Optical mammography using diffuse optical spectroscopy for monitoring tumor response to neoadjuvant chemotherapy in women with locally advanced breast cancer


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**Translational relevance:**
Advances in neoadjuvant chemotherapy, in particular during treatment of breast cancer, have elicited the need for non-invasive treatment monitoring techniques. This prospective study shows the successful use of optical imaging using diffuse optical spectroscopy for tumor response monitoring during neoadjuvant chemotherapy in patients with locally advanced breast cancer. Using diffuse optical spectroscopy it was possible to differentiate between responders and non-responders as early as after the first chemotherapy cycle. Moreover, in this study the predictive power of diffuse optical spectroscopy was higher compared to conventional MRI treatment monitoring in our patient group of patients with HER2-negative breast cancer. These results show that this technique may be used as a novel imaging modality for treatment monitoring to assist patient tailored medicine.
Abstract

Purpose

Diffuse optical spectroscopy (DOS) has the potential to enable monitoring of tumor response during chemotherapy, particularly in the early stages of treatment. This study aims to assess feasibility of DOS for monitoring treatment response in HER2-negative breast cancer patients receiving neoadjuvant chemotherapy and compare DOS to tumor response assessment by MRI.

Experimental Design

Patients received neoadjuvant chemotherapy in 6 cycles of 3 weeks. In addition to standard treatment monitoring by DCE-MRI, DOS scans were acquired after the first, third and last cycle of chemotherapy. The primary goal was to assess feasibility of DOS for early assessment of tumor response. The predictive value of DOS and DCE-MRI compared to pathological response were assessed.

Results

Of the 22 patients, 18 patients had a partial or complete tumor response at pathologic examination, whereas 4 patients were non-responders. As early as after the first chemotherapy cycle a significant difference between responders and non-responders was found using DOS (HbO₂ 86%±25 vs. 136%±25, P=.023). The differences between responders and non-responders continued during treatment (halfway treatment, HbO₂ 68%±22 vs 110%±10, P=.010). Using DCE-MRI a difference between responders and non-responders was found halfway treatment (P=.005) using tumor volume measurement calculations.

Conclusions
DOS allows for tumor response assessment and is able to differentiate between responders and non-responders after the first chemotherapy cycle and halfway treatment. In this study, DOS was equally effective in predicting tumor response halfway treatment compared to DCE-MRI. Therefore, DOS may be used as a novel imaging modality for (early) treatment monitoring of neoadjuvant chemotherapy.
Introduction

Neoadjuvant chemotherapy (NAC) has been established as the standard-of-care treatment for locally advanced inoperable breast cancer, and is increasingly being used for patients with operable cancer (1,2). A pathologic complete response (pCR) has been consistently shown to be associated with increased long-term survival (2). A significant number of patients, however, is unresponsive to NAC or even experience tumor growth under NAC (3,4). A key advantage of NAC is the opportunity to assess response during treatment as a predictor of final pathologic response, with the potential to modify therapy. Therefore, the early knowledge of response to NAC is essential for providing the optimal treatment strategy.

Currently, response of the tumor to NAC is most often monitored by a combination of clinical examination and conventional imaging techniques, such as mammography, ultrasound, ordinaly contrast enhanced MRI (DCE-MRI). However, clinical examination and these imaging techniques are often unable to objectively assess treatment response during the course of treatment (5). Moreover, the correlation between MRI and pCR assessment is limited (6-8). Therefore, novel, non-invasive imaging techniques are needed to improve early monitoring response of the tumor to NAC. In addition to DCE-MRI and PET modalities, optical imaging has received new interest as a non-invasive and non-ionizing technique to assess tumor response (9-14).

Diffuse optical spectroscopy (DOS) uses near-infrared light to provide quantitative spectral information regarding tissue absorption and scattering properties (15,16). These optical properties of tissue can be used to assess tissue microstructure and functional parameters, such as oxygenated hemoglobin, deoxygenated
hemoglobin, relative oxygen desaturation, and water and lipid composition. Hypoxia, blood flow, oxygen saturation and hemoglobin concentration are correlated to tumor response(17). As DOS is non-invasive and does not require contrast agents, it is a promising modality for frequent measurements of tumor response.

