

# Assessment of tumor response to chemotherapy in patients with breast cancer using $^{18}\text{F}$ -FLT: a meta-analysis

Sheng-Ming Deng<sup>1,2,3</sup>, Wei Zhang<sup>1</sup>, Bin Zhang<sup>1,3</sup>, Yi-Wei Wu<sup>1</sup>

<sup>1</sup>Department of Nuclear Medicine, The First Affiliated Hospital of Soochow University, Suzhou 215000, China; <sup>2</sup>School of Radiation Medicine and Protection, Medical College of Soochow University, Suzhou 215000, China; <sup>3</sup>Key Laboratory of Nuclear Medicine, Ministry of Health, Jiangsu Key Laboratory of Molecular Nuclear Medicine, Jiangsu Institute of Nuclear Medicine, Wuxi 214000, China

Correspondence to: Bin Zhang. Department of Nuclear Medicine, The First Affiliated Hospital of Soochow University, Suzhou 215000, China. Email: zbnucmd@126.com.

**Purpose:** To determine the diagnostic performance of 3'-deoxy-3'- $^{18}\text{F}$ -fluorothymidine positron emission tomography/computed tomography (FLT PET/CT) and FLT PET for evaluating response to chemotherapy in patients with breast cancer.

**Methods:** Databases such as PubMed (MEDLINE included) and excerpta medica database (EMBASE), were searched for relevant original articles. The included studies were assessed for methodological quality with quality assessment of diagnosis accuracy studies (QUADAS) score tool. Histopathological analysis and/or clinical and/or radiological follow-up for at least 6 months were used as the reference standard. The data were extracted by two reviewers independently to analyze the sensitivity, specificity, summary receiver operating characteristic (SROC) curve, area under the curve (AUC), and heterogeneity.

**Results:** The present study analyzed a total of 4 selected articles. The pool sensitivity was 0.773 [95% confidence interval (CI): 0.594-0.900]. The pooled specificity was 0.685 (95% CI: 0.479-0.849) on basis of FEM. The pooled LR+, LR-, and DOR were 2.874 (1.492-5.538), 0.293 (0.146-0.589), and 14.891 (3.238-68.475), respectively. The AUC was 0.8636 ( $\pm 0.0655$ ), and the Q\* index was 0.7942 ( $\pm 0.0636$ ).

**Conclusions:** Our results indicate that  $^{18}\text{F}$ -FLT PET/CT or PET is useful to predict chemotherapy response in breast cancer with reasonable sensitivity, specificity and DOR. However, future larger scale clinical trials will be needed to assess the regimen of  $^{18}\text{F}$ -FLT PET/CT or PET in monitoring the response to chemotherapy in breast cancer patients.

**Keywords:** Breast cancer;  $^{18}\text{F}$ -FLT PET; chemotherapy; meta-analysis

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## Introduction

Breast cancer is a leading cause of cancer death in women in the world, accounting for 23% of the total cancer cases and 14% of the cancer deaths (1). Chemotherapy is a widely accepted treatment for breast cancer. However, many patients will still be incurable despite the significant advances in treatment. There is a need to develop imaging methodologies that can enable early and objective assessment of response to chemotherapy. Currently, treatment responses are assessed on the basis of measurement of tumor size before

and after treatment with serial conventional radiography, such as chest X-ray, computed tomography (CT) or magnetic resonance imaging (MRI) (2). However, response monitoring by conventional methods is recommended after 2-3 cycles of chemotherapy. Patients with breast cancer receiving chemotherapy cannot benefit from conventional radiography, since ineffective treatment could not be timely detected and replaced.

A potential novel way of response monitoring is by molecular imaging positron emission tomography (PET) imaging with 3'-deoxy-3'- $^{18}\text{F}$ -fluorothymidine ( $^{18}\text{F}$ -FLT

PET).  $^{18}\text{F}$ -FLT is a pyrimidine nucleoside that is a substrate for the cytoplasmic enzyme, thymidine kinase 1 (TK1). TK1 phosphorylates  $^{18}\text{F}$ -FLT into a highly charged product which is trapped and can be imaged using PET (3). Recently, some studies evaluated the ability of this tracer to monitor response in breast cancer. However, the numbers of cases in studies were insufficient. Thus, we perform a meta-analysis to review the update relevant literature, and assess the diagnostic role of  $^{18}\text{F}$ -FLT PET for evaluating response to chemotherapy in patients with breast cancer.

