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Evaluation of Early Response to Neoadjuvant Chemotherapy in Breast Cancer Patients by ^{18}F-FDG and ^{99m}Tc-HL91 Imaging

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Abstract

By monitor breast cancer mass with ^{18}F-fluorodeoxyglucose (FDG) and ^{99m}Tc-HL91 positron emission tomography (PET) imaging, this study compares the efficacy of the two imaging methods in evaluation of the early response to neoadjuvant chemotherapy in stage II and III breast cancer patients. Images of region of interest were acquired with a hybrid PET/computed tomography scanner in forty patients after administration of ^{18}F-FDG (4.44 MBq/kg) or ^{99m}Tc-HL91 (12.3 MBq/kg) at baseline and after the third course of chemotherapy. And the values of tumor to non-tumor activity ratio (T/N) were compared between the two imaging methods and with the pathologic response. Surgery was performed after three courses of chemotherapy and pathological analysis revealed gross residual disease in 11 patients and minimal residual disease in 29 patients. When 20% reduction in T/N was set as the threshold for differentiation between responders and nonresponders by ^{18}F-FDG imaging, 27 of 29 responders and 10 of 11 nonresponders were identified after three courses of chemotherapy. A linear correlation was observed between the T/N of ^{99m}Tc-HL91 and the T/N of ^{18}F-FDG (r_s = 0.778, p<0.001), but almost lost after chemotherapy (r_s = 0.518, p<0.001).

In conclusion, we suggest that ^{18}F-FDG imaging, but not ^{99m}Tc–HL91 imaging with hybrid PET/CT provides a cost-effective method, which could be well accepted for the low-income population in developing countries, to monitor early tumor response after three cycles of neoadjuvant chemotherapy in stage II and III breast cancer by using the reduction of N/T ratio as predictor.

Keywords: ^{18}F-FDG; ^{99m}Tc-HL91 imaging; Breast cancer; Neoadjuvant chemotherapy; Tumor hypoxia

Introduction

The use of preoperative neoadjuvant chemotherapy in the treatment of breast cancer has been evolving during the past two decades. The benefits of neoadjuvant chemotherapy are: 1) shrinking large cancer tumors so that they are small enough to be removed by breast-conserving surgery instead of radical mastectomy; 2) reducing the chances of spread through the bloodstream, clearing the tiny metastatic lesion, and lowering the possibility of drug fast; 3) understanding the sensitivity of the tumor to chemotherapy and also providing evidence to post-surgery chemotherapy[1-4] . As we know, there are two important endpoint for assessing the therapeutic response of preoperative treatment: clinical and pathological response [5], however both of them have showed limitations. Furthermore, clinical response by measurement of tumor size is often discordant with the pathological evalution, such as the clinically response of approximately 70% in most studies, the partial or complete regression in histopathological biopsy analysis is less than 30% [6]. Additionally, the assessed evaluation of pathological complete response)pCR) based on a complete sectioning and fully step-sectioned are deemed imperative and is difficult to practice particularly by core needle biopsy. It is essential to develop an appropriate, universal assessment criteria used for reaching a judgment in respect to pCR or less than pCR. It is still an unresolved problem or waiting for decision to this day [7].

Because the change in tumor metabolism precedes the decrease in tumor size, positron emission tomography (PET) with ^{18}F-FDG imaging should allow visualization of most tumor responses at an earlier stage than with conventional imaging methods (e.g. ultrasoun digraphy,radiography,etc.) [8,9]. As glucose metabolism is increased pretherapy and decreased post-therapy in most cancer lesions [10-12] so the monitoring of chemotherapy with ^{18}F-FDG imaging has been proposed for the early prediction of response of breast cancer to chemotherapy [13-15].

