The Role of $^{18}$F-FDG PET/CT in the Evaluation of Solid Splenic Masses

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$^{18}$F-Fluorodeoxyglucose–positron emission tomography/computed tomography is a noninvasive imaging modality that appears to have a high negative-predictive value for malignancy in assessing solid splenic masses discovered on conventional imaging modalities. Histological sampling is recommended for fluorodeoxyglucose-avid splenic masses, as the main differential diagnosis includes malignancy, either primary or secondary, or granulomatous disease.

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Focal solid splenic lesions, benign or malignant, are often discovered incidentally. The most common benign entities are hemangioma, granuloma, and hamartoma. Focal infarct and abscess may also occasionally appear as solid masses on imaging. Sporadically, rarer entities such as littoral cell angioma, inflammatory pseudotumor, or Gaucher nodules have been reported.1-5 The most frequent malignancies to involve the spleen are lymphoma, leukemic infiltrates, metastases (most commonly from lung, breast, gastrointestinal cancers, or melanoma), or rarely, primary angiosarcoma of the spleen.6-8

The morphological imaging characteristics of solid splenic masses have been described for most conventional imaging modalities. Hypovascular masses in an enlarged spleen and generalized lymphadenopathy may be suggestive of lymphoma. A hypervascular splenic mass, with metastatic disease, may be suggestive of primary angiosarcoma of the spleen.9 When abnormalities exist in the spleen as well as in other organs, histological sampling is usually performed from nonsplenic sites, to avoid iatrogenic injury to the spleen. However, in most cases making a definitive diagnosis based on imaging alone is difficult, especially if no other abnormalities exist.

Splenic fine-needle biopsies are being performed with increasing frequency in recent years with a high success rate ranging from 63 to 91%10,11 and a complication rate ranging from 1.5 to 13%.10,12 Major hemorrhage secondary to splenic biopsy has been reported not infrequently (7.7% in one series), requiring emergent splenectomy. Major bleeding is usually a result of biopsy from vascular lesions such as littoral cell angioma or angiosarcoma.10 Therefore, judicious use of splenic needle biopsies appears prudent.

In recent years, $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) positron emission tomography (PET) imaging has evolved as a powerful noninvasive imaging modality, mostly for oncology, but also in nononcological indications, such as assessment of fever of unknown origin.13 In-line, hybrid PET/CT scanners have been introduced into routine clinical use in the past several years, enabling metabolic assessment of anatomical abnormalities. The purpose of this review was to describe the potential role of $^{18}$F-FDG PET/computed tomography (CT) in the evaluation of solid splenic lesions.

Positron Emission Tomography—Basic Principles

PET imaging is based on the use of a biochemical molecule labeled with a positron-emitter (such as $^{18}$F, $^{11}$C, $^{15}$O) enabling in vivo tracking of the radioactive compound. During the decay process of the radioisotope, a positron is emitted, which after traveling a short distance (about a millimeter) encounters an electron from surrounding molecules. The two particles annihilate each other, resulting in emission of two $\gamma$-rays of 511 keV at 180 degrees to one another (Fig 1). When detected simultaneously (within 12 nanoseconds) by two opposed detectors, it is assumed that they both originated from the same annihilation event located along a line connecting the two detectors. Data collected are reconstructed into an image using standard algorithms. Attenuation correction is performed traditionally by calculating the ratio between two additional scans, a blank scan and a transmission scan, performed with an external positron-emitting source.
rotating $^{68}$Germanium rod source.\textsuperscript{14} With PET/CT scanners, attenuating correction is performed with a fraction of the time using CT data, thus obviating the need for a transmission scan, reducing acquisition time and improving patient throughput.\textsuperscript{15}

**PET/CT**

The paucity of anatomical data from $^{18}$F-FDG-PET scans hampers lesion localization and thus interpretation of focal uptake of $^{18}$F-FDG. Focal uptake may be physiological or may indicate significant pathology. For example, focal uptake along the chest wall may be due to physiological uptake in intercostal muscles or may be due to a malignant pleural plaque. In-line hybrid PET and CT scanners have been in clinical use for several years.\textsuperscript{16} Several studies have been published on the advantages of fusion imaging, showing better lesion localization, more accurate characterization of lesions as benign or malignant, and better diagnostic accuracy as compared to side-by-side reading of PET and CT.\textsuperscript{17,18}

**$^{18}$F-Fluorodeoxyglucose**

$^{18}$F-FDG is the most common radiotracer used for PET imaging. Much like glucose, it is transported into cells by glucose transporter proteins and is phosphorylated by hexokinase to $^{18}$F-FDG-6-phosphatase. However, since $^{18}$F-FDG-6-phosphatase does not enter subsequent glucose metabolic pathways and since its permeability in membranes is low, it is effectively trapped within cells. The normal biodistribution of $^{18}$F-FDG is the brain, with variable uptake in the myocardium, and gastrointestinal tract. The kidneys excrete $^{18}$F-FDG and therefore $^{18}$F-FDG is normally seen along the genitourinary tract. Physiological uptake in the liver and spleen is generally uniformly low.\textsuperscript{19}

Many types of tumors exhibit overexpression of transporter proteins, high levels of hexokinase, and decreased levels of glucose-6-phosphatase. Therefore, these cells show increased uptake of $^{18}$F-FDG, providing the basis for oncology imaging using $^{18}$F-FDG-PET. It should however be borne in mind that $^{18}$F-FDG is not tumor-specific and increased

![Image of PET/CT process](image_url)

Figure 1 Positron (marked "+") encounters an electron (marked "-"). Annihilation process results in emission of two opposite $\gamma$-rays of 511 keV. Gamma rays are detected by detectors ("D") of PET scanner.