## Materials and methods

### Literature search

A systematic literature search was performed to find articles that evaluate the response of breast cancer to chemotherapy. Two investigators (BZ and SMD) independently searched the PubMed (MEDLINE included) database, EMBASE to identify relevant studies published from January 1, 1993 to October 1, 2013. It was performed with no language restrictions and limited to human studies. The key words used were (“positron emission tomography” OR “PET” OR “positron emission tomography/computed tomography” OR “PET/CT” OR “PET-CT” OR “positron emission tomography-computed tomography” OR “thymidine” OR “fluorothymidine” OR “deoxy-thymidine” OR “deoxy-l-thymidine” OR “ $^{18}\text{F}$ -fluorodeoxy-L-thymidine” OR “3’-deoxy-3’- fluorothymidine” OR “fluorodeoxythymidine” OR “FLT” OR “ $^{18}\text{F}$ -FLT” OR “ $^{18}\text{FLT}$ ”) AND (“breast cancer” OR “breast carcinoma” OR “breast neoplasm” OR “breast neoplasia” ) AND (“prediction” OR “response” OR “response monitoring” OR “chemotherapy” OR “neoadjuvant”) AND (“sensitivity” OR “specificity” OR “false negative” OR “false positive” OR “accuracy”). The list of articles was supplemented with extensive cross checking of the reference lists of all retrieved articles.

### Study identification and selection

#### The inclusion criteria were as follows:

- (I) The study investigated the performance of FLT PET/CT or PET for evaluating chemotherapy in patients with proven breast cancer;
- (II) Histopathological analysis and/or clinical and/or radiological follow-up for at least 6 months were used as the reference standard;
- (III) The reported primary data were sufficient to calculate

- the totals of true and false positives and negatives;
- (IV) The study included more than nine lesions or patients with histological breast cancer;
- (V) When data or subsets of data were presented in more than one article, the one with most details was chosen.

#### Studies were excluded based on the following criteria:

- (I) Animal studies, case report, abstracts, reviews, letters, editorials, comments, *in vitro* studies, studies without raw data;
- (II) PET/CT or PET examination used other radiotracers. Discrepancies in judgment were resolved after discussion.

### Data extraction and quality assessment

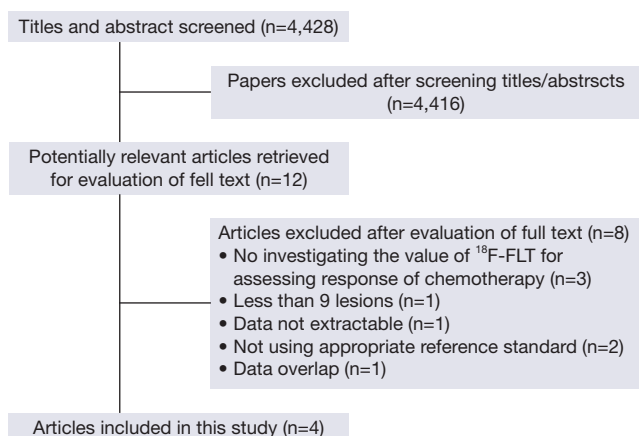
Data collected from the individual studies included: authors, year of publication, sample size, age, study design, initial clinical stage, timing for PET scans, cutoff values, definition of positive PETs, number of responders and non-responders, characteristics of PET/CT or PET imaging, interpretation of the reference standard, and clinical and/or radiological follow-up. The numbers of true and false positives and negatives were also recorded.

The quality assessment of diagnosis accuracy studies (QUADAS) tool was selected to assess the methodological quality of the studies (4,5). QUADAS consists of 14 questions for assessing different categories of bias in a study. If the answer is “yes” then score “1”, and if the answer is “no” or “unclear” then score “0”. Two observers (BZ and SMD) independently assessed the methodological quality. A consensus was reached to resolve any differences between the two reviewers.

