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FDG PET Application for management of breast cancer patient: a narrative review

Saeed Farzanehfar[a], Farahnaz Aghahoseini[a], Marzieh Peyman[a], Mehrshad Abbasi*[a]

[a] *Department of Nuclear Medicine, Vali-asr Hospital, Tehran University of Medical Sciences, Tehran, Iran*

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ABSTRACT

Background: The application of FDG PET/CT scan for assessment of patients with breast cancer is increasing. The cost effectiveness of the application could be different in a developing country with limited PET scanners and treatment priorities

Method: Open discussions of the PET reviewers from 2 out of 4 PET centers of Tehran, the capital city of Iran, were organized to provide insight into their opinions on the indications of FDG PET in breast cancer patients.

Results: The sensitivity of FDG PET scan is high for detection of distant metastases; however, assessment of lymph node pathology and the local extension of the breast cancer are questionable. Considering the cost of the procedure itself and the downstream diagnostic procedures, its application and diagnostic accuracy are hindered for breast cancer screening, staging, and assessment of response to treatment and prognosis. The advantages and disadvantages of FDG PET CT and dedicated breast FDG PET scan have been briefed in different clinical scenarios with a focus on limitations faced by a developing country.

Conclusion: We suggest reserving the use of FDG PET for selected cases of suspected but not proven recurrent disease and in patients with high risk of metastasis before high risk surgery.

Introduction

Functional imaging has comprised a considerable part of medical imaging procedures for 50 years.[1] Many essential physiological facts have been established through functional imaging, and its use has extended into clinical practice. Perfusion imaging, renal function studies, bone scintigraphy and many other functional images have become very common. Breast specific imaging was developed with a focus on MIBI as a surrogate of thallium 201, an important tumor agent. In the advent of state-of-the-art CT scanners, the fine details of anatomy illustrated by cross sectional images, reversed the trend among clinicians to use CT images to focus on the diseases based on the visible shape of the pathology and the changes it causes in organs. Mammography, ultrasonography, and MRI provided high sensitivity[2] and flexibility to guide biopsies[3], and high specificity for breast tumor imaging, respectively.[4] The drawback of functional imaging with lower spatial resolution hindered the scintigraphy images for years. Four decades later professor Abbas Alavi and the team he led used FDG as a new functional brain imaging tracer ; [5] FDG was developed to a potent tumor agent and brought a remarkable advance in the field of oncologic imaging. PET scanners provide superior spatial resolution due to their crystal structure and coincidence acquisition method.[6] Attenuation is lower due to higher photon energy positrons emit. Furthermore, the method benefitted from attenuation corrections using real patient attenuation map provided by gamma emission and transmission data by CT. PET imaging has achieved such a position that many clinicians consider it as a final or even

Address for correspondence:
Mehrshad Abbasi, MD
Associate Professor
Address: Department of Nuclear Medicine, Vali-Asr Hospital
Tehran University of Medical Sciences, Tehran 1419731351,Iran
Tel: +98 21 61192405
Fax: +98 21 66575103
Email: meabbasi@tums.ac.ir

perfect imaging modality, a view we are to oppose for different reasons in the current paper with particular attention to the field of breast cancer.

Methods

The narrative data for this study was accumulated through open discussions among the authors. There are 4 PET scanners installed in Tehran, the capital city of Iran, and the authors of the paper are nuclear physicians in the most advanced (i.e. FA) and the most up to date (i.e. SF and MA) centers there. The essential topics were selected first and then the authors provided their scholarly opinions on the topics. Through directed literature search, the discussed material was approved with scientific citations or changed accordingly.

