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General review

Impact of molecular and histological subtype of breast cancer on ^{18}FDG-PET/CT imaging: Knowledge gained from recent studies

Impact du phénotype moléculaire et de l'histologie du cancer du sein sur l'imagerie TEP/TDM au ^{18}FDG : données récentes

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Abstract

Over the past few years, several studies have focused attention on the impact of breast cancer (BC) histological subtype or BC phenotype, as defined by hormone receptors (HR) and HER2 status, on the results of FDG-PET/CT at staging, or during neoadjuvant chemotherapy (NAC). At staging, sclerotic bone metastases from invasive lobular carcinoma (ILC) demonstrated low or no FDG uptake in comparison to metastases from invasive ductal carcinoma (IDC). The CT component of PET/CT imaging should be carefully analyzed in the staging of ILC. In patients with triple negative or HER2-positive tumors, the proportion of extraskeletal metastases is high; this must be taken into account in the diagnostic strategy. Staging based on PET/CT findings offers higher prognostic stratification value than that defined by conventional imaging workup. The yield and prognostic information are high in patients with clinical stage IIB or higher. Moreover, the intensity of tumor FDG uptake at baseline may have prognostic value for recurrence, with stronger evidence in HR-positive/HER2-negative phenotype. In the assessment of tumor response to NAC, the metabolic response, generally based on the change in SUV_{max} (ΔSUV_{max}), depends on the BC subtypes. In triple negative BC, a good metabolic response early during NAC has been shown to be predictive of pCR, and the predictive value was reinforced by combining ΔSUV_{max} and EGFR status. In 171 patients, no correlation was found between some recently developed PET-derived parameters, i.e. tumor heterogeneity or textural analysis, and BC subtypes. Whether these parameters offer any advantage compared to SUV measurements remains to be demonstrated.

Keywords: PET/CT; ^{18}FDG; Breast cancer; Staging; Prognosis; Neoadjuvant chemotherapy; Response assessment; Pathological complete response; Triple-negative breast cancer; HER2-positive breast cancer; ER-positive breast cancer

Résumé

Ces dernières années, plusieurs études portant sur la TEP/TDM au FDG dans les cancers mammaires (CM) se sont intéressées à l'impact des sous-types histologiques, ou phénotypiques (définis par l'expression ou non des récepteurs hormonaux et de HER2), lors du bilan initial ou de l'évaluation précoce de la réponse à la chimiothérapie néoadjuvante. Lors du bilan d'extension, les métastases osseuses sclérotiques du carcinome lobulaire infiltrant peuvent présenter une fixation du FDG faible, voire absente ; la composante TDM de l'imagerie TEP/TDM doit être

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soigneusement prise en compte. Chez les patientes avec tumeur triple-négative ou HER2-positive, la proportion de métastases extrasquelettiques est élevée ; ceci doit être pris en considération dans la stratégie diagnostique. En plus de l'impact pronostique bien connu d'un bilan d'extension incluant la TEP dans les stades cliniques IIB ou supérieur, l'intensité de fixation du FDG possède une valeur pronostique sur la survie sans récidive, tout particulièrement dans le sous-type HR-positif/HER2-négatif. Dans l'évaluation de la réponse tumorale en cours de chimiothérapie néoadjuvante, la réponse métabolique généralement basée sur la modification du SUV_{max} (ΔSUV_{max}) dépend du sous-type histologique. Pour les CM triple-négatifs, une bonne réponse métabolique est fortement prédictive de la réponse histologique complète. Cette valeur prédictive est renforcée lorsque le ΔSUV_{max} est combiné à l'expression de l'EGFR. Une étude récente incluant 171 patientes n'a pas montré de corrélation entre certains paramètres TEP récemment développés comme l'hétérogénéité tumorale et l'analyse de texture, et les sous-groupes phénotypiques ; l'intérêt de ces paramètres par rapport à la simple mesure du SUV reste à démontrer.