### Statistical analysis

Two reviewers constructed 2×2 contingency tables for each study independently. For studies with zeroes in 1 or more cells, 0.5 was added to all four cells of the 2×2 table. Data on the sensitivity, specificity, positive likelihood ratio (LR+), negative likelihood ratio (LR-), diagnostic odds ratio (DOR), and 95% confidence intervals (CI) were calculated according to the numbers from the original publications. The summary receiver operating characteristic (SROC) curves and  $Q^*$  index ( $Q^*$  index is defined by the point where sensitivity and specificity are equal) were also obtained.

The presence of heterogeneity among different studies was analyzed by chi-square test and quantified by calculating the  $I^2$  statistic with the equation:  $I^2 = (Q-df)/Q$ . Statistical



**Figure 1** Flow diagram for selection of studies.

heterogeneity was defined as an  $I^2$  statistic value of more than 50% (6). According to the heterogeneity, a fixed effects model (FEM) was adopted to calculate the diagnostic indexes if homogeneity existed among different effect sizes, and a random effects model was adopted if heterogeneity existed.

All analyses were executed using Microsoft Excel 2003 (Microsoft, Seattle, WA, USA), and Meta-Disc (version 1.4) software package (7). Meta-Disc is a freeware for performing a systematic review of diagnosis and screening tests, produced by Javier Zamora, free available at [http://www.hrc.es/investigacion/metadisc\\_en.htm](http://www.hrc.es/investigacion/metadisc_en.htm), Madrid, Spain.

## Results

### Search strategy and study selection

A total of 4,428 abstracts were identified by computer search and extensive cross-checking of reference lists. Twelve articles were considered as candidates after the perusal of titles and abstracts. After reading the full texts of the remaining 12 articles, 8 were excluded due to different reasons. Finally, four articles were identified as eligible, all of which were obtained with full-texts. The flow diagram for the selection of the studies is presented in *Figure 1*.

### Methodological quality assessment

On basis of the results of the “QUADAS” quality assessment, all studies met at least 11 of the 14 standards. However, no study met all the 14 questions (*Table 1*). The main weakness was the execution of reference standard was not described

in sufficient detail. Actually, a “clinical and/or radiological follow-up” was introduced as reference standard for all the four studies instead of “histopathological analysis”. Another weakness was blind interpretation of PET or reference standard results. In 2 of the 4 included studies, the time period between reference standard and PET was not short enough for using “follow-up” as standard criteria.

### The characteristics of the studies

Characteristics of the four eligible studies included in the meta-analysis are outlined in *Table 2*. All were in English. There were total 46 patients in the selected studies with ages ranging 18-80 years. The sample size of the studies ranged from 6 to 18. In two studies, several patients had more than one tumor site; therefore, a total of 54 tumors were assessed in the meta-analysis.

There were three studies on PET and 1 on PET/CT. All studies performed a sequential PET or PET/CT both before and after the chemotherapy. All articles assessed treatment of same chemotherapy except one study also using endocrine therapy. In 1 study, an increase in tumor  $^{18}\text{F}$ -FLT uptake was selected as the cutoff criterion for response to chemotherapy after 1 hour of initiation of chemotherapy. The other 3 studies relied on reduction of  $^{18}\text{F}$ -FLT uptake as PET or PET/CT criteria for therapy response.

### Data analysis

Across all four included studies evaluating  $^{18}\text{F}$ -FLT PET/CT or PET, we used a FEM to calculate pooled sensitivity, specificity, LR+, LR-, and DOR on the basis of statistical non-heterogeneity (*Figures 2-6*). The sensitivity of  $^{18}\text{F}$ -FLT PET/CT or PET to assess chemotherapy response in breast cancer ranged from 56.3% to 92.9%. The pool sensitivity was 77.3%. The specificity ranged from 45.8% to 91.7%. The pooled specificity was 68.5%. The detailed sensitivity, specificity, LR+, LR-, and DOR with 95% of CI for individual studies are presented in *Table 3*.

