Appropriateness criteria of FDG PET/CT in oncology

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Abstract

^{18}Fluorine-2-fluoro-2-Deoxy-d-glucose (^{18}F-FDG) positron emission tomography/computerized tomography (PET/CT) is a well-established functional imaging method widely used in oncology. In this article, we have incorporated the various indications for ^{18}FDG PET/CT in oncology based on available evidence and current guidelines. Growing body of evidence for use of ^{18}FDG PET/CT in select tumors is also discussed. This article attempts to give the reader an overview of the appropriateness of using ^{18}F-FDG PET/CT in various malignancies.

Key words: Cancer; ^{18}Fluorine-2-fluoro-2-deoxy-d-glucose; guidelines for PET/CT; oncology; positron emission tomography/computerized tomography ; positron emission tomography

Introduction

Positron emission tomography/computerized tomography (PET/CT) is a technological advancement having a significant impact in oncology. ^{18}Fluorine-2-fluoro-2-deoxy-D-glucose (^{18}F-FDG) is an expensive, short-lived radiopharmaceutical used for PET/CT scanning and is synthesized in a cyclotron by a complex process. The net result is an expensive modality. However, with rising concerns of expenditure and radiation exposure, it becomes necessary to critically evaluate the utility of this modality. Health technology assessment boards of several countries have evaluated available evidence to decide on the appropriateness and cost-effectiveness of ^{18}F-FDG PET/CT in cancer. In 2010, the International Atomic Energy Agency (IAEA) pooled expert evidence in a manual named "Appropriate use of PET/CT for the management of cancer patients."[1] The National Comprehensive Cancer Network (NCCN), which represents a group of cancer institutions in the USA, frames guidelines for tumor groups. "Society of Nuclear Medicine and Molecular Imaging" (SNMMI), a professional body in the USA, produced a summary based on NCCN practice guidelines in March 2013.[2]

Access this article online	
Quick Response Code:	Website: www.ijri.org
	DOI: 10.4103/0971-3026.155823

This article attempts to familiarize the reader with current appropriateness criteria for using ^{18}F-FDG PET/CT in various malignancies based on evidence. The NCCN guidelines are based on availability of reimbursement for FDG PET/CT for various indications. The IAEA appropriateness criteria are recommendations based on the evidence published prior to 2009. This article amalgamates the recommendations of both guideline bodies. Attempt has been made to add evidence generated from 2010 till date and its possible impact on the appropriateness criteria.

Generally, to consider an investigation "appropriate," there must be a clear evidence of better diagnostic performance with higher sensitivity, specificity, and accuracy compared to conventional imaging or existing standard of care. The information obtained from the investigation should change the clinical practice and impact patient outcome. The change could be in the form of adopting better therapeutic strategies or elimination of ineffective, morbid, and expensive practices. "Potentially appropriate" refers to evidence of clear radiological superiority compared to current imaging, but with inadequate evidence about impact on treatment and outcome. "Possibly appropriate" refers to a situation where there is inadequate evidence for use despite a large number of well-planned studies, but a strong rationale exists

due to clinical benefit from PET shown by case reports or inadequately performed studies. "Inappropriate" refers to a situation where performance of PET is inferior to that of conventional imaging.[1]

The various utilities of PET/CT in oncology can be categorized and defined as follows:[1]

Diagnosis

- To characterize a lesion to suggest whether it is benign or malignant
- For the detection of a possible primary when the patient presents with metastases
- To identify an appropriate site from which a biopsy would yield adequate representative tissue for diagnosis
- Detection of malignancy when tumor markers are abnormal

Staging

After the histological diagnosis, to assess the extent of disease before the start of treatment

Response Evaluation

Assessment of response to treatment during or after therapy

Restaging

Assessment of the extent of the disease after treatment or after confirmed recurrence

Suspected Recurrence

Assessment of disease following clinical or biochemical suspicion of recurrence

Follow-up or Surveillance

Assessment of disease in the absence of critical evidence of recurrence

Radiotherapy Planning (RT)

When the study is used for contouring and planning the radiation fields.

The evidence discussed is based on the superior performance of FDG PET or FDG PET/CT compared to contrast-enhanced CT (CECT), which in most situations represents the conventional choice of imaging. CECT may be merged with FDG PET as FDG PET/CECT, as being practiced in many centers, which has shown improved radiological performance compared to FDG PET or FDG PET/CT in a few tumors.

The appropriate timing of the PET/CT study for maximum accuracy is important. To avoid false-positive, results, the best time to perform a PET/CT study is 8-12 weeks after completion of chemotherapy and radiotherapy. Postoperative inflammatory changes are seen till about 12 weeks or, at times, longer. The effect of colony stimulating factor (administered to stimulate production of blood cells after chemotherapy) is seen as intense metabolic activity in the marrow of the bones. This effect is less pronounced after 3 weeks. Ideal timing for performing a postoperative PET/CT study is also after 12 weeks.

Role of FDG PET/CT in Various Cancers

Lymphoma

There is an overwhelming body of evidence regarding the use of PET/CT in staging, restaging, and post-therapy evaluation in Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL), except in a few low-grade lymphomas like small lymphocytic lymphoma (SLL)/chronic lymphocytic leukemia (CLL), marginal zone lymphoma (MZL), mucosa-associated lymphoid tissue (MALT), cutaneous T-cell lymphoma (CTCL), mycosis fungoides, and Sezary syndrome.[1-3]

FDG PET leads to upstaging of disease in about 30% of cases at initial staging[4] [Figure 1]. The sensitivity and specificity of PET/CT is higher as compared to CECT for detection of nodal as well as extranodal disease.[5,6] The International Harmonization Project recommends the use of a baseline FDG PET in HL and aggressive NHL.[7] There is no added advantage of adding CECT in staging or combining it with PET/CT.[8] This only increases the cost and radiation burden. It is also helpful in management of residual masses that are seen

