Int J Clin Exp Med 2016;9(2):1648-1656
www.ijcem.com /ISSN:1940-5901/IJCEM0018907

Original Article

Ultrasonography guided diffuse optical tomography for noninvasive monitoring of breast cancer during neoadjuvant chemotherapy

Yan Dong[1], Jinwei Qiang[1], Cai Chang[2], Shichong Zhou[2]

[1]*Department of Radiology, Jinshan Hospital, Fudan University, Shanghai, China;* [2]*Department of Ultrasonography, Cancer Hospital, Fudan University, Shanghai, China*

Received October 31, 2015; Accepted January 15, 2016; Epub February 15, 2016; Published February 29, 2016

Abstract: Less costly and noninvasive imaging technique is valuable for the diagnosis of breast cancer and monitoring the treatment. This study aimed to evaluate the application of ultrasonography guided diffuse optical tomography (US-DOT) in monitoring tumor response to neoadjuvant chemotherapy (NAC) in breast cancer patients. We prospectively evaluated 90 patients with breast cancer. All patients underwent surgery after NAC. Ninety patients were scanned with US-DOT prior to, during, and at the completion of NAC. Total hemoglobin concentration (THC) and tumor diameter were measured by US-DOT. Tumor response was assessed using the Miller-Payer system. All 90 patients completed the whole NAC cycles, 20 (20%) patients showed complete disappearance of all cancerous tissue (Grade 5). Only 3 (3.44%) patients had no pathological response (Grade 1). The other 67 (76.56%) patients showed varying degrees of necrosis of cancerous tissue (Grade 2-4). The tumor diameter and THC value decreased during NAC. Tumor diameter correlated significantly with THC value of breast cancers (R=0.6). After four or six cycles of NAC, the relative variation rates (RVRs) of THC values were significantly different among the grades ($P < 0.05$), but THC values had no difference in three chemotherapy regimens. In conclusion, US-DOT is a powerful technique to monitor tumor response during NAC.

Keywords: Ultrasonography, diffuse optical tomography, breast cancer, neoadjuvant chemotherapy, total hemoglobin concentration

Introduction

Breast cancer remains one of the most deadly diseases for women. Neoadjuvant chemotherapy (NAC) is increasingly used for patients with breast cancer to reduce tumor volume and eliminate possible micrometastasis [1]. Because there are many drugs available for the treatment of breast cancer, it is imperative to find a noninvasive and inexpensive modality to diagnose disease and monitor treatment response. Traditional methods of monitoring tumor response including X-ray mammography and ultrasound are useful but have considerable limitations [2-4]. Magnetic resonance imaging (MRI) and positron emission tomography (PET) scans are generally considered beneficial but are expensive [5, 6]. Less costly imaging technique would be of great value, especially diffuse optical tomography (DOT) using near-infrared (NIR) light is an emerging noninvasive method to provide functional information on breast cancer [7-10].

By probing the absorption and scattering properties of tissues, DOT using NIR provides an assessment of angiogenesis, a critical factor in the autonomous growth and spread of cancer. Optically derived functional images of the major absorption chromophores of oxyhemoglobin (HbO_2) and hemoglobin (Hb) can be obtained. Although functional imaging with DOT in comparison with conventional imaging modalities provides less spatial resolution, it can potentially provide valuable functional information soon after the initiation of cancer treatment. Recent developments that combine DOT with other imaging techniques such as ultrasonogra-

Table 1. Characteristics of 90 patients with breast cancer

Clinicopathologic variables	Patients (%)
Tumor diameter	
≤2 cm	8.88%
>2 cm	91.11%
ER status	
Negative	73.33%
Positive	26.67%
PR status	
Negative	35.56%
Positive	64.44%
HER2 status	
Negative	58.89%
Positive	41.11%
Neoadjuvant Chemotherapy	
CEF-T	45.56%
PCarH	41.11%
PDP	13.33%
Miller-Payer system	
Grade 1	3.33%
Grade 2	15.56%
Grade 3	38.89%
Grade 4	20%
Grade 5	22.22%

ER, estrogen; ER, estrogen receptor; PR, progesterone receptor; HER2, receptor for human epidermal growth factor; N/A, not available; CEF-T, cyclophosphamide, 5-fluorouracil and tamoxifen; PCarH, paclitaxel, carboplatin, trastuzumab; PDP, Paclitaxel.

