Using DOSI to predict response to Neoadjuvant chemotherapy in patients with locally advanced Breast Cancer

Diffuse Optical Spectroscopic Imaging, or DOSI, is a hand-held laser breast scanner invented by scientists at University of California Irvine’s Beckman Laser Institute and Medical Clinic which could become an integral part of treating locally advanced breast cancer. i

Locally advanced breast cancer does not have one definition. Usually this means that a particular breast cancer tumor has a combination of some or all of the following features:

- tumor may be larger than five centimetres and can often be too big to remove at time of diagnosis,
- cancer may have spread to other tissues around the breast, such as the skin, muscle or ribs,
- cancer may have spread extensively to the lymph nodes.

Pre-surgical or neoadjuvant chemotherapy is an option in patients with locally advanced breast cancer and has become a standard treatmentii. The neoadjuvant chemotherapy treatment has two benefits. Firstly, neoadjuvant chemotherapy may shrink the tumor so that it can be removed with less extensive surgery. Secondly neoadjuvant chemotherapy given before the tumor is removed, allows doctors to see how the cancer responds to the treatment. In theory, the event of a poor response could lead to modifications of the treatment plan. If the first set of drugs does not shrink the tumor, other drugs may be needed to achieve that goal.iii

Standard clinical and radiographic monitoring during neo adjuvant chemotherapy to predict pathological complete response (pCR) is notoriously inaccurate. iv

Pathological complete response is a way of measuring and assessing response to neoadjuvant chemotherapy given to patients before surgery to shrink the particular tumor in the breast and in any involved lymph nodes. A pCR is defined as the absence of residual invasive disease in the breast and in the axillary lymph nodes at the completion of the neoadjuvant chemotherapy treatment. Patients who achieve a pCR with neoadjuvant chemotherapy treatment tend to have a very good prognosis. Elimination of the visible disease in the breast and lymph nodes correlates with eradication of micrometastatic disease. Therefore patients who achieve a pCR are at much lower risk for subsequent distant disease recurrence. v

Conventional therapeutic endpoints for cancer treatments are 5–10 year overall survival and disease-free survival. This means a long wait to see response to treatment. Surrogate endpoints obtained prior to and during treatment are desirable to facilitate more rapid assessment of therapeutic strategies. Complete pathological response (pCR) is an important endpoint that correlates with survival in patients receiving neoadjuvant chemotherapy. A major advantage of pCR is that assessment is performed at the completion of neoadjuvant
chemotherapy (i.e. within a few months of diagnosis) and it provides a good projection for 5 year survival/disease-free survival. vi

Although pCR is obtained relatively quickly (compared with 5 year survival), there is a significant interest in developing molecular and imaging-based biomarkers to enhance or replace pCR. Imaging biomarkers could provide dynamic feedback during therapy, giving oncologists new methods for clinical decision-making that optimize therapeutic outcomes and minimize collateral tissue damage. Research continues in this area.

Standard clinical assessments (e.g. physical examination, ultrasound and mammography) have been shown to be inadequate for predicting neoadjuvant chemotherapy pCR. Moreover it is thought unlikely that early changes in tumor size alone are predictive of final pathological response. Functional imaging with advanced techniques such as MRI, magnetic resonance spectroscopy (MRS) and positron emission tomography (PET) has shown improved response assessment capabilities over conventional anatomic imaging. However, these functional methods can be difficult to perform in advanced stage cancer patients for reasons of lengthy scan times, exogenous contrast, and high cost. This is particularly so when frequent measurements are desired. In addition, there is currently no consensus on optimal time-points and quantitative response measures. vii These advanced imaging techniques are large, expensive, confined to a hospital building space and the patient must come, or be brought to the site of the equipment.

This is where Diffuse Optical Spectroscopic Imaging (DOSI) comes in. DOSI is a portable scanner that detects breast cancer and produces images based on the composition of the tumor, including water, fat and blood content. Oncologists can compare the images of the tumor, before neoadjuvant chemotherapy treatment and after, to determine if the cancer is shrinking. viii

**How DOSI works**

DOSI is a non-invasive scanning tool. Using a hand-held laser probe, broadband near-infrared light goes deep inside the tissue and interacts with the tumor. Some of this light emerges from the tissue, bearing detailed information about the composition of the tumor and surrounding tissue. This light signal is detected by sensors and rendered in an image that tells researchers about the metabolism and composition of the tumor and surrounding tissue. It measures the amount of water, lipid and haemoglobin in the breast tissue. The pictures taken with these measurements clarify how the breast tissue uses blood and oxygen. Because this information helps doctors to tell the difference between what is a tumor and what is normal tissue, it helps them to see how tumors respond to chemotherapy. Malignant tumors have more water and blood vessels, less fat and low oxygen levels. Cancerous tumors have a higher density of cells which are made up of mostly water. ix
Oncologists/physicians can compare DOSI images of the tumor obtained prior to neoadjuvant chemotherapy to images obtained throughout the course of a six-month neoadjuvant chemotherapy treatment to determine early if the treatment is likely to be successful. Doctors can use DOSI scans to alter the course of treatment and improve the patient’s outcome.