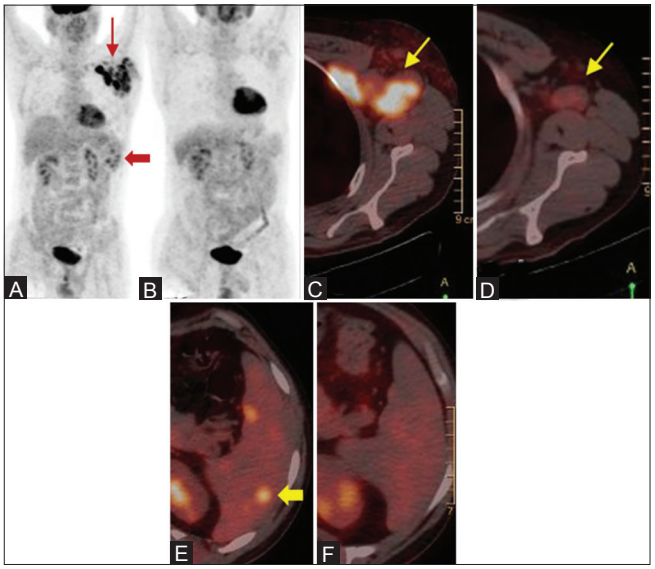

Figure 1(A-F): A case of Hodgkin's lymphoma. (A) The maximum intensity projection (MIP) PET pretreatment scan shows bulky left axillary adenopathy (arrows) and hypermetabolic splenic lesions - disease upstaged (block arrow). (B) MIP image of the same patient done after two cycles of chemotherapy (interim response assessment) shows complete metabolic resolution. The fused PET/CT image in the pretreatment scan (C) shows hypermetabolic left axillary nodes. The interim scan in (D) shows residual morphologic nodes with no significant FDG uptake. Hypermetabolic splenic lesions in (E) show complete metabolic and morphologic resolution in (F)

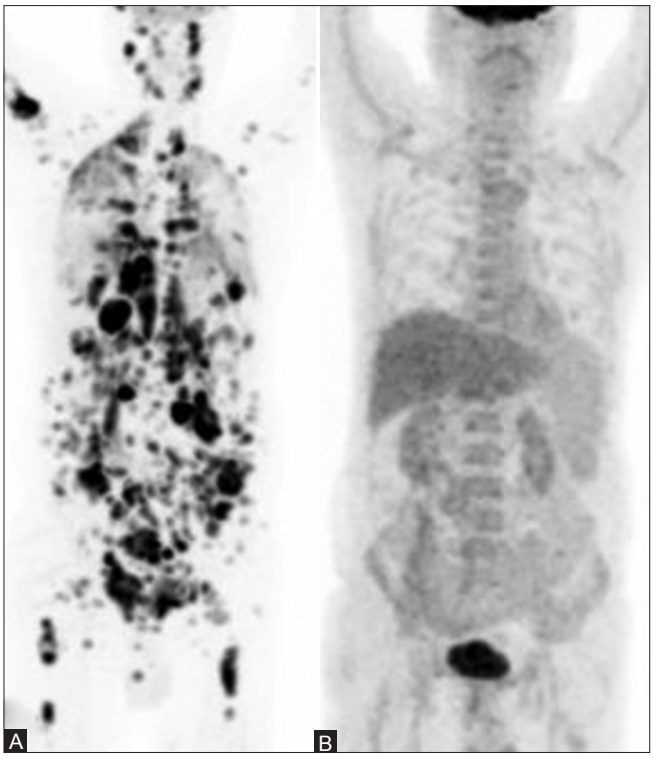

Figure 2 (A and B): A 65-year-old male, a case of NHL. (A) The pretreatment PET MIP image shows extensive nodal and extranodal involvement (B) PET scan done after completion of six cycles of chemotherapy (post-treatment response assessment) shows complete metabolic resolution of disease

after completion of therapy by correctly predicting the presence or absence of viable disease [Figure 2]. CECT is the imaging modality of choice in staging all low-grade lymphomas,[9] except in MALT where FDG PET/CT may have a potential role.[10]

Bone marrow biopsy is an integral part of the work-up of lymphoma. FDG PET/CT has shown increased sensitivity in detection of marrow involvement, especially when the disease is focal in nature. Interim PET or early treatment response after two cycles of chemotherapy helps in prognostication and may modify treatment in some lymphomas[11] [Figure 1], if there is no response or there is progression of the disease seen on PET/CT.

Bone and soft tissue tumors

Both NCCN and IAEA recommend the use of PET in staging, restaging, and in surveillance with options of using either PET or bone scan.[1,2] A recent meta-analysis has shown that FDG PET is a valuable tool for staging and detecting recurrences in patients with Ewing's sarcoma (ES).[12] The pooled sensitivity and specificity of FDG PET/CT in detection of ES is 95%. It is more sensitive in detection of recurrent bone lesions, as compared with other imaging modalities.[13-16] It is also superior to bone scintigraphy and magnetic resonance imaging (MRI) in detection of bone metastases and may lead to change in management.[16] Earlier studies have reported low sensitivity of PET as compared to CT for detection of pulmonary metastases.[15-17] But now, with the availability of PET with diagnostic quality CT, lung nodules can be diagnosed using the CT component of PET/CT with similar accuracy, making it a one-stop-shop staging modality. A prospective multicenter trial has shown the usefulness of PET in detection of primary tumor and metastases with higher sensitivity and specificity as compared to conventional imaging modalities in ES, osteosarcoma, and rhabdomyosarcoma.[16]

There is growing evidence to suggest the role of FDG PET/CT in predicting the response to neoadjuvant chemotherapy (NACT) prior to surgery in osteosarcoma with a pooled sensitivity and specificity of 73% and 86%, respectively.[18] FDG PET/CT has shown promise in demonstrating sarcomatous change in osteochondromas by identifying the hypermetabolic sarcomatous focus.[19] It has also demonstrated clinical impact and outcome in chondrosarcomas.[20]

Breast cancer

FDG PET/CT is useful in providing more accurate metastatic (M) stage and metabolic information in locally advanced breast cancer and inflammatory breast cancer. It has limited/no role in initial detection of the primary and axillary nodes. It also predicts outcome after NACT.[21,22]

