



Correction by the skin-to-chest wall distance in near-infrared spectroscopy and assessment of breast cancer responses to neoadjuvant chemotherapy

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Abstract

Background The measurement of hemoglobin (Hb) concentrations in breast cancer by near-infrared spectroscopy is useful for the assessment of responses to neoadjuvant chemotherapy (NAC). However, the chest wall muscles may affect this measurement. We corrected Hb concentrations based on the skin-to-chest wall distance. Corrected Hb was compared with uncorrected Hb as a marker of treatment responses in breast cancer patients.

Methods We measured total Hb (tHb) in breast cancer using a near-infrared time-resolved spectroscopy system in 10 patients before chemotherapy and after the first and second courses of NAC. To assess the skin-to-chest wall distance and thickness of tumors, ultrasound images were obtained using an ultrasonography probe with the spectroscopic probe. Net tHb (tHb_{net}) was calculated by subtracting tHb in normal breast tissue from cancer tHb. Patients underwent positron emission tomography with [¹⁸F] fluorodeoxyglucose (FDG) before chemotherapy and after the second course of NAC. FDG uptake was evaluated using the maximum standardized uptake value (SUV_{max}).

Results tHb, tHb_{net}, and SUV_{max} in cancer significantly decreased in the course of chemotherapy. The change in tHb_{net} was larger than that in tHb. Although a correlation was not observed between the change in tHb and that in SUV_{max}, a positive correlation was noted between the change in tHb_{net} and that in SUV_{max}.

Conclusions Corrections by the skin-to-chest wall distance in spectroscopy led to the change in Hb concentrations being more similar to that in FDG uptake after NAC in breast cancer. tHb_{net} has potential as a reliable biomarker of breast cancer.

Keywords Breast cancer · Near-infrared time-resolved spectroscopy · Hemoglobin · Neoadjuvant chemotherapy

1 Introduction

Neoadjuvant chemotherapy (NAC) is the standard treatment for locally advanced breast cancer and a standard option for early breast cancer depending on the histological subtype [1]. Disease-free survival and overall survival are equivalent in patients treated with the same adjuvant or neoadjuvant regimen [1]. However, NAC is a useful treatment for downsizing tumors and increasing breast conservation rates [1, 2]. Previous studies demonstrated that the response to NAC is a predictor of long-term outcomes, and a pathological complete response is associated with improved disease-free survival and overall survival [1, 3].

The accurate assessment of the effects of NAC leads to an appropriate treatment strategy for breast cancer. Ultrasonography and MRI have been used to monitor treatment responses. Ultrasonography is an easy and non-invasive

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modality; however, fibrotic changes after chemotherapy are difficult to differentiate from residual tumors. The diagnostic accuracy of contrast-enhanced MRI is high. However, the use of contrast media and associated costs make MRI difficult to repeat.

Positron emission tomography (PET) using [^{18}F] fluorodeoxyglucose (FDG) is used for staging, evaluating responses to treatments, and predicting the prognosis of various cancers [4–7]. FDG-PET is also useful for monitoring treatment responses in breast cancer [8–11]. The accumulation of FDG depends on the metabolic activity of the lesion and may be a more suitable indicator of therapeutic responses than morphological changes [12–14]. FDG uptake has been reported to predict pathological responses [15, 16]. However, FDG-PET is also difficult to repeat because of the high associated costs and radiation exposure.

Near-infrared diffuse optical spectroscopy and diffuse optical tomography have been developed for the detection of primary cancer [17–20] and monitoring of responses after neoadjuvant chemotherapy in breast cancer [21–24]. Since these are not expensive procedures and do not expose patients to radiation, frequent measurements are possible.

We measured the optical properties of breast cancer using a near-infrared time-resolved spectroscopy system. We demonstrated that measurements were influenced by the chest wall muscles in a manner that depended on the skin-to-chest wall distance, and to reduce the effects of the chest wall, we proposed a subtraction method [25]. The net hemoglobin (Hb) concentration in cancer was calculated by subtracting Hb in normal breast tissue.

In the present study, Hb in breast cancer was measured in the course of NAC and corrected Hb was compared with uncorrected Hb as a marker of treatment responses. TRS was compared with FDG-PET in monitoring the response of breast cancer to NAC.