Table 2. Relative variation of THC and histological response in 90 cases

Grade	N	After NAC	*P* value
		Relative variation of THC	
1	3	-0.01±0.19	P<0.05
2	14	-0.28±0.16	
3	35	-0.35±0.21	
4	18	-0.52±0.31	
5	20	-0.57±0.18	

phy (US) and MRI may potentially overcome these limitations [11-14]. Accordingly, several studies using DOT demonstrated that total hemoglobin concentration (THC) was much higher in malignant than in benign conditions [13-16]. Given its limitations in spatial resolution and difficulty in using DOT as a diagnosis tool, interest has shifted to the use of DOT in monitoring treatment response. The application of DOT in NAC response evaluation is based on tumor angiogenesis. Breast cancer tissues have more blood vessels than normal tissues, and the tumor vessels have greater permeability than normal vessels due to the weaker integrity of the vessel wall. Breast cancer is an obvious candidate because of the use of neoadjuvant treatment and pathologic data available after surgery. Multiple studies have shown the utility of DOT in predicting early tumor response to neoadjuvant treatment [17-21].

Therefore, in this study we aimed to assess the feasibility of using US-DOT for monitoring tumor responses to neoadjuvant chemotherapy (NAC) in patients with breast cancer. In a series of 90 breast cancer patients we evaluated the correlation of functional US-DOT parameter (THC) with clinical and final pathologic outcomes of the patients during NAC.

Patients and methods

Patients

This study was performed at Ultrasonography Department of Fudan University Shanghai Cancer Center from February 2013 to July 2014. The approval was obtained from Ethics Committee of Jinshan Hospital, Fudan University, and written informed consent was obtained from the participants. One hundred and twenty patients were enrolled at the beginning, undergoing conventional US, US-DOT, MRI, and open biopsy either 1 or 2 days after recruitment. However, eighteen patients did not complete the study due to the change in treatment plan. Nine patients were unwilling to continue to participate, and three patients quitted before definitive surgery. The final study group included 90 women with mean age 48.6 years (range 36-60 years). **Table 1** presented the clinical characteristics of the final study group. The tumor diameter was assessed by US at the initial examination. The histologic type of these patients was invasive ductal carcinoma. In this study, only patients with one lesion were recruited, and the number of lesion was assessed by MRI. Pathologic response of tumors was graded by Miller-Payer system, status of ER, PR and HER2 expression. Patients received a variety of neoadjuvant treatment regimens. designed by the oncologist's discretion depending on toxicity and response.

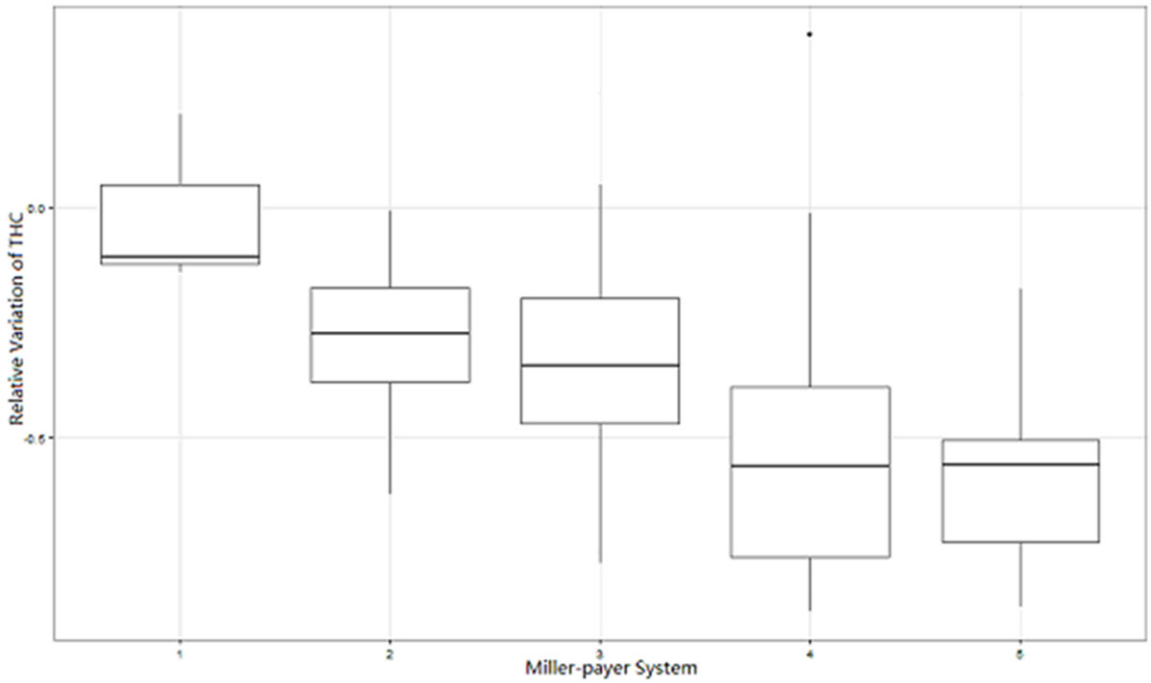

Figure 1. Relationship between relative variation of THC and histological response (Grade 1-5) in 90 cases.