Many malignant tumours are hypoxic in tumor regions [16-18]. This is clinically important as tumor hypoxia may increase resistance to radiation therapy and to some forms of chemotherapy [19]. There has been much interest in noninvasive methods such as imaging of radiophamaceuticals like ^{99m}Tc-HL91, which are selectively retained in regions of hypoxia. Cook,G et al had performed a pilot evaluation using ^{99m}Tc-HL91 to assess imaging characteristics and efficacy in malignant tumor detection and correlated results with ^{18}F-FDG imaging as a gold standard scintigraphic method of tumor localization [20,21].

Whether current neoadjuvant chemotherapy may be employed to improve the degree of hypoxia and whether hypoxia imaging with ^{99m}Tc-HL91 can predict the effect of that neoadjuvant chemotherapy? In order to answer these questions, fourty patients suffered from stage II and III primary breast cancer patients were enrolled in this study. All of them accepted ^{99m}Tc-HL91 imaging and ^{18}F-FDG imaging simultaneously pre- and post-chemotherapy. This preliminary study explored the possibility of ^{99m}Tc-HL91 imaging like ^{18}F-FDG imaging

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in identification of malignant tumors and prediction of the efficacy of neoadjuvant chemotherapy.

Patients and Methods

Patients

This prospective study was approved by the ethic committee of the Fourth Military Medical University and all patients gave their written informed consent before enrollment. Inclusion criteria were the following: age older than 18 years; no pregnancy; without prior breast surgery, chemotherapy, nor radiotherapy; with surgery indication. From August 2004 to April 2006, forty consecutive patients with newly diagnosed, noninflammatory, stage II and III breast cancer undergoing neoadjuvant chemotherapy were enrolled. Diagnosis of invasive carcinoma was done by core needle biopsy in all patients and the stage of cancer was determined by x-ray, ultrasound and bone scan investigations according to TNM classification (AJCC Cancer Staging Manual, 6th edition, 2002). Tumor size and location were established by ultrasound at baseline and after the third course of chemotherapy. Both axillary fossa and breast ultrasound were performed using an 11- to 13.5-MHz transducer.

Neoadjuvant chemotherapy

All the enrolled patients received CAF neoadjuvant regimen without radiotherapy. The regimen consists: 1) Cytoxan (CTX) 100 mg/m^2, per oral (PO) on day 1-14; 2) Adriamycin (ADM) 30 mg/m^2, intravenous injection (IV) on day 1 and day 8; 3) Fluorouracil (5-FU) 500 mg/m^2, IV on day 1 and day 8. A three-week treatment is a cycle. Surgery was performed less than 2 weeks after the last course of chemotherapy.

^{18}F-FDG PET imaging

Tumors scans were performed with a hybrid PET/CT scanner (Millennium, VG5 with Hawkeye, GE medical systems) pre- and post-neoadjuvant chemotherapy. The patients were kept fasting 6 h and their fasting blood glucose were measured to ensure glucose levels were less than 7.0 mmol/L. Scanning was carried out 50 min after an intravenous injection of ^{18}F-FDG)4.44 MBq/kg), including 10 min CT and 30 min scintigraphy. For semiquantitative analysis of the ^{18}F-FDG uptake, the average ratio of the radioactivity in each ROI (region of interest) was calculated and recognized as the tumor to non-tumor ratio (T/N). Chemotherapy induced decrease of glucose metabolism in tumors was defined as the reduction rate of T/N of FDG.

^{99m}Tc-HL91 imaging

HL91 (4,9-diaza-2, 3-10, 10-tetramethyldodeca-2, 11-dione dioxime) was produced by the Xinke Sida Company in Beijing. The procedure of ^{99m}Tc labeling HL91 is as follows: firstly adding fresh $^{99m}TcO_4^-$ elutriator (1.11 – 2.22 GBq) into HL91 freeze-dry product (lyophilized form), then dissolving and shaking the solution thoroughly, and leaving it at the room temperature for 10 minutes, finally using the double system measurement to inspect the labeling rate and radiochemical purity; labeling rate should be above 95% for effective application. The image instrument was equipped with low energy high resolution parallel hole collimator. Section imaging was performed 4 hours after injecting ^{99m}Tc-HL91 of 12.3 MBq/kg, which was followed by imaging processing. The T/N of ^{99m}Tc--HL91 imaging in each ROI was calculated.

