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## FDG-PET/CT in surgical oncology

By Seza A Gulec, M.D.

### LEARNING OBJECTIVES

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

- Explain the limitations and potentials of FDG-PET/CT in oncologic surgery applications.
- List current clinical indications of FDG-PET/CT in oncologic surgery.
- Assess the value of FDG-PET as a prognostic marker.
- Describe the clinical importance of the PET/CT integrated system.

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**P**ET imaging is the most sophisticated functional imaging technique to date. Due to PET's unique detection mechanism and image analysis physics, the sensitivity and resolution of its images are superior to those of conventional nuclear medicine images. The development of integrated PET/CT technology, which also provides satisfactory anatomic detail, has remarkably increased the diagnostic value of PET and has emerged as the new paradigm in imaging.

Contemporary integrated scanners have up to a 64-slice CT component and a high-resolution PET device. Special viewing tools provided with the standard integrative software allow the viewer to scroll through any of the individual and combined image sets. Imperfections arising from breathing motion can be corrected with the use of respiratory gating techniques.

PET/CT also broadens the concept of contrast enhancement in imaging. The standard iodine-based contrast enhancement, which is the basis of tumor/lesion characterization in anatomical imaging, is merely a reflection of the blood pool in the microvascular compartment and does not correlate with biologic characteristics of the tumors.

F-18 fluorodeoxyglucose (FDG) essentially serves as a biologic contrast agent, enhancing the tissue function to be examined. Metabolically active tissues, tumors, or non-neoplastic lesions are enhanced with FDG. PET/CT imaging not only provides the surgeon a detailed road map for tumor localization with much improved sensitivity and precision, but it also allows a comprehensive tumor/tissue characterization and in vivo quantitative assessment of tumor metabolism.

The use of FDG as the metabolic contrast in PET/CT imaging provides an additional phase to standard contrast-enhanced CT studies. A typical integrated protocol involves a whole-body non-contrast CT scan followed by PET data acquisition. Noncontrast CT images are used for attenuation correction in PET image reconstruction. These steps are completed in less than 20 minutes with contemporary PET/CT scanners. The third phase is the conventional contrast imaging of the anatomic compartment of interest using specific acquisition parameters.

The total image set is completed in 30 to 40 minutes. There is no good reason not to add the FDG phase to all standard imaging protocols. Obviously, this transition will require the gradual replacement of conventional CT scanners with PET/CT integrated systems. This change may take place parallel to the development of new molecular probes and biologic contrast agents.

### DIAGNOSTIC PERFORMANCE OF FDG-PET

A large body of clinical studies and reviews attests to the clinical value of FDG-PET in staging, restaging, evaluation of response to systemic and regional therapies, and radiation treatment planning.<sup>1</sup> Optimal utilization of a new technology, however, requires a thorough understanding of its inherent limitations as well as its potential.

FDG-PET certainly is no exception. Although FDG is an outstanding tumor localizing molecular probe, it is not tumor-specific. FDG uptake indicates high or heightened metabolic/glycolytic activity. All metabolically active tissues, including