Gastrointestinal and hepatobiliary cancers

Though the NCCN and IAEA do not recommend the use of PET/CT in hepatocellular cancer (HCC), the role of functional imaging with PET/CT and PET/MR is gradually evolving. Triple-phase CECT and MRI are the gold standard for diagnosis and staging of HCC.[23] The uptake of FDG in HCC is dependent on the size and differentiation with well-differentiated tumors showing low FDG avidity and more undifferentiated tumors showing high FDG uptake.[24] It is useful in the detection of multifocal lesions and extra-hepatic disease with detection rates of 83-89.6%.[25-27] Preoperative PET helps in predicting tumor differentiation and post-surgical outcome. Higher standardized uptake values (SUVs) are associated with poor differentiation and worse prognosis.[28,29] PET is used in pre-transplant evaluation in HCC, with high recurrence rates seen in patients with positive PET.[30]

The work-up of cholangiocarcinoma is mainly by CECT and MRI with cholangio-pancreatography. Few studies have evaluated the role of PET/CT in diagnosis and staging of cholangiocarcinoma. PET has high sensitivity for the detection of intrahepatic cholangiocarcinoma, whereas the sensitivity is very low for extrahepatic cholangiocarcinoma (91-95% vs 60%).[31,32] Reported sensitivities for detection of distant metastases are in the range of 65-100%, with very low sensitivity for detection of lymph nodal metastases.[33,34] PET/CT is useful in detection of recurrences where anatomical

imaging has limited use due to post-surgical distortion and fibrosis, with sensitivity and specificity of 94% and 100%, respectively, for PET/CT and 82% and 43%, respectively, for CT.[35]

There is scarcity of literature on the role of PET/CT in evaluation of gall bladder cancer, primarily because most of these are detected incidentally. FDG PET/CT seems to have a potential role in staging, as these cancers are intensely FDG avid. PET/CT has an overall diagnostic accuracy of 95.9% for the primary disease and 85.7% and 95.9% for the detection of lymph nodes and metastatic disease, respectively.[36] In our own experience, PET/CT scores over multi-detector CT (MDCT) in detection of occult metastatic disease.[37]

Pancreatic cancer

The primary imaging modality in staging pancreatic carcinoma is MDCT or MRI with/without MRCP (Magnetic Resonance cholangiopancreatography). FDG PET/CT may have a role in triaging patients for curative versus palliative treatment depending on the absence or presence of metastasis in locally advanced disease.[38] A recent meta-analysis has shown pooled sensitivity of 90% and specificity of 76% for FDG PET/CT. It has no additional benefit over the current conventional imaging modalities in diagnosing primary pancreatic cancer.[39] Current evidence regarding the role of FDG PET/CT in the evaluation of intraductal papillary mucinous neoplasms (IPMN) is limited.

Gastric cancer

CT is the modality of choice in defining resectability of gastric cancer due to exquisite anatomic detail, whereas FDG PET/CT has a role in predicting the biological behavior and in prognostication based on the metabolic activity.[40-42] PET/CT has low sensitivity for detection of the primary gastric tumor[43,44] because of normal physiological uptake of FDG in the stomach and due to certain histologies like signet cell and mucinous adenocarcinomas which are low FDG avid.[45] For nodal (N) staging, PET/CT has similar diagnostic performance as compared to CECT, with a sensitivity of 50% for detection of N2, N3 disease and a specificity of about 90%.[44,46,47] CECT has higher sensitivity than PET/CT (77% vs 35%) and lower specificity than PET/CT (92% vs 99%) for the detection of peritoneal metastases.[48] PET/CT has moderate sensitivity and specificity in the detection of recurrent gastric cancers, with pooled sensitivity of 76% and 86% and specificity of 82% and 88%, respectively.[49,50]

Colorectal cancer

The standard imaging work-up includes CT for colonic cancer, and MRI and CT with or without endorectal ultrasound for rectal cancer. NCCN guidelines recommend the use of FDG PET/CT as a problem-solving tool in the initial staging of colorectal cancer (CRC).[1,51] It is particularly useful in characterizing indeterminate liver lesions on CT. There is emerging evidence to suggest the role of PET/CT in evaluating extrahepatic disease before the surgical resection of liver metastases. PET/CT is more sensitive than CT for detection of extrahepatic disease with equal specificity.[52] There has been conflicting evidence regarding the use of PET/CT for response assessment post neoadjuvant chemo-radiotherapy (NACT-RT) in locally advanced rectal cancer.[53,54] But a recent systematic review has shown that PET predicts early response to NACT-RT with high accuracy.[55] However, PET/CT has an undisputed role in the evaluation of recurrent CRC with elevated CEA (carcinoembryonic antigen) and often with equivocal/negative CT [Figure 3]. A recent meta-analysis has quoted pooled sensitivity of 94.1% and specificity of 77.2% of PET/CT for detection of recurrence.[56]

Gastrointestinal stromal tumors

FDG PET/CT has a definite role in staging and evaluation of the response to imatinib mesylate in gastrointestinal stromal tumors (GIST). CT-based Response Evaluation in Solid Tumors (RECIST) criteria are not very useful is assessing the treatment response as the size may not change in these tumors; whereas responses on PET/CT based on change in the metabolic activity are in tandem with the clinical response.[57-59]

Anal cancer

PET/CT can be considered for staging of anal cancer as it alters the stage as compared to conventional imaging

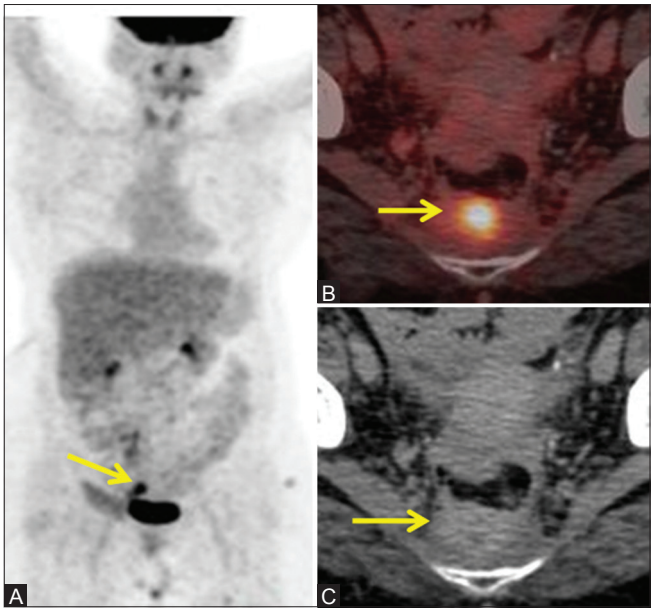

Figure 3 (A-C): A case of carcinoma rectum post abdomino-perineal resection, 9 months post surgery with increasing CEA. (A) The MIP image of the PET scan shows a hypermetabolic focus in the pelvis (arrow) (B) Fused PET/CT image shows FDG-avid pre-sacral mass (arrow) suspicious for recurrent disease (C) CT image shows a pre-sacral mass. Indeterminate whether it is benign fibrosis or disease recurrence. Biopsy confirmed recurrence of adenocarcinoma

modalities in 20-25% cases.[60-62] The role of FDG PET/CT in RT planning in delineation of the target volume is evolving.[63]