The SROC curves with  $Q^*$  index are shown in *Figure 7*. Of all four studies, the AUC ( $\pm$  standard error) was 0.8636 ( $\pm 0.0655$ ), the  $Q^*$  index was 0.7942 ( $\pm 0.0636$ ).

## Discussion

Recently, whole-body imaging with fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-

**Table 1** The distribution of methodological characteristics

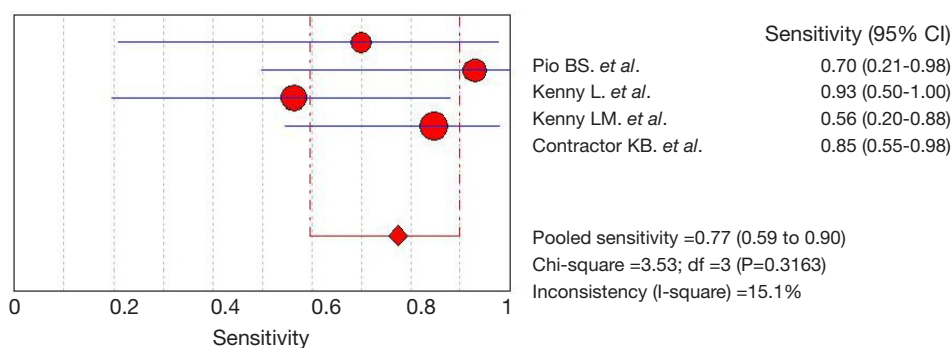
First author (reference)	Representative spectrum of patients	Selection criteria	Reliable reference standard	Short time interval	Whole or random sample received verification	Same reference standard	Reference standard independent of the PET	Description of execution of PET	Description of execution of reference standard	Interpretation of PET blinded from reference standard	Interpretation of reference standard blinded from PET	Clinical data available	Uninterpretable test results reported	Withdrawals explained
Plo BS, et al. (8)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Unclear	Yes	Yes	Yes
Kenny L, et al. (9)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Unclear	Yes	Yes	Yes
Kenny LM, et al. (10)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Unclear	Yes	Yes	Unclear
Contractor KB, et al. (11)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Unclear	Yes	Yes	Yes

PET, positron emission tomography.

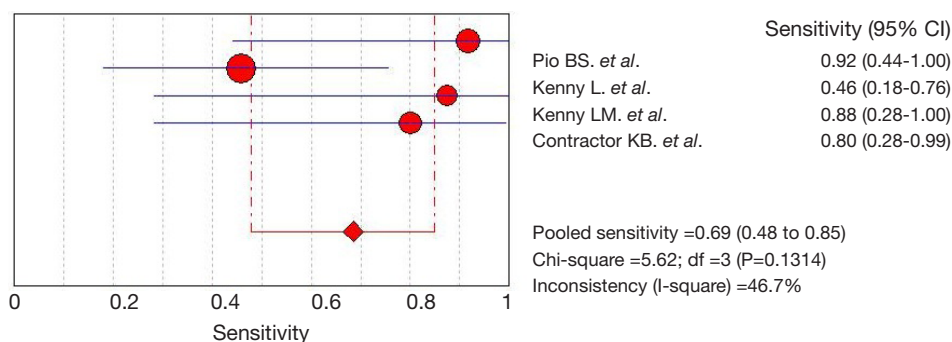
**Table 2** Characteristics of studies of <sup>18</sup>F-FLT PET or PET/CT for assessing response to chemotherapy in breast cancer

First author, year (reference)	No. of patients	No. of tumors	Age range	Tumor stage	Regimen	Study type	Reference standard	No. of responders	Imaging modality	Timing of PET	PET criteria
Plo BS, 2006 (8)	9	9	NR	Metastatic breast cancer	Chemotherapy and hormonal therapy	Prospective	CT follow-up	3	PET	Before, 2 weeks following the end of the first cycle of the new regimen	Not mentioned
Kenny L, 2007 (9)	13	17	18-80	Stage II-IV	FEC Chemotherapy	NR	RECIST criteria	6	PET	Before, 1 week after chemotherapy	Reduction of SUV <sub>90</sub> ≥ 18%
Kenny LM, 2009 (10)	6	10	NR	Stage III-IV	Capecitabine chemotherapy	NR	RECIST criteria	4	PET	Before, 1 hour after the first oral dose of capecitabine	Increase in imaging variable of >95% CI
Contractor KB, 2011 (11)	18	18	41-69	Stage II-IV	Docetaxl chemotherapy	Prospective	RECIST criteria	11	PET/CT	Before, 2 weeks after chemotherapy	Reduction of SUV <sub>90,av</sub> ≥ 20%