Image analysis

FDG-PET images and HL91-PET images were respectively analyzed by different observers who were blinded to the histopathologic response status as well as the size measurements on ultrasound. To quantify tumor FDG uptake, a circular region of interest with a diameter of 1.5 cm was placed at the site of maximum FDG uptake as previously described.

Clinical assessment

The sizes of the breast tumor were assessed by means of ultrasonography before and after chemotherapy. The clinical response to treatment was classified as complete response (CR), partial response (PR), no change (NC) and progressive disease (PD) according to the RECIST (Response Evaluation Criteria in Solid Tumors) and WHO classification system. CR was defined as the disappearance of all clinical evidence of the breast tumor; PR was defined as a decrease in tumor size of at least 50%; NC was defined as a decrease of less than 50% or increased less than 25% in tumor size; The tumor size increased greater than 25% or the appearance of new lesions was defined as PD.

Histopathologic assessment

One pathologist, who was blinded to PET and ultrasound data, analyzed all specimens in a standard fashion as previously described. Each specimen was bisected along the greatest diameter, and the perimeter of the tumor was defined. The entire cross sectional area of the bisected tumor was partitioned into 2.0-cm^2 (average) blocks and processed for histologic examination, along with additional randomly sampled areas. The histological changes was classified as three stages: catagenesis or apomorphosis (stage I), granuloma (stage II), and fibrous degeneration (stage III). At stage I, degeneration of tumor cells, including swollen cytoplasm, pultaceous and vacuolus appearance; swollen nucleus, dissolve, pycnotic and fragmentation, could be observed. At stage II, there appears obvious degeneration and necrosis of cancer cells, decreased number of tumor cells, and granuloma-like change. At stage III, progressive degeneration results in difficult to identify the cancer cells or disappearance of cancer cells, the fibroplasias of interstitial tissue and glassy degeneration fill in apomorphosis necrosis area.

Statistical analysis

Comparisons between groups were made by *t* test. Correlation analysis of the T/N reduction rate of ^{18}F-FDG and therapeutic responses or the T/N reduction rate between ^{18}F-FDG and ^{99m}Tc-HL91 was analyzed using Spearman rank correlation coefficient.

Results

Patients and assessment of clinical and pathological responses

Patients and tumor characteristics are listed in Table. The median primary tumor size was 34mm (range, 20 to 72mm). All the patients received three courses of primary chemotherapy and the median duration of treatments was 110days (range, 98 to 132 days). Median tumor size after chemotherapy was 21mm (range, 5 to 70mm). Among the 40 breast cancer patients, the overall response (OR) rate was 72.5% (29 out of 40 patients), in which three patients were in the CR group (7.5%), 26 in the PR group (65.0%), 11 in the NC group (27.5%), and none in the progressive disease group. After completion of chemotherapy, based on pathology finding, 29 patients were considered as responders. A Sataloff grade I response was identified in 7 patients, a grade II response was identified in 13 patients, and a grade III response was identified in 9 patients.

The correlation between the T/N of ^{99m}Tc-HL91 and that of ^{18}F-FDG

Before the chemotherapy, all 40 tumors were well visualized on Hybrid PET/CT images as enhancing ^{18}F-FDG and ^{99m}Tc-HL91 accumulation in breast cancer lesions. A linear correlation was observed between the T/N of ^{99m}Tc-HL91 and the T/N of ^{18}F-FDG (r_s = 0.778, p<0.001) (Figure 1). The mean rate of T/N of ^{18}F-FDG (4.35 ±1.95) was significantly higher than that of ^{99m}Tc-HL91 (3.24 ± 1.03) in 40 breast cancer lesions (t = 3.193 p <0.01). For example : in case 6 image, the T/N of ^{18}F-FDG (4.79) was obvious higher than that of ^{99m}Tc-HL91)3.73) and in case 12 image, the T/N of ^{18}F-FDG)8.90) was also obvious higher than that of ^{99m}Tc-HL91)3.30). However, there was less correlation between the T/N of ^{99m}Tc-HL91 and the T/N of ^{18}F-FDG after chemotherapy.(r_s = 0.518, p<0.001).