ACRIN 6691 study results

One study leading to this goal of improving patient treatment is the ACRIN 6691 clinical trial which determined whether the baseline to mid-therapy changes in the DOSI measurement of the quantitative tumor tissue optical index (TOI) could predict final complete pathologic response (pCR) in breast cancer patients undergoing pre-surgical neoadjuvant chemotherapy treatment. Results from the multi-center ACRIN 6691 study reported by Bruce J Tromberg PhD at the San Antonio Breast Cancer Symposium 2014 evaluated the performance of a bedside DOSI platform in 34 breast cancer patients followed for several months. Baseline to mid-therapy changes in the tumor to normal (T/N) Tissue Optical Index (TOI) ratio were evaluated from DOSI images as the primary imaging endpoint for predicting clinical outcome (pCR). 60 female breast cancer patients (ages 28-69 years), with locally advanced disease (tumors >2cm) were enrolled across the 6 participating institutions in the USA. DOSI measurements were performed at baseline, during the first week of therapy, at midpoint, and at the completion of neoadjuvant chemotherapy. Of the 34 participants with complete and evaluable data, 10 (29%) achieved pCR as determined by central pathology review.

The results of the ACRIN 6691 presented in San Antonio were inconclusive. They presented the results of 34 participants. They used the criteria of a change TOI of \( \leq \) or \( > 40\% \). For the patients with the criteria of a TOI of \( > 40\% \) (who were predicted not to attain a pCR) 16 of 19 did not attain a pCR. For the patients with the criteria of a change in TOI of \( < 40\% \) predicted attain a pCR 7 of 15 did. The predictive accuracy was therefore \((16 + 7)\) of \((19 + 15)\) which is 68\% which is not particularly impressive and did not attain statistical significance. The authors of this study concluded that additional studies would need to be done. As an outsider looking at the results this is a conceptually interesting result but only a bigger study with perhaps other criteria for prediction of pCR is needed.

Conclusions: DOSI has been successfully implemented in a multi-center setting and changes in T/N TOI are a promising predictor of neoadjuvant chemotherapy clinical outcome (pCR).

Potential benefits of DOSI

This approach is well suited to monitoring breast tumor response and may provide feedback for optimizing therapeutic outcomes and minimizing side-effects. Therapeutic drug monitoring in the neoadjuvant setting is an ideally suited application for diffuse optical methods like DOSI because it accentuates the strengths (functional, portable) and offsets the
limitations (low spatial resolution) of the technique. DOSI resolution limits are a consequence of multiple-light scattering in a relatively large sample volume, providing macroscopically averaged tissue absorption and scattering properties at depths up to several centimetres. Consequently, the resolution of DOSI methods is of an order, which is similar to PET.  

Because of its portability and low cost, the bedside DOSI platform as used in the ACRIN 6691 study is shown to be effective as well as a low barrier-to-access technology for patients. As such, it potentially creates new opportunities for patients to receive personalized treatment and for oncologists/physicians to gain insights into mechanisms of cancer appearance and response to therapy. An important practical advantage of the DOSI approach is that it can be used frequently in unconventional settings such as a doctor's surgery or clinic. Portable optical imaging platforms can easily supplement existing radiological methods either as standalone devices or as units integrated into established technologies such as ultrasound, mammography or MRI.

Unlike MRI and PET scanning machines, DOSI is mobile and non-invasive, safe and easy to perform. There are no known side effects with DOSI. There isn’t any radiation or pain or the uncomfortable compression that accompanies a mammography. During a breast DOSI scan, the patient lies in a comfortable chair while a hand held scanner is moved in a specific pattern over the area, without pressure to the breast. A typical DOSI scan takes from 20 to 40 minutes to complete.

Because of its easy portability, physicians can take it to a rural area or a patient’s bedside, DOSI’s other primary advantage is its cost. A typical clinical MRI machine costs about US$1 million and has substantial recurring maintenance costs. An individually built DOSI scanner costs about US$35,000.

DOSI has components that are similar to a smartphone. The laser breast scanner has evolved from a “benchtop” technology requiring large lasers and electronics in a big laboratory space to firstly, a refrigerator-sized device, and now the latest version that is a compact unit about the size of two stacked laptops. Researchers hope to make the final version of DOSI even smaller.

In summary the DOSI technology may possibly have the potential to be used in a clinic setting and offers the potential for rapid feedback to the physician that shows functional tumor response (how well neoadjuvant chemotherapy is working in an individual breast cancer patient) so that better treatment decisions can be made more quickly. One hopes that it will be confirmed to have a broad and universal use because of its portability and ready access for patients.

A larger study population is needed to fully assess the utility of TOI and other DOSI imaging endpoints for guiding therapies and predicting neoadjuvant chemotherapy response in individual subjects, and then to combine DOSI with biomarkers to give a more complete picture for each patient.
References


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