Multiple studies have assessed DOS for monitoring NAC treatment in breast cancer patients(9-14). These studies have suggested that DOS may provide clinically useful information on tumor response on NAC treatment. In previous studies, patients using different chemotherapeutic regimes were included. This study aims to assess the feasibility and predictive power of DOS for monitoring treatment response in breast cancer patients receiving NAC directly after the start of NAC until surgery. Moreover, this study compares the tumor response assessment by DOS to tumor response assessment by MRI.
Methods

This prospective, single-arm, single-center study was approved by the Medical Ethics Committee of the Leiden University Medical Center and was performed in accordance with the ethical standards of the Helsinki Declaration of 1975. Inclusion criteria were breast cancer patients with HER2 negative tumors larger than 2 cm or HER2 negative tumors with lymph node metastases, without distant metastases and eligible for neoadjuvant treatment. Patients with known allergies to materials used in the DOS apparatus, prior breast surgery or chemotherapy or radiation therapy were excluded. Patients were included in the period from March 2011 to October 2012. All included patients gave informed consent and the acquired data was anonymized.

Clinical trial

Patients received TAC (docetaxel, doxorubicin and cyclophosphamide) with or without zoledronic acidin 6 cycles of 3 weeks. Patients were mainly enrolled in the context of the NEOZOTAC trial (NCT01099436). Standard monitoring of treatment response of the tumor to NAC was based on clinical examination before each cycle and 3 dynamic contrast enhanced MRI (DCE-MRI) scans (before NAC, before 4th cycle, before surgery) performed on a 1.5 Tesla system (Philips Medical Systems, Best, The Netherlands). In addition, patients were scheduled for 4 optical mammographies using DOS (before NAC, before 2nd cycle, before 4th cycle, before surgery). DOS was performed using a commercially available breast imaging system (Softscan, Softscan Healthcare Group, Montreal, Canada) as described previously (18). Briefly, Softscan is a bed-based imaging system on which the patient has to lie down with the
breast inserted into an aquarium filled with optical compensation media (OCM). OCM is an oil-in-water emulsion that mimics average optical properties of the human breast. It is used to minimize light reflections at the breast surface to improve image quality. The system consists of four individual pulsed diode lasers operating at 690, 730, 780, and 830 nm. Light is collected by a mobile detector in a 1 cm-X constellation composed of five optical fibers and detected by a photomultiplier. The breast is scanned in approximately 10 to 20 minutes. The count by the detector was time correlated with the synchronization signal provided by the laser system driver. Using the measured absorption and scattering, an accurate estimate of the oxyhemoglobin (HbO₂), deoxyhemoglobin (Hb), total hemoglobin (HbT), and Scattering Amplitude (SA) and Power (SP) can be obtained. Water (H₂O) and % lipids have low, but non-negligible absorption coefficients at the higher NIR wavelengths and were estimated as well. Patients were positioned into the Softscan aperture under guidance of a radiology technician. Breasts were scanned in the craniocaudal (CC) angle and the scanning area encompassed the whole breast. To ensure consistency, stabilizing plates were used to secure the breast in place. The acquired data were reconstructed using the software associated with the Softscan device, and three-dimensional tomographic images were created from the optical parameters with a typical voxel size of 3x3x7mm³ (Figure 1).

**MRI- and pathologic assessment of tumor response to neoadjuvant chemotherapy**

* DCE-MRI response assessment
Tumor response to NAC on DCE-MRI was assessed in two ways: a) according to the response evaluation criteria in solid tumors (RECIST 1.1) guidelines, b) by semi-automated measurement of tumor volume using a dedicated software program. All measurements were performed by a single observer (MW).

Following RECIST 1.1 tumor response was measured by changes in the longest diameter of the enhancing tumor target lesions. Complete reduction of the target lesions was termed as a complete response (CR). Partial response (PR) was deemed to have occurred if tumor size was reduced by at least 30%. Progressive disease (PD) was defined as an increase in tumor size of at least 20%. The remaining cases were considered to have stable disease (SD).

