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The Use of PET and PET/CT in Radiation Oncology

By Vinai Gondi, Robert Jeraj, Ph.D., and Minesh Mehta, M.D.

LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

- Describe how the physiologic basis of FDG-PET imaging allows it to be a powerful tool in radiation oncology.
- Summarize the importance of FDG-PET and FDG-PET/CT in improving the accuracy with which cancer is staged and in enhancing the therapeutic ratio of radiotherapy.
- Explain how FDG-PET and FDG-PET/CT can help predict outcome of radiotherapy.
- Describe the potential for other PET biomarkers to provide valuable information regarding tumor kinetics and tumor microenvironment parameters.

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For the last two decades, radiation oncology has relied on the conventional imaging technologies of CT and MRI to provide anatomic visualization of tumor, involved lymph nodes, and dose-limiting normal tissues. This information has enabled the delineation of target volumes for precise 3D delivery of radiotherapy. The ability of these anatomic imaging techniques to distinguish tumor from normal tissues is based solely on morphologic characteristics such as density, size, vascularity, fat, and water content. Functional information regarding normal tissues and the specificity of the diagnosis of neoplastic involvement is missing, however, limiting the value of this information for radiotherapy planning.

Functional imaging in the form of PET has allowed for visualization of tumors and involved lymph nodes based on their metabolic characteristics. PET is based on the emission of positrons by a radioactive isotope tagged to a molecule with properties that impart it with functional specificity. The most frequently used tracer is F-18-2-fluoro-2-deoxylucose (FDG), a molecule that, similar to glucose, is transported into cells and phosphorylated by hexokinase. Unlike glucose, FDG is not further metabolized through glycolysis.

The use of FDG-PET in tumor imaging is based on the preferential accumulation of FDG in cancer cells. Highly metabolic malignant cells tend to have higher FDG uptake, presumably due to the upregulation of the glucose transporter proteins and the glucose phosphorylating enzyme hexokinase. FDG can also accumulate in many other tissues such as the brain, where glucose is the exclusive source of energy, and the urinary tract, since FDG is not reabsorbed by renal tubular cells.

Without accompanying anatomic information, however, pathologic sites of FDG uptake can easily be confused with normal physiologic uptake, and sometimes the precise location of uptake can be misinterpreted, resulting in potential false-positive and false-negative readings. Historically, this limitation has been addressed by coupling the interpretation of FDG-PET data with CT or MR, but the problems resulting from inexact anatomic superimposition of data sets has generally resulted in rather crude interpretation. The development of combined FDG-PET/CT technology has overcome these barriers. FDG-PET/CT allows for the correlation of almost simultaneously obtained anatomic and functional imaging findings and provides more precise anatomic defini-

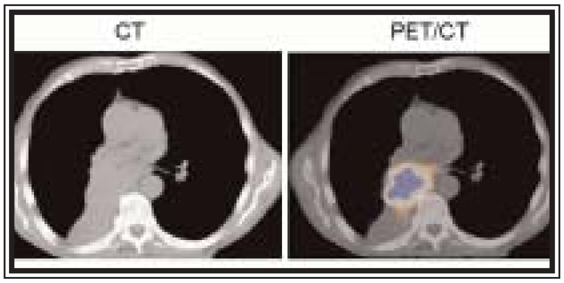

Figure 1. Value of FDG-PET/CT in defining gross tumor volume (GTV) in atelectasis. Left: collapse and consolidation of right lower lobe is obvious on CT, but tumor location cannot be delineated. Right: Tumor is readily apparent on FDG-PET/CT, enabling radiotherapy planning to proceed. (Adapted with permission from Mac Manus M, Hicks RJ, Everitt S. Role of PET/CT in the optimization of thoracic radiotherapy J Thoracic Oncology 2006;1(1):81-84)

tion of physiologic and pathologic FDG uptake. This advantage becomes especially important for neoplastic lesions of smaller size and/or those near sites of physiologic uptake. Hybrid FDG-PET/CT scanners hold technical advantages over FDG-PET scanners through increased spatial resolution and the potential to incorporate time as another dimension of imaging.