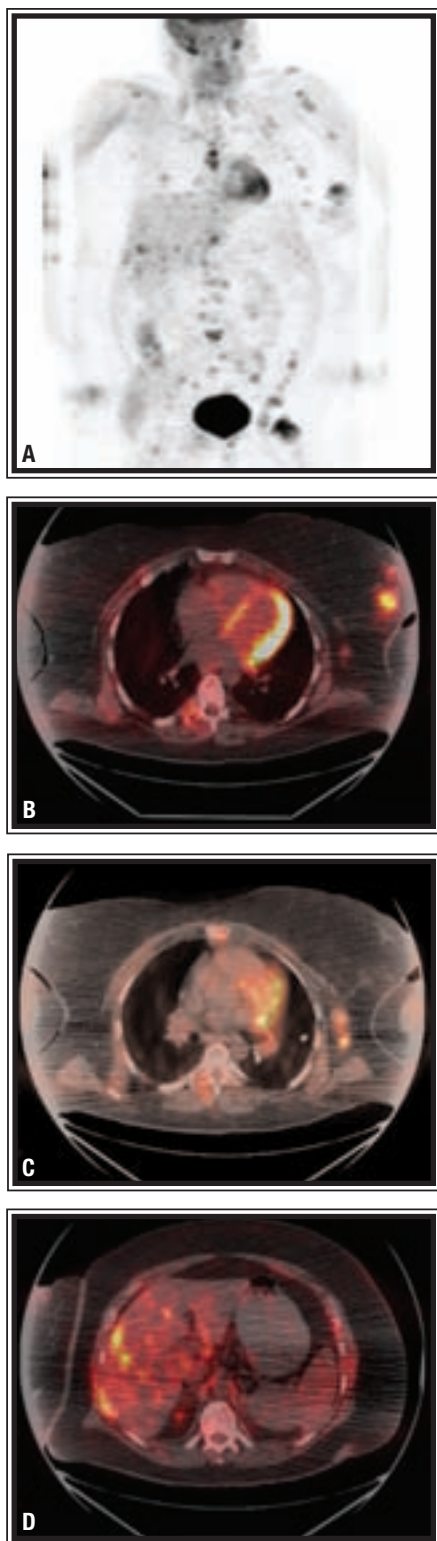


Figure 1. 35-year-old woman presented with left breast 3-cm cancer. Left axilla was clinically negative. A: Maximum intensity projection image shows widespread metastatic disease. Precise localization of lesions is difficult to assess without CT framework. B: PET/CT shows left breast cancer. C: Axillary lymph nodes. D: Liver and rib metastases.

those involved in active and chronic inflammatory processes, are expected to show enhanced FDG uptake. This should by no means be regarded as false positivity but rather as a biologic phenomenon that needs to be taken into account when interpreting FDG images. An analogy can be made to elevation in white blood cell count, which can be associated with many altered physiologic states and not necessarily due to the presence of an infection.

One intrinsic limitation of PET derives from the nature of positron decay and the principle of coincidence detection. A positron generally must travel a certain distance in tissues before colliding with an electron. Annihilation often occurs approximately 1 to 2 mm away from the positron's origin. This phenomenon places a theoretical limit on PET's achievable spatial resolution, which is estimated at 2 to 3 mm. Understanding this limitation of PET has practical value in the appropriate use of the technology. Numerous studies, particularly those published in surgical literature, have demonstrated that the sensitivity of PET for detecting microscopic metastatic disease is low. In general, for most lesions less than 1 cm, the detection sensitivity of PET is approximately 10%.

### FDG-PET AND TUMOR BIOLOGY

There is a direct correlation between tumor aggressiveness (and prognosis) and the rate of glucose consumption, as demonstrated by FDG-PET imaging, and glucose transport protein (mainly Glut-1) expression shown by immunohistochemistry studies. The end result of accelerated glycolysis is increased tumor cell acid production. An acid-mediated tumor invasion hypothesis was developed to explain the clinical correlations between FDG uptake and tumor prognosis.<sup>2</sup>

The general concept is that the tumor cells become invasive because they perturb the environment to make it optimal for their own proliferation and toxic to the normal cells with which they compete for space and substrate. Through a variety of mechanisms, acidification of the extracellular environment leads to destruction of normal tissue. These mechanisms include caspase-mediated activation of p53-dependent apoptosis pathways, promotion of angiogenesis through acid-induced release of vascular endothelial growth factor and interleukin 8, extracellular matrix degradation by proteolytic enzymes such as cathepsin B, and inhibition of immune function.

FDG-PET imaging data provide substantially more information beyond merely locating tumors. FDG-PET is an in vivo quantifiable prognostic marker. In this context, false-negativity in FDG-PET is an incorrect con-

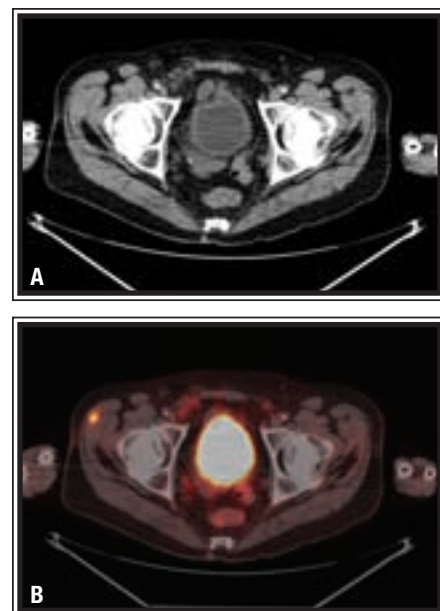


Figure 2. 44-year-old man with history of melanoma. Clinical exam was negative. A: Axial CT image shows no appreciable abnormality. B: PET/CT shows distinct intramuscular focal uptake consistent with metastatic nodule.

notation. Rather, tumor(s) should be denoted as FDG-positive or FDG-negative, analogous to markers such as estrogen/progesterone receptors.