Neoadjuvant chemotherapy and the evaluation of tumor regression

In this study, 41 patients received NAC treatment with paclitaxel, carboplatin, and trastuzumab (PCarH) for estrogen or progesterone receptor positive and HER2 positive breast cancer with six cycles. The other 37 patients received preoperative treatment consisting of cyclophosphamide, 5-fluorouracil and tamoxifen (CEF-T) for estrogen or progesterone receptor positive and HER2 negative breast cancer with six cycles. The other 12 patients received preoperative treatment consisting of paclitaxel and cisplatin for estrogen and progesterone receptor negative and HER2 negative breast cancer with four cycles.

Tumor regression was judged based on Miller-Payer system [22]: Grade 1: No change or some alteration to individual malignant cells but no reduction in overall cellularity. Grade 2: A minor loss of tumor cells but overall high cellularity; up to 30% loss. Grade 3: Between an estimated 30% and 90% reduction in tumor cells. Grade 4: A marked disappearance of tumor cells such that only small clusters or widely dispersed individual cells remain; more than 90% loss of tumor cells. Grade 5: No malignant cells identifiable in sections from the site of the tumor; only vascular fibroelastoticstroma remain, often containing macrophages.

US-guided DOT technique

In US imaging, the largest tumor diameter was measured in spatial dimensions and in depth. OPTIMUS type II breast diagnostic system (XinaoMDT Technology Co., Ltd., Beijing, China) was used. The probes of OPTIMUS consisted of a 7-12 MHz US probe (Terason T3000 ultrasound, TeraTech, Rockville, MD, USA) in the middle, an array of nine optical fibers on one side and an array of 10 optical guides (Edmund Scientific, Barrington, NJ, USA) on another side. All examinations were performed by one radiologist who had manipulated breast US-DOT system for three years.

Because the maximal diameter of the lesion was chosen as the optical horizontal plane, it was not always equal to sonographic coronal scan. Likewise, optical vertical plane was not always equal to sagittal scan. Based on the optical parameters of the four planes (two affected side planes, two contralateral side planes), the region of interest (ROI) was defined. The total examination time required for DOT was approximately 5-6 min for each patient. Reconstructed images of optical absorption

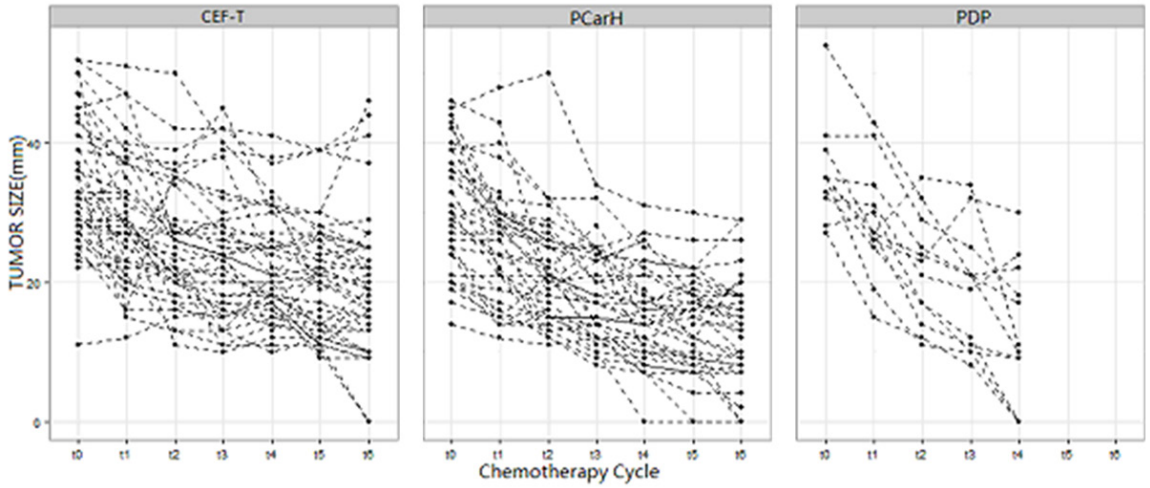

Figure 2. Changes in tumor diameter during NAC. The three graphs illustrated each of the parameters plotted from pretreatment at 4 or 6 weeks.