Measurement of tumor volumes on the subtracted threedimensional T1-weighted DCE-MR images was done using dedicated software (Vitrea Enterprise Suite version 6.6.3 software, Vital Images Inc.). Calculation of tumor volume consisted of semi-automated summing of all voxels with enhancement above background parenchymal enhancement.

Pathology

Following definitive surgery, the excised specimens were cut in multiple serial sections of approximately 5 mm, fixed in 10% formalin, paraffin-embedded as tissue blocks, stained by hematoxylin and eosin, and evaluated by an experienced pathologist to determine the degree of pathological tumor response of the primary breast lesion. Pathological response was scored according to the Miller and Payne criteria(19).

Diffuse optical spectroscopy assessment of neoadjuvant chemotherapy
Tumor regions in each of the four DOS scans were manually annotated. The tumor in the baseline scan was annotated as an ellipsoid with axes of the sizes reported in the first radiological assessment. The annotated region was centered on the maximum scatter amplitude in breast section containing the tumor based on conventional radiology. In DOS scans 2 to 4, an annotated region of the same size and shape as in the first scan was centered at the maximum scatter amplitude in these respective scans. Within each annotated region the mean Hb and HbO$_2$ contents were measured in μM. Hb and HbO$_2$ contents in follow-up scans were normalized by the baseline scan for inter-subject comparison. Subjects where the baseline scan was unreliable were completely excluded. Subjects where a follow-up scan was unreliable were removed from the respective groups. Criteria for unreliable scans were: tumor on the edge of the scan or outside the scan; severe reconstruction artifacts in the breast section containing the tumor. Severe reconstruction artifacts were identified as physically improbable measurements, particularly zero scattering amplitude and negative scatter power.

**Patient and tumor characteristics**

A total of 25 patients were initially included in the study. Two patients were excluded due to a failed baseline DOS scan and one patient due to a failed scan after 1 cycle. Patient and tumor characteristics of the 22 analyzed patients are summarized in Table 1. The median age was 50 years (range, 38 - 66), median tumor size prior to NAC was 30 mm (range, 16 – 81). Of the patients, 6 patients had lobular carcinoma, 16 had ductal carcinoma, 20 had an ER positive tumor and 15 had a PR positive tumor. All patients received a DOS scan before NAC and before the 2nd cycle. In 2 patients the DOS scan
halfway therapy and in 4 patients the DOS scan before surgery was not performed due to patient complications (not-related to Softscan) or logistic reasons.

Data analysis and statistics

The primary goal of this study was to assess feasibility of DOS for assessment of tumor response to NAC based on pathological response before the second NAC cycle. Failure of a missed first or second DOS scan resulted in exclusion from further DOS scans. All subjects were divided in two groups based on the Miller and Payne criteria: non-responders (MP 1; i.e. 0% decrease of tumor cellularity after NAC) and (partial) responders (MP 2-5). For DOS time points, the changes in Hb and HbO\textsubscript{2} with respect to baseline were compared between the two groups and tested for significant differences using the Mann-Whitney U-test. To test the predictive power of the DOS scans for identification of non-responders a linear logistic classifier was trained. For the DOS scans HbO\textsubscript{2} was used as the feature. The classification performance was tested by training on 50% of the data, using the other 50% for testing. The classifier was evaluated by estimating a receiver-operator curve (ROC). Due to the small number of patients, the training and testing was repeated 100 times with different permutations of training and test data sets. The average ROC was computed for final predictive power evaluation.

To compare DOS to DCE-MRI, the sensitivity and specificity of both RECIST and MRIVolume measurements to predict tumor response (pathological) to chemotherapy were assessed. The radiological assessment by RECIST criteria was converted into a numerical ordering as: PD: 1, SD: 2, PR: 3 and CR: 4. Volume measurement after 3 and 6 cycles were normalized to the baseline tumor volume. Subjects were divided in two
groups based on the same Miller and Payne criteria: non-responders (MP 1) and (partial) responders (MP 2-5). The RECIST criteria and normalized volumes after 3 and 6 cycles were compared between the two groups and tested for significant differences using the Man-Whitney U-test. Moreover, the predictive power of MRI was assessed. Both assessment by MRI using the RECIST 1.1 criteria and MRI volume were used to predict tumor response to NAC (MP criteria) by training a logistic classifier as for DOS.