2 Patients and methods

2.1 Patient characteristics

We measured optical properties and FDG uptake in 11 patients with breast cancer before and after NAC between April 2014 and October 2016. We excluded one patient whose ultrasonography data were not recorded. We enrolled 10 patients. The mean age of the patients was 50.5 years with a range between 39 and 67 years. Five patients were premenopausal and five were post-menopausal. Three patients had more than one tumor. One tumor was excluded because it was mostly occupied by a cystic component. Therefore, we analyzed 10 patients and 14 tumors. The median thickness of tumors was 13.5 mm with a range between 6 and 23 mm. All tumors were invasive ductal carcinoma.

The study protocol was approved by the Ethical Review Committee of Hamamatsu University School of Medicine. All patients provided written informed consent.

2.2 Chemotherapy

Patients received four courses of FEC (fluorouracil 500 mg/m², epirubicin 100 mg/m², cyclophosphamide 500 mg/m², every 3 weeks) followed by four courses of docetaxel or a combination of docetaxel and trastuzumab. One patient received two courses of docetaxel and two courses of FEC instead of docetaxel after four courses of FEC.

The optical properties of cancer were measured before chemotherapy, after the first course, and after the second course of FEC. Patients underwent FDG-PET before chemotherapy and after the second course of FEC. Blood samples were obtained before every course of chemotherapy.

2.3 Near-infrared time-resolved spectroscopy

We used a single-channel time-resolved spectroscopy system with near-infrared light of three wavelengths: 758 nm, 795 nm, and 833 nm (TRS-20SH, Hamamatsu Photonics KK, Hamamatsu, Japan). The principle of the measurements was described in detail previously [25]. The distance between the light source and detector was 3 cm. The absorption coefficient and reduced scattering coefficient were obtained at each wavelength. The concentrations of oxygenated and deoxygenated Hb were calculated from the absorption coefficient at each wavelength after subtracting water and lipid absorption in breast tissue. Because we could not measure the amounts of water and lipid only using three wavelengths, we used the mean values of water and lipid for normal breast tissue, which were 18.7% and 66.1%, respectively [26]. In our prior study, there was no significant difference between the result tHb obtained using the mean values of water and lipid for normal breast tissue and for breast cancer (about 1.6% on average). Based on the result, we calculated tHb concentration in breast cancer using the value for normal breast tissue to simplify the analysis. The concentration of total Hb (tHb) was the sum of the concentrations of oxygenated and deoxygenated Hb.

To assess the skin-to-chest wall distance and thickness of tumors, ultrasound images were obtained using an ultrasonography system (EUB-7500, Hitachi Medical Corporation, Tokyo, Japan) with a linear probe (EUP-L65, Hitachi Medical Corporation). The spectroscopic probe was attached to the ultrasound probe in a rectangular direction. A skin-to-chest wall distance of more than 36 mm was assumed to be 37 mm in one patient because the maximal depth was initially set at 36 mm. A previous study revealed that when the skin-to-chest wall distance was 20 mm or more, the

influence of the chest wall was negligible and the tHb concentration was constant.

We measured tHb prior to the treatment, 3 weeks after the first infusion of FEC, and 3 weeks after the second infusion of FEC. The spectroscopic probe attached to the ultrasound probe was lightly placed above the tumor, and optical parameters and ultrasound images were obtained. The optical parameters of normal breast tissue were measured in the contralateral breast.

We defined net tHb (tHb_{net}) by subtracting tHb in normal breast tissue at the same skin-to-chest wall distance as cancer from tHb in cancer. tHb in normal breast tissue was obtained from fitting curves of tHb concentrations as a function of the skin-to-chest wall distance. Curves were generated in our previous study [25].

Changes in tHb and tHb_{net} were shown by the percentage of the change between the baseline and post-chemotherapy.

$$\Delta tHb = \frac{\text{post-therapy tHb} - \text{baseline tHb}}{\text{baseline tHb}} \times 100 (\%)$$

$$\Delta tHb_{net} = \frac{\text{post-therapy } tHb_{net} - \text{baseline } tHb_{net}}{\text{baseline } tHb_{net}} \times 100 (\%)$$

2.4 FDG-PET

After fasting for at least 6 h, patients received an intravenous injection of FDG (4.0 MBq/kg). None of the patients had blood glucose levels that exceeded 200 mg/dl. After a 60-min uptake period, image acquisition was performed using a PET system combined with a 16-slice CT scanner (TruePoint Biograph16, Siemens Healthineers, Erlangen, Germany). Tumor FDG uptake was quantified by the maximum standardized uptake value (SUV_{max}). FDG-PET was evaluated prior to the treatment and 3 weeks after the second infusion of FEC. The change in SUV_{max} was shown by the percentage of the change between the baseline and post-therapy.

