REVIEW ARTICLE

FDG-PET IN ONCOLOGY

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ABSTRACT

Positron Emission Tomography (PET) is very sensitive modality that depicts the cellular processes underlying tumor metabolic activity, such as glucose metabolism, cell proliferation, cell membrane metabolism and receptor expression. Since 2001 in oncology, PET is being used for tumor detection and differentiation between benign and malignant tumors, tumor staging and prognostic stratification, evaluation of treatment response, restaging and detection of recurrent disease, radiation treatment planning and the development of new anticancer drugs. 2-(18F) fluoro-2-deoxy-D-glucose(FDG), a glucose analogue first tested in humans in 1976, is by far the most widely used metabolic tracer globally. Pioneering work since its conception has helped to solidify FDG-PET as a powerful diagnostic imaging modality in oncology and has generated a growing interest in molecular imaging.

Key words: Positron Emission Tomography (PET); FDG; Oncology

FDG is an analogue of glucose transported into tumor cells by glucose transporters (glut-1, glut-3) and phosphorylated by hexokinase inside the cell to form fluorodeoxyglucose-6-phosphate. The phosphorylated deoxyglucose is not a substrate for further biochemical pathways, and is therefore trapped within cells (Fig.1).

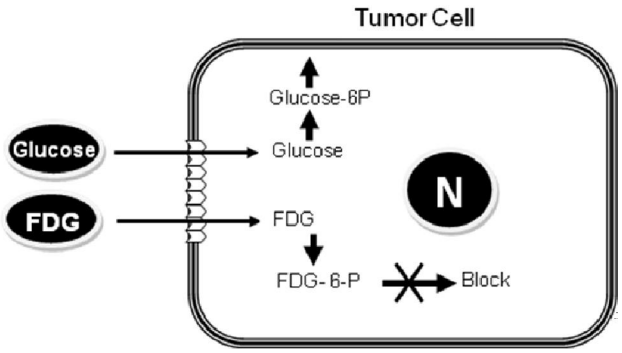

Figure 1: FDG uptake in Cancer Cell

The upregulation of glycolytic rate is a characteristic feature of many types of malignant cells and is partially related to an over-expression of the GLUT-1 glucose transporters and an increased hexokinase activity. These tumors exhibit increased FDG uptake on PET scan.[1,2] Metabolic activity in brown adipose tissue, physiological gut activity, infectious and inflammatory processes, physiologic or pathologic sequelae of surgical or interventional procedures, etc may pose some difficulties in the image interpretation. Modest hexokinase activity in well differentiated tumors and certain tumor such as prostate cancer and mucinous carcinomas may result in only insignificant FDG-uptake and thus may not be detected on PET scan.[3,4]

Limited spatial resolution and poor anatomical localization of FDG-PET warranted the incorporation of anatomical imaging modality i.e. computerized tomography (CT) resulting in dual-mode imaging. These hybrid systems allow acquisition of anatomic transmission (CT) and functional emission (PET) during single sitting by using a single imaging device. This has significantly improved the diagnostic accuracy and also provided data to improve therapeutic decisions thus enhancing patient care. The hybrid imaging is now being extended to PET/MRI and further improvements are foreseen in this new modality.[5]

PET/CT Procedure

In order to address the concerns of misinterpretation, it is imperative to observe a standardized patient