Predictive power is estimated from classification results. The classification result is a trade-off between the desired fraction of true positives (non-responders classified as non-responders) and the accepted fraction of false positives (responders classified as non-responders). The area under the curve (AUC) is a measure for the predictive power and is 1 for a perfect classifier (100% true positives for 0% false negatives), 0.5 for a random classification (similar to a coin-flip) and 0 for a completely wrong classification (0% true positives for 100% false negatives).
Results

MRI and pathologic assessment of tumor response:

A summary of DCE-MRI response (RECIST criteria) and pathological response (Miller and Payne criteria) measurements is given in Figure 2. In 4 patients after 3 cycles and in 2 patients after 6 cycles RECIST criteria could not be applied because of scattered presentation of the contrast-enhanced lesions and as in 1 patient no MRI was obtained. Tumor volume could not be accurately measured in 1 patient after 6 cycles because of too scattered presentation.

MRI response measurements after 3 cycles (halfway treatment) indicated zero patients with progressive disease, 5 patients with stable disease, 9 patients with a partial response, and 4 patients with a complete response.

After 6 cycles and prior to surgery MRI response measurements indicated 0 patients with progressive disease, 5 patients with stable disease, 11 patients with a partial response, 4 patients with a complete response.

The distribution of the pathological response classification, following Miller and Payne, was as follows: grade 1, 4 patients; grade 2, patients 9, grade 3, 3 patients; grade 4, 3 patients; grade 5, 3 patients.

Comparison between responders and non-responders

Diffuse optical spectroscopy

In all 22 patients the tumor could be located on the optical mammography. The mean HbO₂ content (standard deviations between parentheses) for tumors at baseline were 25.9 (7.8) µM for responders and 16.7 (3.8) µM for non-responders. Corresponding Hb content
was 10.5 (3.8) µM and 8.2 (0.8) µM. These differences were non-significant: P = 0.064 (HbO₂), P = 0.335 (Hb). In follow-up scans inter-patient variability remained and Hb and HbO₂ content (µM) was not significantly different between responders and non-responders: P > 0.500 for all follow-up scans.

However, the average Hb and HbO₂ contents relative to baseline in Table 2 show clear significant differences between responders and non-responders that are distributed based on pathological criteria. The relative HbO₂ content (compared to baseline) is significantly lower in all 3 treatment stages: P = 0.023 after 1 cycle, P = 0.010 after 3 cycles and P = 0.009 after therapy completion. Representative examples of DOS in responders (n = 18; decrease of HbO₂ content) and non-responders (n = 4; stable or increasing HbO₂ content) are shown in Figure 3. The average Hb content for responders is lower for all cycles, but this is not statistically significant.

**Dynamic Contrast Enhanced MRI**

The Mann-Whitney U-test shows no significant difference in DCE-MRI assessment using RECIST for pathological responders (MP 2-5, n = 18) and non-responders (MP 1, n = 4) both after 3 cycles (p=0.10) and after 6 cycles (p=0.77). This is further illustrated in Figure 2. After both 3 and 6 cycles a weak trend is visible in which a better response seems to correspond to a higher Miller and Payne ranking. This is however far from statistically significant. Correlation coefficients between Miller and Payne and RECIST assessment were 0.43 after both 3 and 6 cycles of NAC.

MRI volume measurements show statistically significant differences between responders and non-responders after both 3 cycles (P = 0.005) and 6 cycles (P = 0.011)
In both responders and non-responders the tumor has decreased halfway through therapy and decreased even further in the scan before surgery. The decrease in tumor volume is much stronger in the group with responders. Correlations between normalized MRI volumes and normalized Hb/HbO$_2$ content after 3 cycles were 0.46 and 0.69 for Hb and HbO$_2$, respectively, and 0.64 (Hb), 0.70 (HbO$_2$) after 6 cycles.