### CLINICAL USE: SURGICAL PERSPECTIVES

FDG-PET imaging has a number of applications in oncologic surgery.

- **Breast cancer.** The diagnostic performance of FDG-PET is most prominent in the recurrent/metastatic setting, with sensitivity and specificity rates of 90% and 80%, respectively.<sup>3</sup> PET, not surprisingly, has a better diagnostic accuracy in evaluation of anatomic regions that have been previously treated with surgery or radiation, where the anatomical imaging techniques are highly challenged. Supraclavicular, internal mammary, and mediastinal nodal recurrences can be best mapped with PET/CT. Nonosteoblastic bone metastases are detected with better sensitivity than by conventional bone scan.

Bender et al correctly identified 28 of 29 (97%) patients with lymph node involvement, 15 of 15 (100%) with bone metastases, five of six (83%) with lung metastases, and two of two (100%) with liver metastases.<sup>4</sup> Eubanks et al have shown a superior diagnostic performance with FDG-PET in the assessment of the extent of disease in advanced breast cancer.<sup>5</sup> These studies clearly indicate that PET is a highly effective method for evaluating the extent of disease in patients with

advanced stage or recurrent/metastatic breast cancer (Figure 1).

PET imaging initially instigated excitement in the search for noninvasive staging of axilla. Some early studies reported sensitivity rates as high as 90% in axillary staging of breast cancer using FDG-PET.<sup>6</sup> Subsequent prospective studies, however, have demonstrated that the sensitivity is only in the range of 40% to 60%.<sup>7,8</sup> Micrometastatic disease remains beyond the detection limits of current imaging technology.

The sensitivity of PET in axilla, however, is correlated with the size of the primary tumor. Therefore, PET imaging does have a more well-defined role in T2 and larger tumors. Patients with larger tumors might be better served with PET imaging before a sentinel lymph node biopsy (SLNB). In fact, this approach has been adapted by several institutions clinically. More recent studies highlight the prognostic importance of FDG-PET-detected axillary metastases. The clinical importance of FDG-PET-based primary staging of breast cancer compared with standard histopathologic staging is yet to be studied.

The pursuit of cost-effective screening for early diagnosis of breast cancer continues. A similar need exists for the characterization of mammographically or ultrasonographically

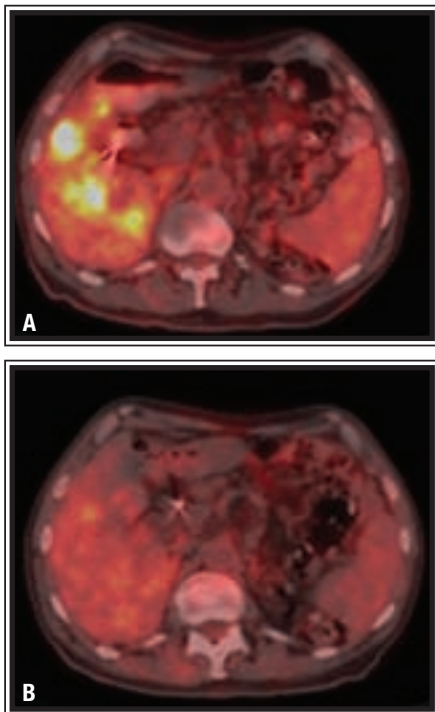


Figure 3. 67-year-old man with history of colorectal cancer liver metastases. Patient was treated with yttrium-90 microspheres in combination with chemotherapy. A: Pretreatment PET/CT axial images show multiple liver metastases. B: Post-treatment PET/CT shows complete resolution of tumor activity.

detected nonpalpable abnormalities. The limitations in spatial resolution of current whole-body imaging systems challenge the practical use of PET for these indications. The development of dedicated breast systems that interface with digital mammography, however, has the potential to improve detection sensitivity and specificity.