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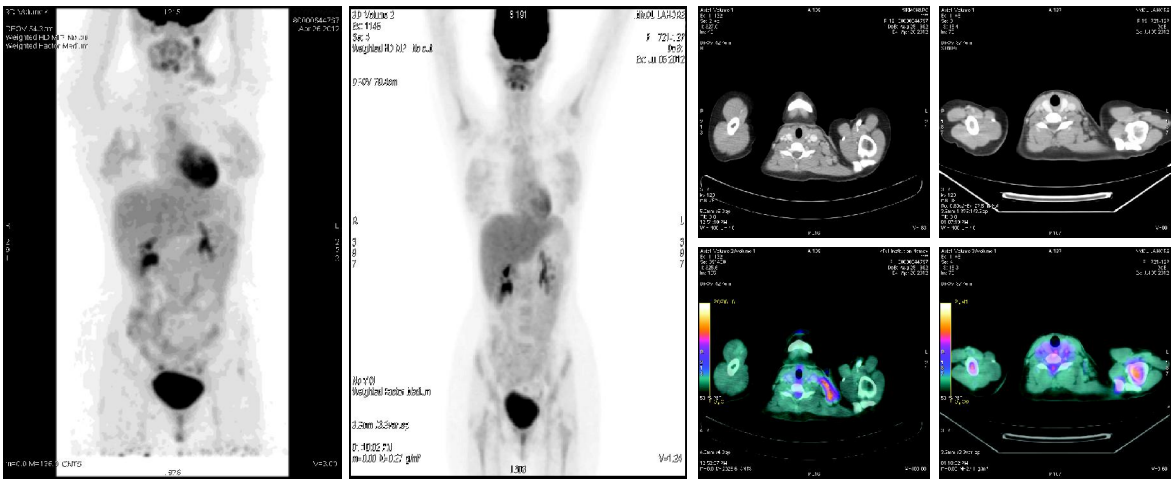
preparation protocol for FDG PET/CT imaging. A 4-6 hour fasting is recommended prior to administration of FDG with euglycemic state at the time of FDG injection. Patient should be well hydrated. Other important factors requiring attention are effects of physiological activity, and the timing of acquisition relative to the type of treatment. For diabetic patients, blood glucose level is to be checked. If the level is <200 mg/dl, FDG is injected intravenously through the IV catheter with a dosage of 0.22 mCi/kg (8.1 MBq/kg) or as prescribed by the physician. The cutoff value for glucose level varies with the institution. In lymphoma and colorectal studies, catheterization is desirable to eliminate extraneous activity in the bladder. The patient waits for 40 to 60 minutes with instructions to remain calm and quietly seated during this waiting period. A blank CT transmission scan is acquired at the beginning of the day. The patient lies supine on the scan table with the head toward the gantry. The table advances by computer control toward the gantry (first CT). A topogram is acquired to define axial range of the body for scanning. Patient is asked to close eyes and breath normally and not to move during this phase. Patient is then positioned in the CT scan field and a spiral CT transmission scan that takes less than 1min is acquired. The table then automatically advances into the PET scanner with the patient in the scan field. The number of bed positions is automatically ascertained from the axial range defined by the topogram obtained from head to thigh. Data are acquired for a set time (usually 3-4 minutes) for each bed.

PET has a wide range of clinical applications with varying degrees of supporting evidence in literature for each indication. However there are many potential applications for which the current literature is limited. Some of the common oncologic indications are discussed.

Lymphoma

The lymphoproliferative disorders, represent a heterogeneous group of lymphoid malignancies which can be broadly divided into two large subgroupings, Hodgkin's (HL) and non-Hodgkin's (NHL) lymphoma[6] Though both lymphoma groups are characterized by upgraded glucose metabolism with subsequently increased FDG uptake in tumor sites, the degree of uptake is variable and does not correlate with a specific histologic subtype or grade. Based on the avidity of FDG Weiler-Sagie M, et al classified 766 cases of lymphoma, the sensitivity of FDG-PET was 100% for Hodgkin's disease, Burkitt's lymphoma, mantle cell lymphoma, nodal marginal zone lymphoma (MZL), and lymphoblastic lymphoma, 97% for DLBCL and 95% for follicular lymphoma.[7] whereas some studies have reported marginal zone lymphoma, peripheral T-cell lymphoma, and small lymphocytic lymphoma as less reliably FDG-avid.

Several indications for FDG-PET have been established in patients with malignant lymphoma (ML) like staging, evaluation of early response to chemotherapy, assessment of end response to therapy, radiation therapy planning and during follow-up.[8] (Fig. 2)