Predictive power of diffuse optical spectroscopy and MRI

The ROC curves in Figure 4 show the prediction sensitivity and specificity for different trade-offs for DOS, RECIST and DCE-MRI volumes normalized to baseline. For DOS assessment after only 1 cycle, accepting incorrect classification of 5% of the responders as non-responders would correctly identify 75% of the non-responders and allow them to change therapy. Similarly, accepting 10% incorrectly identified responders would correctly identify 87% of the non-responders as responders.

The ROC curves show that DOS and normalized volume measurements have a comparable predictive power, both far better than RECIST. For example, predicting if a patient is a non-responder after 3 cycles with a 20% false positive rate is correct in 86% of the DOS scans and volume measurements, while this is only correct in 58% of the RECIST assessments. Considering the AUC, the predictive power for DOS is similar for all timepoints, with AUC values of 0.92, 0.96 and 0.89 after respectively 1, 3 and 6 cycles. The MRI volume AUC is 0.97 after 3 cycles and 0.71 after 6 cycles. The RECIST AUC is 0.62 after 3 cycles and only 0.47 after 6 cycles. These RECIST figures are much lower than for DOS and MRI volume measurements, especially when taking into account that an AUC of 0.5 corresponds to a random prediction. The MRI volume measurements
at 6 cycles have a decreased predictive power due to tumors that were non-responders based on the MP criteria, but showed no contrast enhancement after 6 cycles. The large standard deviation of 64 in Table 3 is indicative for the wide spread of non-responding tumor volumes after 6 cycles.
Discussion

The present study demonstrates the clinical use of DOS for treatment monitoring of NAC in patients with breast cancer. Treatment monitoring using DOS showed a significant difference in the physiological tumor parameters between responders and non-responders as early as after the first gift of NAC. Moreover, the predictive value of DOS to determine tumor response corresponded to MRI volume measurements after 3 cycles but appeared to outperform DCE-MRI evaluation based on RECIST.

DOS showed a decrease in Hb and HbO$_2$ content in the patients with a response of the tumor to NAC. We found this decrease to be only statistically significant for HbO$_2$, but not for Hb. Similar results were obtained in previous studies (9-13, 20). In comparative studies between Hb and HbO$_2$ levels in tumor tissue and healthy tissue, tumor tissue shows a nearly a two-fold increased level of Hb and HbO$_2$ as a result of increased vascular supply (17). The decrease of Hb and HbO$_2$ levels observed in the study suggest a decrease of tumor tissue and an increase of non-tumorous tissue in the region of interest where the tumor was located. The reason we did not find a statistically significant decrease of Hb can be partly attributed to the small number of non-responders (N = 4), compared to the large number of responders. Under these circumstances the Mann-Whitney U-test has a strongly decreased sensitivity and only large group differences as in the relative HbO$_2$ changes were tested as statistically significantly different.

The absolute quantities of Hb and HbO$_2$ at baseline were varying greatly between tumors and did not show significant differences between potential responders and non-responders. This large inter-patient variability was also present in the follow-up scans and responders and non-responders could not be separated based on absolute Hb and HbO$_2$
content (µM). Normalization with respect to the baseline scan is thus essential. Apart from Hb and HbO₂, the two most important absorbers in NIR are water and lipids. The low absorption coefficients of the latter two, compared to Hb and HbO₂, prevented reliable estimates, with frequent erroneous estimates (0% or 100% water/lipids content).

Correlating the normalized DOS parameters Hb, HbO₂ with normalized MRI volume measurements showed a strong positive relationship between changes in MRI volume and changes in (de)oxyhemoglobin content. Although it is likely that tumor volume and oxygenation have a positive relationship, a confounder may be in the hemoglobin measurements where a constant volume is used to measure these parameters, while the tumor volume has decreased and additional normal tissue can be in the measurement volume. One should therefore be careful with interpreting the absolute hemoglobin measurements in relation to tumor viability.