The incorporation of FDG-PET and FDG-PET/CT technology into the practice of radiation oncology has enabled the biologic delineation of tumors and has improved the accuracy with which neoplastic targets can be defined and staged, radiotherapy can be delivered, and prognosis during and after treatment can be estimated (see table). For these uses, FDG-PET has been studied in a wide range of tumors: brain, breast, colorectal, head and neck, lung, lymphoma, melanoma, cervix, and pancreas. We focus here on non-small cell lung cancer (NSCLC), a tumor for which the use of FDG-PET has been rigorously studied and clinically accepted.

ROLE IN STAGING

Precise staging of tumors requires accurate detection of the primary tumor, lymph nodes, and distant metastases. It is essential for individualized cancer management and provides valuable prognostic information. While anatomic imaging techniques can detect subcentimeter lesions, determination of the presence of tumor is based predominantly on morphology. This limitation allows small but biologically active lesions to be overlooked and assumes that tumors of similar morphology have similar biological behavior. Enlarged lymph nodes, irrespective of the etiology, are presumed to be malignant.

FDG-PET and FDG-PET/CT technologies mitigate these uncertainties by characterizing the biological behavior of tumors more completely. Research on the accuracy of FDG-PET has revealed its high sensitivity (82% to 91%) and specificity (82% to 94%) across most oncologic applications.[1] The management of NSCLC, the leading cause of cancer death in men and women worldwide, has benefited considerably from the incorporation of FDG-PET technology.

Accurate staging of NSCLC necessitates an evaluation of potential spread of disease to locoregional lymph nodes and to distant sites. This evaluation has important implications on radiation oncology, as the decision to offer curative or palliative radiotherapy can be altered by the discovery of distant metastases. Radiotherapy target volumes can be expanded or reduced depending on the status of locoregional nodes. Conventional anatomic imaging methods are suboptimal for this purpose, often requiring confirmatory surgical procedures (e.g., cervical mediastinoscopy) for more accurate staging. FDG-PET and FDG-PET/CT have consistently been shown to be more accurate than CT.

CURRENT STATUS OF CLINICAL INDICATIONS FOR FDG-PET IN SELECTED TUMORS

Site	Staging	Disease Monitoring		Local recurrence
		Early during treatment	After treatment	
Head and neck squamous cell carcinoma	++ (cervical LN metastasis)	++	++	+++
Breast cancer	++ (large primary tumor and axillary metastasis)	+++	+++	++++
Non-small cell lung cancer	+++++ (mediastinal LN and distant metastasis)	+++	+++	++++
Lymphoma	++++	++++	++++	+
Cervix	++++ (pelvic and paraaortic LN metastasis)	+	+++	++++
Colorectal	++ (primary tumor)	+	++	++++
Melanoma	+++ (systemic metastasis) ++ (LN metastasis)	+	+	+++

+++++ : Established clinical use
++++ : Strongly supported by acceptable, published literature
+++ : Promising benefit but further studies needed
++ : Potentially helpful but limited/conflicting data
+ : Lack of data

Adapted with permission from Apisanthrax S, Chao KSC. Current imaging paradigms in radiation oncology. Radiation Research 2005;163:1-25.

In the evaluation of mediastinal involvement, both surgicopathologic prospective studies[2,3] and meta-analyses[4-6] have consistently shown higher sensitivity and specificity with FDG-PET (81% to 93% and 86% to 95%, respectively) than with CT (57% to 75% and 63% to 82%, respectively). These studies also showed a high negative predictive value (93% to 95%) for FDG-PET,[2,3] a statistic that might obviate or reduce the need for mediastinoscopy in patients with an FDG-PET-negative mediastinum. In the detection of distant metastases, whole-body FDG-PET has been shown to be more sensitive and specific than conventional imaging methods (thoracic CT, bone scintigraphy),[2,3] an important consideration in NSCLC since 40% of newly diagnosed patients have distant metastases at the time of presentation.[7]