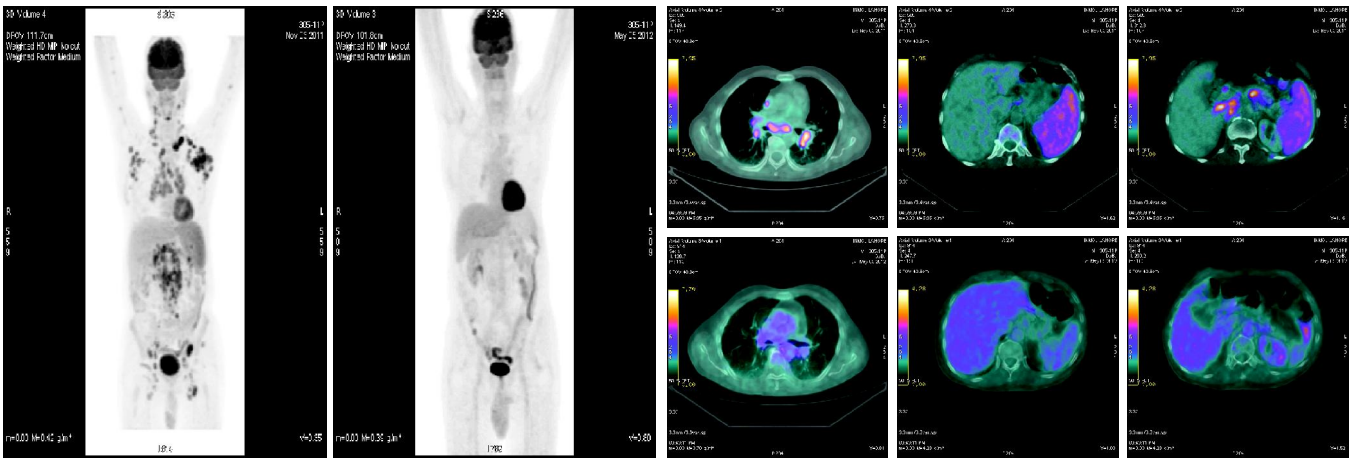


HD Pre-Treatment HD Post-Treatment HD Pre-Treatment HD Post-Treatment

Figure 2: Hodgkin Disease Scan showing complete metabolic remission after 6 cycles of chemotherapy.

The role of PET/CT in the staging of lymphoma is now well established. A number of studies have concluded that PET/CT scan suffice as stand alone modality for staging and re-staging of patients with lymphoma. Multiple studies have shown FDG to be very sensitive for the detection of nodal and extranodal lymphoma at baseline staging of patients prior to commencement of treatment.[9] Isohashi et al evaluated the diagnostic accuracy of positron emission tomography (PET) with FDG for staging/restaging, evaluating the treatment response, and screening of recurrence in patients with ML during long-term follow-up.[10] The accuracy of FDG-PET versus CT/MRI was 92% versus 84% ($p < 0.06$) for staging/restaging. In the pretreatment staging of lymphoma, PET can add to conventional diagnostic testing with CT, leading to upstaging in 10-20% of cases. Typical examples of upstaging include FDG-avidity in sub-centimeter lymph nodes, which are not significant by CT criteria, and splenic and hepatic infiltration which may not be obvious on CT studies. FDG-PET revealed that 90-100% of early-stage HL patients achieved a metabolic complete response after two to three cycles of chemotherapy.[11] FDG-PET at mid-treatment can predict the outcome of patients with aggressive lymphoma and should be a useful tool to modify an ineffective therapy.

Zijlstra et al., in a meta-analysis study estimated the diagnostic accuracy of PET-CT in lymphoma. The pooled sensitivity and specificity of FDG PET for detection of residual disease after completion of firstline therapy were 84% (95% confidence interval, 71%-92%) and 90%(95%confidence interval, 84%-94%), respectively, for HD and 72% (95% confidence interval, 61%-82%) and 100% (95% confidence interval, 97%-100%), respectively, for NHL.[12] Terasawa et al reviewed 19 studies consisting of 474. HD and 254 aggressive NHL patients. Reported ranges for the sensitivity and specificity of FDG-PET in predicting disease relapse were 0.50-1.00 and 0.67-1.00, respectively, for HD and 0.33-0.77 and 0.82-1.00, respectively, for NHL.[13] Both reviews show a very high, somewhat less variable, negative predictive value (NPV) for FDG. PET in post-therapy evaluation of HD, with the NPV ranging from 84% to 100% in the 5 studies reported by Zijlstra et al. and from 71% to 100% in the 10 studies included by Terasawa et al., with a weighted average of 94% for the latter studies. FDG PET has been incorporated into revised response criteria for aggressive lymphomas.[14] (Fig. 3)



NHL Baseline Scan | Post-treatment scan | NHL Stage III Pre and Post-treatment FDG PET scan

Figure 3: Non-Hodgkin Lymphoma Stage III showing complete response after chemotherapy