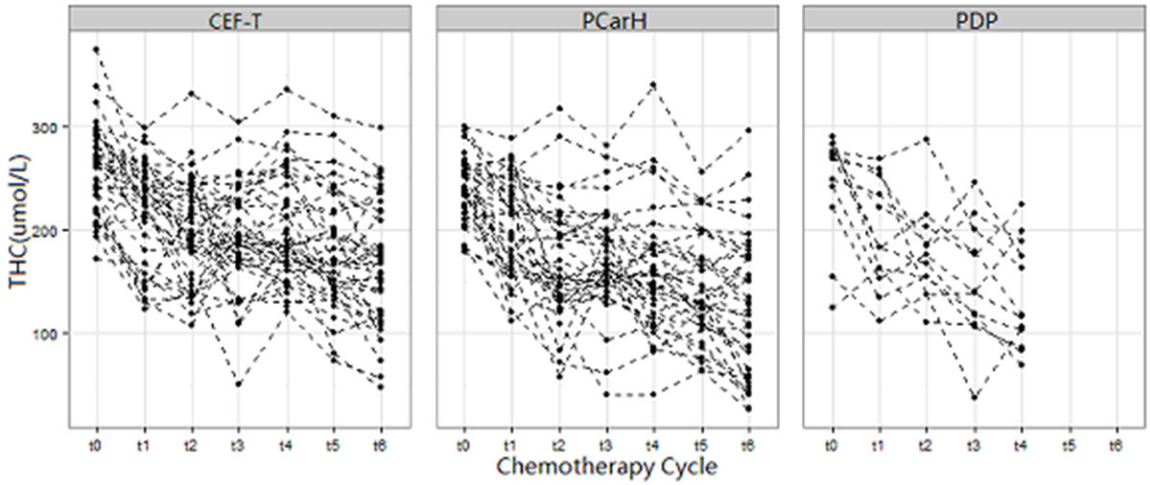

Figure 3. Changes in THC during NAC. The three graphs illustrated each of the parameters plotted from pretreatment at 4 or 6 weeks.

and scattering at each of the four wavelengths were produced as above, and the functional parameter THC was generated.

Data source and statistical analysis

The statistics software SPSS was used for the statistical data analysis. Data were expressed as means ± SD. One way-ANOVA was used to determine the differences of THC within the grades. A forward Pearson correlation analysis was used to test the correlation of THC with tumor diameter. A *P* value of less than 0.05 was considered significant difference.

Results

Twenty cases (22%) showed almost complete disappearance of all cancerous tissue, indicating that the patients had excellent responses to primary treatment (Grade 5). Three (3%) cases did not show any reduction in tumor diameter after chemotherapy. The tumors showed no regressive changes in the tissue sections, indicating that the tumors had not responded to chemotherapy (Grade 1). The remaining 67 (75%) patients showed some degree of response to chemotherapy. The post-operative histological changes showed varying degrees

Table 3. Correlations between mean maximum THC and clinicopathologic variables of breast cancer

Clinicopathologic variables	THC				*P* value
Tumor size	Min	Max	Mean	SD	0.91
≤2 cm	184.41	303.88	247.22	38.99	
>2 cm	374.21	125.35	248.88	39.80	
ER status	Min	Max	Mean	SD	0.29
Negative	125.35	374.21	251.01	42.58	
Positive	178.34	299.28	242.46	29.35	
PR status	Min	Max	Mean	SD	0.6
Negative	125.35	300	245.82	40.33	
Positive	171.49	374.21	250.34	39.32	
HER2 status	Min	Max	Mean	SD	0.12
Negative	125.35	374.21	253.87	44.23	
Positive	178.34	300.00	241.38	30.67	
Neoadjuvant Chemotherapy	Min	Max	Mean	SD	0.19
CEF-T	171.48	374.20	256.89	41.82	
PCarH	178.34	300	241.37	30.67	
PDP	125.34	290.16	243.52	52.32	

of necrosis of cancerous tissue, the degenerative changes of residual carcinoma, intercellular substance edema, fibrous hyperplasia and inflammatory cell invasion (Grade 2-4). One way-ANOVA showed that relative variation of THC value was different among the grades according to Miller-Payer system ($P<0.05$, **Table 2**). We further drew a plot to show the relationship of relative variation of THC value in each grade (**Figure 1**).

We measured tumor diameter after each cycle of NAC by US, and found that tumor diameter was significantly reduced by chemotherapy in all three chemotherapy regimens (**Figure 2**). We further measured THC after each cycle by US-DOT and found that THC was significantly reduced by chemotherapy too (**Figure 3**).

We also analyzed the correlations between mean maximum THC and clinicopathologic variables of breast cancer patients and the results were shown in **Table 3**. To investigate the relationship between THC and tumor diameter, we performed Pearson correlation analysis and found a significant relationship between THC and tumor diameter in all three chemotherapy regimens (**Figure 4**). Finally, we estimated the relationship between tumor diameter and THC by mixed-effects models and the results showed the equation of this model as: THC=4.2*T+94.58, T indicated tumor diameter (**Figure 5**).