In the current study, a homogenous HER2-negative group of patients with locally advanced breast cancer was used receiving the same NAC regime. It is important to validate DOS in a homogenous patient group as tumor variables such as HER2-status and tumor size have a significant effect on the optical properties of tumors. Positive HER2 tumors have a significant higher Hb level by DOS assessment (21). This is most likely related to angiogenesis as HER2 overexpression is associated with increased angiogenesis. As the difference between Hb levels between HER2 positive tumors and healthy tissue is larger compared to HER2-negative tumors it can be expected that DOS assessment of NAC in HER2 positive tumors will result in even a more distinct difference between responders and non-responders.

Moreover, in addition to NAC, neoadjuvant hormonal therapy is also increasing
rapidly and has shown similar patient outcomes compared to NAC(22). Many different anti-cancer agents are available (chemotherapy, hormonal therapy, monoclonal agents), all have different anti-tumor and anti-angiogenic effects. Therefore, when assessing early treatment response it is crucial to use a homogenous treatment regime. As the therapeutic effect of hormonal therapy acts on a different mechanism compared to chemotherapy, validation of using DOS for treatment monitoring in neoadjuvant hormonal therapy is essential to provide wide clinical use of DOS in the treatment monitoring of patients with breast cancer(23).

With the increasing interest in neoadjuvant treatment, improved imaging modalities that can provide early prediction of tumor response will be required to select patient who may benefit from a different treatment. In case of locally advanced breast cancer, early detection of non-responders could prevent unnecessary toxic NAC treatment and allows to select patient who would benefit from a different neoadjuvant treatment regime or early surgery. In the current study, after 1 cycle of NAC DOS would correctly identify most non-responders, allowing them to change treatment strategy early. Prediction accuracies were evaluated as AUCs of 0.92, 0.96 and 0.87 after 1, 3 and 6 cycles, respectively. The lower AUC after 6 cycles is due to a smaller number of available scans for classifier training. Previous studies have shown similar results showing specificity of 80 – 83%(9,11). These data suggests that DOS is able to identify a large set of patients early during treatment that would benefit from a different treatment regime. Though, it should be emphasized that prospective studies are necessary to validate these results.
In the current study the predictive value of DOS to determine tumor response corresponded to MRI volume measurements after 3 cycles but appeared to outperform DCE-MRI evaluation based on RECIST. To date, DCE-MRI is the most accurate response assessment (24). However, this modality is not in all breast tumors equally reliable. Several breast tumor subtypes, such as HER2-negative and ER-positive breast tumors are associated with reduced accuracy (25). This might explain the poor adequacy of MRI in our study, as our study population consisted almost completely of HER2-negative and ER-positive patients. The biological explanation for this may be that HER2-negative breast cancer is associated with decreased angiogenesis, resulting in impaired tumor tissue perfusion of MRI contrast (26). Also, hormone receptor-positive tumors have a different growth pattern than hormone receptor-negative tumors, with less often (unifocal) mass-like lesions, making it more difficult to accurately determine the residual tumor diameter (8, 27).

Limitation of the used DOS-device in our study is that determination of the correct region of interest for the DOS was difficult because DOS provided limited anatomical context. Therefore, the region of interest at baseline was partly based upon data of conventional mammography and MRI acquired before therapy. Localization of the region of interest was not trivial during data analysis and incorrect region of interest placement can lead to an underestimation of tissue changes and consequently decrease the sensitivity. A 5 mm displacement of the ROI introduces variations in Hb/HbO₂ estimates of about 2% for tumors of about 30 cm³, while for smaller tumors of approximately 5 cm³, estimates could differ by up to 8%. The possibility of merging MRI
and DOS could therefore improve DOS assessment and provide more functional parameters to the MRI and further increases sensitivity.