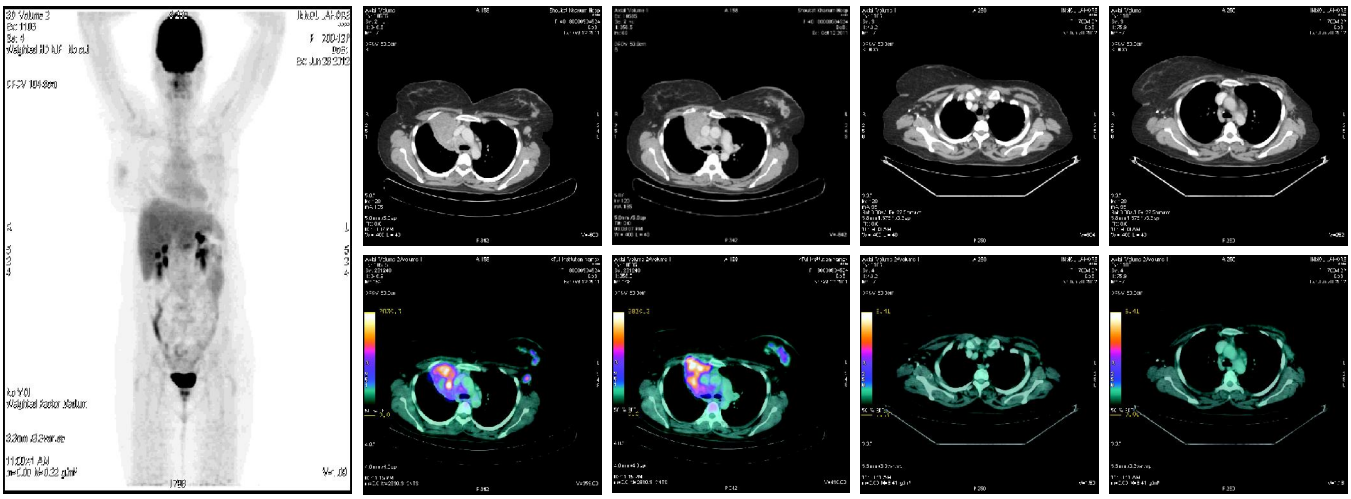
Breast Cancer

Cancer of the breast in women is a major health burden worldwide. It is the most common cause of cancer among women in both high-resource and low-resource settings. Although standard imaging methods, such as ultrasonography, mammography, and magnetic resonance imaging, are used for the initial diagnosis and follow-up of primary breast cancer, the information obtained is structural and does not provide any information regarding the metabolic activity. PET imaging with FDG is a valuable tool for evaluating metabolic activity of tumor. Available evidence in literature currently does not recommend FDG-PET-CT as a primary diagnostic procedure in breast cancer, but it role in detection of nodal and distant metastases and for monitoring response to chemotherapy is widely accepted.

Accurate staging of breast cancer at the time of initial diagnosis has a major impact on the treatment strategy and follow-up. Nodal and distant metastases are two important prognostic factors in patients with breast cancer. Cermik et al in a prospective study on 271 patients revealed that extra-axillary regional node or distant metastatic lesions by PET scan in 22 of 24 patients resulted in a significant change in the TNM stage. Distant metastasis without axillary lymph node metastasis was found in 21% (5/24) of patients. The results revealed that FDG-PET upgraded TNM stage in 9.2% (22/240) of patients.[15] Other studies also potential role in the workup of patients with less advanced, clinical stage II disease.[16]

Peare R et al carried an aggregated ROC analysis of 25 studies involving 2460 subjects found an area under the curve of 0.95 (95% CI 0.91–0.97) and a Q* value of 0.89 (95% CI 0.85–0.92).[17] Groheux et al showed that several biological features usually considered as bad prognostic factors like higher tumor grade, triple negative tumors, p53 mutation, were associated with an increase in FDG uptake. Over-expression of c-erb B-2 had no effect on the SUV value.[18]