With this improved accuracy for the detection of mediastinal nodal and distant metastases, FDG-PET-assisted staging was shown to be a powerful predictor of survival in a recent prospective study of radiotherapy patients with unresectable NSCLC.[8] In another prospective study, routine FDG-PET imaging led to the downstaging of 12% and the upstaging of 36% of patients.[9]

While the accuracy of FDG-PET in staging cancer is quite high, limitations exist. FDG accumulates in the brain and urinary tract, rendering evaluation of metastases at these sites challenging. Its limited anatomic resolution means that FDG-PET allows evaluation of nodal disease only by lymph node levels and not by individual lymph nodes. The use of CT with PET, however, helps pinpoint anatomic locations of FDG uptake. This advantage is helpful, for instance, when disease in intrapulmonary lymph nodes is mistaken for disease in mediastinal lymph nodes, an error that would incorrectly upstage a patient from N1 to N2. Despite this theoretical improvement in accuracy, studies are conflicting regarding the benefit of FDG-PET/CT over FDG-PET in the staging of NSCLC.[2,4,10]

Confusion arises over FDG-PET-positive lesions due to the possibility of false positives caused by inflammation (e.g., postobstructive pneumonia or peritumoral granulocytic reactions). Yet compared with CT, which often requires comprehensive exploration of the mediastinum, the higher accuracy of FDG-PET may limit the requirement for surgical evaluation to sites of FDG uptake.

ROLE IN RADIOTHERAPY PLANNING

Like surgical planning, effective radiotherapy planning requires accurate delineation of disease extent in order to determine the volume to be treated. In the past, this delineation relied upon externally visible or palpable anatomic landmarks, relatively inaccurate x-ray imaging, and clinical judgment. The advent of cross-sectional anatomic imaging enabled a 3D target-driven approach that has significantly improved the accuracy of radiotherapy delivery.

Despite this advance, the accuracy of radiotherapy planning has been limited by situations in which tumor cannot be easily differentiated from normal tissues. In these cases, conventional imaging techniques have led to some areas of tumor being missed and other areas of normal tissue being irradiated unnecessarily. The possibility of radiation toxicity to normal tissues has limited the dose of radiation that can be delivered to the tumor target. The emergence of functional imaging allows for the differentiation of benign from malignant tissue and has ushered in the possibility of optimizing the therapeutic ratio of radiotherapy.

The role of FDG-PET-based radiotherapy planning has been intensively examined in the management of patients with NSCLC. Prospective studies[8,11,12] have shown that the incorporation of FDG-PET or FDG-PET/CT imaging alters radiotherapy volumes in 30% to 60% of patients. The improved accuracy of FDG-PET or FDG-PET/CT to define the NSCLC tumor target is partly due to its abilities to radiographically distinguish atelectasis from tumor and eliminate the need for elective nodal irradiation (ENI).

Atelectasis, a sequela of tumor-induced obstruction in NSCLC, is difficult to distinguish from tumor using solely the morphologic information of conventional anatomic imaging. The ability to make this distinction is critical to sparing normal lung tissue from the toxicity of radiotherapy. The incorporation of FDG-PET imaging has shown a powerful capacity to make this distinction less challenging and reduce radiotherapy treatment volume in patients with atelectasis[13] (Figure 1).

ENI is defined as the treatment of locoregional lymph nodes at high risk for harboring micrometastases. Its use in the management of NSCLC has been scrutinized recently due to the irradiation of a large volume of normal tissue. The resulting toxicities limit the radiotherapeutic dose that can be delivered and curtail the ability of radiotherapy to accomplish maximal local control of the primary tumor, the most common site for disease recurrence in NSCLC.[14,15] Recent efforts to replace ENI with targeted nodal irradiation, especially in high-risk patients, have been aided by the improved accuracy with which FDG-PET or FDG-PET/CT imaging can differentiate between benign and malignant nodal disease.