Cervical cancer

Lymph nodal involvement is an important prognostic factor in cervical cancer management. FDG PET/CT has a potential role in detection of lymph nodal metastasis in locally advanced cervical carcinoma (≥IB2) in which extra-pelvic spread is common. PET can detect nodal metastasis when CT findings are normal.[64-66] In a retrospective study, Grigsby *et al*. compared CT and FDG PET in the evaluation of nodal metastasis and demonstrated that PET picked up more number of nodal metastasis as compared to CT and also that PET is a better predictor of survival.[66] PET/CT is valuable in treatment planning with external beam RT and brachytherapy. PET results in extension of the involved field radiation in about 18% of cases.[67] In brachytherapy, PET improves the tumor coverage without increasing the dose to the surrounding critical structures.[68] PET/CT has high accuracy of 92% in detection of recurrent disease with a sensitivity of 82% and specificity of 97%.[69] The role of predictive volumetric parameters derived from PET, such as metabolic tumor volume and total lesion glycolysis, is evolving.[70]

Ovarian cancer

CT is the primary imaging modality in the work-up of ovarian cancer. PET/CT has no additional benefit over CT in early ovarian cancer, but is useful in differentiating stage IIIC–IV from other stages with a sensitivity of 100% and specificity of 91%, whereas CT has a sensitivity of 97% and specificity of 64%.[71] PET has a higher sensitivity in the detection of peritoneal deposits and metastasis in normal-sized nodes. It is useful in the detection of recurrent ovarian cancer with increasing cancer antigen 125 (CA125) levels and negative CT or MRI, showing a high sensitivity and specificity of 94.5% and 100%, respectively.[72,73] A recent meta-analysis has shown that PET/CT has the highest sensitivity of 91% when compared with CA125, CT, and MRI.[74]

Head and neck cancers

FDG PET has a well-established role in the detection of distant metastasis and second primary in locally advanced head and neck cancers. In a recent meta-analysis, Xu *et al*. have shown PET and PET/CT to have a sensitivity of 83% and specificity of 96% for detection of distant malignancies, whereas for conventional imaging, the values are 44% and 96%, respectively.[75,76] Detection of distant metastasis early in the work-up algorithm leads to change in the treatment plan and in prognosis. A negative PET/CT study has nearly 100% accuracy in predicting the absence of distant metastatic disease and second primary.[77,78] Accurate response assessment after chemo-radiotherapy (CRT) is essential to plan salvage surgery in patients with advanced disease. PET/CT is not recommended before 8 weeks of completion of CRT because of high false-positive rates. The negative predictive value (NPV) of PET/CT done after 8–12 weeks is 95%.[79] In a meta-analysis of 51 studies, Gupta *et al*. have reported an NPV of 95% for both primary and nodal disease for response assessment.[80] In the post-treatment setting, the best timing for doing a PET/CT for response assessment is after 12 weeks of completion of treatment, but can be done sooner if there is clinical suspicion of recurrent disease,[81] though not before 8 weeks. PET/CT is the best modality for detection of recurrence in head and neck cancers [Figure 4].

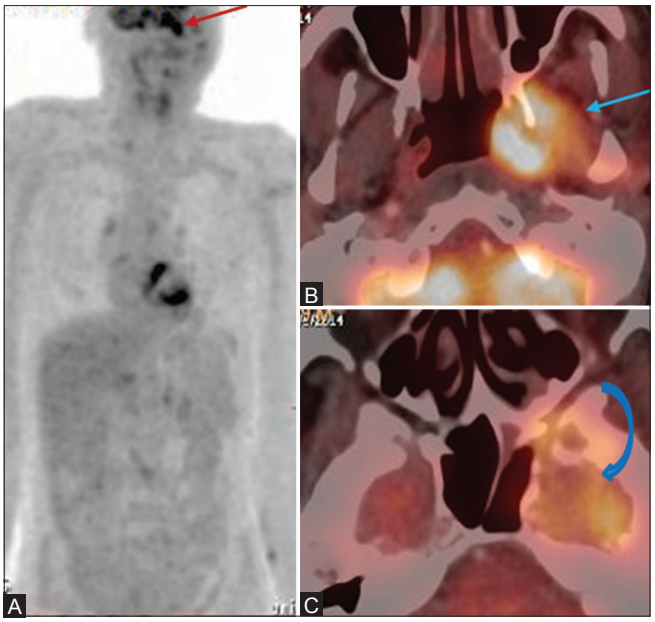

Figure 4 (A-C): A 59-year-old male, a case of squamous carcinoma of left buccal mucosa, post surgery, chemotherapy, and external radiotherapy given a year back, presented with left facial palsy with no clinical evidence of disease. (A) The MIP image of the PET scan shows a hypermetabolic focus in the left infra-temporal fossa (ITF) (arrow) (B and C) Fused PET/CT image shows hypermetabolic mass in the left ITF involving the pterygoid muscles (arrow) with intracranial extension into the left cavernous sinus and left temporal lobe (curved arrow) suggestive of recurrent disease

Unknown primary

It is important to identify the primary in patients who present with metastatic cervical adenopathy. Inability to detect the primary leads to futile tonsillectomies and untargeted neck dissections. Varying detection rates of 29-54%, with sensitivity ranging from 62 to 97% and specificities of 33–93% have been reported[82-85] [Figure 5]. PET/CT leads to change in management in 38.9% of patients.[85] PET/CT done prior to pan-endoscopy and biopsy reduces futile endoscopies and false-positive PET studies[86] [Figure 5].

