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Clinical applications of ^{18}F fluoro-2-deoxy-D-glucose (FDG) positron emission tomography--computed tomography (PET/CT)

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Abstract

Positron emission computed tomography (PET) is a functional diagnostic imaging modality. Coupled with computed tomography (CT), it has a high accuracy, adding morphological informations. F-18 fluoro-2-deoxy-D-glucose (FDG), an analogue of glucose, is the most commonly used radiotracer. Its uptake reflects glucose metabolism in the cells which is increased several times in malignant tumors. However FDG is not a cancer specific agent and its uptake has been described in a number of non-neoplastic inflammatory lesions. The aim of our paper is to summarize its major indications in the clinical practice.
Key words: fluorodeoxyglucose, positron emission tomography, computed tomography

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Introduction

Positron emission computed tomography (PET) is a functional diagnostic imaging modality which can accurately assess the biodistribution of an injected radiotracers. The ability of PET to study different biological processes increased its application not only in research but even in clinical practice. In addition PET coupled with computed tomography (CT) has a high accuracy, as the hybrid imaging can provide functional and morphological informations in the same setting. F-18 fluoro-2-deoxy-D-glucose (FDG), an analogue of glucose, is the most commonly used radiotracer. Its uptake reflects glucose metabolism in the cells: it is mediated by a family of structurally related glucose transporter proteins (GLUT receptors) present on the cell membrane, phosphorylated by the enzyme hexokinase to FDG-6-phosphate and then biochemically trapped within the cell. PET images show preferential higher FDG uptake in malignant cells as compared to normal cells since glucose metabolism is increased several times in malignant tumors. Indeed PET is a valuable tool for staging and restaging many tumors and has an important role in the detection of recurrence in asymptomatic patients with rising tumor marker levels and patients with negative or equivocal findings on conventional imaging techniques. It is also useful in monitoring response to therapy. In this regard, it can also improve patient management by identifying responders early, before tumor size is reduced; non-responders could therefore discontinue futile therapy and escalate doses or change treatment strategy. Moreover, a reduction in the metabolic activity within days or weeks of initiating therapy (e.g. in lymphoma, non-small cell lung, and esophageal cancer) significantly correlates with prolonged survival.However FDG is not a cancer specific agent and its uptake has been described in a number of non-neoplastic inflammatory lesions like sarcoidosis, tuberculosis, fungal infection and abscesses.Although such uptake can produce false-positive results in patients with known or suspected malignancy, FDG represents a potentially useful radiotracer in the setting of infection and inflammation.

Main recommendations

Here below the summarized nine cancer indications approved by the Centers for Medicare and Medicaid Services (CMS) according to the Society of Nuclear Medicine (SNM), National Comprehensive Cancer Network (NCCN), and other professional organizations regarding the use of FDG PET/CT in oncology.

Head and neck cancer

1. Detection of occult primary tumors in patients presenting with metastatic disease. Patients with cervical lymph node metastasis from an unknown primary tumor represent a big diagnostic dilemma. FDG PET can be a valuable tool in this particular subset as an early identification of the primary tumor may allow more accurate tumor staging and targeted radiotherapy.
2. Initial staging, including detection of cervical lymph node metastases in the clinically node negative neck, and detection of distant metastases in patients with locally advanced disease. Lymph node metastasis in head and neck tumors and distant metastases are associated with poor prognosis. Accurate pre-therapy lymph node staging is essential for therapeutic planning. FDG PET has a major impact in patient management compared with PET alone and conventional morphological imaging like CT/MRI and avoids unnecessary neck surgery. In addition the impact of FDG PET on radiotherapy planning is important: it has been reported that the gross tumor volume is statistically significantly larger with FDG PET/CT-based assessment than with CT-based assessment.
3. Detection of residual or recurrent disease. FDG PET provides high diagnostic accuracy of 100% compared to 28% alone for CT for residual disease, when performed eight weeks after the conclusion of radiation therapy. A positive scan obtained at least six weeks after the end of therapy suggests residual disease, unless there are clinical signs of inflammation/infection to explain the abnormalities on PET. FDG PET is also more sensitive and specific in detecting residual and recurrent lymph node metastasis. Moreover it can be used in prognostic stratification and has significant clinical impact on management.

Pitfalls: Benign inflammatory/infective diseases show increased lymph node uptake and cause false positive results. Head and Neck cancers can be low-grade tumors and therefore only mildly FDG avid.