Discussion

NAC has been used in breast cancer patients to prevent cancer metastasis [1]. Consequently, breast-conserving treatment is performed in patients who are deemed to be inoperable [22, 23]. During the process of treatment, it is vital to assess tumor response to NAC and distinguish responders from non-responders in case of unfavorable response. This can prevent patients from experiencing unnecessary drug toxicity. Studies have shown that breast tumor became clinically relevant once they developed blood supply. US-DOT is an emerging imaging modality that provides information regarding the angiogenesis of tissue. It is noninvasive and portable, and less expensive than other imaging modalities such as MRI or FDG-PET. In addition, US-DOT does not involve the use of exogenous contrast agents, which makes it ideal for multiple scans typically required for treatment monitoring.

US-DOT combines DOT and ultrasonography and thus the tumors could be imaged by both ultrasound and DOT [24, 25]. In general, the ultrasound system is used to localize the tumor and determine the structural or anatomical parameters, such as the depth and diameter. Optical microscopy can provide high spatial resolution by detecting nonscattered light in tissue, but this method makes it extremely difficult to image deeper than 1 mm in most biological tissues [26]. By contrast, significantly scattered light (usually called diffuse light) can travel much deeper into tissue. By taking advantage of this fact, near-infrared spectroscopy has been developed to measure the change of hemoglobin concentration in deep tissues. However, near-infrared spectroscopy can not provide an image to show the spatial distribution of the measured signal. To achieve deep-tissue imaging, DOT has been developed to image HbO_2, Hb, total hemoglobin and oxygenation in breast and prostate tumors.

Bruce et al. concluded that response monitoring with DOT during NAC was promising,

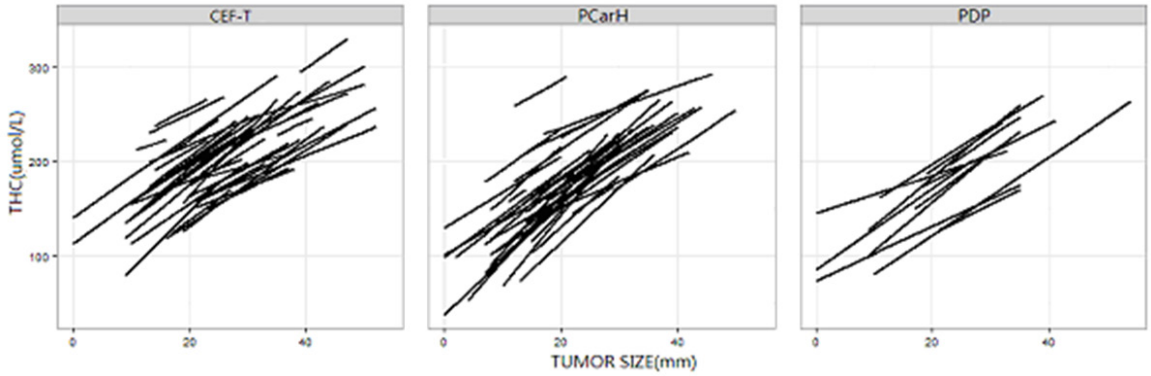

Figure 4. The correlation of THC value with tumor diameter.