$$\Delta SUV_{max} = \frac{\text{post-therapy } SUV_{max} - \text{baseline } SUV_{max}}{\text{baseline } SUV_{max}} \times 100 (\%)$$

2.5 Statistical analysis

Statistical analyses were performed using Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) and StatFlex version 6.0 (Artech Co., Ltd., Osaka, Japan). Differences in blood Hb and SUV_{max} in cancer before and after two courses of chemotherapy were assessed using the Wilcoxon signed-rank test. Differences between tHb and tHb_{net} before chemotherapy, after one course, and after two courses of chemotherapy in cancer were evaluated using Dunn's test. Pearson's correlation coefficient analysis and simple regres-

sion were used to assess the relationship between ΔtHb and ΔSUV_{max} and between ΔtHb_{net} and ΔSUV_{max} . Differences in the correlation coefficients of the regression lines obtained from ΔtHb and ΔtHb_{net} were assessed by testing the t value. $P < 0.05$ was considered to be significant.

3 Results

tHb in normal breast tissue plotted on the reference curve obtained from our previous study (Fig. 1). Baseline blood Hb was 13.1 g/dl (median) and decreased to 11.5 g/dl (median) after two courses of FEC ($P < 0.01$). However, breast tHb did not significantly decrease after two courses of FEC. Cancer tHb plotted above the curve, even after two courses of FEC (Fig. 2).

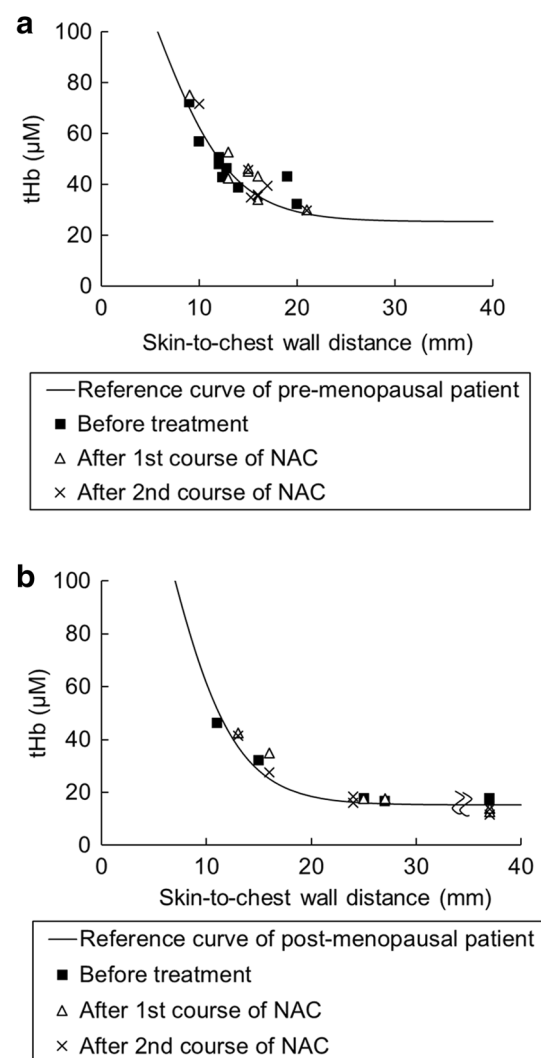


Fig. 1 tHb of normal breast tissue in pre-menopausal patients (a) and post-menopausal patients (b). The reference curve was obtained from our previous study [25]. tHb at the baseline and after one and two courses of chemotherapy plotted on the curve

