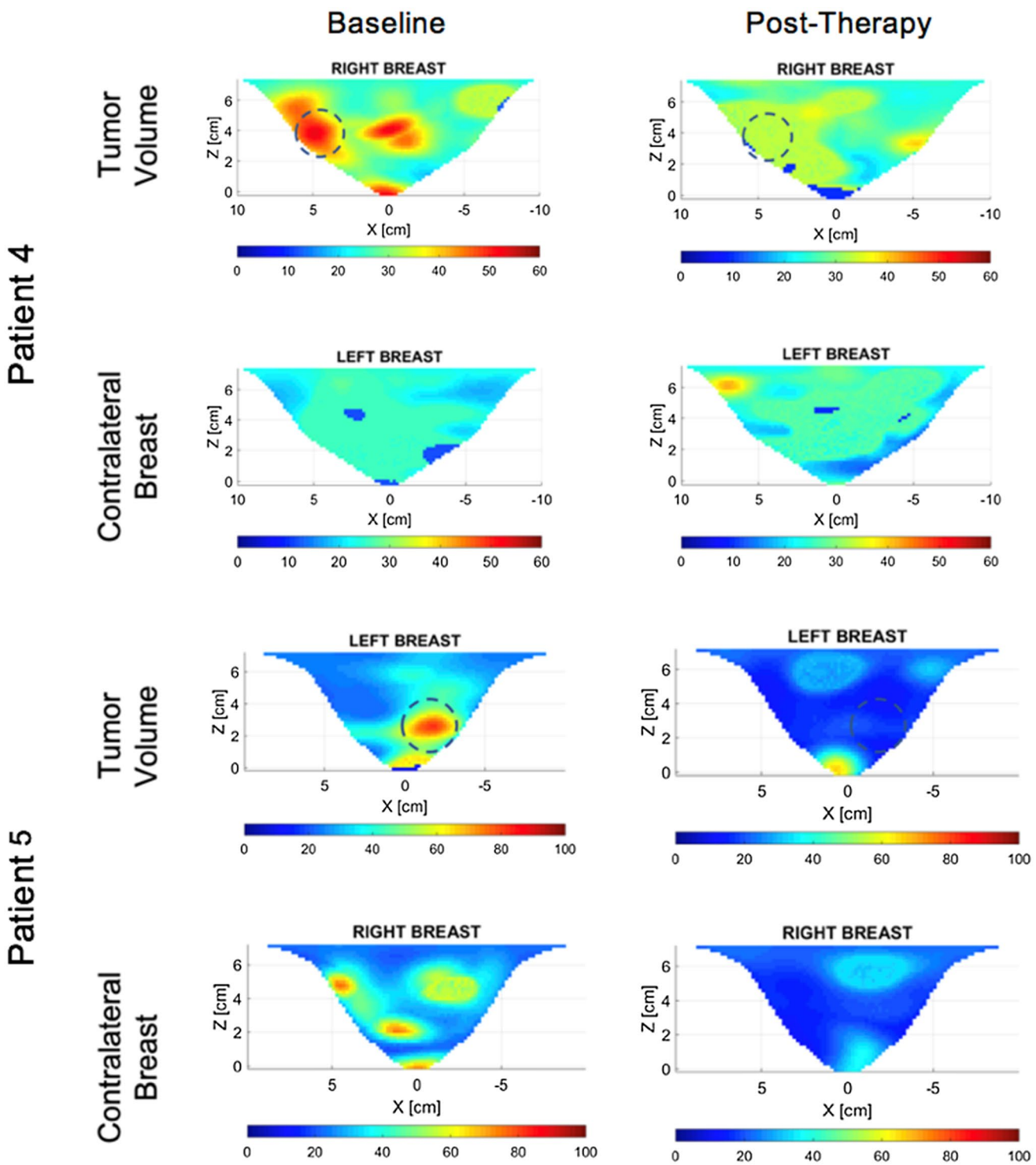

Fig. 2 Axial MIP of the reconstructed 3D ctTHb maps within the affected breast (*i.e.* tumor volume) and the contralateral breast for two representative patients before and after pre-surgical therapy administration. Dashed circle indicates tumor volume localization. Patient 4 received the AKT inhibitor MK-2206, and Patient 5 received letrozole

undergoing NACT for early stage breast cancer was modifiable with chemotherapy and correlated with mammographic density [22], a known biomarker of breast cancer risk that shows dynamic change and is predictive of breast cancer recurrence among women who receive adjuvant tamoxifen [23–25]. While we did not compare

DOTBIS measurements to mammographic density in this study nor evaluate if changes in contralateral DOTBIS measurements correlated with clinical outcomes, this is an area of potential research, particularly with neoadjuvant endocrine-based therapies. Changes in contralateral as well as tumor volume DOTBIS measurements might also be explained by altered angiogenesis in breast tissue as a result of pre-surgical therapies, particularly among those who received MK-2206, given the role of the PI3K/AKT/mTOR pathway in angiogenesis [26].