Sequential FDG-PET imaging has been widely studied as a method for assessing tumor response to neoadjuvant chemotherapy. The concept of using FDG-PET for predicting a therapeutic response is based on early changes in tumor glucose use. (Fig.4) Isasi CR et al in a meta-analysis of studies that evaluated the diagnostic performance of FDG-PET in the assessment of breast cancer recurrence and metastasis, estimated the pooled sensitivity, false positive rate, and the maximum joint sensitivity and specificity of FDG-PET. Among the 18 studies with patient-based data and sample size of 808 subjects, the median sensitivity was 92.7%, and the median specificity was 81.6%. The pooled sensitivity was 90% (95% confidence interval (86.8–93.2)), and the pooled false positive rate was 11% (95% confidence interval (7.8–14.6)), after the exclusion of outliers. The maximum joint sensitivity and specificity, was 88% (95% confidence interval (86.0–90.6)).[19]



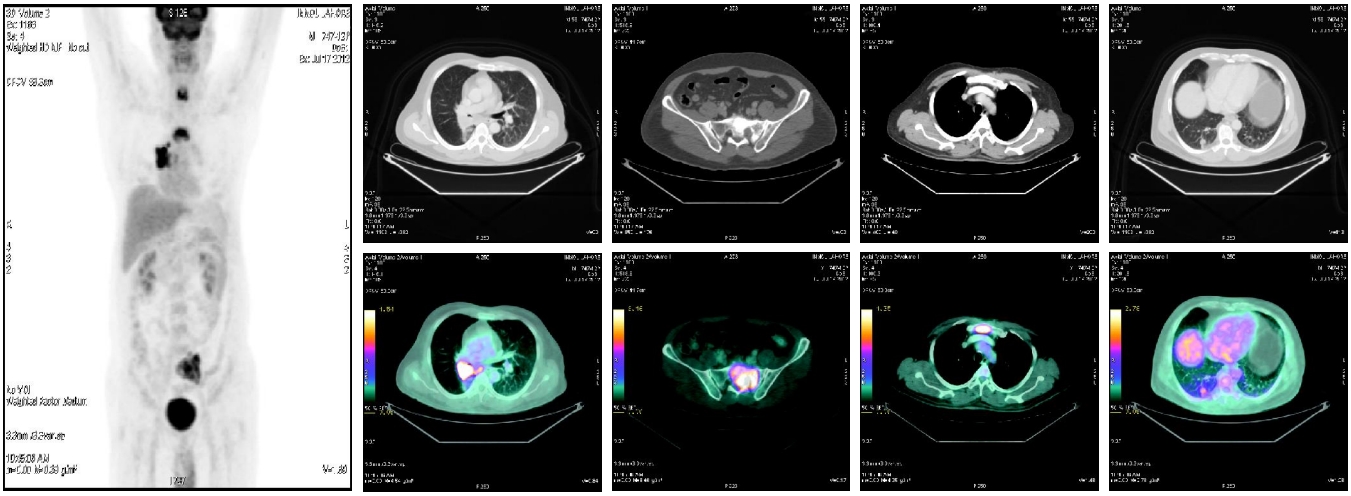
Ca Breast Post-Surgery and Chemotherapy | Primary Tumor (Pre-treatment) | Primary Tumor (Post-treatment)

Figure 4: 54 year old female with primary breast cancer and lung mets Pre and Post-treatment scans

Lung Cancer

The diagnostic workup of lung cancer typically includes history and physical examination, chest X-ray, high resolution contrast-enhanced computed tomography, bronchoscopy and biopsy. While CT is the cornerstones of the structural imaging workup, FDG-PET plays an increasing role in the diagnosis, staging and follow-up of lung cancer patients. Accurate staging of patients with non-small-cell lung cancer is critical in determining treatment strategy and predicting prognosis. The role of FDG-PET in lung cancer has expanded beyond staging, such as the evaluation of biological characteristics of the tumor and prediction of prognosis and the early assessment of tumor response to therapy. Wever et al. showed that integrated PET/CT correctly

predicted the T staging in patients with NSCLC in 86% of cases versus 68% with CT.[20] Integrated PET/CT provides important information on mediastinal infiltration, chest wall infiltration, and differentiation between tumor and peritumoral atelectasis. For N staging, PET/CT scanning possessing high negative predict value can reduce unnecessary media - stinoscopy.[21] (Fig. 5)



Ca Lung with Nodal and Bone Mets | Primary Tumor | Sacral Mets | Sternal Mets | Suspicious Satellite