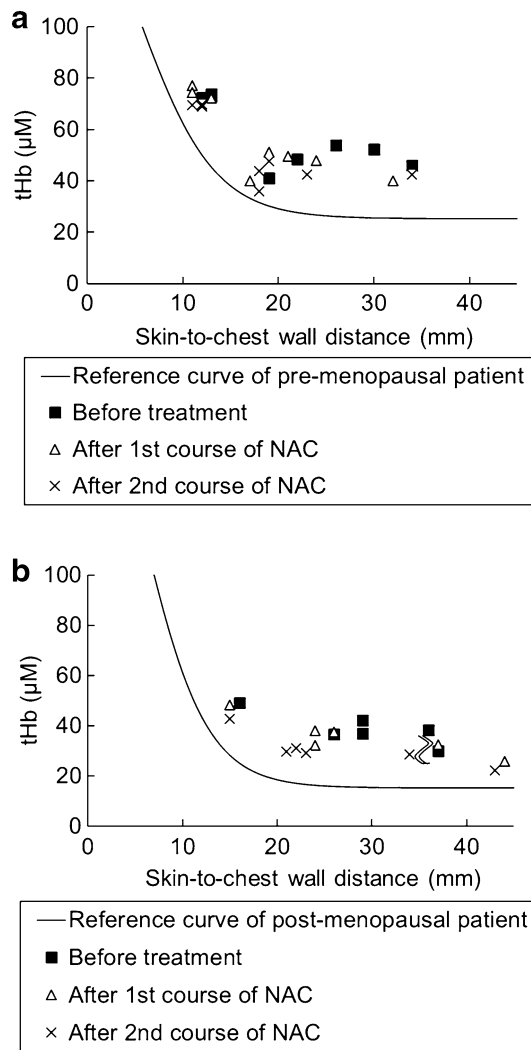


Fig. 2 tHb of breast cancer in pre-menopausal patients (a) and in post-menopausal patients (b). The reference curve represents the tHb of normal breast tissue obtained in our previous study [25]. The tHb of all cancers plotted above the curve

Although the decrease in tHb in cancer was small after one course of chemotherapy, tHb_{net} in cancer significantly decreased ($P < 0.05$) (Fig. 3). tHb and tHb_{net} in cancer both decreased after two courses ($P < 0.01$). Δ tHb between the baseline and after two courses of chemotherapy was $-14.7 \pm 8.2\%$ (mean \pm SD) and Δ tHb_{net} was $-40.0 \pm 13.1\%$ (mean \pm SD). The change in tHb_{net} was significantly larger than that in tHb ($P < 0.001$). SUV_{max} in cancer decreased after two courses of chemotherapy ($P < 0.001$) (Fig. 4). The thickness of the tumor also decreased after two courses of chemotherapy ($P < 0.01$) (Fig. 5).

A correlation was not observed between Δ tHb and Δ SUV_{max}. On the other hand, a positive correlation was noted between Δ tHb_{net} and Δ SUV_{max} ($P < 0.05$) (Fig. 6).

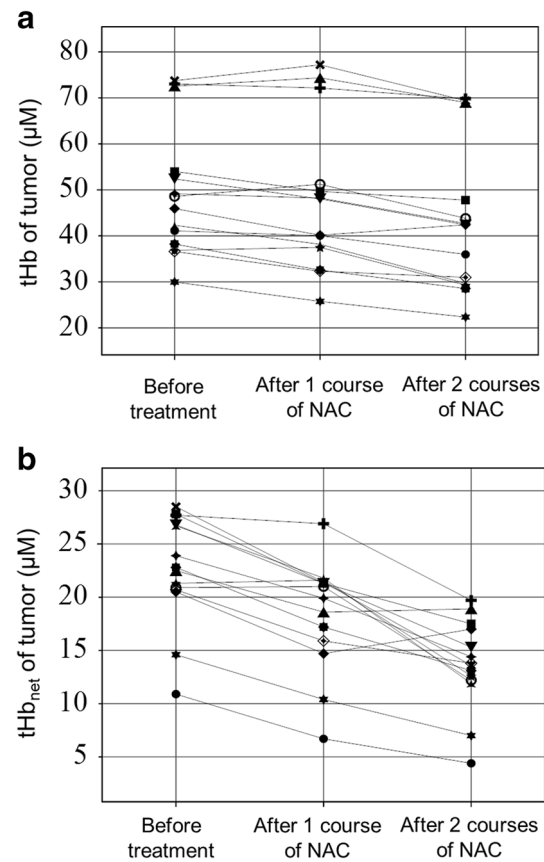


Fig. 3 tHb of cancer (a) and tHb_{net} of cancer (b) before chemotherapy, after one course, and after two courses of chemotherapy. tHb and tHb_{net} both decreased after chemotherapy