- **Melanoma.** The clinical stage/extent of disease in malignant melanoma is mostly dependent on the depth of the primary tumor (Breslow thickness/Clark's level). At present, assessment of regional nodal status is considered very important in intermediate thickness melanomas (Breslow 1 to 4 mm), and this is most accurately done with SLNB. Patients who were diagnosed with stage III disease might require further imaging for complete evaluation of its extent. PET/CT offers better sensitivity compared with CT alone. The management of patients who present with melanomas deeper than 4 mm is more complicated, and the incidence of remote metastatic disease in this group of patients is high. Initiating a diagnostic workup with PET/CT, with consideration of SLNB only if a remote metastatic disease is ruled out, is clinically appropriate.

The management of stage IV disease is largely dependent on its pattern of distribution. Systemic disease is approached by immunotherapy or biochemotherapy. Patients with isolated or limited disease, however, may benefit from surgical treatment, which also can prevent gastrointestinal bleeding complications in patients with small bowel disease. An accurate evaluation of the extent of stage IV disease thus has paramount importance in the management of melanoma patients.<sup>9-11</sup>

The superiority of PET/CT in this setting is undeniable. Small bowel disease and soft-tissue nodules are detected by FDG-PET more readily than by anatomical imaging alone (Figure 2). One caveat with FDG-PET is its low sensitivity in detecting brain metastases. Metabolically very active brain tissue masks small metastatic lesions. Although sensitivity could be improved with dedicated brain imaging, a more reliable modality to complement whole-body PET/CT is MRI of the brain. Brain metastases are quite common in stage IV melanoma, and unless solitary and treatable, they might preclude aggressive surgical plans for other metastatic lesions.

- **Colorectal cancer.** FDG-PET/CT has become indispensable for evaluating the extent of disease in colorectal cancer (CRC). PET is most useful in detecting peritoneal disease, where CT is known to be notoriously insensitive. Unusual remote nodal involvements can also be disclosed with PET/CT in

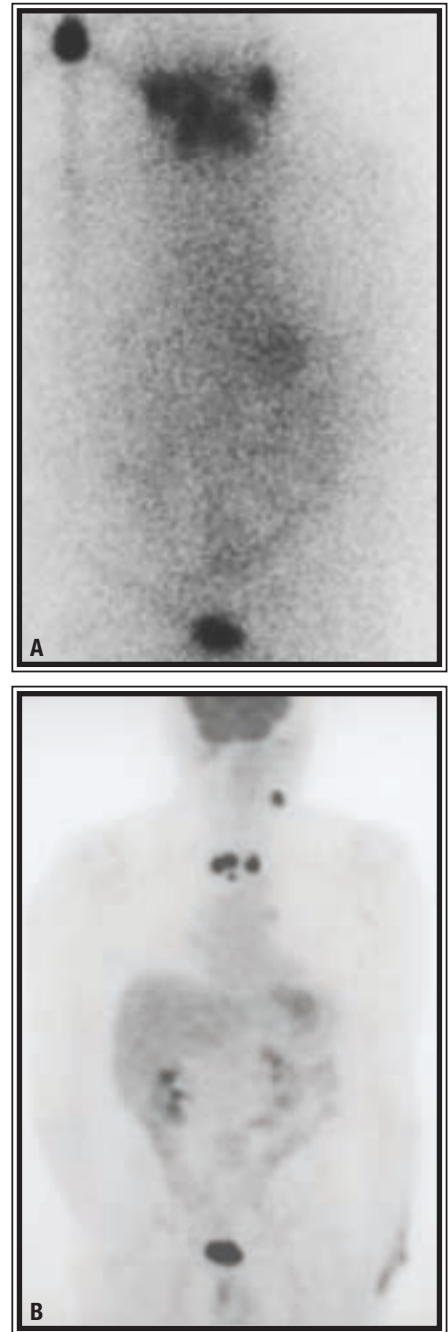


Figure 4. 71-year-old man with history of follicular thyroid cancer presented with elevated thyroglobulin. A: Negative radioactive iodine scan. B: FDG-PET shows left neck level-1 and multiple superior mediastinal lymph nodes. Patient underwent successful PET probe-guided lymph node dissection in both regions.

regions that normally may not be in the standard abdominal CT field.

