

# Role of Fludeoxyglucose in Breast Cancer Treatment Response

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## KEYWORDS

- FDG-PET/CT • Breast cancer • Treatment response • Neoadjuvant chemotherapy
- Metastatic breast cancer

## KEY POINTS

- Changes in metabolic activity generally occur earlier than changes in tumor size.
- The metabolic information provided by PET has been shown to be valuable for the early assessment of the response to neoadjuvant chemotherapy, but the methodology for image acquisition and analysis needs to be standardized; breast cancer subtype and treatment type need to be considered in interpreting the change in fludeoxyglucose uptake with therapy.
- In the metastatic setting, there is evidences that PET/computed tomography (CT) performed better than CT alone, especially to assess the response in bone metastases.
- In the metastatic setting, PET/CT has the ability to evaluate different sites of metastases in a single examination and to detect a heterogeneous response (coexistence of responding and nonresponding lesions within the same patient).
- The use of PET/CT in patients with metastatic breast cancer is hampered by the absence of consensus of the criteria to use to assess the response, of the number of metastatic sites to analyze, and of the optimal date to perform PET during treatment.

## INTRODUCTION

The role of fludeoxyglucose (FDG) PET in the management of patients with breast cancer (BC) is evolving. Combined PET and computed tomography (CT) systems (PET/CT) have replaced PET alone in most nuclear medicine departments. The CT portion of PET/CT provides the anatomic information useful for accurate interpretation of PET signal.

Most patients with stage II-III BC are treated by neoadjuvant chemotherapy (NAC). This strategy allows more patients to undergo breast-conserving surgery and increases the chances of surgery in patients with primary inoperable disease; it also provides precious information on the

efficacy of chemotherapy. Early assessment of the response to NAC should be helpful, as it might reduce the toxicity from inefficacious chemotherapy or allow a refinement of treatment. The number of studies has pointed out the efficacy of FDG PET/CT in early assessing the response to NAC.<sup>1-12</sup> Nevertheless, PET/CT for assessment of the response to NAC has not yet entered routine clinical practice.

Early response of treatment is also important in the metastatic setting to use the most efficient drugs and to stop early ineffective chemotherapy. Changes in metabolic activity generally occur earlier than changes in tumor size. FDG PET/CT has shown high performances to assess the response in metastatic patients with BC.<sup>13-25</sup>

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When compared with conventional imaging, FDG PET/CT has shown better accuracy, especially to assess the response in bone lesions. However, PET is not currently used in the metastatic setting.

In this review, the author briefly describes the principles of PET/CT imaging in BC and the tools that could be used to assess the treatment response. Then, the author assesses the advantages and limits of FDG PET/CT to early evaluation of the response in the neoadjuvant setting and afterward in the metastatic setting.

## GENERAL INFORMATION

### *Fludeoxyglucose PET/Computed Tomography Procedure*

Imaging usually starts 60 minutes after the intravenous injection of FDG. CT and PET data are acquired sequentially before being fused. Patients are imaged from the base of the skull to the mid-thigh, except for specific situations. Imaging usually begins with CT acquisition. Questions remain as to whether the CT part of PET/CT should be performed as a contrast-enhanced full-dose diagnostic CT or as a nonenhanced, low-dose CT, with additional focused segmental examination in case of inconclusive findings. Some technical constraints imposed by the PET component, such as free breathing, might limit the full diagnostic power of CT when performed as part of PET/CT imaging.

Modern whole-body PET systems typically have a reconstructed spatial resolution of 5- to 6-mm full width at half maximum, based on phantom measurements. However, detection depends not only on tumor size but also on the degree of FDG avidity, tumor-to-background ratio, impact of motion (respiration), and so forth.

### *Fludeoxyglucose Uptake Depends on Breast Tumor Characteristics*

Most malignant breast tumors overexpress glucose transporters (especially Glut-1 and Glut-3) and show increased hexokinase activity.<sup>26,27</sup> However, FDG uptake can be undetectable or weak in some tumors. In the case of low FDG uptake at baseline, PET/CT has limited value to assess the treatment response.

Invasive ductal carcinoma exhibits higher FDG uptake than invasive lobular carcinoma.<sup>28–30</sup> FDG uptake in carcinoma in situ is usually weak as compared with invasive tumors.<sup>29</sup> FDG uptake increases with the tumor proliferation index (Ki67 expression).<sup>29</sup> High-grade tumors exhibit higher FDG uptake than intermediate- and low-grade tumors.<sup>29,30</sup> FDG uptake is higher in tumors that are negative for hormone receptors.<sup>29,30</sup> Triple-negative breast tumors (negative for estradiol

and progesterone receptors and without human epidermal growth factor receptor 2 [HER2] overexpression) are usually highly FDG avid.<sup>30,31</sup>

### *Available Fludeoxyglucose PET/Computed Tomography Parameters to Assess Treatment Response*

Tumor FDG uptake can be expressed by using a so-called standardized uptake value (SUV). This index is calculated based on the amount of activity injected and the patients' body mass, as follows:  $SUV = \text{measured activity in the volume of interest} / [\text{injected activity/body weight of patients}]$ . Different methods to define the SUV are available, the most used being maximum SUV ( $SUV_{\max}$ ) (value of the voxel with the highest SUV),  $SUV_{\text{peak}}$  (mean of voxels intensities in a spherical region of interest of 1 cm<sup>3</sup> around the  $SUV_{\max}$  voxel<sup>32</sup>), and  $SUV_{\text{mean}}$  (mean of voxels intensities within the tumor volume). The ability of  $SUV_{\max}$  to assess the treatment response has been evaluated in numerous series. This robust parameter is the most used in clinical practice.

Some parameters mixing volume and FDG intensity can also be used to assess the treatment response. The metabolic active tumor volume (MATV) is determined as the tumor volume with significant FDG uptake.<sup>33</sup> Different methods can be used to define the MATV. The total lesion glycolysis (TLG) corresponds to the MATV multiplied by the  $SUV_{\text{mean}}$ .

Recently, some texture features, such as the entropy and the heterogeneity, were evaluated to define the breast tumor.<sup>34–36</sup> However, the ability of those parameters to assess the treatment response needs to be evaluated in large series.

The question remains open on whether 60 minutes after injection is the optimal timing for FDG PET/CT imaging. No optimal time has been defined in the literature. Uptake in breast tumors (and so the SUV value) continues to increase beyond 60 minutes.<sup>37</sup> Nevertheless, this time point, which has the advantage of simplicity, is widely used. It is a key point within a given institution to apply the same time delay after injection. The delay used at baseline imaging should be reproduced if patients are referred for response evaluation. Some investigators developed methods to make appropriate time corrections for tumor SUVs.<sup>37,38</sup> Also, when performing SUV measurements for response assessment, there is a risk of underestimation of SUV values when the residual tumor is small (partial volume effect). The time delay between the last chemotherapy use and FDG imaging might also influence the response assessment.

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