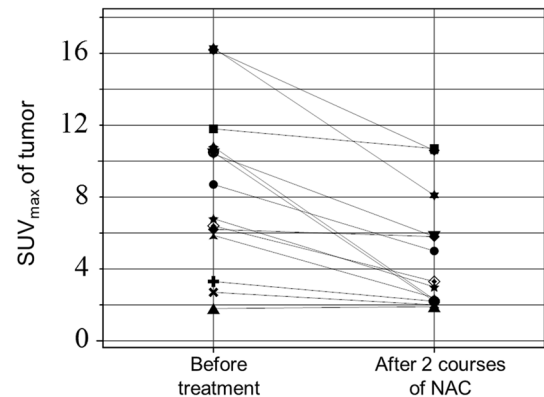


Fig. 4 The SUV_{max} in cancer before chemotherapy and after two courses of chemotherapy. The SUV_{max} significantly decreased after chemotherapy

The regression coefficient of the Δ tHb_{net} regression was slightly larger than that of Δ tHb.

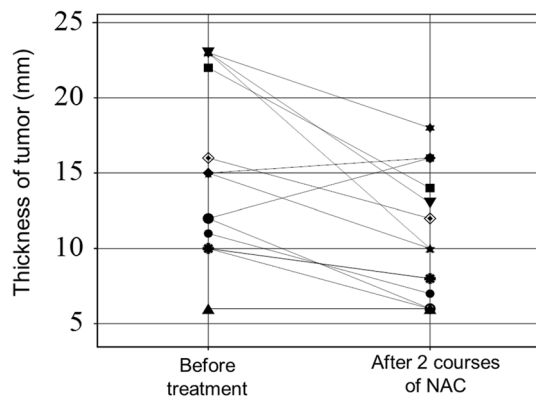


Fig. 5 The thickness of cancer before chemotherapy and after two courses of chemotherapy. Tumors reduced in size after chemotherapy

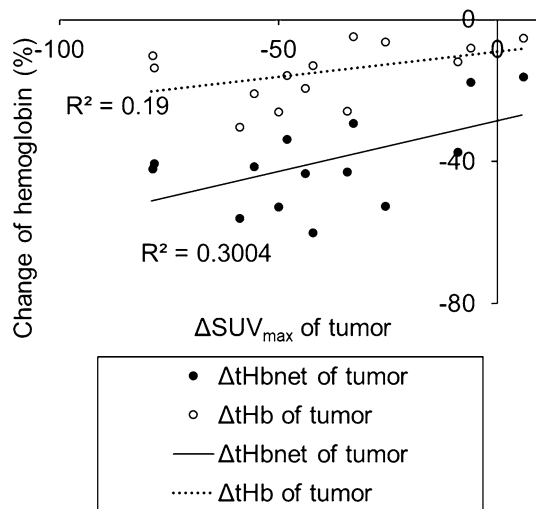


Fig. 6 Relation between ΔtHb (white circle) and ΔSUV_{max} and between ΔtHb_{net} (black circle) and ΔSUV_{max} . Although there was no significant correlation between ΔtHb and ΔSUV_{max} (dotted line, $R^2=0.19$), a positive correlation was found between ΔtHb_{net} and ΔSUV_{max} (solid line, $R^2=0.3004$, $P<0.05$)

4 Discussion

We herein proposed tHb_{net} , which reflects the skin-to-chest wall distance. Since tHb_{net} is calculated by subtracting tHb in normal breast tissue from cancer tHb , tHb in normal breast tissue is essential. tHb was lower in post-menopausal patients than in pre-menopausal patients; therefore, we used reference curves for pre- and post-menopausal patients individually [25]. tHb in normal breast tissue in the present study plotted on the lines that were generated in our previous study, showing the reliability of the curves. Although blood Hb decreased after chemotherapy, tHb in normal breast tissue did not change after two courses of chemotherapy.

Spectroscopy may not be sensitive for small changes in blood Hb. No significant differences between pre- and post-chemotherapy, suggesting that it is justifiable to apply the same curves before and after two courses of chemotherapy. However, tHb in normal breast tissue may decrease after several courses of NAC. Therefore, we need to carefully observe tHb in normal breast tissue when we apply this subtraction method to that situation.

All cancer cases had tHb above the reference curves, which coincided with the previous study. In the course of chemotherapy tHb_{net} showed a stronger correlation with FDG uptake than uncorrected tHb . The decrease observed in tHb_{net} , even after the first course of NAC, and the positive correlation between the change in tHb_{net} and that in FDG uptake indicate that tHb_{net} is a good marker of treatment responses. FDG-PET shows glycolytic activity in cancer, while Hb concentrations reflect blood volumes. Spectroscopy is more easily performed than FDG-PET and may provide a different aspect of proliferation other than glycolytic activity.