Figure 5: 54 year old male with lung mass, cough, hemoptysis and weight loss

Wang J et al in a metanalysis concluded that combined PET and CT provide a favorable NPV for mediastinal metastases in T1N0.[22] Ten studies with a total of 1122 patients with stage I (T1-2N0) NSCLC were analysed. The NPVs of combined PET and CT for mediastinal metastases were 0.94 in T1 disease and 0.89 in T2 disease. Including both T1 disease and T2 disease, the NPVs were 0.93 for mediastinal metastases and 0.87 for overall nodal metastases. By integrating functional and anatomic data, PET/CT improved N staging compared with PET or CT alone. Initial studies demonstrated a pooled average sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of PET/CT for detecting metastatic lymph nodes of, respectively, 73%, 91%, 71%, 90%, and 86% versus 83%, 81%, 71%, 89%, 82% of PET alone and 74%, 73%, 52%, 88%, 73% of CT alone. PET/CT has a low sensitivity in detecting brain metastases because of brain cells with high glucose uptake in nature. In a recent metaanalysis, Chang MC et al (23) observed that the pooled patient-based sensitivity, specificity and AUC of FDG-PET or PET/CT was 0.93 (95% confidence interval (CI), 0.88-0.96), 0.95 (95% CI, 0.91-0.98), 0.94 respectively. The pooled sensitivity, specificity and AUC of bone scans was 0.87 (95% CI, 0.79-0.93), 0.82 (95% CI, 0.62-0.92), and 0.91 respectively. The pooled lesion-based sensitivity, specificity and AUC of FDG-PET or PET/CT was 0.93 (95% CI, 0.84-0.97), 0.91 (95% CI, 0.80-0.96), and 0.97 respectively. The pooled sensitivity, specificity and AUC of bone scans was 0.92 (95% CI, 0.87-0.95), 0.57 (95% CI, 0.09-0.95), and 0.92 respectively.

The degree of FDG uptake is of prognostic value at initial presentation, after induction treatment prior to resection and in the case of relapse of non-small cell lung cancer (NSCLC). A prospective study of 57 patients with advanced NSCLC revealed that early metabolic response (defined as a reduction in SUV mean of >20% after the first cycle of chemotherapy) was associated with a significantly longer time to disease progression and more frequent survival to 1 year (44% vs 10%).[24]

The total number of tumors and number of nodal metastases, as metabolic tumor burden measurements in FDG PET/CT, are prognostic markers independent of clinical stage, age, gender, and SUV measurement in non-surgical patients with NSCLC.[25]

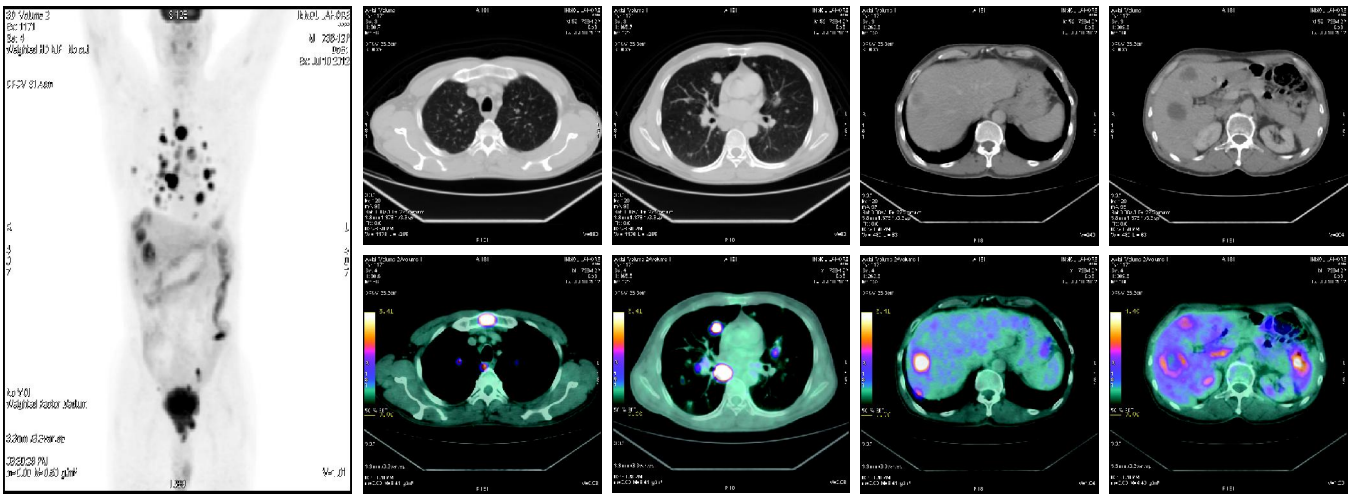
PET by itself does not add much to the assessment of local resectability, because its inferior spatial resolution does not provide more detail of the exact tumor extent or infiltration of neighboring structures. Despite an extensive literature documenting the sensitivity and specificity of PET/CT scanning, literature demonstrating an increased survival of patients with NSCLC due to the use of PET scanning is almost non-existent. Fontaine et al.[26] showed that the introduction of routine PET scanning did not result in improved survival.