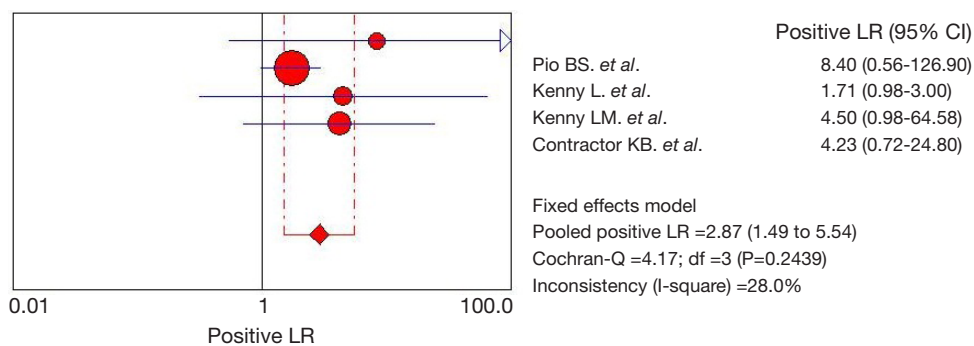
NR, not reported; PET, positron emission tomography; CT, computed tomography.



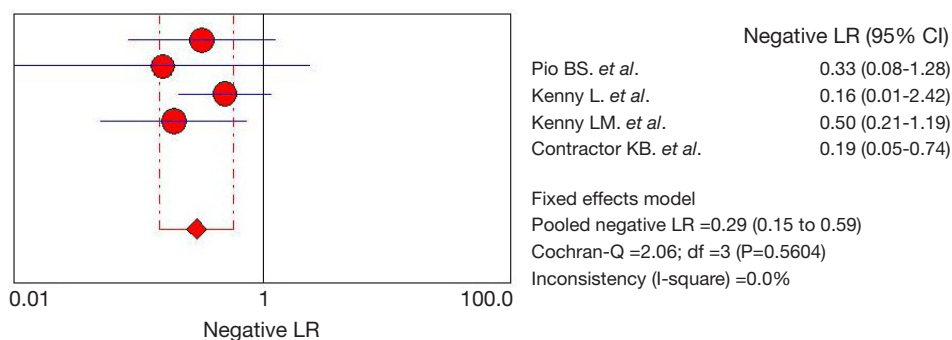
**Figure 2** Pooled and individual studies estimating the sensitivity of <sup>18</sup>F-FLT PET or PET/CT in monitoring response to chemotherapy in breast cancer. Studies are identified by the name of first author to the right of the graph. PET, positron emission tomography; CT, computed tomography.



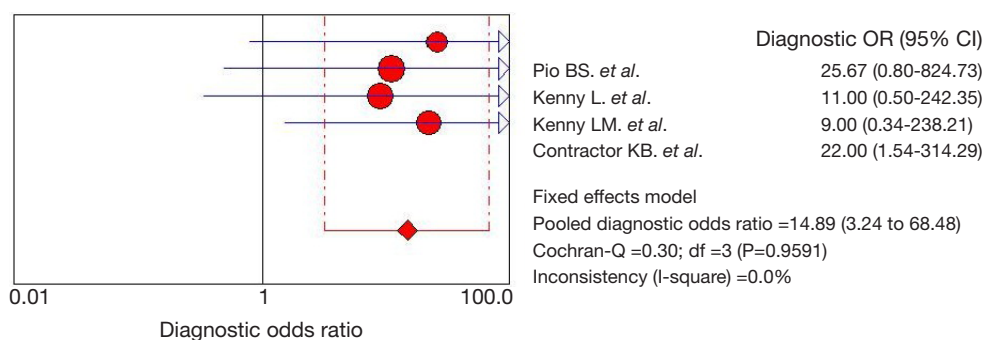
**Figure 3** Pooled and individual studies estimating the specificity of <sup>18</sup>F-FLT PET or PET/CT in monitoring response to chemotherapy in breast cancer. Studies are identified by the name of first author to the right of the graph. PET, positron emission tomography; CT, computed tomography.