Thyroid cancer

Poorly differentiated and undifferentiated thyroid cancers are FDG avid due to over-expression of glucose transporter (GLUT) receptors and negative on radioiodine scintigraphy due to loss of sodium iodide symporter

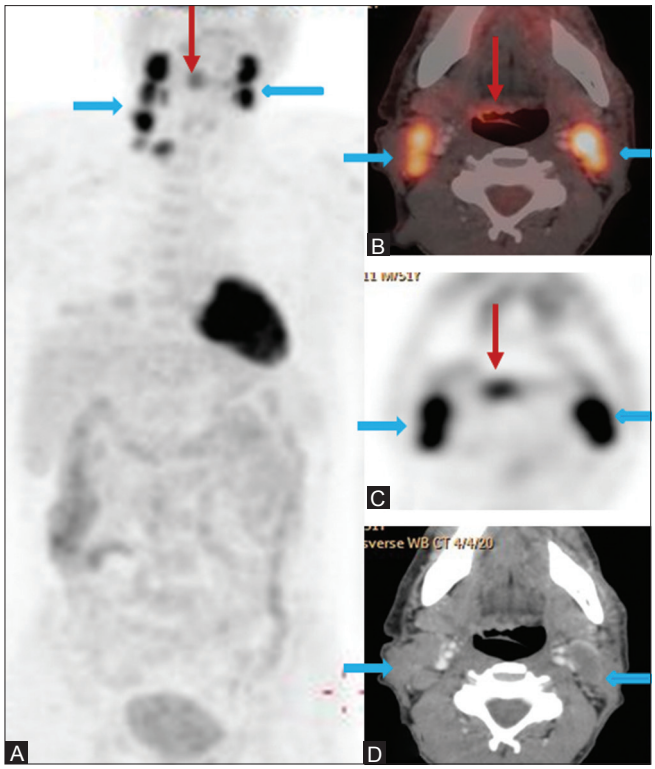

Figure 5 (A-D): A 51-year-old old male presented with bilateral cervical adenopathy; biopsy revealed it as metastatic squamous cell cancer, unknown primary. (A) PET image shows hypermetabolic bilateral cervical adenopathy (block arrows) (B) Fused PET/CT image shows a subtle hypermetabolic lesion involving the right base tongue (BOT) and vallecula (arrow) (C) PET image shows the same (D) CECT image shows bilateral necrotic cervical nodes, but the primary lesion is not evident. Biopsy of the BOT and vallecula showed squamous cell carcinoma (primary detected)

responsible for iodine uptake in a thyroid follicular cell. This is in contrast to well-differential thyroid cancers which are radioiodine avid and negative on PET. This is known as flip-flop phenomenon and sets the basis of the appropriateness of FDG PET study in thyroid malignancies. It is considered appropriate to perform FDG PET in thyroid malignancies with high-risk pathology subtypes like tall cell, solid, insular variants, etc. In metastatic thyroid disease, current evidence suggests that FDG PET scan identifies the metastatic lesions not identified by radioiodine scan. This has important treatment implications. For undifferentiated and anaplastic thyroid tumors, FDG PET/CT is the imaging of choice.[1,2,87]

CNS lymphoma

FDG PET/CT has a potential role in the detection of primary CNS lymphoma (PCNSL). Though PET is not very useful in the detection of metastatic lesions due to high physiological uptake of FDG in the brain parenchyma, PCNSL usually demonstrates very intense FDG uptake, which is 2-2.5 times higher than normal physiological uptake. It also has high sensitivity in differentiating PCNSL from glioblastoma and metastatic disease.[88]

Lung cancer

FDG PET combined with CECT is an efficient modality for staging of lung cancers. PET/CT is the best modality to differentiate tumor from adjacent atelectasis, in identifying chest wall invasion, and in detection of pleural metastases.[89-91] PET has a high sensitivity of 95%, positive predictive value (PPV) of 95%, accuracy of 92%, and moderate specificity of 67% in the detection of pleural metastasis.[92] PET/CT has higher sensitivity and specificity in the mediastinal staging of lymph nodes with a sensitivity and specificity of 81% and 90%, respectively, as compared to CT which has a sensitivity and specificity of 59% and 79%, respectively.[93] PET has the added advantage of detection of metastatic nodes < 1 cm, but with a low PPV of 64%.[94-96] However, PET-positive nodes should still undergo mediastinoscopic sampling for confirmation of metastatic involvement.[97,98] On the contrary, PET has a high NPV of 95% and invasive mediastinoscopy can be omitted in PET-negative nodes,[98] except in centrally situated masses where perilesional mediastinal nodes can be masked due to high metabolic activity of the tumor.[99] PET detects occult metastatic disease in about 29% of cases.[100] It detects adrenal metastasis with a high sensitivity and specificity of >95% and >80%, respectively.[101,102] An invasive biopsy can usually be obviated in most cases. In cases of isolated adrenal metastasis with equivocal PET/CT, a biopsy or adrenalectomy can be contemplated. A meta-analysis comparing FDG PET/CT, MRI, and bone scintigraphy has shown that PET/CT is the best modality for detection of bone metastasis, with a pooled sensitivity and specificity of 92% and 98%, respectively, for PET/CT, 77% and 92%, respectively, for MRI, and 86% and 88%, respectively, for bone scintigraphy[103] [Figure 6]. For brain metastases, MRI is the imaging modality of choice. FDG PET/CT is not very suitable due to normal physiological FDG activity in the brain parenchyma. PET/CT-based RT planning reduces the inter-observer variability and leads to change in treatment plan in about 50% of patients, with enhanced tumor coverage.[89,104]

PET is a better predictor of response to treatment and the metabolic response correlates with outcome.[105] PET/CT detects recurrences with a high sensitivity and specificity of 93% and 89%, respectively, and an accuracy of 92%.[106]

Small cell lung cancer

PET/CT has higher sensitivity and specificity in the detection of distant metastases of small cell cancer as compared to CT, except for brain metastasis. PET leads to change in stage of the disease in 17% of cases, when compared to conventional imaging modalities.[107,108] PET-based RT planning also leads to change in radiation field in about 37% cases.[109]