The standard imaging approach for the detection and characterization of liver lesions is a multiphase liver scan. The initial examination is a noncontrast acquisition. This is followed by three acquisitions obtained at

various times during the different phases of contrast medium distribution: arterial, portal, and delayed phase (also termed equilibrium phase). Portal phase imaging has the highest yield in terms of lesion detection in CRC liver metastases, as it shows the liver during its highest parenchymal enhancement and consequently allows the depiction of lesions with greater lesion-to-liver contrast when compared with other phases.

FDG-PET/CT clearly improves diagnostic yield in patients with CRC liver metastases.<sup>12-14</sup> It is superior in the detection of extrahepatic metastases and has also been shown to be very useful in the evaluation of response in liver-directed therapies.<sup>15,16</sup> A five-phase liver scan is a new standard in the evaluation of patients with CRC liver metastases (Figure 3).

A typical clinical scenario, in which a CRC patient presents with a rising carcinoembryonic antigen level, should prompt PET/CT evaluation. One debatable issue is the frequency and extent of diagnostic imaging in asymptomatic patients with normal CEA who were treated for Dukes A-C disease. Although a more lenient approach is acceptable in patients with early-stage disease and no risk factors, stage III patients, due to a substantial risk for recurrence and metastases, deserve a more thorough periodic imaging assessment. FDG-PET/CT imaging should be regarded as standard in this group of patients and should be considered at three to six-month intervals, depending on the risk stratification.

• **Thyroid cancer.** Differentiated thyroid cancers have a relatively indolent course. Most patients are effectively treated with

thyroidectomy followed by radioactive iodine (RAI) ablation. Metastatic disease can also be managed successfully with RAI treatment. During its protracted course, however, thyroid cancer may gradually dedifferentiate and lose its ability to concentrate RAI. A typical clinical presentation is negative RAI diagnostic imaging in the presence of an elevated thyroglobulin.

In the past, this group of patients posed a major diagnostic challenge. It has been clearly demonstrated that the loss of iodine concentration ability during the dedifferentiation process is associated with the acquisition of a more aggressive tumor phenotype characterized by enhanced glycolytic activity. FDG-PET/CT successfully detects locoregional recurrences and remote metastatic lesions when RAI scanning fails to identify the dedifferentiated disease (Figure 4).<sup>17</sup>

Nodular thyroid disease is very common. Only a fraction of patients with thyroid nodules prove to have thyroid cancer. Thyroid ultrasound iodine-123 scans have been used in the characterization of nodules with limited value. Fine-needle aspiration biopsy is a very sensitive technique in the diagnosis of thyroid nodules, and it is currently the standard diagnostic tool. The malignant nodules of the thyroid accumulate FDG, but a similar degree of FDG uptake may also be seen in adenomas, limiting the utility of PET in the differential diagnosis of nodules. Incidentally found focal FDG positivity in the thyroid carries an approximate 50% possibility for cancer. Surgical intervention might be warranted with or without an FNA confirmation.

## MERGING PARADIGMS OF SURGERY AND IMAGING

Oncologic surgery has entered a new age with advances in systemic therapy. The mortality and morbidity of many of the major surgical procedures have decreased parallel to improvements in anesthetic and surgical techniques. Radical surgery, once considered only when a complete excision of the tumor could be achieved in early-stage disease, is now increasingly being used for locally advanced and metastatic disease chromomodulated with chemotherapy and radiation. The most important factors in determining the appropriateness of surgical intervention and the prognosis are the extent of disease and, more important, the biology of individual tumors.

Many early cancers (stage I or II) are surgically treated with a curative intent, but management decisions are more complicated in more advanced presentations. Surgical decisions are made based on the calculated chance of locoregional control for a stage III setting and anticipated protraction of the disease course for a stage IV setting (in the context of cytoreduction).

Since tumor biology governs clinical outcomes, the actual extent of disease and the biology of individual tumor types must be evaluated before extensive efforts using surgical treatment are made. PET/CT has become an invaluable diagnostic tool in the contemporary practice of oncologic surgery. The development of new molecular probes will continue to expand its role in the surgical decision-making.

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