**Figure 4** Pooled and individual studies estimating the LR+ of <sup>18</sup>F-FLT PET or PET/CT in monitoring response to chemotherapy in breast cancer. Studies are identified by the name of first author to the right of the graph. PET, positron emission tomography; CT, computed tomography.



**Figure 5** Pooled and individual studies estimating the LR- of  $^{18}\text{F}$ -FLT PET or PET/CT in monitoring response to chemotherapy in breast cancer. Studies are identified by the name of first author to the right of the graph. PET, positron emission tomography; CT, computed tomography.



**Figure 6** Pooled and individual studies estimating the DOR of  $^{18}\text{F}$ -FLT PET or PET/CT in monitoring response to chemotherapy in breast cancer. Studies are identified by the name of first author to the right of the graph. PET, positron emission tomography; CT, computed tomography.

PET) has gained widespread acceptance for assessing tumor response to chemotherapy in patients with breast cancer (12-14). However, it has been demonstrated that inflammatory tissues can accumulate  $^{18}\text{F}$ -FDG and that chemotherapy-induced inflammation can lead to misinterpretation of results.  $^{18}\text{F}$ -FLT has been used to demonstrate proliferative activity in various tumors. Most researchers have demonstrated that  $^{18}\text{F}$ -FLT is more specific than  $^{18}\text{F}$ -FDG for malignant tumors and is not susceptible to uptake due to inflammatory changes (15). Moreover,  $^{18}\text{F}$ -FLT PET images showed high tumor-to-background contrast. In a meta-analysis, 19 studies with total 786 breast cancer patients who received neoadjuvant treatment were included (16). In 15 studies  $^{18}\text{F}$ -FDG PET scan was performed before and at different moments during chemotherapy. The pooled analysis showed that  $^{18}\text{F}$ -FDG PET with a sensitivity of 84% and a DOR of 11.9 have a beneficial value to assess response of

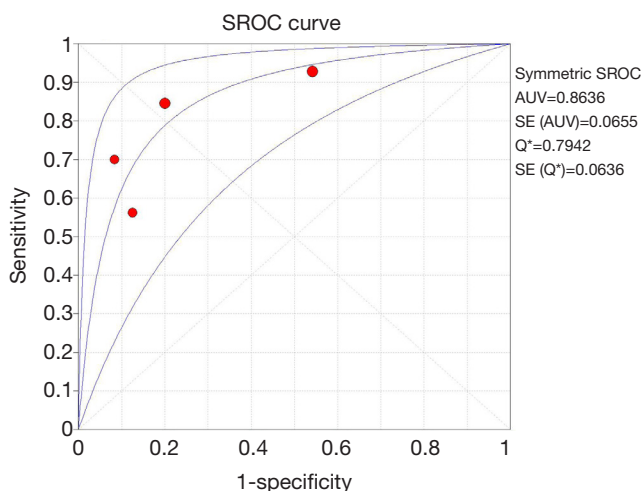
chemotherapy. However, the specificity (66%) is relatively low. Our statistical results confirmed that  $^{18}\text{F}$ -FLT PET/CT or PET has an important role in assessing response to chemotherapy in breast cancer, with relatively lower pooled sensitivity (77.3%), higher pooled specificity (68.5%) and DOR (14.891).