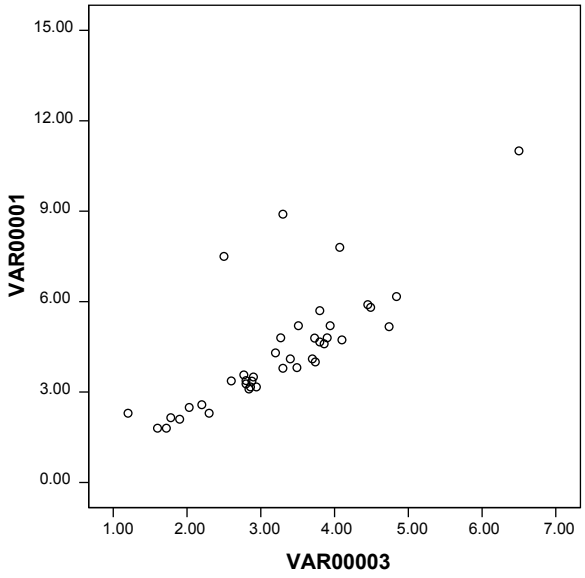

Figure 1: Correlation of the tumor to non-tumor ^{18}F-FDG and ^{99m}Tc-HL91 radioactivity ratio (T/N) in forty breast cancer patients before neoadjuvant chemotherapy. Each data point represents the T/N change of ^{18}F-FDG (VAR00001) and ^{99m}Tc-HL91 (VAR00003) radioactivity in an individual tumor. Spearman rank correlation analysis detected a linear correlation between the T/N of ^{99m}Tc-HL91 and the T/N of ^{18}F-FDG (r = 0.778, p<0.0001)

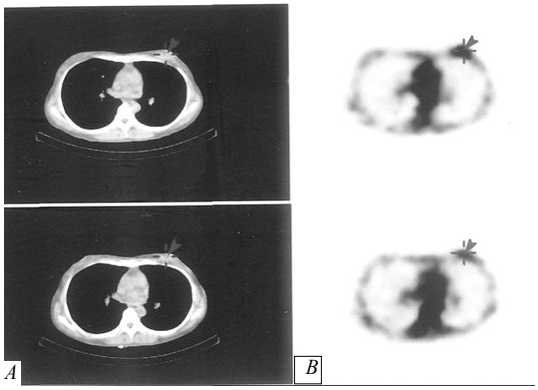

Figure 2: The pre-(above) and post-treatment (below) CT imaging(A) and hybrid ^{18}F-FDG PET imaging (B) in a breast cancer patient with a response to neoadjuvant chemotherapy. After neoadjuvant chemotherapy, the radioactivity of ^{18}F-FDG in breast cancer area decreased significantly, with the tumor to non-tumor FDG radioactivity ratio decreasing from 2.58 to 1.94.

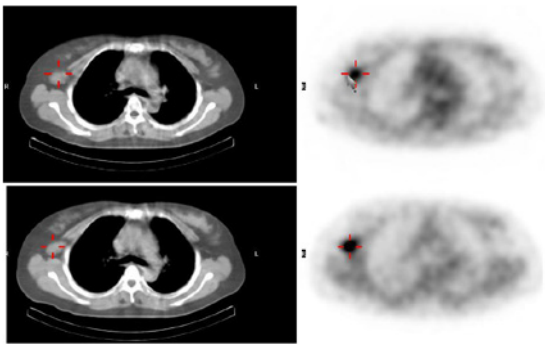

Figure 3: The pre-(above) and post-treatment (below) CT imaging(A) and hybrid ^{18}F-FDG PET imaging (B) in a breast cancer patient with non-response to neoadjuvant chemotherapy. After neoadjuvant chemotherapy, the radioactivity of ^{18}F-FDG in breast cancer area was no significant difference, the tumor to non- tumor FDG radioactivity ratio was 2.76 (pre-treatment) and 2.68 (post-treatment) respectively.