Malignant pleural mesothelioma

PET/CT is recommended for staging and restaging of malignant mesothelioma. It correctly differentiates between benign and malignant pleural lesions with a sensitivity of

95-97% and specificity ranging from 78 to 92%.[110,111] FDG avidity with an SUVmax value >2-2.2 is helpful for this differentiation.[111] PET/CT identifies more sites of nodal involvement and distant metastases, as compared to CT.[112,113]

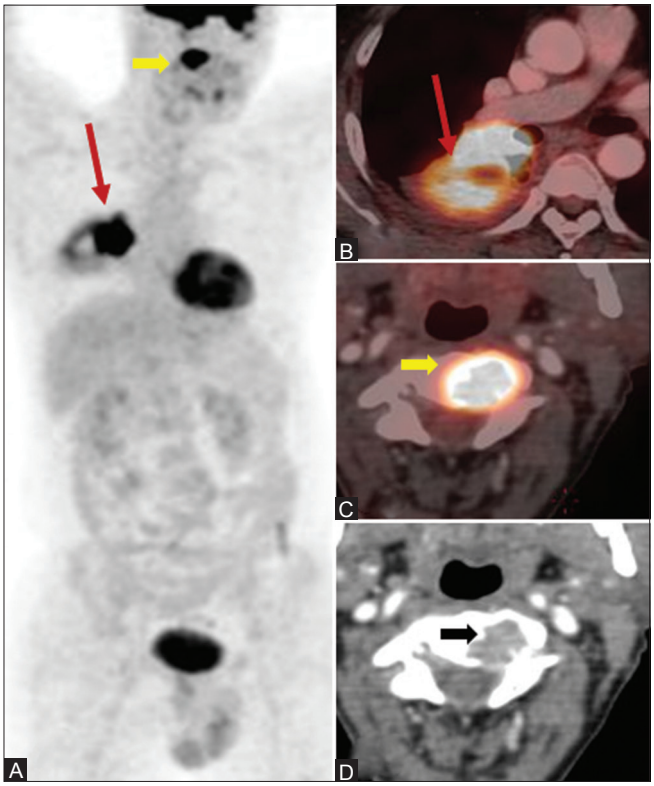

Figure 6 (A-D): A 54-year-old male, diagnosed case of adenocarcinoma of the right lung. PET/CT scan done for initial staging shows hypermetabolic right lower lobe mass (arrows in A and B) and an unsuspected metastatic lesion in C2 vertebral body (block arrows in A, C, and D)

Thymic tumors

FDG PET/CT is recommended for the diagnosis and staging of thymic tumors. Studies have shown that PET can differentiate between low-risk thymomas (A, AB, B1 histological types), high-risk thymomas (B2, B3 histological types), and thymic carcinomas based on SUV values. The SUV values show an increasing trend from low to high-risk tumors.[114-117] PET/CT is better in identifying involved nodes of size <1 cm.[114]

Esophageal cancer

For initial tumor (T) staging of esophageal cancer, endoscopic ultrasound is the preferred modality of choice as it measures the depth of invasion most accurately.[118] PET/CT lacks the spatial resolution to demarcate the depth of invasion. The sensitivity increases with increasing depth of invasion, the value being 83% for T2 tumors, 97% for T3, and 100% for T4 tumors.[119] For detection of nodal disease, PET/CT has the highest sensitivity and specificity of 96% and 95%, respectively.[120] PET/CT is the best modality for detecting distant metastasis and prevents unnecessary surgical explorations by detection of metastatic disease.[121] In a study by Duong *et al*., PET/CT changed the clinical management from either curative to palliative or vice versa or changed the treatment modality in 40% of patients.[122] In our own experience, PET/CT detects unsuspected distant metastases in 16% of patients, changing the plan of treatment from curative to palliative.[123] PET/CT is useful in evaluating the response

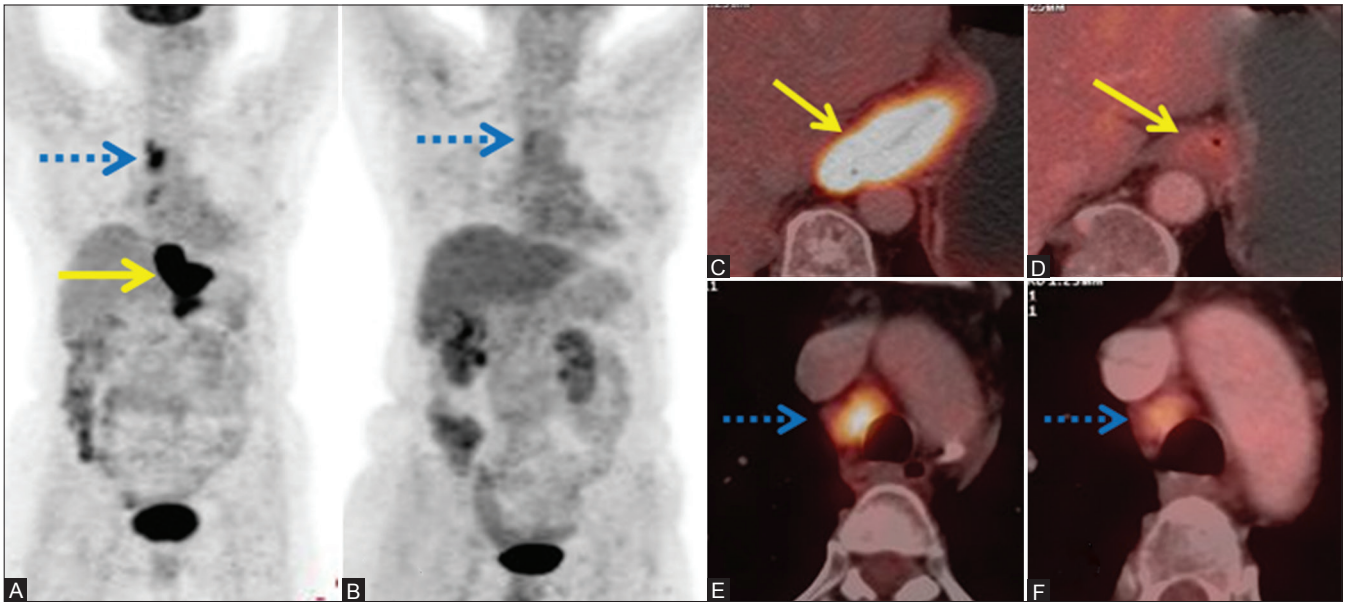

Figure 7 (A-F): A case of adenocarcinoma of the distal esophagus. (A) Pretreatment MIP image shows hypermetabolic mass in the distal esophagus (arrow) and hypermetabolic metastatic mediastinal nodes (dashed arrow). (C and E) Fused PET/CT images showing the same. (B) Response assessment PET scan done after three cycles of neoadjuvant chemotherapy (NACT) shows complete metabolic and morphologic regression of the mass with partial metabolic and morphologic regression of the mediastinal nodes (dashed arrow) on MIP. (D), (F) The same is depicted in fused PET/CT images (arrow in d and dashed arrow in F)

