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The prognostic value of SUV_{max} measuring on primary lesion and ALN by ^{18}F-FDG PET or PET/CT in patients with breast cancer

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ABSTRACT

Purpose: To evaluate the prognostic value of maximum standardized uptake values (SUV_{max}) measured in the primary lesion and axillary lymph nodes (ALN) by pretreatment fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) or positron emission tomography/computed tomography (PET/CT) in patients with breast cancer.

Methods: We systematically searched PubMed, Embase, and the Cochrane Library. The primary prognosis endpoint was event-free survival (EFS), and the secondary endpoint was overall survival (OS). The pooled hazard ratio (HR) was estimated by using random-effects model according to the results of heterogeneity.

Results: Fifteen eligible studies with 3574 breast cancer patients were included. For EFS, patients with higher primary SUV_{max} showed a poorer survival prognosis with pooled HR of 1.96 (95% confidence interval (CI) 1.40–2.73). The combined HR of high SUV_{max} in ALN and ALN-to-primary SUV_{max} ratio (N/T ratio) were 1.89 (95% CI 0.70–5.07) and 2.06 (95% CI 0.59–7.21), respectively. In analyzing invasive ductal carcinoma (IDC) patients, the pooled HR was 1.91 (95% CI 1.40–2.64). For OS, the pooled HR of SUV_{max} in primary lesion and ALN were 0.64 (95% CI 0.23–1.84) and 1.09 (95% CI 0.07–16.53), respectively.

Conclusions: Our meta-analysis suggested that patients with high primary SUV_{max} may experience a higher risk for recurrence or a poor progression. Moreover, the SUV_{max} of ^{18}F-FDG showed a significant prognostic value in IDC patients.

1. Introduction

Breast cancer (BC) is the most commonly diagnosed cancer accounting for 29% of all newly diagnosed cancers and the second commonest cause of cancer-related death in the United States women [1]. Estimated 40,450 women per year die from BC and most of them die of the progressive metastatic disease in the United States [1]. Although newly imaging tools and adjuvant systemic treatment have improved the survival BC patients, local relapses still were found in about 10–15% of the early stage invasive BC patients after suitable treatment [2]. Therefore, it is crucial to identify those who may experience recurrence or progression.

Prediction of prognosis is quite essential for BC patients before designing therapy strategy. Many factors seem effective to predict patients who have a high risk of recurrence or progression. These factors include tumor size, nuclear grade, axillary lymph node (ALN) involvement, the status of hormone receptors (e.g., estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2)), and Ki-67 proliferation index [3]. Except for all these factors, increasing evidence has proved that fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) has a promising role in predicting prognosis of malignant tumors [4].

^{18}F-FDG PET/CT has been widely used in malignant tumors not only for initial stage or restage, early treatment response assessment, but for recurrence or metastasis detection and prognosis prediction [5]. Several recent systematic reviews and meta-analyses found that the maximum standardized uptake value (SUV_{max}) of ^{18}F-FDG could serve as a prognostic factor in various malignant tumors, such as diffuse large B cell lymphoma, uterine cervical cancer and non-small cell lung cancer [6–8]. Buck et al. [9] suggested that higher FDG uptake was correlated with the more clinically aggressive behavior of BC. However, it is still controversial whether high or low SUV_{max} predicts reduced survival of BC patients. Some studies found significant relationships between high SUV_{max} and poor prognoses in patients with BC [10–12], whereas De

Abbreviations: PET/CT, positron emission tomography/computed tomography; ^{18}F-FDG, fluorine-18-fluorodeoxyglucose; BC, breast cancer; IDC, invasive ductal carcinoma patients; EFS, event-free survival; DFS, disease-free survival; HR, hazard ratio; OS, overall survival; SUV_{max}, maximum standardized uptake value; ALN, axillary lymph node