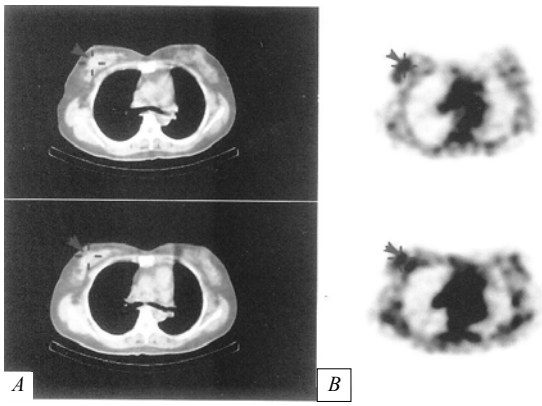

Figure 4: The pre-(above) and post-treatment (below) CT imaging(A) and hybrid ^{99m}Tc-HL91 SPECT imaging (B) in a breast cancer patient with response to neoadjuvant chemotherapy. After neoadjuvant chemotherapy, the radioactivity of ^{99m}Tc-HL91 in breast cancer area was no significant difference, with the tumor to non- tumor HL91 radioactivity ratio was 2.33(pre-treatment) and 2.46(post-treatment) respectively.

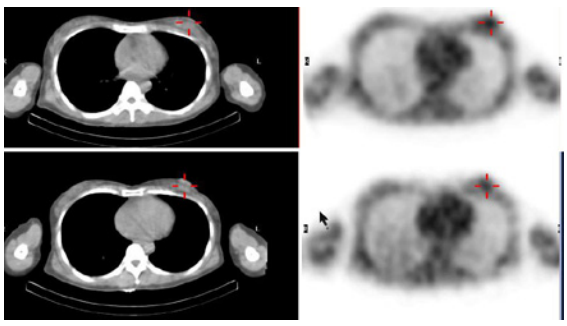

Figure 5: The pre-(above) and post-treatment (below) CT imaging(A) and hybrid ^{99m}Tc-HL91 SPECT imaging(B) in a breast cancer patient with non-response to neoadjuvant chemotherapy. After neoadjuvant chemotherapy, the radioactivity of ^{99m}Tc-HL91 in breast cancer area was no significant difference, with the tumor to non- tumor HL91 radioactivity ratio was 2.15(pre-treatment) and 2.07(post-treatment) respectively.

Assessment of treatment response by ^{18}F-FDG imaging

The mean T/N of ^{18}F-FDG (3.02 ± 0.98) post-chemotherapy for the 40 tumor lesions was with significant decreased from that pre-chemotherapy (4.35 ±1.95) (t= 3.861 p<0.01); the mean

T/N of ^{18}F-FDG in OR group (n 29) and NC group (n 11) post-chemotherapy were 2.92 ± 1.05 and 3.30 ± 0.74, respectively. The T/N was significantly decreased in patients with a good response to neoadjuvant chemotherapy)$t = 3.863$ $p< 0.01$) (Figure 2) whereas it was not significant in patients with non-response to neoadjuvant chemotherapy ($t = 0.842$ $p >0.05$) (Figure 3). When 20% reduction in T/N was set as the threshold for differentiation between responders and nonresponders, 27 of 29 responders and 10 of 11 nonresponders were identified after three courses of chemotherapy.