There were some limitations in the present study. The number of patients was small. Furthermore, we did not compare changes in tHb or tHb_{net} with pathological changes. Difficulties are associated with performing an interim pathological examination. FDG-PET was instead used as the comparison.

Previous studies showed that FDG-PET predicts responses to neoadjuvant chemotherapy in breast cancer [8–11]. Another limitation is that we assumed that the water and lipid contents of cancer were constant. To calculate Hb accurately, we need to assess the water and lipid contents of cancer patients individually. We have recently developed a spectroscopic device that used six wavelengths (762 nm, 802 nm, 838 nm, 908 nm, 936 nm and 976 nm) to measure water and lipid contents in addition to tHb concentration [27]. We are planning to conduct measurement with this system.

In conclusion, corrections by the skin-to-chest wall distance in spectroscopy resulted in the change in Hb concentrations being more similar to that in FDG uptake after NAC in breast cancer. tHb_{net} has potential as a reliable biomarker of breast cancer.

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Compliance with ethical standards

Conflict of interest S. Ueda has research funding from Hamamatsu Photonics K.K. T. Saeki received honoraria for a speech from Ono Pharmaceutical Co., Ltd., Kyowa Hakko Kirin Co., Ltd., Taiho Pharmaceutical Co., Ltd., and Novartis Pharma K.K., T. Saeki has research funding from Ono Pharmaceutical Co., Ltd., Kyowa Hakko Kirin Co., Ltd., Taiho Pharmaceutical Co., Ltd., and Chugai Pharmaceutical Co.,