to NACT [Figure 7] and CRT by distinguishing residual viable tumor from fibrosis/necrosis based on the metabolic activity of the tumor.[124]

Prostate cancer

FDG PET has a limited role in the staging and diagnosis of prostate cancer (PC) because of overlap of FDG uptake in normal, benign, and malignant lesions in the prostate.[125,126] Few recent studies have shown increased FDG uptake in aggressive lesions as compared to the indolent ones, with a sensitivity of 80%.[127,128]

Renal cell cancer

FDG PET/CT has limited a role in staging of renal cell cancer (RCC), but is useful in the detection of metastatic disease and in restaging. Wang *et al*. have shown in a meta-analysis that the pooled sensitivity and specificity for detection of metastases is 91% and 88%, respectively.[129]

Urinary bladder cancer

FDG PET/CT has a limited role in staging of bladder cancer due to excretion of FDG via the kidneys and subsequent accumulation in the bladder, masking the uptake in the primary. Many interventions like hydration, delayed imaging, and diuretic administration are performed to enhance the visualization of FDG uptake in the primary, showing good results.[130,131] A recent meta-analysis has reported good diagnostic accuracy for detection of metastatic lesions with a pooled sensitivity and specificity of 82% and 89%, respectively, for restaging patients.[132]

Testicular cancer

Presence of viable tumor in residual masses after chemotherapy is a major problem in germ cell tumors (GCT). Currently FDG PET/CT is the best imaging modality to solve this problem. De Santis *et al*., in a study of 56 seminomatous GCT patients, have shown that PET is the best predictor of viable disease in residual masses with a sensitivity of 80% and specificity of 100%, in comparison to CT which has a sensitivity of 70% and specificity of 74%.[133] The accuracy is 100% for masses >3 cm and 95% for masses <3 cm. Similar results were confirmed by a recent meta-analysis.[134,135] The use of PET in non-seminomatous GCT (NSGCT) is controversial. In NSGCT, PET has a PPV of 91% and NPV of 62% in differentiating viable from non-viable disease. This means that PET can predict the presence of viable disease with a reasonable accuracy, but a negative PET study cannot exclude the presence of disease.[136] PET has a definite role in the evaluation of seminoma, but cannot predict the presence of disease in NSGCT with negative PET study.

Melanoma

FDG PET/CT is the best modality for N and M staging of advanced cutaneous melanoma[137] [Figure 8] and for detection of metastasis in mucosal melanomas of head and neck and anorectum.

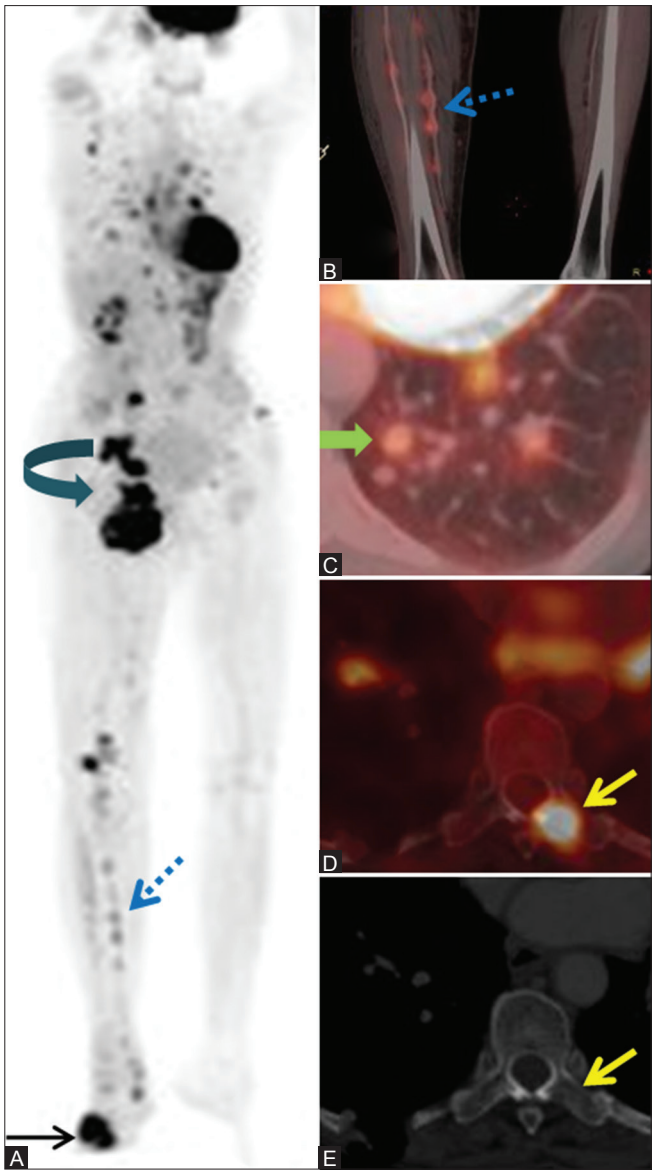

Figure 8 (A-E): (A-E) A 65-year-old lady, a case of malignant melanoma of the right foot. PET/CT done for staging shows FDG-avid mass in the right foot [site of primary (arrow)], multiple interstitial nodules in the right lower leg (dashed arrows in A and B), right inguinal and pelvic nodal masses (curved arrow), multiple metastatic lung nodules (block arrow), and marrow metastasis in the dorsal vertebra (yellow arrow). PET/CT is a one-stop-shop imaging for detection of metastases in malignant melanoma

The indications for the use of PET/CT are summarized in Table 1.