Assessment of treatment response by ^{99m}Tc–HL91 imaging

The mean T/N of ^{99m}Tc–HL91 (2.35 ±0.74) post-chemotherapy for the 40 tumor lesions was no significant difference from that pre-chemotherapy (3.24 ± 0.74, $p <0.05$). Comparing the T/N of ^{99m}Tc–HL91 pre- and post-chemotherapy, ten cases had decreased in the responders group, whereas eight cases had decreased in the non-responders group; the rest patients' T/N of ^{99m}Tc–HL91 increased with variable extent. The mean T/N of ^{99m}Tc–HL91 in a breast cancer patient with response or non-response to neoadjuvant chemotherapy was 2.18±0.74 or 2.81±0.56, respectively ($p<0.05$) (Figure 4, Figure 5), suggesting ^{99m}Tc–HL91 PET does little value in predicting early response of tumors to neoadjuvant chemotherapy.

Discussion

Substantial results from clinical research proved that patients suffer from breast cancer could benefit from neoadjuvant chemotherapy before surgery. And the effectiveness of neoadjuvant chemotherapy is usually accessed by the size of the tumor determined by ultrasonography or mammography. However, measurement of the tumor size could neither differentiate the viable cancer cells from inflammatory reaction, edema and scar resulted from chemotherapy nor reflect the blood supply and metabolism of the lesion. In this study, we found that the clinical evaluation is not in agreement with the pathological evaluation completely. For example, the two patients in the CR group showed stage I pathological changes, on the other hand, four patients in the ineffective group showed stage III pathological changes. It is identical to the results and view of Chollet,P. and Kurosumi M et al.[6,7].

Since the change of tumor metabolism precedes the change of tumor size, researchers had explored using ^{18}F-FDG PET, a functional imaging method which could reflect the level of glucose metabolism, to evaluate the early response of tumor tissue to neoadjuvant chemotherapy and pronounced prediction value of the decrease of SUV was found to be superior to the change of tumor size in breast cancer and other cancers. As hybrid PET/CT is more popular than PET in developing country for their relatively low cost, in this study we explored whether the T/N ratio of hybrid PET/CT could be an good substitute for SUV of PET/CT in evaluation of the early response to neoadjuvant chemotherapy and found that when 20% reduction in T/N was set as the threshold, responders and nonresponders could be differentiated with high accuracy. So we proposed that T/N ratio could substitute SUV in prediction of the early tumor response to neoadjuvant chemotherapy which is more acceptable for the low-income population but should be further confirmed in prospective randomized studies.

^{99m}Tc–HL91 had been proved to have good affinity to tumor's hypoxia tissues, and it is a kind of widely used tumor hypoxia imaging agent, including in vitro cell tests, animal tumor model experiments and clinical tests. In this study, we found that T/N ratio determined by ^{99m}Tc-HL91 imaging with hybrid PET/CT correlated well with that determined by ^{18}F-FDG imaging before neoadjuvant chemotherapy, suggesting that the glucose metabolic rate of the tumor tissues correlate with the degree of hypoxia in stage II and III breast cancer. However, the linear correlation decreased after chemotherapy, suggesting that the T/N ratio of ^{18}F-FDG imaging could not fully delineate the hypoxia region inside the tumor mass after therapy. As hypoxia-inducible factor 1 has been considered as an independent predictor of tumor radioresistance, the T/N ratio of ^{18}F-FDG imaging was no better than that of ^{99m}Tc-HL91 imaging in adjusting the dose of radiation when radiotherapy is combined with neoadjuvant chemotherapy to further improve the tumor response.

Conclusion

In summary, we suggest that ^{18}F-FDG imaging with hybrid PET/CT provides a cost-effective method, which could be well accepted for the low-income population in developing countries, to monitor early tumor response after three cycles of neoadjuvant chemotherapy in stage II and III breast cancer by using the reduction of N/T ratio as predictor. And ^{99m}Tc-HL91 imaging would be more helpful than ^{18}F-FDG imaging in adjusting the dose of radiation when radiotherapy is combined with neoadjuvant chemotherapy to further improve the tumor response.

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