DOS is a relatively novel imaging modality in the field of breast cancer and is rapidly evolving by increasing spatial resolution and by increasing analytic techniques to provide more accurate assessment of functional parameters (28, 29). A recent study by Roblyer et al. indicated that DOS as early as the first day after NAC may possibly discriminate non-responding from responding patients (30). Remarkably, this study found an increase in HbO$_2$ for responders, compared to non-responders, while monitoring in the first week. Roblyer, et al. hypothesized that this increase can be attributed to an acute inflammatory reaction in the responding tumors. Measurements with the same device as Roblyer, et al. at mid-therapy and before surgery showed lower HbO$_2$ values for responders, comparable with our findings (30). We therefore hypothesize that after the acute inflammatory reaction stops, the responding tumors have a lower metabolism and that our measurement after three weeks (1 cycle) is measuring the same decrease in metabolism in the tumor as response to NAC as the measurements after 3 and 6 cycles. A future study with frequent measurements during the first three weeks after NAC therapy starts could provide further insight.

Moreover, several optical contrast agents are available, which may improve contrast and sensitivity (31, 32). Furthermore, DOS can be combined with other imaging modalities, such as ultrasound, for improved tumor localization accuracy (11). These developments will allow further improvement of DOS sensitivity and accuracy.

In conclusion, DOS allows early response monitoring of tumor tissue to chemotherapy and is able to differentiate between responders and non-responders in early
stages of therapy. Therefore, DOS could be used as a novel imaging modality for
treatment monitoring of NAC to assist patient tailored medicine.
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# TABLES

## Table 1 - Patient and Tumor Characteristics

<table>
<thead>
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<th>Characteristic</th>
<th>All patients (N=22)</th>
<th>Responders (N=18)</th>
<th>Non-responders (N=4)</th>
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* staging according to AJCC guidelines
Table 2– Differentiation between responders and non-responders using DOS and MRI volumes

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<th>Diffuse optical spectroscopy measurements</th>
<th>MRI volume measurements</th>
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<td>Responder Hb (%)</td>
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<td>Non-responder Hb (%)</td>
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<td>U-test p-value</td>
<td>1</td>
<td><strong>0.023</strong></td>
</tr>
</tbody>
</table>

Average Hb and HbO₂ content measured by diffuse optical spectroscopy and tumor volumes measured by MRI relative to baseline for responders and non-responders selected based on pathology criteria. Standard deviations are between parentheses. The Mann-Whitney U-test p-values estimate significance of the differences between the two groups. Bold text highlights p-values indicating statistically significant differences (P<0.05).
FIGURE LEGENDS

Figure 1
Acquired DOS data of HbO$_2$(µM) was reconstructed to allow 3D analysis (BreastViewer 3.1).

Figure 2
Agreement between Miller and Payne (MP) criteria and radiology assessment by DCE-MRI using RECIST criteria after 3 cycles (A) and after 6 cycles (B) of neoadjuvant chemotherapy (NAC). The values indicate the patient count. The blue arrow denotes the expected relation, while the red arrow shows the linear regression between MP and DCE-MRI. MRI was assessed according to the RESIST criteria. NE not evaluated, CR complete response, PR partial response, SD stable disease, PD progressive disease.

Figure 3
Transverse DOS images (after interpolation) before and after NAC of a typical responder, which shows a significant decrease of HbO$_2$(µM) in the area of the tumor after NAC (upper row), and non-responder, which shows increase of HbO$_2$ in the area of the tumor after NAC (lower row). The circle indicates where the tumor is located.

Figure 4
Predictive value of DOS and MRI - receiver-operator curve curves for DOS and conventional radiology by MRI using RECIST (REC) and volume measurements (VOL) after 1, 3 and 6 cycles of NAC. AUC denotes the area under the curve. The dashed diagonal shows a receiver-operator curve for a completely random classification result with an AUC of 0.5.
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A

B

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Schaafsma and van de Giessen et al. Fig 4

1 cycle

3 cycles

6 cycles

DOS: AUC=0.92
REC: AUC=0.82
VOL: AUC=0.97

DOS: AUC=0.89
REC: AUC=0.47
VOL: AUC=0.71
Optical mammography using diffuse optical spectroscopy for monitoring tumor response to neoadjuvant chemotherapy in women with locally advanced breast cancer

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