Thyroid cancer

1. Detection of residual or recurrent thyroid cancer when serum thyroglobulin is elevated and radioiodine scan is negative.
2. Staging of patients with poorly differentiated thyroid cancers and invasive Hurtle cell carcinomas.
3. Evaluation of treatment response following systemic or local therapy of metastatic or locally invasive disease.More than 90% of thyroid cancers are differentiated, including papillary and follicular carcinoma. In de-differentiated thyroid cancer, recurrent or metastatic tumor cells may lose the expression of sodium iodide symporter and have a decreased ability to concentrate radioiodine.

Breast cancer

1. Initial staging of patients with locally advanced or metastatic breast cancer when conventional staging studies (e.g. CT or bone scan) are equivocal or suspicious.Metastatic lymphadenopathy is one of the most important prognostic factors in breast cancer patients. PET has been shown to have limitations in detecting lymph node metastasis when compared to sentinel lymph node biopsy. However, a clearly positive result in the particular setting of patients with a high risk of nodal metastases has as high positive predictive value and may identify patients with evidence of nodal metastases.
2. Follow-up or surveillance patients with breast cancer when conventional studies (e.g. CT or bone scan) are equivocal or suspicious. A recent meta-analysis on 13 studies provided the following results: pooled sensitivity 0.878 (95% CI: 0.838–0.909), pooled specificity 0.693 (95% CI: 0.553–0.805), and pooled accuracy 0.828 (95% CI: 0.762–0.878) confirming the potential of PET/CT in detecting occult soft tissue and bone metastases in the presence of a progressive increase of serum tumor markers.

Pitfalls: Acute and chronic inflammation, physiologic lactation, and benign breast masses, including silicone granuloma, fat necrosis, fibroadenoma, and postsurgical changes, may show increased FDG uptake. Patients with carcinoma in situ, low-grade tumors, well differentiated ductal and lobular breast cancer, usually have significantly lower uptake and can be misinterpreted as benign lesions. In addition, smaller lesions (<5 mm) and micrometastatic axillary lymph nodes can be missed.

Characterization of solitary pulmonary nodule > 8–10 mm

The results of main meta-analyses show that the sensitivity and specificity of FDG PET for determining malignancy of SPN are close to 95% and 80% respectively. Furthermore FDG PET shows a slightly better specificity than comparators (dynamic contrast-enhanced CT and dynamic contrast-enhanced MR). Pitfalls: False negative results are mainly due to certain histological types with low metabolic activity (such as bronchiolo-alveolar carcinoma and typical carcinoid), or small size nodules (less than 8 mm). False positives are mainly represented by granulomatous and infectious processes.However malignant nodules show increased FDG uptake over time, while pulmonary nodules of benign origin have a declining pattern of uptake.

Non small cell lung cancer

1. Initial staging in patients eligible for surgery. CT is the imaging modality of choice to define the extent of the primary tumor and to assess the tumor involvement of the pleural surfaces and the thoracic wall, however it is well known its low sensitivity and specificity in mediastinal nodal staging. Mediastinoscopy is considered the Gold Standard for lymph node staging. However, it is an invasive procedure and sampling errors cannot be excluded. PET added value is mainly related to accurate staging of nodal and metastatic sites changing the course of management in up to 52% of cases.
2. Delineation of gross-tumor volume in patients receiving radiation therapy. FDG PET is useful for radiation therapy planning since it provides more accurate initial staging, allowing omission of elective radiation of clinically uninvolved nodal stations.

Esophageal cancer

1. Initial staging. Endoscopic ultrasound (EUS) provides more accurate and cost-effective T-staging and N-staging than

FDG PET and conventional CT and remains the standard for local tumor evaluation. The most important role of PET lies in M-staging thanks to its ability to identify unexpected metastases (i.e. metastases not visible on conventional imaging), which are present in up to 30% of the patients.
2. Restaging after neoadjuvant chemoradiation therapy. Assessment of tumor response to neoadjuvant therapy by FDG PET has been found to be an important prognostic factor, with a reported diagnostic accuracy of 85% which is similar to EUS (86%) and significantly higher than conventional CT (54%).
3. Delineation of gross tumor volume in patients receiving radiation therapy.