Conclusion

It is evident that the appropriateness criteria for FDG PET/CT in various malignancies are constantly evolving. The impact of FDG PET/CT on treatment management, as evident by the National Oncologic PET

Table 1: Indications of PET/CT

Type of malignancy	Diagnosis	Staging	Restaging	Therapy evaluation	Follow-up/ surveillance	Radiation planning	Remarks
Hodgkin's lymphoma	x	!!!	!!!	!!!	!x	!	8 weeks minimum for post RT evaluation
NHL	!x	!!!	!!!	!!!	!x	!	IAEA considers appropriate across NHL
NHL follicular grade 1-2	x	!x	!!!	!!!	x	x	Biopsy required if used for follow-up to confirm progression
Non-gastric MALT lymphoma, marginal zone lymphoma (nodal, splenic), Burkitt lymphoma, lymphoblastic lymphoma, peripheral (non-cutaneous) T-cell lymphoma, primary cutaneous B-cell lymphoma, adult T-cell leukemia/lymphoma	x	!x	!!!	!!!	x	x	NCCN recommends certain NHL subtypes
Mantle cell lymphoma	x	!x	!!!	!!!	x	x	
CLL/SLL	!!	x	d	d	x	x	Directing nodal biopsy if Richter's transformation is suspected
Post-transplant lymphoproliferative disorder	x	!x	d	x	x	x	
Sarcomas							
Ewing's sarcoma and osteosarcoma	x	!!!	!!!	!x	!!!	!	Chemo-response to predict necrosis
Chondrosarcoma	x	x	x	x	x	x	
Soft tissue sarcoma (extremity and trunk)	!!	!!	x	!!	x	x	
Retroperitoneal and abdominal sarcoma and desmoid tumors	x	x	x	x	x	x	
Melanoma	x	!!!	!!!	x	!x	x	Up to 5 years follow-up
Breast cancer	x	!!!	!!	!!	x	!	Staging in LABC Locally advanced breast cancer
Occult primary	!!!	!!!	x	x	x	x	
Non-melanoma skin cancers	x	x	x	x	x	x	
Merkel cell carcinoma	!x	!x	x	x	x	x	
Gastrointestinal and hepatobiliary cancers							
Colorectal cancer	x	!x	!!!	!	!	!	
Anal canal	x	!x	x	x	x	x	
Gastric cancer	x	!!!	!!!	!	!	x	
Hepatocellular cancer	x	!x	x	x	x	x	May be useful as a prognostic marker
Gall bladder	!	!	x	!	x	!x	May be useful to detect distant metastases in otherwise resectable disease
Pancreatic cancer	!x	!	!!	!	x	!	Can be used in high-risk patients to detect extrapancreatic metastases
Gynecological cancers							
Cervical cancer	x	!!!	!!!	!	!!!	!!!	
Ovarian cancer	x	!!	!!!	!!!	!!!	x	
Endometrial carcinoma	x	x	x	x	x	x	
Uterine sarcoma	x	!x	!x	x	x	x	
Head and neck cancers							
Squamous cell cancer	!!!	!!!	!!!	!!!	!!	!	Diagnosis for unknown primary presenting as neck nodes
Nasopharyngeal carcinoma	x	!!!	!!!	!	!	!	
Differentiated thyroid cancer	x	x	!!!	x	x	x	When Tg>2–5 ng/ml and I-131 imaging is negative in papillary, follicular, and Hurthle cell carcinoma and rising thyroglobulin level
Thyroid cancer- anaplastic	x	!!!					
Medullary cancer thyroid	x	c	!!!	!!	x	x	Increasing calcitonin or CEA level
CNS lymphoma	!!!	!!!	x	x	x	!	
Glioblastoma	x	x	!!!	x	x	!	>1 Brain metastases in occult primary, spinal metastases in known or unknown primary, PET-guided biopsy

Contd...

Table 1: Contd...

Type of malignancy	Diagnosis	Staging	Restaging	Therapy evaluation	Follow-up/ surveillance	Radiation planning	Remarks
Thoracic cancers							
Solitary pulmonary nodule	!!!	x	x	x	x	x	
Non-small cell lung cancer	x	!!!	!!!	x	x	!!!	
Small cell lung cancer	x	!!!	x	x	x	!!!	
Malignant pleural mesothelioma	x	!!!	!!!	x	x	x	
Thymic malignancies	!!	!!!	x	x	x	x	
Esophageal cancer	x	!!!	!!	!!	x	!!	
Urological cancers							
Prostate cancer	x	x	x	x	x	x	
Kidney cancer	x	!	!!	x	x	x	
Urinary bladder cancer	x	x	x	x	x	x	
Testicular cancer seminoma	x	x	!!!	!	!!	x	
Testicular cancer non-seminoma	x	x	x	x	x	x	

!x: Useful under some circumstances, !!!: Appropriate, !!: Potentially appropriate, !: Possibly appropriate, x: Inappropriate, CLL: Chronic lymphocytic leukemia, IAEA: International atomic energy agency, MALT: Mucosa-associated lymphoid tissue, NCCN: National Comprehensive Cancer Network, NHL: Non-Hodgkin's lymphoma, PET: Positron emission tomography, SLL: Small lymphocytic lymphoma

Registry (NOPR)[138,139] which is a collaboration of the American College of Radiology Imaging Network (ACRIN) to ensure access to Medicare reimbursement for various PET scan indications, has added a new dimension to the appropriateness criteria. The above recommendations provide an insight into the usefulness of PET/CT in oncology and can help the radiologist and clinician in choosing this hybrid technology appropriately to maximize information for optimal patient care.

Acknowledgement

We would like to thank Dr. Abhijith Singh and Mr. Ashish Jha for their help in preparing the manuscript.

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Cite this article as: Agrawal A, Rangarajan V. Appropriateness criteria of FDG PET/CT in oncology. Indian J Radiol Imaging 2015;25:88-101.

Source of Support: Nil, **Conflict of Interest:** None declared.