Results and discussion

The application of PET can be categorized into different strata summarized as screening, initial staging, follow up for recurrence, re-staging, and response to treatment and prognosis. With a focus on a developing country, the following overall views could be considered for aforementioned applications in the field of breast cancer:

Screening

The use of whole body FDG PET for breast cancer screening is discouraging. Many biological cancer-related characteristics may influence the degree of uptake in a sizable breast malignant lesion. Well-differentiated cancers as well as certain histopathological subtypes, including those with indolent behavior, infiltrative pattern of growth and low cellular density such as infiltrative lobular carcinoma and tubular carcinoma do not take up FDG to the same extent as many FDG avid tumors do.[7] Other factors such as receptor status and specific mutation have a controversial correlation with degree of FDG uptake for a given histopathology subtype.[8] It is worth noting that a screening tool should have the capability of detection of very small size and non-palpable malignant lesions in the early stage of development. This may be the most important drawback for current PET scanners with sensitivity of less than 60% for malignant lesions <1 cm to be considered as the imaging modality of choice for breast cancer screening. The overall sensitivity for primary lesion ranges from 48 to 96; with lower performances reported from studies including smaller lesions.[9] However, metabolic criteria derived from FDG PET scan may have a complementary role in improving risk stratification of incidentally-detected breast lesions in PET/CT scan in non-breast cancer patients.10 To sum up, the use of whole body PET for screening is questioned.

Even so, particular cases may benefit from screening by breast dedicated PET scans, with higher spatial resolution for limited breasts' field in contrast to whole body PET imaging, including young high risk genetically predisposed patients or contralateral breasts predisposed to higher-grade tumors with more aggressive clinical courses.[11-13]

FDG accumulates in invasive ductal cancers[14, 15], breast dedicated PET scanners developed to do breast screening.[16, 17] However, there is no global consensus to support the benefit of dedicated breast FDG PET. The accuracy of the dedicated breast PET images are high, i.e., 0.95, ranging from 0.82 to 1.0[18], and considerably superior to the accuracy of mammography . The reason why dedicated PET scans did not take place as a screening tool is that the cost to a breast dedicated PET scan is 10 times of a mammography alongside the fact that instrumentation is expensive and not widely available.[19]

Initial Staging

Due to whole body nature, FDG PET scan is useful for detection of metastasis[20, 21], and in certain scenarios for detection of LN invasions.[22] The role for whole body FDG PET/CT in T staging is limited. In breast cancer, FDG illustrates axillary LN invasions in about two thirds of the cases involved, which is not an accountable figure[23] considering the detection rate of more than 95% achieved by sentinel LN biopsy. Although PET/CT is not a suitable substitute for routine axillary N staging, in patients who are at high risk for axillary metastasis, PET-detected positive nodes may be proceeded for US-guided biopsy, and hence, obviate the need for sentinel node biopsy in patients with biopsy-proven nodal involvement.[24] Furthermore, currently, distant metastasis at the time of primary tumor diagnosis is very rare as a result of powerful screening and diagnostic methods.[25] Lastly, the need for systemic therapy in low T tumors does not obviate definitive surgery. Consequently, the evaluation of distant metastasis could be postponed until after definitive surgery. Potential use of PET for certain locally advanced breast cancers is advocated for the assessment of prognosis and to monitor future therapy.[26, 27] It should also be considered that breast cancer is the most frequent cancer in females;[28] initial staging of many common cancers by PET scan is hindered due to financial considerations. Some patients may benefit from initial staging by FDG PET scan, but the overall health system and community may not afford the cost, considering the fact that the procedure is not definitely cost effective.[19] In the era of individualized practice however, physicians may consider a particular patient eligible for FDG PET scan e.g. an old patient with comorbidities with a small tumor in which detection of an axillary or internal mammary LN or a distant metastasis may change the approach, or a young patient with large breast tumors, where the detection of a distant metastasis may change the plan for neoadjuvanttherapy.