Pitfalls: False positive results in patients with inflammatory/infective diseases of esophagus. Limited value for early nodal disease or detection of lymph nodes very close to the primary lesion.

Colorectal cancer

1. Preoperative evaluation of patients with potentially resectable hepatic or other metastases.The routine use of PET is not recommended for the diagnosis or staging of clinical stage I–III colorectal cancers.
2. Determining location of tumors when rising CEA level suggests recurrence.PET is not recommended for routine surveillance in patients with colorectal cancer treated with curative surgery at high risk for recurrence. It is recommended to determine the site of recurrence in the setting of rising CEA when conventional work-up fails to unequivocally identify metastatic disease.

Pitfalls: Fistulas, abscesses, diverticulitis and adenomas can cause false positive results. Normal physiological bowel activity can mask lesions. Mucinous adenocarcinoma and microscopic lymph node metastasis can cause false negative results.

Cervical cancer

1. Initial treatment planning assistance, including determination of nodal status and systemic spread.Invasive cancer of the cervix is the second most common genital malignancy in women, worldwide. The applications of PET in cervical cancer patients include: assessing metabolic tumor activity and possible endometrial involvement, evaluating pelvic nodal involvement (even in cases with negative CT or MRI studies), detection of distant metastases, radiation therapy planning of metabolically active nodal lesions.
2. Detection of residual or recurrent disease following initial treatment.

Pitfalls: False positive results in patients with fibroid, cervicitis and other inflammatory/infective pathologies. Increased FDG uptake is also noted during menstrual cycle. Limited value in detection of primary cervical cancer in early stages and disease activity in pelvic lymph nodes.

Malignant melanoma

1. Detection and localization of potential extranodal metastatic lesions in initial evaluation of patients with advanced stage disease.
2. Evaluate the extent of metastatic disease burden in patients with recurrent disease following treatment. Melanoma metastasizes very widely (to skin, muscle, bone, bowel, myocardium, omentum, leptomeninges, mesentery etc.). FDG PET, showing a high tumor-to-background ratio, can highlight metastases at unusual sites that are easily missed with conventional imaging modalities.

Pitfalls: Limited value for early cutaneous melanoma (stage I–II) of the disease.Low sensitivity compared to sentinel lymph node biopsy for detection of early nodal disease.

Lymphoma

1. Routine pre-treatment staging of patients with Hodgkin Disease (HD) and most non-Hodgkin Lymphoma (NHL) subtypes. FDG PET can detect more lesions than CT and may lead to a upstaging of up to 15% of patients. A number of studies have assessed the value of PET in the diagnosis of extra nodal involvement like bone marrow, bone, gastrointestinal and splenic involvement, which may be present in 10–25% of newly diagnosed patients of lymphoma. Another major advantage of PET is that being a whole body imaging method, it can suggest a suitable and easily accessible biopsy site.
2. Routine restaging after chemotherapy and/or radiation therapy. Residual post-therapy masses are seen in up to 85% of HL and up to 40% of NHL. It is well known the limitation of CT to distinguish between viable tumour and necrosis or fibrotic tissue while PET performed after treatment is highly predictive of Progression Free Survival and Overall Survival with and without residual masses detected on CT. In 2007 new recommendation were developed by International Harmonization Project.

Pitfalls: Benign inflammatory/infective diseases show increased lymph node uptake, as well as post-surgical/radiotherapy/chemotherapy inflammatory changes. Increased bone marrow uptake due to post chemotherapy rebound can be noted. Low-grade lymphoma (in particular small lymphocytic and marginal zone) are usually poorly FDG avid.

Infection and inflammation

In patients with acquired immunodeficiency syndrome, FDG PET helps to localize foci of infection and is particularly useful for differentiating central nervous system lymphoma from toxoplasmosis. FDG PET can also identify the source of fever of undetermined origin, thereby guiding additional testing. Equally important is its high negative predictive value (NPV): negative FDG PET findings make it very unlikely that a morphologic origin of the fever will be identified. In addition this modality may represent a reliable non-invasive imaging in the specific clinical setting of endocarditis and infected vascular graft and pacemaker device. In the musculoskeletal system, FDG PET accurately helps diagnose spinal osteomyelitis. Finally, in inflammatory conditions such as sarcoidosis and vasculitis, it appears to be useful for defining the extent of disease and monitoring response to treatment. FDG PET will likely assume increasing importance in assessing inflammatory and infectious processes.

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