Mots clés : TEP/TDM ; ^{18}FDG ; Cancer du sein ; Bilan initial ; Pronostic ; Chimiothérapie néoadjuvante ; Réponse thérapeutique ; Cancer triple-négatif ; HER2+ ; Cancer hormonodépendant

1. Introduction

Positron emission tomography/computed tomography (PET/CT) with ^{18}F-fluorodeoxyglucose (^{18}FDG) is gaining importance for the staging of patients with large or locally-advanced breast cancer (BC) and for evaluation of tumor response to chemotherapy, especially in the neoadjuvant setting. Almost all breast tumors are ^{18}FDG-avid although the intensity of ^{18}FDG uptake is related to cancer subtype. In clinical practice, there are 3 main entities based on immunohistochemical analysis of hormone receptors (HR) and human epidermal growth factor receptor 2 (HER2): HR-positive/HER2-negative BC, HER2-positive BC and triple-negative breast cancer (TNBC; lacking estrogen and progesterone receptors and without HER2-overexpression). On ^{18}FDG-PET imaging, the Standard Uptake Value (SUV) is usually higher in cases of estrogen-receptor (ER)-negative or TNBC than in ER-positive tumors [1,2]. ^{18}FDG uptake also depends on certain histopathological characteristics of the tumor: invasive ductal carcinoma (IDC) exhibits higher uptake than invasive lobular carcinoma (ILC) [1,3,4] and tumors with SBR grade-3 exhibit higher ^{18}FDG uptake than lower grade tumors [1,4]. There is also a positive correlation between the tumor proliferation index (Ki67 expression) and the intensity of ^{18}FDG uptake [4].

Awareness of the determinants of ^{18}FDG uptake by oncologists and nuclear physicians is important as it could influence clinical use of ^{18}FDG-PET/CT, including the sensitivity in detecting regional and distance disease spread, and evaluation of tumor response to chemotherapy. In this review, we will assess the impact of molecular and histological subtype of BC on ^{18}FDG-PET/CT imaging for staging and response assessment in the light of recent studies.

2. Impact of molecular and histological subtype on BC staging with ^{18}FDG-PET/CT

Two recent papers from the Memorial Sloan-Kettering Cancer Center of New York focused on ^{18}FDG uptake based on BC histologic subtype.

A first study included 95 patients with bone metastases at presentation. The histologic subtypes of the primary were as follows: 74 IDC; 13 ILC; 8 mixed ductal/lobular (MDL) [5]. In all IDC and MDL patients with bone metastases, at least one lesion was ^{18}FDG-avid. ILC bone metastases were more commonly sclerotic and demonstrated lower SUV_{max} than IDC metastases. For ILC patients with lytic or mixed bone metastases, at least one metastasis was ^{18}FDG-avid. However, in only three out of seven patients, sclerotic bone metastases were apparent on ^{18}FDG-PET. In summary, this study showed that the histologic subtype of BC affects the appearance of untreated bone metastases on ^{18}FDG-PET/CT. In particular, non-FDG-avid sclerotic bone metastases were more common in patients with ILC than in patients with IDC.

In a second study, the authors evaluated the impact of histologic subtype on PET/CT staging [6]. PET/CT revealed unsuspected distant metastases in 12 of 146 (8%) ILC patients: 0/8 initial stage I, 2/50 (4%) stage II, and 10/88 (11%) stage III. However, 3 of the 12 patients were upstaged based only on the CT component of PET/CT, as their metastases were not ^{18}FDG-avid. In a subgroup of stage III IDC patients used for comparison, PET/CT revealed distant metastases in 22% (20/89) and in all these patients, metastases were ^{18}FDG-avid. The relative risk of PET/CT revealing unsuspected distant metastases in stage III IDC patients was 1.98 times (95% CI: 0.98–3.98) that of stage III ILC patients ($P = 0.049$) [6].

Beyond tumor histology, some biological characteristics of the primary tumor may have an impact on ^{18}FDG-PET/CT staging. In another study from the Memorial Sloan-Kettering Cancer Center that retrospectively included patients younger than 40 years, grade and receptor phenotype were not found to influence the rate of distant metastases [7]. Again, in the study from Saint-Louis hospital, the rates of distant involvement did not differ according to grade and BC phenotype. However, the sites of involvement differed. TNBC patients and HER2-positive patients had a higher proportion of extraskeletal metastases than in the case of patients with HR-positive/HER2-negative BC [8].

Further studies are needed to evaluate the yield of PET/CT according to the biomarkers of tumor aggressiveness in patients with large or locally advanced BC. Considering the high proportion of extraskeletal metastases in the case of TNBC and HER2-positive BC [8], the potential role of brain MRI in addition to whole-body ^{18}FDG-PET/CT should be evaluated in these subtypes.