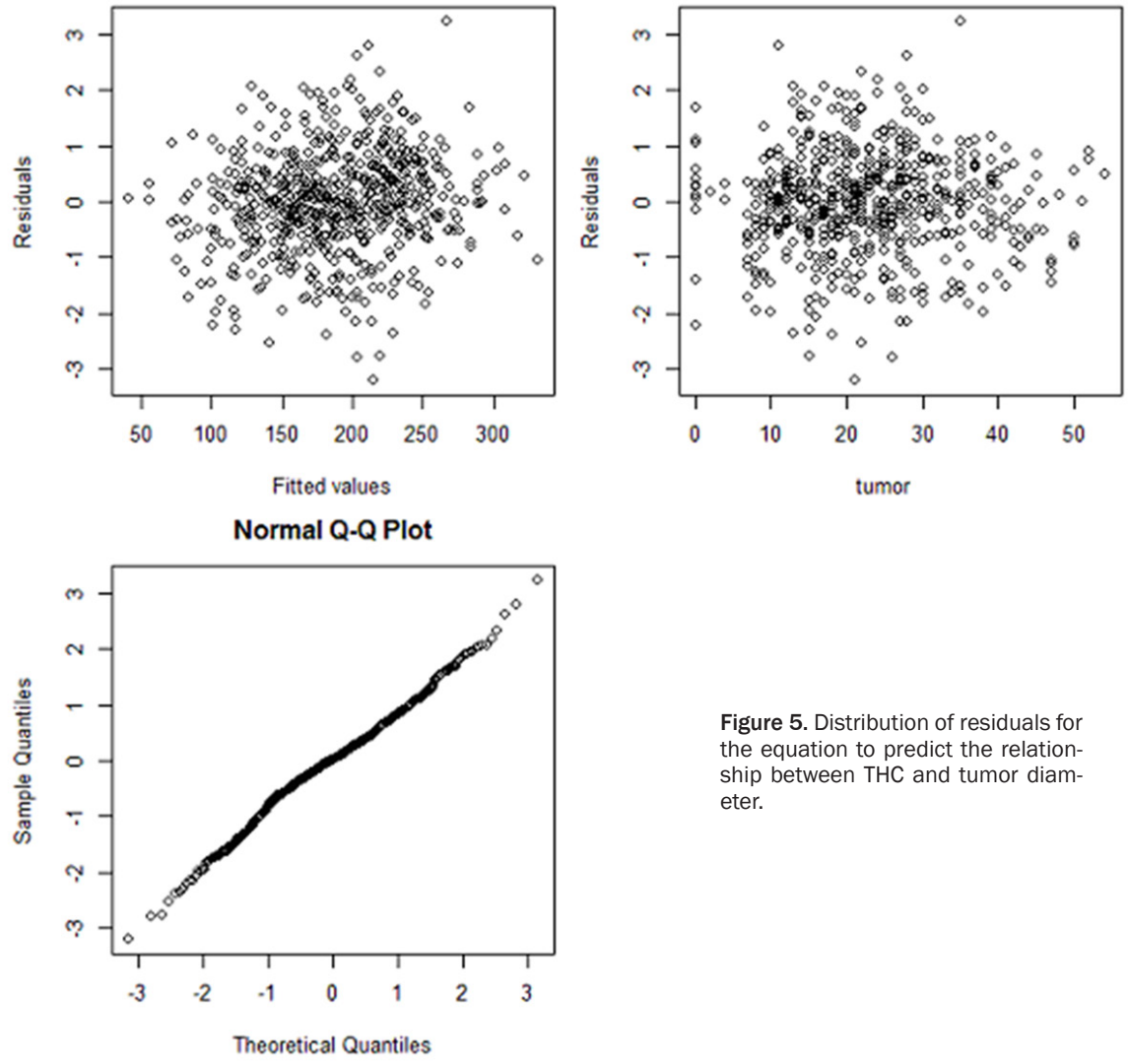

Figure 5. Distribution of residuals for the equation to predict the relationship between THC and tumor diameter.

although there was lack of standardization [27]. In this study, we reported the results of 90 patients with breast cancer whose tumor responses to NAC were monitored using US-DOT. Subtype was stratified according to receptor status based on immunohistochemis-

try analysis of ER, PR and Her2, and all 90 patients were given different chemotherapy drugs according to different subtypes. If US-DOT can accurately monitor tumor response repeatedly and easily, the most efficacious drugs could be used. Ideally, chemotherapy should be monitored at earlier cycles as this could facilitate the modification of the regimen to enable the lesion to be maximally treated [28, 29]. In this study only 22 patients (22%) had complete pathologic responses (Grade 5) to NAC. Thus most of the patients could not get complete remission after NAC and it is very important to monitor tumor response.

By using US-DOT to monitor tumor diameter during chemotherapy, we found that the majority of tumor diameter decreased. We also analyzed the relationship between THC and tumor pathologic grades. Cancerous tissues have more blood vessels than normal tissues, so chemotherapy drugs inhibited tumor angiogenesis, resulting in decreasing tumor diameter. We used Pearson correlation analysis to demonstrate the relationship between THC and tumor diameter. Mixed-effects models provided an efficient means of analyzing repeatedly measured data and making accurate prediction. We estimated the relationship between tumor diameter and THC by mixed-effects models and got the equitation THC=4.2*T+94.58, where T indicated tumor diameter. THC and tumor diameter were mutually dependent ($P<0.05$). Therefore, THC has the potential to be used for *in vivo* monitoring of the response of tumors to NAC.

Because our sample size is small, more patients are needed to validate our conclusion. Therefore we could not conclusively state that US-DOT could identify tumor response to NAC according to THC status. Further multi-center studies on US-DOT would test the power of US-DOT to monitor tumor response during breast cancer NAC.

The application of US-DOT in predicting the response of breast cancer to neoadjuvant chemotherapy is still not clear. The number of patients in our study was too small to determinate the cut-off points in predicting responders and non- responders. However, our data suggest that US-DOT is a quick and noninvasive method that may prove invaluable for neoadjuvant treatments to monitor tumor response to NAC.