Systematic evaluation of FDG-PET/CT data regarding their impact on contouring gross tumor volumes (GTVs) has been limited. We compared CT-derived GTVs for lung and esophageal cancer with GTVs drawn based on FDG-PET/CT planning studies. Lung and esophageal cancer patients undergoing FDG-PET/CT were positioned and immobilized using standard radiotherapy techniques. Noncontrast low-dose total-body spiral CT scans were obtained first, followed by FDG-PET imaging, and the two coregistered. Immediately, without moving the patient, we obtained contrast-enhanced CT scans of the thorax. This secondary CT data set was fused with the primary CT data set in the treatment planning software module.

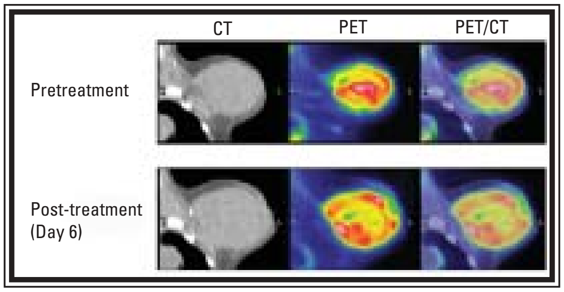

Figure 2. Imaging proliferation changes during radiotherapy. PET and PET/CT using FLT enables visualization of proliferation changes during radiotherapy of a dog sarcoma. The ability to image such proliferation changes during radiotherapy allows for additional radiation to be "painted" to areas of "residual proliferation" at the end of treatment.

The investigators were initially blinded to the FDG-PET data, and GTVs were contoured on the CT data set. The FDG-PET data, superimposed and fused to the CT data sets, were then presented, with the CT-derived GTV contours turned off. FDG-PET/CT-based GTV contours were then generated. To standardize FDG-PET GTV margin definition, background liver FDG-PET activity was standardized in all images. When available, the results of other diagnostic tests, such as esophogastroduodenoscopy (EGD), were used in CT-derived GTV design.

The CT-based GTVs were compared with the FDG-PET/CT-based GTVs by means of a conformality index (CI) (the intersection of the two GTVs divided by their union). A CI of 1.00 would imply that the CT-based and the FDG-PET/CT-based GTVs were identical. A CI of 0.00 would mean no overlap at all between the two contoured tumor volumes.

Fourteen patients with lung cancer and 16 with esophageal carcinoma were evaluated. All had diagnostic-quality contrast-enhanced CT scans of the thorax, and all esophageal cancer patients had EGD results available at the time of GTV design. The mean CI for lung and esophageal cancer was 0.44 (range 0.00 to 0.70) and 0.46 (range 0.13 to 0.80), respectively, suggesting that the use of FDG-PET/CT scanning in radiation treatment planning significantly changes the design of GTVs in a large proportion of patients. This finding served as the basis for an ongoing prospective trial evaluating the use of FDG-PET/CT-based treatment plans for patients with esophageal cancer, lung cancer, lymphoma, and head and neck cancer.[16]

Despite its utility in radiotherapy planning, FDG-PET and FDG-PET/CT imaging is not without its challenges. The interpretation of FDG-PET and FDG-PET/CT images can lead to considerable interobserver variability.[17] Close collaboration between nuclear medicine physicians, who are highly qualified to provide qualitative and quantitative interpretations, and radiation oncologists, who translate the quantitative threshold for tumor uptake into viable treatment plans, could reduce this imprecision. The threshold for tumor uptake has been inadequately studied, leading to considerable ambiguity for standardized uptake values between four and 10. This ambiguity further leads to challenges in defining the "tumor edge," and no consensus has been drawn on this controversial matter.[18] Critical to maintaining the accuracy of radiotherapy planning is ensuring precise patient alignment between FDG-PET image acquisition and radiotherapy delivery. Variability can be reduced during FDG-PET image acquisition by mimicking the flat tabletop and custom body molds used during radiotherapy.