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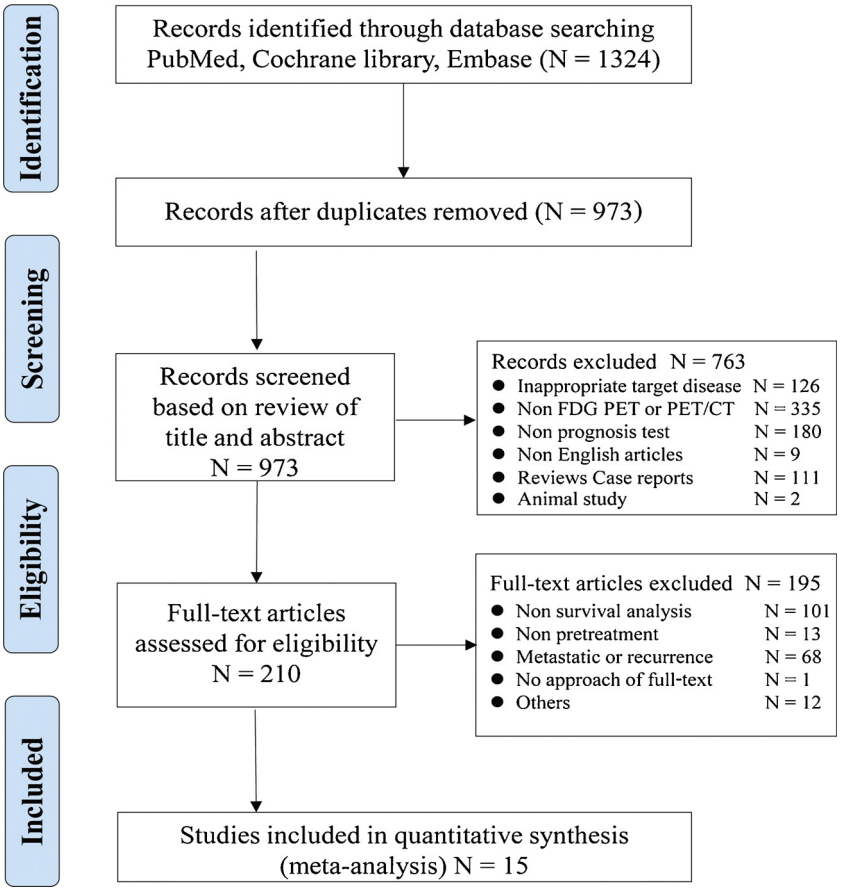

Fig. 1. Flowchart of the selection process for eligible studies; Illustration of the number of articles identified in the literature search and reasons for exclusion.

Cicco et al. [13] did not find such a correlation. Therefore, we conducted this meta-analysis to investigate the prognostic value of SUV_{max} measured in primary lesions and ALN by pretreatment ^{18}F-FDG PET or PET/CT scans in patients with BC.

2. Materials and methods

2.1. Search strategy and eligible criteria

We performed a systematic search of PubMed, Embase and the Cochrane Library (1993 to April 2018). The following keywords were employed: "breast neoplasms" or "breast cancer" or "breast carcinoma"; "positron emission tomography" or "PET/CT" or "fluorine-18-fluorodeoxyglucose" or "^{18}F-FDG"; "standardized uptake value" or SUV_{max} and "prognosis" or "prediction" or "outcome" or "survival". All searches were limited to human studies. Only articles published in English were included.

The inclusion criteria were as follows: (1) studies involved patients with histologically diagnosed BC; (2) ^{18}F-FDG PET/CT was used as an imaging tool before the treatment; (3) the metabolic level of primary lesions or axillary lymph node was measured with SUV_{max}; (4) studies reported at least one form of survival data. The exclusion criteria were as follows: (1) studies only focused on diagnosis, staging, or monitoring recurrence or progression; (2) studies involved patients with recurrent or distant metastatic disease before treatment; (3) studies only included luminal or Her2 positive or triple negative subtype breast cancer patients; and (4) reviews, case report, conference abstracts and editorial materials.

Two authors independently performed the initial screening by reviewing the titles and abstracts according to the inclusion and exclusion criteria. Any discrepancy was resolved by discussion. Full-text would be reviewed if the records reported the prognosis of BC with pretreatment ^{18}F-FDG PET or PET/CT.

2.2. Data extraction and quality assessment

Two reviewers independently extracted the relevant data, and the following information was recorded: first author, year of publication, study design, sample size, follow-up duration, median or mean age, histology types, treatment measures, PET protocols, endpoint, and cut-off value.

Three investigators independently reviewed and scored each study using the quality scale that had been widely used (Supplementary Table 1) [6,14,15]. This quality scale consisted of four categories: scientific design, generalizability, analysis result, and PET reports. Each item in these categories was assigned 0, 1, or 2 points. As a result, each category had a maximum score of 10 points. After the assessment, each investigator could acquire a total quality score. The final score was obtained by averaging these three total scores and was expressed in percentage with higher score reflecting higher quality.

2.3. Statistical analysis

The event-free survival (EFS) was defined as the time from initiation of therapy until recurrence or progression [16,17]. In some included studies, disease-free survival (DFS), relapse-free survival (RFS) and recurrence or progression-free survival (PFS) were obtained as the primary outcomes, but they were all redefined as EFS in this meta-analysis. The overall survival (OS) was defined as the time from the initiation of therapy to death regardless of the causes [6,17].

To aggregate the estimated effect, we measured the impact of SUV_{max} on survival by hazard ratio (HR). We extracted the multivariate