The main limitation of our trial is the small number of enrolled patients at a single academic institution, which might limit generalizability and, as mentioned, did not allow us to statistically evaluate for associations between change in DOTBIS measurements and validated pathologic outcomes, including pCR or change in Ki67. The heterogeneity in pre-surgical therapy and treatment duration among patients also limited our ability to assess for such associations, particularly given that most patients received pre-surgical treatment for a month or less and would be unlikely to achieve pCR with such a short duration of treatment.

Conclusion

We demonstrated that DOTBIS-derived measurements are modifiable with neoadjuvant targeted and endocrine therapies among women with early stage breast cancer, and therefore warrants further investigation in larger, multicenter prospective studies to determine the potential clinical utility of DOTBIS-derived images as a marker of response to these therapies.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10549-021-06320-6.

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Data availability Supporting data can be made available upon written request for non-commercial purposes to researchers subject to a non-disclosure agreement with all relevant parties, and by contacting the corresponding author.

Declarations

Conflict of interest JEM, MLA, AM, LEF, SL, HKK, MT, MST, MKA, KDC, DLH, AHH declare no conflict of interest. KK declares the following potential conflicts of interest: *Medical Advisor*—Immunomedics, Pfizer, Novartis, Eisai, Eli-Lilly, Amgen, Immunomedics, Merck, Seattle Genetics, and Astra Zeneca; *Institutional Support*—Immunomedics, Novartis, Incyte, Genentech/Roche, Eli-Lilly, Pfizer, Calithera Biosciences, Acetylon, Seattle Genetics, Amgen, Zentalis Pharmaceuticals, and CytomX Therapeutics; *Speakers Bureau*—Eli-Lilly; *Spouse*—Array Biopharma, Pfizer, Grail.

Ethical approval The institutional review board at Columbia University Irving Medical Center approved the study protocol (AAAI9154).

Informed consent Informed consent was obtained from all patients prior to their enrollment.

References

1. Fisher B, Brown A, Mamounas E, Wieand S, Robidoux A, Margolese RG, Cruz AB Jr, Fisher ER, Wickerham DL, Wolmark N et al (1997) Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. J Clin Oncol 15(7):2483–2493
2. Makris A, Powles TJ, Ashley SE, Chang J, Hickish T, Tidy VA, Nash AG, Ford HT (1998) A reduction in the requirements for mastectomy in a randomized trial of neoadjuvant chemoendocrine therapy in primary breast cancer. Ann Oncol 9(11):1179–1184
3. Mauriac L, MacGrogan G, Avril A, Durand M, Floquet A, Debled M, Dilhuydy JM, Bonichon F (1999) Neoadjuvant chemotherapy for operable breast carcinoma larger than 3 cm: a unicentre randomized trial with a 124-month median follow-up. . Ann Oncol 10(1):47–52
4. Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, Bonnefoi H, Cameron D, Gianni L, Valagussa P et al (2014) Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. The Lancet 384(9938):164–172
5. Chagpar AB, Middleton LP, Sahin AA, Dempsey P, Buzdar AU, Mirza AN, Ames FC, Babiera GV, Feig BW, Hunt KK et al (2006) Accuracy of physical examination, ultrasonography, and mammography in predicting residual pathologic tumor size in patients treated with neoadjuvant chemotherapy. Ann Surg 243(2):257–264
6. Schott AF, Roubidoux MA, Helvie MA, Hayes DF, Kleer CG, Newman LA, Pierce LJ, Griffith KA, Murray S, Hunt KA et al (2005) Clinical and radiologic assessments to predict breast cancer pathologic complete response to neoadjuvant chemotherapy. Breast Cancer Res Treat 92(3):231–238
7. Buck AK, Herrmann K, Stargardt T, Dechow T, Krause BJ, Schreyögg J (2010) Economic evaluation of PET and PET/CT in oncology: evidence and methodologic approaches. J Nucl Med Technol 38(1):6–17
8. Huang B, Law MW, Khong PL (2009) Whole-body PET/CT scanning: estimation of radiation dose and cancer risk. Radiology 251(1):166–174
9. Flexman M, Kim H, Gunther J, Lim E, Alvarez M, Desperito E, Kalinsky K, Hershman D, Hielscher A (2013) Optical biomarkers for breast cancer derived from dynamic diffuse optical tomography. J Biomed Opt 18(9):096012