Follow up for Recurrence

FDG accumulates in recurrence sites and metastasis very sensitively; but the inflammation at surgery site is highly metabolic for weeks and granulation tissues for months. Specificity of the findings could be optimized with clinical reasoning concerning the possibility of malignancy as the reason for the findings.[29] There are two definite scenarios where FDG PET provides future insight for the clinician: First, the recurrence is biochemically suspected but conventional images do not document its site. The oncologist/surgeons actively search for recurrence sites and then closely follow up the patient if the images are not indicative of the site of recurrence.[30] Particularly, when metastasis is difficult to follow up with conventional anatomical imaging like intramedullary bone metastasis[31] it could be optimally assessed by FDG PET scan.[32] Furthermore, in certain situations, the conventional images including lung and abdominopelvic CT scans and bone scans point to a suspicious recurrence site. The extent of the finding is not so that the biopsy could be indicated or metastasis/recurrence confirmed. FDG uptake may support the clinician's decision to follow up or act on the findings. One of the major privileges of the FDG PET in this setting could be discrimination of post-radiation and post-surgery changes including fibrosis from recurrent tumors.[33] Although granulation tissue, as mentioned above, and inflammation and fibrosis in early stages may occur with high FDG uptake[34, 35], the absence of high metabolic activity remarkably reduces the possibility of malignancy.[33] The PET is reimbursed for breast cancer recurrence follow up in many health systems.

Re-staging

In a scenario where the patient may benefit from a second surgery which could be either a metastasectomy at liver or lung, or local recurrence completion surgery, precise assessment of distant metastases would be a must. Obviation of surgery of a site in presence of another metastasis elsewhere is de facto. Obviously, repeated surgeries are more costly both for the patient and the health system, and detection of another recurrence site, which is considered as the strength of whole body sensitive FDG PET scan[33,36], dramatically changes the decision to opt for surgery. In the era when there is a growing desire to eradicate disease more powerfully by surgeries in patients with metastasis and with the advent of effective chemotherapy agents, FDG PET may provide a rather complete map of the recurrence/metastasis sites[37] to plan for the most reasonable action. It is noteworthy to mention when a malignant disease becomes systemic, certain malignant cells may disseminate and develop to very small nests bellow the spatial resolution of PET or visible but ignorable. Consequently, although the sensitivity of FDG PET is considered high, the extent of the systemic diseases is higher than what is visualized.

Response to treatment and prognosis

In certain malignancies including lymphoma, FDG uptake provides particular insight into the effectiveness of therapy. This finding could change the chemotherapy line or intensify the treatment.[38] At the end of treatment, a PET scan without abnormal FDG uptake site confirms the completeness of the treatment and obviates further investigations for months.[39] Nevertheless, the absence of FDG uptake does not exclude the possibility of recurrence and the necessity to follow up. This application is not highlighted for breast cancer. The local surgical tumor eradication is directly observed by the surgeon and pathologist, and the effect of systemic therapies could be assessed by anatomical images.[26, 40] For example, the number and size of lesions in lung and liver metastases could be optimally followed by lung and 3 phase liver CT scans. There are particular scenarios in which FDG PET plays a remarkable role.[41] After curative surgeries or ablations of bone and liver metastases by surgery, external beam radiation, radiofrequency, or microwave, discrimination of post therapy changes from remnant, or recurrent tumor is difficult using conventional images.[42] The effectiveness of surgery with or without RF on a set of liver metastases could be optimally documented by FDG PET scan.[43] The assessment of prognosis is another less useful application of FDG PET according to which high grade or more invasive tumors present with higher FDG uptake requiring more intensive treatments[37], an application which is neither robust nor cost effective in breast cancer setting.

In a developing country like Iran where there are only 8 PET scanners installed and less than 10 are planned for forthcoming years, considering the import limitations, the request for PET scans plausibly should be limited. In this country, about 100 PET scans could be performed a day and there are more than 18000 new cancer cases a year.[44] Regarding the fact that screening, initial staging, and follow up of breast cancers patients could be done delicately with other imaging methods, FDG PET/CT scan could be preserved for patients with suspected but not confirmed recurrent disease and particular cases before proceeding to surgery with high risk of metastases which precludes a difficult or life threatening surgery in a high risk patient with various comorbidities.

Conflict of Interest

None

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