There were also drawbacks of  $^{18}\text{F}$ -FLT. Firstly,  $^{18}\text{F}$ -FLT PET or PET/CT had low sensitivity for the detection of regional lymph node metastases, which may be related to the lower uptake of  $^{18}\text{F}$ -FLT compared with  $^{18}\text{F}$ -FDG. Thus  $^{18}\text{F}$ -FLT scans showed more false-negative findings compared with  $^{18}\text{F}$ -FDG scans. Secondly, there was no standard regimen of  $^{18}\text{F}$ -FLT PET or PET/CT for assessing response to chemotherapy in breast cancer. The optimal moment of scanning, the quantification method and cutoff value of PET are issues. Most studies demonstrated that a decrease in  $^{18}\text{F}$ -FLT uptake after treatment of malignant tumors (8,9,11,17). SUV reduction rate was

**Table 3** True and false positives and negatives associated with the sensitivity, specificity, accuracy, and diagnostic odds ratios for the meta-analysis of chemotherapy assessment

Author	Year	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)	DOR (95% CI)
Pio BS, <i>et al.</i> (8)	2006	3	0	1	5	0.700 (0.209-0.977)	0.917 (0.442-1.000)	8.400 (0.556-126.90)	0.327 (0.084-1.276)	25.667 (0.799-824.73)
Kenny L, <i>et al.</i> (9)	2007	6	6	0	5	0.929 (0.499-1.000)	0.458 (0.180-0.757)	1.714 (0.980-3.000)	0.156 (0.010-2.416)	11.000 (0.499-242.35)
Kenny LM, <i>et al.</i> (10)	2009	4	0	3	3	0.563 (0.199-0.881)	0.875 (0.284-1.000)	4.500 (0.314-64.581)	0.500 (0.210-1.192)	9.000 (0.340-238.21)
Contractor KB, <i>et al.</i> (11)	2011	11	1	2	4	0.846 (0.546-0.981)	0.800 (0.284-0.995)	4.231 (0.722-24.796)	0.192 (0.050-0.740)	22.000 (1.540-314.29)
Pooled results		24	7	6	17	0.773 (0.594-0.900)	0.685 (0.479-0.849)	2.874 (1.492-5.538)	0.293 (0.146-0.589)	14.891 (3.238-68.475)
Heterogeneity test						( $I^2=15.1%$ , $P=0.316$ )	( $I^2=46.7%$ , $P=0.131$ )	( $I^2=28.0%$ , $P=0.244$ )	( $I^2=0.0%$ , $P=0.560$ )	( $I^2=0.0%$ , $P=0.959$ )

TP, true positive; FP, false positive; TN, true negative; FN, false negative; LR+, positive likelihood ratio; LR-, negative likelihood ratio; DOR, diagnostic odds ratio; CI, confidence intervals.



**Figure 7** The SROC curve for <sup>18</sup>F-FLT PET or PET/CT. Solid circle represents each study in the meta-analysis. The size of the circle indicates the study size. SROC, summary receiver operating characteristic. PET, positron emission tomography; CT, computed tomography.

recommended as PET or PET/CT criterion. However, the increase in <sup>18</sup>F-FLT uptake after treatment was also reported (10,18,19). In one included study, a repeat <sup>18</sup>F-FLT PET was performed to assess the response and an increase in tumor <sup>18</sup>F-FLT uptake was selected as the criterion of

PET. Since no statistical heterogeneity was identified in this study, we did not performed subgroup analyses.

There are some limitations with the present study. Firstly, the number of studies is small. It may lead to imprecise and inconclusive results. Secondly, there was verification bias or workup bias, because not all patients were subjected to the same reference test. The most valid reference test for response of chemotherapy is histopathology. But not all patients and lesions were biopsied consistently. Therefore, the present study used histopathological analysis and/or close clinical and/or radiological follow-up for at least 6 months as reference standard. Other potential limitations include publication bias, selector bias.

**Conclusions**

To our knowledge, this is the first report using meta-analysis to assess the overall diagnostic role of <sup>18</sup>F-FLT PET or PET/CT for evaluating response to chemotherapy in patients with breast cancer. As examined by the QUADAS tool, methodological quality of reports was relatively high. Despite some limitations, meta-analysis demonstrated a beneficial value of <sup>18</sup>F-FLT PET or PET/CT to monitor the response to chemotherapy in breast cancer, with reasonable sensitivity, specificity and DOR. Studies with larger scale are warranted to further assess the regimen of <sup>18</sup>F-FLT PET.

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*Disclosure:* The authors declare no conflict of interest.

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