10. Flexman M, Khalil M, Kim H, Fong C, Hielscher A, Abdi RA, Barbour R, Desperito E, Hershman D (2011) Digital optical tomography system for dynamic breast imaging. J Biomed Opt 16(7):076014
11. Wang J, Jiang S, Li Z, diFlorio-Alexander RM, Barth RJ, Kaufman PA, Pogue BW, Paulsen KD (2010) In vivo quantitative imaging of normal and cancerous breast tissue using broadband diffuse optical tomography. Med Phys 37(7Part1):3715–3724
12. Zhu Q, Cronin EB, Currier AA, Vine HS, Huang M, Chen N, Xu C (2005) Benign versus malignant breast masses: optical differentiation with US-guided optical imaging reconstruction. Radiology 237(1):57–66
13. Gunther JE, Lim EA, Kim HK, Flexman M, Altoe M, Campbell JA, Hibshoosh H, Crew KD, Kalinsky K, Hershman DL et al (2018) Dynamic diffuse optical tomography for monitoring neoadjuvant chemotherapy in patients with breast cancer. Radiology 287(3):778–786
14. Lim EA, Gunther JE, Kim HK, Flexman M, Hibshoosh H, Crew K, Taback B, Campbell J, Kalinsky K, Hielscher A et al (2017) Diffuse optical tomography changes correlate with residual cancer burden after neoadjuvant chemotherapy in breast cancer patients. Breast Cancer Res Treat 162(3):533–540
15. Kalinsky K, Sparano JA, Zhong X, Andreopoulou E, Taback B, Wiechmann L, Feldman SM, Ananthakrishnan P, Ahmad A, Cremers S et al (2018) Pre-surgical trial of the AKT inhibitor MK-2206 in patients with operable invasive breast cancer: a New York Cancer Consortium trial. Clin Transl Oncol 20(11):1474–1483
16. Guerrieri-Gonzaga A, Thomas P, DeCensi A, Crew KD, Kumar N, Gandini S, Vornik L, Heckman-Stoddard B, Szabo E, Dimond E et al (2020) Abstract OT1-04-03: Alternative dosing of exemestane before surgery in postmenopausal patients with stage 0–II estrogen receptor positive breast cancer: design and methodology. Cancer Res. https://doi.org/10.1158/1538-7445.SABCS19-OT1-04-03
17. Khan QJ, O'Dea A, Bardia A, Kalinsky K, Wisinski KB, O'Regan R, Yuan Y, Ma CX, Jahanzeb M, Trivedi MS et al (2020) Letrozole + ribociclib versus letrozole + placebo as neoadjuvant therapy for ER+ breast cancer (FELINE trial). J Clin Oncol 38:505–505
18. Kim HK, Flexman M, Yamashiro DJ, Kandel JJ, Hielscher AH (2010) PDE-constrained multispectral imaging of tissue chromophores with the equation of radiative transfer. Biomed Opt Express 1(3):812–824
19. Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, Bonnefoi H, Cameron D, Gianni L, Valagussa P et al (2014) Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 384(9938):164–172
20. Smith I, Robertson J, Kilburn L, Wilcox M, Evans A, Holcombe C, Horgan K, Kirwan C, Mallon E, Sibbering M et al (2020) Long-term outcome and prognostic value of Ki67 after perioperative endocrine therapy in postmenopausal women with hormone-sensitive early breast cancer (POETIC): an open-label, multicentre, parallel-group, randomised, phase 3 trial. Lancet Oncol 21(11):1443–1454
21. Dowsett M, Smith IE, Ebbs SR, Dixon JM, Skene A, A'Hern R, Salter J, Detre S, Hills M, Walsh G (2007) Prognostic value of Ki67 expression after short-term presurgical endocrine therapy for primary breast cancer. J Natl Cancer Inst 99(2):167–170
22. Altoe ML, Marone A, Kim HK, Kalinsky K, Hershman DL, Hielscher AH, Ha RS (2019) Diffuse optical tomography of the breast: a potential modifiable biomarker of breast cancer risk with neoadjuvant chemotherapy. Biomed Opt Express 10(8):4305–4315
23. Boyd NF, Guo H, Martin LJ, Sun L, Stone J, Fishell E, Jong RA, Hislop G, Chiarelli A, Minkin S et al (2007) Mammographic density and the risk and detection of breast cancer. N Engl J Med 356(3):227–236
24. Ko KL, Shin IS, You JY, Jung SY, Ro J, Lee ES (2013) Adjuvant tamoxifen-induced mammographic breast density reduction as a predictor for recurrence in estrogen receptor-positive premenopausal breast cancer patients. Breast Cancer Res Treat 142(3):559–567
25. Cuzick J, Warwick J, Pinney E, Duffy SW, Cawthorn S, Howell A, Forbes JF, Warren RM (2011) Tamoxifen-induced reduction in mammographic density and breast cancer risk reduction: a nested case-control study. J Natl Cancer Inst 103(9):744–752
26. Jiang BH, Liu LZ (2009) PI3K/PTEN signaling in angiogenesis and tumorigenesis. Adv Cancer Res 102:19–65