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References

- Kaufmann, M., Hortobagyi, G.N., Goldhirsch, A., Scholl, S., Makris, A., Valagussa, P., Blohmer, J.U., Eiermann, W., Jackesz, R., Jonat, W., Lebeau, A., Loibl, S., Miller, W., Seeber, S., Semiglazov, V., Smith, R., Souchon, R., Stearns, V., Untch, M., von Minckwitz, G.: Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: an update. *J. Clin. Oncol.* **24**(12), 1940–1949 (2006). <https://doi.org/10.1200/jco.2005.02.6187>
- Mieog, J.S., van der Hage, J.A., van de Velde, C.J.: Preoperative chemotherapy for women with operable breast cancer. *Cochrane Database Syst. Rev.* **2**, CD005002 (2007). <https://doi.org/10.1002/14651858.CD005002.pub2>
- Kong, X., Moran, M.S., Zhang, N., Haffty, B., Yang, Q.: Meta-analysis confirms achieving pathological complete response after neoadjuvant chemotherapy predicts favourable prognosis for breast cancer patients. *Eur. J. Cancer (Oxford, England)*. **47**(14), 2084–2090 (2011 (1990)). <https://doi.org/10.1016/j.ejca.2011.06.014>
- Antoch, G., Saoudi, N., Kuehl, H., Dahmen, G., Mueller, S.P., Beyer, T., Bockisch, A., Debatin, J.F., Freudenberg, L.S.: Accuracy of whole-body dual-modality fluorine-18-2-fluoro-2-deoxy-D-glucose positron emission tomography and computed tomography (FDG-PET/CT) for tumor staging in solid tumors: comparison with CT and PET. *J. Clin. Oncol.* **22**(21), 4357–4368 (2004). <https://doi.org/10.1200/jco.2004.08.120>
- Fletcher, J.W., Djulbegovic, B., Soares, H.P., Siegel, B.A., Lowe, V.J., Lyman, G.H., Coleman, R.E., Wahl, R., Paschold, J.C., Avril, N., Einhorn, L.H., Suh, W.W., Samson, D., Delbeke, D., Gorman, M., Shields, A.F.: Recommendations on the use of ¹⁸F-FDG PET in oncology. *J. Nucl. Med.* **49**(3), 480–508 (2008). <https://doi.org/10.2967/jnumed.107.047787>
- Weber, W.A.: Use of PET for monitoring cancer therapy and for predicting outcome. *J. Nucl. Med.* **46**(6), 983–995 (2005)
- Weber, W.A., Figlin, R.: Monitoring cancer treatment with PET/CT: does it make a difference? *J. Nucl. Med.* **48**(Suppl 1), 36 s–44 (2007) s
- Wahl, R.L., Jacene, H., Kasamon, Y., Lodge, M.A.: From RECIST to PERCIST: evolving considerations for PET response criteria in solid tumors. *J. Nucl. Med.* **50**(Suppl 1), 122 s–150 (2009). <https://doi.org/10.2967/jnumed.108.057307> s).
- Mghanga, F.P., Lan, X., Bakari, K.H., Li, C., Zhang, Y.: Fluorine-18 fluorodeoxyglucose positron emission tomography-computed tomography in monitoring the response of breast cancer to neoadjuvant chemotherapy: a meta-analysis. *Clin. Breast Cancer*. **13**(4), 271–279 (2013). <https://doi.org/10.1016/j.clbc.2013.02.003>
- Duch, J., Fuster, D., Munoz, M., Fernandez, P.L., Paredes, P., Fontanillas, M., Guzman, F., Rubi, S., Lomena, F.J., Pons, F.: ¹⁸F-FDG PET/CT for early prediction of response to neoadjuvant chemotherapy in breast cancer. *Eur. J. Nucl. Med. Mol. Imaging*. **36**(10), 1551–1557 (2009). <https://doi.org/10.1007/s00259-009-1116-y>
- Kumar, A., Kumar, R., Seenu, V., Gupta, S.D., Chawla, M., Malhotra, A., Mehta, S.N.: The role of ¹⁸F-FDG PET/CT in evaluation of early response to neoadjuvant chemotherapy in patients with locally advanced breast cancer. *Eur. Radiol.* **19**(6), 1347–1357 (2009). <https://doi.org/10.1007/s00330-009-1303-z>
- Wahl, R.L., Zasadny, K., Helvie, M., Hutchins, G.D., Weber, B., Cody, R.: Metabolic monitoring of breast cancer chemohormonotherapy using positron emission tomography: initial evaluation. *J. Clin. Oncol.* **11**(11), 2101–2111 (1993). <https://doi.org/10.1200/jco.1993.11.11.2101>
- Chen, L., Yang, Q., Bao, J., Liu, D., Huang, X., Wang, J.: Direct comparison of PET/CT and MRI to predict the pathological response to neoadjuvant chemotherapy in breast cancer: a meta-analysis. *Sci. Rep.* **7**(1), 8479 (2017). <https://doi.org/10.1038/s41598-017-08852-8>
- Pahk, K., Kim, S., Choe, J.G.: Early prediction of pathological complete response in luminal B type neoadjuvant chemotherapy-treated breast cancer patients: comparison between interim ¹⁸F-FDG PET/CT and MRI. *Nucl. Med. Commun.* **36**(9), 887–891 (2015). <https://doi.org/10.1097/mnm.0000000000000329>
- Andrade, W.P., Lima, E.N., Osorio, C.A., do Socorro Maciel, M., Baiocchi, G., Bitencourt, A.G., Fanelli, M.F., Damascena, A.S., Soares, F.A.: Can FDG-PET/CT predict early response to neoadjuvant chemotherapy in breast cancer? *Eur. J. Surg. Oncol.* **39**(12), 1358–1363 (2013). <https://doi.org/10.1016/j.ejso.2013.08.025>
- Ueda, S., Saeki, T., Shigekawa, T., Omata, J., Moriya, T., Yamamoto, J., Osaki, A., Fujiuchi, N., Misumi, M., Takeuchi, H., Sakurai, T., Tsuda, H., Tamura, K., Ishida, J., Abe, Y., Imabayashi, E., Kuji, I., Matsuda, H.: ¹⁸F-fluorodeoxyglucose positron emission tomography optimizes neoadjuvant chemotherapy for primary breast cancer to achieve pathological complete response. *Int. J. Clin. Oncol.* **17**(3), 276–282 (2012). <https://doi.org/10.1007/s10147-011-0287-2>
- Tromberg, B.J., Pogue, B.W., Paulsen, K.D., Yodh, A.G., Boas, D.A., Cerussi, A.E.: Assessing the future of diffuse optical imaging technologies for breast cancer management. *Med. Phys.* **35**(6), 2443–2451 (2008). <https://doi.org/10.1118/1.2919078>
- Ueda, Y., Yoshimoto, K., Ohmae, E., Suzuki, T., Yamanaka, T., Yamashita, D., Ogura, H., Teruya, C., Nasu, H., Ima, E., Sakahara, H., Oda, M., Yamashita, Y.: Time-resolved optical mammography and its preliminary clinical results. *Technol. Cancer Res. Treat.* **10**(5), 393–401 (2011). <https://doi.org/10.7785/tcrt.2012.500217>
- Fantini, S., Sassaroli, A.: Near-infrared optical mammography for breast cancer detection with intrinsic contrast. *Ann. Biomed. Eng.* **40**(2), 398–407 (2012). <https://doi.org/10.1007/s10439-011-0404-4>
- Wu, T., Feng, J.C., Tuerhong, S., Wang, B., Yang, L., Zhao, Q., Dilixiati, J., Xu, W.T., Zhu, L.P.: Ultrasound-guided diffuse optical tomography for differentiation of benign and malignant breast lesions: a meta-analysis. *J. Ultrasound Med.* **36**(3), 485–492 (2017). <https://doi.org/10.7863/ultra.16.03063>
- Ueda, S., Yoshizawa, N., Shigekawa, T., Takeuchi, H., Ogura, H., Osaki, A., Saeki, T., Ueda, Y., Yamane, T., Kuji, I., Sakahara, H.: Near-infrared diffuse optical imaging for early prediction of breast cancer response to neoadjuvant chemotherapy: a comparative study using ¹⁸F-FDG PET/CT. *J. Nucl. Med.* **57**(8), 1189–1195 (2016). <https://doi.org/10.2967/jnumed.115.167320>
- Nakamiya, N., Ueda, S., Shigekawa, T., Takeuchi, H., Sano, H., Hirokawa, E., Shimada, H., Suzuki, H., Oda, M., Osaki, A., Saeki, T.: Clinicopathological and prognostic impact of imaging of breast cancer angiogenesis and hypoxia using diffuse optical spectroscopy. *Cancer Sci.* **105**(7), 833–839 (2014). <https://doi.org/10.1111/cas.12432>
- Tromberg, B.J., Zhang, Z., Leproux, A., O'Sullivan, T.D., Cerussi, A.E., Carpenter, P.M., Mehta, R.S., Roblyer, D., Yang, W., Paulsen, K.D., Pogue, B.W., Jiang, S., Kaufman, P.A., Yodh, A.G., Chung, S.H., Schnall, M., Snyder, B.S., Hylton, N., Boas, D.A., Carp, S.A., Isakoff, S.J., Mankoff, D.: Predicting responses to neoadjuvant chemotherapy in breast cancer: ACRIN 6691 trial of diffuse optical spectroscopic imaging. *Cancer Res.* **76**(20), 5933–5944 (2016). <https://doi.org/10.1158/0008-5472.can-16-0346>