Acknowledgements

This work was supported by grants from Shanghai Health and Family Planning Commission (No. 201440395) and Jinshan Science and Technology Committee (No. 2014-3-01).

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Jinwei Qiang, Department of Radiology, Jinshan Hospital, Fudan University, 1508 Longhang Road, Shanghai 201508, China. E-mail: dr.jinweiqiang@163.com; Cai Chang, Department of Ultrasound, Cancer Hospital, Fudan University, 270 Dong'an Road, Shanghai 200032, China. Tel: 86-21-34189990; Fax: 86-21-67226910; E-mail: changcai@sina.com

References

[1] Buchholz TA, Lehman CD, Harris JR, Pockaj BA, Khouri N, Hylton NF, Miller MJ, Whelan T, Pierce LJ, Esserman LJ, Newman LA, Smith BL, Bear HD, Mamounas EP. Statement of the science concerning locoregional treatments after preoperative chemotherapy for breast cancer: a National Cancer Institute conference. J Clin Oncol 2008; 26: 791-797.

[2] Herrada J, Iyer RB, Atkinson EN, Sneige N, Buzdar AU, Hortobagyi GN. Relative value of physical examination, mammography, and breast sonography in evaluating the diameter of the primary tumor and regional lymph node metastases in women receiving neoadjuvant chemotherapy for locally advanced breast carcinoma. Clin Cancer Res 1997; 3: 1565-1569.

[3] Helvie MA, Joynt LK, Cody RL, Pierce LJ, Adler DD, Merajver SD. Locally advanced breast carcinoma: accuracy of mammography versus clinical examination in the prediction of residual disease after chemotherapy. Radiology 1996; 198: 327-332.

[4] Chagpar AB, Middleton LP, Sahin AA, Dempsey P, Buzdar AU, Mirza AN, Ames FC, Babiera GV, Feig BW, Hunt KK, Kuerer HM, Meric-Bernstam F, Ross MI, Singletary SE. Accuracy of physical examination, ultrasonography, and mammography in predicting residual pathologic tumor diameter in patients treated with neoadjuvant chemotherapy. Ann Surg 2006; 243: 257-264.

[5] Kim SJ, Kim SK, Lee ES, Ro J, Kang S. Predictive value of [18F]FDG PET for pathological response of breast cancer to neoadjuvant chemotherapy. Ann Oncol 2004; 15: 1352-1357.

[6] Mankoff DA, Dunnwald LK, Gralow JR, Ellis GK, Schubert EK, Tseng J, Lawton TJ, Linden HM, Livingston RB. Changes in blood flow and me-

