Review Article

Examining the evolving utility of ^{18}FDG-PET/CT in breast cancer recurrence

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Abstract: Many studies have demonstrated the utility of ^{18}fluorodeoxyglucose-positron emission tomography/computed tomography (^{18}FDG-PET/CT) scan in evaluating breast cancer recurrence in subsets of patients based on age, histological subtype and cancer stage to guide response to conventional chemoradiation guidelines during treatment of metastatic breast cancer disease. This literature review focuses on the breakthrough of ^{18}FDG-PET/CT imaging within the paradigm of breast cancer oncology centered toward improving risk stratification and prognostication of disease relapse based on cancer molecular phenotypes, tumor markers, early metabolic activity and response to neoadjuvant chemotherapy (NAC). The authors consider the rapid shift toward biomarker based molecular tracers to quantify treatment response and pathologic complete response with more recent imaging modalities such as dedicated breast positron emission tomography (dbPET), and the advantages afforded by this multisystem approach.

Keywords: Breast cancer; ^{18}Fluorodeoxyglucose-positron emission tomography/computed tomography (^{18}FDG-PET/CT); staging; SUVmax; neoadjuvant; dedicated breast position emission tomography (dbPET); metabolic activity

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Introduction

^{18}Fluorodeoxyglucose-positron emission tomography/computed tomography (^{18}FDG-PET/CT) has proven over time to be at the forefront of diagnostic staging in recurrent breast cancers, most notably in women with advanced local disease or equivocal findings on CT or MRI. While mammograms and ultrasounds are still used to elucidate the diagnosis of benign breast lesions or primary breast cancers, the highly sensitive tracking modality of ^{18}FDG-PET/CT during subsequent patient encounters keep it as a highly valuable tool in radiation oncology (1). However, given the resurgence of disease relapse during the first two to three years after primary treatment, with localized, regional or distant metastatic involvement, the utility of ^{18}FDG-PET/CT in the detection and subsequent management of breast cancer patients during chemoradiotherapy has become more common (2). In addition to the ongoing evaluation of pre- and post-operative usage of ^{18}FDG-PET/CT, current studies are focusing on understanding the novel features of PET/CT. ^{18}FDG-PET/CT has already been measured for accuracy of tumor detection, but is now being examined with concomitant profiling of serum markers, risk stratification of metastasis, and response to neoadjuvant chemotherapy (NAC) based on radionuclide uptake metrics. In this paper, we searched the English language literature databases of PubMed, Web of Science, and Google Scholar for recent breakthroughs in ^{18}FDG-PET/CT based on

breast tumor characteristics, different treatment points in relation to NAC, and modified PET/CT modalities to better understand tumor metabolic profiles.

Staging and monitoring recurrence

As the dilemma of multiple treatment strategies for patients with breast cancer recurrence presents to practitioners and oncologists, the timely and accurate diagnosis of failed outcomes from primary or even relapsed therapy must be recognized to tailor optimal treatment management. In patients with suspected breast cancer recurrence, ^{18}FDG-PET/CT has been well established in impacting patient discourse in the clinical setting from a non-treatment to treatment approach, based on positive findings discovered on ^{18}FDG-PET/CT (3). Furthermore, the National Comprehensive Cancer Network guidelines recommended ^{18}FDG-PET/CT for the detection of suspicious or equivocal metastatic lesions without the recommendation of the systematic use of PET/CT in breast cancer staging (4). Although the decreased sensitivity of ^{18}FDG-PET/CT hinders the accuracy in staging early stage breast cancer, the utility in high-risk patients, "intermediate-risk" patients (stage IIB disease or higher), inflammatory or locally advanced breast cancer (LABC) disease has been highlighted through various studies (3-5). Understandably, the known limitations of PET/CT spatial resolution and subsequent proclivity of false-positive results has led for the continued need to perform sentinel node biopsy when considering small nodal metastases.

Recurrence

The gap in 5-year survival rate in advanced disease is currently at 15%, substantially reduced from the 80% survival rate in early disease. The recurrence rate is nearly 30% in early stage disease, with a 6% 5-year recurrence after primary therapy in stage I-II disease (6,7). Therefore, making the detection of an early relapse is not only critical in the treatment of the patient but as well as the prognostication of breast cancer survivors. Current limitations of ^{18}FDG-PET/CT for breast cancer follow-ups are detecting loco-regional recurrence and distant metastasis in relapsed disease.