24. Zhi, W., Liu, G., Chang, C., Miao, A., Zhu, X., Xie, L., Zhou, J.: Predicting treatment response of breast cancer to neoadjuvant chemotherapy using ultrasound-guided diffuse optical tomography. *Transl. Oncol.* **11**(1), 56–64 (2018). <https://doi.org/10.1016/j.tranon.2017.10.011>
25. Yoshizawa, N., Ueda, Y., Nasu, H., Ogura, H., Ohmae, E., Yoshimoto, K., Takehara, Y., Yamashita, Y., Sakahara, H.: Effect of the chest wall on the measurement of hemoglobin concentrations by near-infrared time-resolved spectroscopy in normal breast and cancer. *Breast Cancer (Tokyo, Japan)*. **23**(6), 844–850 (2016). <https://doi.org/10.1007/s12282-015-0650-7>
26. Cerussi, A., Shah, N., Hsiang, D., Durkin, A., Butler, J., Tromberg, B.J.: In vivo absorption, scattering, and physiologic properties of 58 malignant breast tumors determined by broadband diffuse optical spectroscopy. *J. Biomed. Opt.* **11**(4), 044005 (2006). <https://doi.org/10.1117/1.2337546>
27. Ohmae, E., Yoshizawa, N., Yoshimoto, K., Hayashi, M., Wada, H., Mimura, T., Suzuki, H., Homma, S., Suzuki, N., Ogura, H., Nasu, H., Sakahara, H., Yamashita, Y., Ueda, Y.: Stable tissue-simulating phantoms with various water and lipid contents for diffuse optical spectroscopy. *Biomed. Opt. Express*. **9**(11), 5792–5808 (2018). <https://doi.org/10.1364/BOE.9.005792>

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