Colorectal Cancer

FDG-PET has an established role in staging patients before surgical resection of recurrence and metastases, in the localization of recurrence in patients with an unexplained rise of serum carcinoembryonic antigen, and distinguishing fibrosis and scar from viable tumor in residual masses of rectal cancer after treatment.[27] A meta-analysis of 14 observational studies by Mass M et al concluded that both whole-body PET and PET/CT are very accurate for the detection of local and/or distant recurrent disease in CRC patients with a (high) suspicion of recurrent disease. Area Under Curve (AUCs) for PET, PET/CT and CT were 0.94 (0.90–0.97), 0.94 (0.87–0.98) and 0.83 (0.72–0.90), respectively.[28] In a meta-analysis of thirty-nine articles (3391 patients) by Niekel MC et al., the sensitivity estimates of CT, MR imaging, and FDG PET on a per-lesion basis were 74.4%, 80.3%, and 81.4%, respectively. On a per-patient basis, the sensitivities of CT, MR imaging, and FDG PET were 83.6%, 88.2%, and 94.1%, respectively. The per-patient sensitivity of CT was lower than that of FDG PET (p=.025). Specificity estimates were comparable.[29]

De Geus-Oei LF et al in a study on 50 patients with CRC concluded that the degree of chemotherapy-induced changes in tumor glucose metabolism in advanced colorectal cancer is highly predictive of patient outcome.[30,31] 18 F-FDG PET predicted therapy outcomes significantly better than endorectal ultrasound, CT, and MRI.[32]

Metastatic disease in colorectal cancer is most common in liver and lung, but can affect the whole body. FDG-PET showed greatest accuracy in the detection of liver metastases with reported accuracy up to 99%, sensitivity up to 100% and specificity up to 98%.[33] (Fig. 6)



Ca Rectum Post-Surgery | Sternal Mets | Pulmonary Mets | Liver Mets | Liver Mets

Figure 6: 45 yr old case of post-surgical Ca Rectum for staging.

Uro-oncology

The use of FDG-PET in uro-oncology has not been very successful partly due to the excretion of tracer through the renal tract, potentially making structures and tumors difficult to see against this high background. Considerable heterogeneity exists in the current clinical experience with FDG-PET in prostate cancer (PCa), because of variability in disease states, validation criteria, and end points among studies. PET has been evaluated for diagnosis and staging of prostate cancer. FDG uptake in PCa was reported to correlate with the prostate-specific antigen (PSA) level, thus it can be used as a measure of tumor aggressiveness.[34] FDG-PET can also be useful in monitoring the therapeutic responses of patients with aggressive or hormone refractory diseases.[35] However the results are generally poor with PET unable to distinguish benign prostatic hypertrophy (BPH) from cancer in a number of cases.[36] Widespread metastatic disease remains a problem in prostate cancer. In particular, bony metastases are a common site for spread. The best examination for detection remains radionuclide bone scanning. FDG-PET can certainly detect bone disease with positive predictive values up to 98%.[36] It can also discriminate active bone lesions from radioistopically quiescent

lesions[37] but it has poorer sensitivity, and does miss some metastases seen on bone scintigraphy. In 35.1% of prostate cancer cases, PET findings changed clinical management (95% CI, 33.8%–36.4%), although the odds ratio for change in management compared with that for other cancers in the NOPR trial was less than 1 (0.86; 95% CI, 0.81–0.92), suggesting that change in management was lower for prostate cancer than for all other types of cancer.[38]