CA 15-3

Commonly evaluated tumor markers in breast cancer disease have been an emphasis in multi-center studies attempting to correlate the level of tumor markers to cancer recurrence. However, in patients with early disease burden ^{18}FDG-PET/CT demonstrates significant accuracy in assessing the site and extent of recurrence when confronted with elevated serum tumor markers in asymptomatic breast cancer patients following primary treatment (8-13). This event may be due in part from the lack of tumor marker level increase before clinical or radiological findings of recurrence (14,15). CA 15-3 in addition to carcinoembryonic antigen (CEA) trends have provided research insight not previously studied about performing ^{18}FDG-PET/CT to detect recurrent disease. In different studies' sensitivity and specificity of CA 15-3 in recurrent disease has ranged from 38–80% for sensitivity and 91% for specificity, making an appropriate cut-off value difficulty to identify (16,17). Retrospective studies have revealed that serial measurements of CA 15-3, up to nine months before ^{18}FDG-PET/CT evaluation in relapsed breast cancer patients, correlated with positive ^{18}FDG-PET/CT findings that confirmed the cancer recurrence (18). Although promising data has been presented, the value of ^{18}FDG-PET/CT in evaluating breast cancer recurrence with elevated tumor markers remains unclear (2,8-12).

Metabolic activity

In addition to the detection of cancer metastasis through the most common secondary sites (e.g., lungs, liver, bone, axillary lymph nodes), picking up on subtle changes in metabolic activity has provided insight into the prognostic values of standardized uptake values (SUVmax) derived from ^{18}FDG-PET/CT. Although targeted endocrine therapies for breast cancer treatment have a substantial impact on metabolic activity and tumor size, more studies are needed to understand the characteristics of breast cancer metabolism of molecular subtypes (4-12). Recently, hybrid modalities of ^{18}FDG-PET/CT and PET/MRI have provided anatomical-metabolic imaging as an approach for predicting response to treatment, although more studies are needed to establish the standardization in treatment guidance. Moving forward with current clinical trials, parameters such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG) are now being used to evaluate total tumor burden and metabolic activity to predict response to chemotherapy.

Molecular phenotypes: SUV and role of dedicated breast position emission tomography (dbPET)

As various PET scan modalities are brought to the forefront

of breast cancer staging in the hopes of minimizing irradiation exposure or surgery to vital tissue structures, efforts are now shifting towards apprehension of the metabolic characteristics of breast cancer molecular subtypes. Several studies have focused on this premise in lieu of improved imaging techniques to evaluate correlations between phenotypical prognostic factors and standard uptake value in tumors (19-22).

SUV profiles are an important characteristic of tumor pathophysiology that needs further clarification in understanding the aggressive tendencies and prognoses of these cancers. For example, studies have shown that primary lesions in triple-negative breast cancer (TNBC) have substantially higher SUV than non-TNBC groups although the latter have a lower pre-chemotherapy SUV than TNBC patients (9.8 *vs.* 6.4) (20,21). While focus on estrogen receptor (ER) lesions have shown that ER negative tumors have a higher change in SUV and pre-chemotherapy SUV than other phenotypes. In ER-positive/HER2-negative subtypes, early metabolic non-response to treatment was always considered pathologic non-response and hence a poor prognosis, causing speculation that ^{18}FDG-PET/CT would be beneficial to certain patients who would conceivably benefit from early strategic therapeutic modifications (23,24). ^{18}FDG-PET/CT monitoring was much more accurate in the ER-positive/HER2-negative and triple-negative subtypes than in the HER2-positive cancers, a conclusion that this response may be due to an initial inflammatory response induced by trastuzumab treatment in HER2-positive subtype patients (25). Many analogous studies have also exhibited the positive effect of ^{18}FDG-PET/CT in monitoring responses of such cancer subtypes to neoadjuvant chemotherapy (NAC).