PROGNOSTIC VALUE

After radiotherapy or other cancer therapy, the early detection of recurrence, currently achieved by physical examination and anatomic imaging, improves the chances of successfully implementing salvage therapy and is an important aspect of cancer management. The limited ability of anatomic imaging to distinguish between recurrence and treatment sequelae, such as scar tissue, may allow tumor progression to go undetected. Salvage treatment becomes less effective as the tumor becomes markedly enlarged. FDG-PET and FDG-PET/CT have been shown to be especially valuable and accurate in detecting early recurrence in head and neck cancer, esophageal cancer, NSCLC, and cervical cancer.[19-24] One study highlighted the accuracy (sensitivity 97%, specificity 100%) with which FDG-PET imaging can distinguish between benign sequelae of radiotherapy and actual tumor recurrence.[25]

Cancer management would also be greatly improved by the capacity to predict tumor responsiveness early during treatment. This would allow alterations in the treatment regimens of potential nonresponders, such as dose escalation of radiotherapy or the addition of chemotherapy or targeted agents, early in the course. Detection of the morphologic changes of nonresponding tumor by conventional imaging has been ill suited for this application, since such changes do not occur until very late. The detection of early metabolic changes through FDG-PET imaging has shown tremendous potential for the monitoring of treatment response in such tumors as lymphoma, esophageal cancer, gastric cancer, head and neck cancer, and NSCLC.[26-31]

For this application, however, FDG might not be the optimal tracer. The relationship between tumor response and FDG uptake does not appear to be entirely linear, as reduced FDG uptake by the tumor may indicate only partial responsiveness by radiosensitive cells while other radioresistant cells remain metabolically active. Radiation-induced inflammation can lead to false-positive FDG uptake. Incorporation of other recently developed tracers into PET imaging, however, offers hope for the improved accuracy of PET imaging in monitoring tumor response.

EXPERIMENTAL AREAS

While most studies on PET and PET/CT have focused on FDG as a radiotracer, the potential for other radiotracers to offer additional dimensions of information is being explored. One process involves tumor hypoxia. Regions of hypoxia within a tumor are believed to foster radioresistance and may limit cure in patients receiving radiotherapy. The capacity to identify these regions and quantify their degree of hypoxia would enable radiation oncologists to enhance the radiotherapy delivered to these regions through either dose escalation or the use of radiosensitizers. Two classes of radiotracers allowing for hypoxia imaging are the 2-nitroimidazoles (e.g., F-18 fluoromidonidazole) and the nonimidazoles. The mechanism of these tracers is not fully understood but seems to involve a bioreductive property that enables them to be retained in regions of hypoxia.

Cell proliferation, another tumor process that can provide important prognostic information, can also be imaged with PET. A potential marker for this property is F-18-labeled fluorothymine (FLT), a radiolabeled analog of the pyrimidine base thymine. This marker provides information regarding tumor cell proliferation by indirectly measuring DNA synthesis via the DNA salvage pathway.

Imaging of hypoxia, proliferation, and other dimensions of tumor kinetics and tumor microenvironment via PET or PET/CT technology opens possibilities for dose-painting, a potentially revolutionary approach to radiation oncology (Figure 2). This approach stems from the recent development of intensity-modulated radiation therapy, a technique that allows for the precise delivery of nonuniform intensities of radiation to create a tumor-specific, heterogeneous distribution of dose. The technique allows for additional radiation to be "painted" to areas of higher proliferation, hypoxia, or other biologically relevant markers of resistance. Integral to fulfilling this potential is the capacity to image tumors in the framework of biological, spatial, and temporal dimensions, a process termed theragnostic imaging (i.e., treatment according to knowledge derived from the tumor's responsiveness, as assessed by imaging).

CONCLUSION

The use of PET and PET/CT imaging remains integral to the current practice of radiation oncology and renders promising the future efficacy of radiotherapy. Close collaboration and mutual understanding between practitioners of nuclear medicine and radiation oncology is essential for continued, and potentially deeper, incorporation of PET and PET/CT technology into radiotherapeutic treatment and for the improved care of cancer patients. ■

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