Undoubtedly the most useful place for FDG-PET in uro-oncology is in testicular cancers, especially in residual/recurrent disease. Except for mature teratomas, germ cell tumors and their secondaries are generally characterized by a high FDG uptake, particularly seminomas, which accumulate even more FDG than non-seminomatous lesions.[39] A positive PET is an accurate marker of disease location. Certainly, in complicated multiple relapse patients, the use of FDG-PET has been shown to change the decision on therapy in 57% of cases. In post-chemotherapy seminoma, the results also suggest direct management implications based on PET.[40]

Few studies have examined PET and bladder cancer. Certainly the excretion of FDG through the renal tract may make visualization of the bladder difficult particularly in assessing primary disease. It can be useful in specific cases particularly with equivocal conventional imaging. It is of value in local staging. For the diagnosis of NM-positive disease, the sensitivity, specificity and accuracy of PET-CT is 60%, 88% and 78%, respectively.[41] It may also differentiate fibrosis from recurrent disease in the treatment bed. Where metastatic disease is an issue away from the renal tract, bladder metastases are FDG avid and in this instance PET would be complementary to other imaging.

Primary renal cancer is undoubtedly FDG positive despite excretion of tracer through the kidney. While having no advantage over CT for identification of primary masses, PET is efficient for detection of metastatic disease. Safaei et al. found a diagnostic accuracy of 89% overall and of 84% for classifying biopsy-confirmed suspicious lesions of unknown significance.[42]

Head & Neck

FDG-PET imaging is a valuable imaging tool in evaluation of patients with head and neck carcinomas (HNSCC). PET has a higher sensitivity (87% versus 62%) and specificity (89% versus 73%) compared to CT for staging cancer.[43]

It has higher sensitivity and specificity for detecting both occult and palpable lymph node metastases. The reported sensitivity and specificity ranged from 67-79% and 82-95%, respectively, in cases of occult nodal disease.[44,45]

FDG-PET also is considered superior to CT and MR imaging for local staging and detection of malignant characteristics in cervical lymph nodal enlargements.[46]

The main limitations of PET are poor anatomic localization of the primary tumor and metastases. These limitations are overcome by fusing the anatomic data of CT with functional data of FDG-PET.[47] Although anatomic localization is improved by combined PET/CT, FDG-PET and PET/CT have similar diagnostic accuracy for detecting metastatic neck disease.

Lymph node metastases are common in patients who have head and neck cancers. In up to 20% to 30% of patients, lymph nodal spread of the disease is found, even though it may not be apparent on physical examination. As distant metastases are less common, the role of screening for distant metastases in patients who have HNSCC is controversial. There is no role yet for pretreatment FDG PET as a predictor of (chemo)radiotherapy outcome in HNC in daily routine.[48]

Brain Tumors

MRI is still the gold standard for diagnosing and staging brain cancers, but PET may be useful in identifying nonenhancing, low-grade gliomas undergoing malignant conversion. Imaging of brain tumors with FDG was the first oncologic application of PET.[49] As in other malignancies, glucose consumption is increased in brain tumors, especially in malignant gliomas, but differentiating tumors from normal tissue or nontumorous lesions is often difficult because of the high metabolism in normal cortex. The amount of accumulation of FDG in a primary brain tumor correlates with histologic tumor grade,[50] cell density,[51] and survival.[52] Gliomas are often heterogeneous and may contain regions of different histologic grades. High uptake in a previously known low-grade tumor establishes the diagnosis of anaplastic transformation Patients with brain tumors have decreased metabolism in the contralateral cortex, and the degree of decrease correlates with tumor size. This phenomenon may partly be caused by corticosteroids, but a functional inactivation of the contralateral hemisphere cannot be excluded.[53] While interpreting FDG PET images of a treated brain to distinguish tumor recurrence from

radiation necrosis, it is critical to have the MRI structural information available for correlation. In a series of 44 lesions treated with stereotactic radiosurgery, FDG PET alone had a sensitivity of 65% in subjects with metastases but reached 86% when MRI and PET images were coregistered.[54]

The role of PET in treatment planning and monitoring is an active area of investigation. With the development of targeted therapies, PET biomarkers might be used to select patients who are likely to respond to treatment, as well as to monitor treatment response.

In conclusion despite the variable evidence and limited efficacy for certain cancers, FDG-PET is now mature enough and its general use in cancer is understood sufficiently for clinicians to be empowered to use it intelligently as they think best for individual cases.

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