tabolism in locally advanced breast cancer treated with neoadjuvant chemotherapy. J Nucl Med 2003; 44: 1806-1814.
[7] Grosenick D, Moesta KT, Wabnitz H, Mucke J, Stroszczynski C, Macdonald R, Schlag PM, Rinneberg H. Time-domain optical mammography: Initial clinical results on detection and characterization of breast tumors. Appl Opt 2003; 42: 3170-3186.
[8] Jiang H, Xu Y, Iftimia N, Eggert J, Klove K, Baron L, Fajardo L. Three-dimensional optical tomographic imaging of breast in a human subject. IEEE Trans Med Imaging 2001; 20: 1334-1340.
[9] Pogue BW, Poplack SP, McBride TO, Wells WA, Osterman KS, Osterberg UL, Paulsen KD. Quantitative hemoglobin tomography with diffuse near-infrared spectroscopy: Pilot results in the breast. Radiology 2001; 218: 261-266.
[10] Tromberg BJ, Cerussi A, Shah N, Compton M, Durkin A, Hsiang D, Butler J, Mehta R. Imaging in breast cancer: Diffuse optics in breast cancer: Detecting tumors in pre-menopausal women and monitoring neoadjuvant chemotherapy. Breast Cancer Res 2005; 7: 279-285.
[11] Brooksby B, Pogue BW, Jiang S, Dehghani H, Srinivasan S, Kogel C, Tosteson TD, Weaver J, Poplack SP, Paulsen KD. Imaging breast adipose and fibroglandular tissue molecular signatures by using hybrid MRI-guided near-infrared spectral tomography. Proc Natl Accad Sci U S A 2006; 103: 8828-8833.
[12] Ntziachristos V, Yodh AG, Schnall MD, Chance B. MRI-guided diffuse optical spectroscopy of malignant and benign breast lesions. Neoplasia 2002; 4: 347-354.
[13] You SS, Jiang YX, Zhu QL, Liu JB, Zhang J, Dai Q, Liu H, Sun Q. US-guided diffused optical tomography: A promising functional imaging technique in breast lesions. Eur Radiol 2010; 20: 309-317.
[14] Zhu Q, Cronin EB, Currier AA, Vine HS, Huang M, Chen N, Xu C. Benign versus malignant breast masses: Optical differentiation with US-guided optical imaging reconstruction. Radiology 2005; 237: 57-66.
[15] Zhu Q, Hegde PU, Ricci A Jr, Kane M, Cronin EB, Ardeshirpour Y, Xu C, Aguirre A, Kurtzman SH, Deckers PJ, Tannenbaum SH. Early-stage invasive breast cancers: Potential role of optical tomography with US localization in assisting diagnosis. Radiology 2010; 256: 367-378.
[16] Kim MJ, Kim JY, Youn JH, Kim MH, Koo HR, Kim SJ, Sohn YM, Moon HJ, Kim EK. US-guided diffuse optical tomography for breast lesions: The reliability of clinical experience. Eur Radiol 2011; 21: 1353-1363.
[17] Cerussi A, Hsiang D, Shah N, Mehta R, Durkin A, Butler J, Tromberg BJ. Predicting response to breast cancer neoadjuvant chemotherapy using diffuse optical spectroscopy. Proc Natl Acad Sci U S A 2007; 104: 4014-4019.
[18] Zhu Q, Kurtzma SH, Hegde P, Tannenbaum S, Kane M, Huang M, Chen NG, Jagjivan B, Zarfos K. Utilizing optical tomography with ultrasound localization to image heterogeneous hemoglobin distribution in large breast cancers. Neoplasia 2005; 7: 263-270.
[19] Jakubowski DB, Cerussi AE, Bevilacqua F, Shah N, Hsiang D, Butler J, Tromberg BJ. Monitoring neoadjuvant chemotherapy in breast cancer using quantitative diffuse optical spectroscopy: a case study. J Biomed Opt 2004; 9: 230-238.
[20] Choe R, Corlu A, Lee K, Durduran T, Konecky SD, Grosicka-Koptyra M, Arridge SR, Czerniecki BJ, Fraker DL, DeMichele A, Chance B, Rosen MA, Yodh AG. Diffuse optical tomography of breast cancer during neoadjuvant chemotherapy: a case study with comparison to MRI. Med Phys 2005; 32: 1128-1139.
[21] Shah N, Gibbs J, Wolverton D, Cerussi A, Hylton N, Tromberg BJ. Combined diffuse optical spectroscopy and contrast-enhanced magnetic resonance imaging for monitoring breast cancer neoadjuvant chemotherapy: a case study. J Biomed Opt 2005; 10: 051503.
[22] Fisher B, Bryant J, Wolmark N, Mamounas E, Brown A, Fisher ER, Wickerham DL, Begovic M, DeCillis A, Robidoux A, Margolese RG, Cruz AB Jr, Hoehn JL, Lees AW, Dimitrov NV, Bear HD. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol 1998; 16: 2672-2685.
[23] Mieog JS, van der Hage JA, van de Velde CJ. Neoadjuvant chemotherapy for operable breast cancer. Br J Surg 2007; 94: 1189-1200.
[24] Jiang Z, Piao D, Xu G, Ritchey JW, Holyoak GR, Bartels KE, Bunting CF, Slobodov G, Krasinki JS. Trans-rectal ultrasound-coupled near-infrared optical tomography of the prostate, part II: experimental demonstration. Opt Express 2008; 16: 17505-17520.
[25] Ardeshirpour Y, Biswal N, Aguirre A, Zhu Q. Artifact reduction method in ultrasound-guided diffuse optical tomography using exogenous contrast agents. J Biomed Opt 2011; 16: 046015.
[26] McDonald DM, Choyke PL. Imaging of angiogenesis: from microscope to clinic. Nat Med 2003; 9: 713-725.
[27] Bruce J. Tromberg and Albert E. Cerussi: Imaging Breast Cancer Chemotherapy Response with Light. Clin Cancer Res 2010; 16: 2486-2488.

[28] Martincich L, Montemurro F, De Rosa G, Marra V, Ponzone R, Cirillo S, Gatti M, Biglia N, Sarotto I, Sismondi P, Regge D, Aglietta M. Monitoring response to primary chemotherapy in breast cancer using dynamic contrast-enhanced magnetic resonance imaging. Breast Cancer Res Treat 2004; 83: 67-76.

[29] Manton DJ, Chaturvedi A, Hubbard A, Lind MJ, Lowry M, Maraveyas A, Pickles MD, Tozer DJ and Turnbull LW. Neoadjuvant chemotherapy in breast cancer: early response prediction with quantitative MR imaging and spectroscopy. Br J Cancer 2006; 94: 427-435.