dbPET is a newer iteration of PET technology with improved spatial resolution that targets specific breast cancer lesions of intratumoral heterogeneity. This imaging modality has already provided a clinical breakthrough in heterogeneous endocrine expressing malignancies, as identification by biopsy for tumor complexity becomes difficult given the limited number of samples at any one stage (26). Described in several reviews is the higher sensitivity for detecting sub-centimeter lesions in dbPET compared to ^{18}FDG-PET/CT while having the patient in a prone position (27,28). Given the use of ligands labeled with radionuclides, information about the various phenotypes of breast cancer have enabled investigators to quantify the proliferation of tumors and target their therapy based on tracer uptake. One such example is ^{18}F-fluoroestradiol (FES)-PET/CT, using estradiol, as an agonist for ER, to allow for imaging of ER-positive breast cancers (29,30). Furthermore, highlighting the potential of FES-PET/CT in guiding therapy response were clinical studies that demonstrated FES-PET/CT has high overall sensitivity and specificity at 84% and 98% respectively, in assessing the ER status in breast cancer (31).

Different uptake tracers with respect to breast cancer phenotypes have far fewer studies demonstrating improvement in patient care outcomes and detection of recurrence. HER2-positive cancers have shown a promise with [Zr89]-trastuzumab in detecting metastatic HER2-positive breast cancer in patients with HER2-negative primary breast cancer (32). Similarly, 18F-fluorofurany lnorprogesterone (FFNP)-PET/CT has shown to be a safe and non-invasive method for evaluating progesterone receptor positive tumors with high affinity and selectivity for progesterone receptors (PR) (33,34). As previously mentioned there remains a tremendous potential for these endocrine receptor tracers to advance drug discovery with enhancement of personalized treatment approaches and understanding of tumor phenotype biology in heterogeneous cancers.

SUVmax and response after neoadjuvant chemotherapy

Many patients with stage II and III breast cancer undergo NAC with four sequential courses of anthracycline (12,35). Tumor size, measured routinely by ultrasonography or MRI generally determines the therapeutic outcomes of patients undergoing NAC. While the elimination of residual cancer cells following NAC for primary tumors are associated with an improved overall disease-free, in most NAC studies, less than 30% complete response has been observed in patients (35).

The SUVmax, which reflects tumor viability, has shown good treatment predictability when used together with ^{18}FDG-PET/CT. Tracking of SUVmax in lymph nodes was reported to correlate well in many studies examining lymph node metastases in axillary sites of breast cancer disease. With the correlation of SUVmax and treatment response after NAC having been formed, relative changes in SUV and SUVmax were proposed as a means to differentiate non-metabolic from metabolic responders or between pathological complete response (pCR) and non-pCR (36-38). Achievement of pCR, or the lack of residual cancer after NAC, is an important period in the therapeutic course of breast cancer with an understanding that tumor grade, size and SUVmax can alter the chemotherapeutic or surgical management of cancer (39-

41). In one study evaluating the predicative usefulness of SUVmax before and after NAC, the post-SUVmax showed a significant correlation with achievement of pCR, specifically in patients HER2+ and TNBC (39). Another clinical trial used the change in SUVmax, or SUV reduction rates, calculated from ^{18}FDG-PET/CT images to demonstrate a better prognosis among certain responders from additional chemotherapy during NAC (42). However, SUVmax demonstrated have limitations in comparison to the uptake of FDG, due to the partial volume effect (43).

Conclusions

The studies examined in this literature review have broad implications supporting the following conclusions: (I) given the high recurrence rate of primary breast cancer after systemic therapy, early detection of relapse is vital in achieving early intervention and shift in chemoradiotherapy treatment; (II) cohort studies have demonstrated that serial tumor marker tracking in conjunction with ^{18}FDG-PET/CT is more specific than either study alone in detecting tumor recurrence; (III) there is an understood positive impact in detection accuracy of tumors with heterogeneous distribution when ^{18}FDG-PET/CT scan is employed; (IV) after the completion of NAC, post-SUVmax shows a significant correlation with pCR with breast cancer tumors, but further studies are needed to substantiate this finding with breast cancer molecular phenotypes, as HER2+ and TNBC are examples of this principle. There is still much to be discovered from metabolic characteristics of specific tumor markers and relation with next generation parameters such as MTV and TLG. More studies are needed using these newer modified PET/CT or PET/MRI modalities to better understand tumor behavior characteristics, such as SUVmax, with respect to the time frame of implementing chemoradiation to improve the clinical utility of these imaging techniques. With an increased recognition of the inflammatory and cell pathways that cancer potentiates with disease relapse, especially among the elderly population, improved therapeutic treatments are on the horizon.

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Footnote

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