![Image of PET/CT comparison](image_url)

Figure 2 Splenic infarct simulating mass lesion (CT, left; PET, middle; fused PET/CT, right). A subtle hypodense lesion is seen in posterior aspect of spleen on CT. PET and fused PET/CT images show lesion to be photopenic (arrow), consistent with an infarct. (Color version of figure is available online.)
18F-FDG uptake may be seen in a variety of benign conditions including inflammation.20

18F-FDG-PET/CT in Solid Splenic Masses

Benign Solid Splenic Masses

Most benign solid splenic masses such as hemangiomas or hamartomas of the spleen are not expected to show abnormal uptake of 18F-FDG. Focal infarcts which may on occasion appear “mass-like” are photopenic on 18F-FDG-PET (Fig 2). However, some benign lesions exhibit abnormal uptake of 18F-FDG, most commonly splenic abscess and active granulomatous diseases involving the spleen. Activated leukocytes, especially monocytes, show increased glucose uptake due to elevated levels of glucose transporter proteins. Furthermore, cytokines and growth factors increase the affinity of these transporters to glucose.21,22 Granulomatous disease involving the spleen may be infectious (eg, tuberculosis, Brucella) or inflammatory (eg, sarcoidosis). In routine clinical practice, granulomatous disease may be suggested prospectively on whole-body imaging due to multisite involvement and typical imaging patterns (Fig 3).

Activated macrophages may also be the mechanism for increased uptake of FDG in inflammatory pseudotumor of the spleen. Inflammatory pseudotumor is a benign, yet potentially locally aggressive lesion. Although its etiology is unknown, several factors have been implicated including infection and autoimmune processes.23 It may mimic malignancy on both conventional imaging (sonography, CT, and MRI) and 18F-FDG-PET (Fig 4).

Gaucher disease is a rare hereditary lysosomal storage disorder with accumulation of glucocerebroside in reticuloendothelial cells throughout the body, resulting in hepatosplenomegaly. Splenic infarcts and focal splenic nodules representing clusters of macrophage-like cells (termed “Gaucher cells”) can be found in approximately a third of patients with type I disease on magnetic resonance (MR), likely an
underestimate of their true frequency on pathology.24 No studies have been performed to date on 18F-FDG-PET and Gaucher nodules in the spleen. Although expression of pro-inflammatory mediators is not always apparent on Gaucher cells, markers characteristic of alternatively activated macrophages are found.25 Therefore, Gaucher nodules may potentially be FDG-avid (Fig 5).

**Splenic Metastases**

Metastases in the spleen are uncommon, usually occurring as part of disseminated metastatic disease.26 In postmortem examination of cancer patients the prevalence of splenic metastases was between 2.3 and 12.9%, most commonly from carcinoma of lung, breast, ovary, and melanoma.26,27 Statistically, most solitary splenic lesions in cancer patients are benign, as solitary splenic metastases are rare.28 Nonetheless, solitary or multiple splenic masses warrant further evaluation and specific characterization to rule out malignancy, even when other metastatic disease is documented, as in some clinical settings they may alter patient management (Fig 6).

A metabolically active splenic mass in a patient with known FDG-avid malignancy would likely represent a malignant splenic deposit. Conversely, lack of 18F-FDG uptake in a splenic mass would indicate a lesion that is not related to the patient’s known FDG-avid malignant disease and therefore would likely be benign. In a recent study performed on 68 oncology patients with FDG-avid malignancy and solid splenic masses on anatomical imaging, 18F-FDG-PET/CT had 100% accuracy in characterizing lesions as benign or malignant. In 20 additional patients without previously diagnosed malignancy and a solid splenic mass, lack of uptake of 18F-FDG-PET also had a 100% negative-predictive value for malignancy.29 It should however be kept in mind that non-FDG-avid tumors, such as some renal or thyroid cancers, may metastasize to the spleen. Therefore, when encountering a non-FDG-avid splenic mass, the CT portion of the PET/CT study should be meticulously assessed for potential non-FDG-avid malignancy.

**Primary Malignancies of the Spleen**

The spleen is a frequent site of involvement in patients with non-Hodgkin’s lymphoma and may be involved in one-third of patients with Hodgkin’s disease.24 On imaging, lymphomatous involvement of the spleen may manifest as either focal lesions or diffuse infiltration. A solid splenic mass may occasionally be the presenting sign of disseminated lymphoma (Fig 7). Recent reports have shown that 18F-FDG-PET is more accurate than CT and 67Ga-citrate scintigraphy for identifying splenic involvement by lymphoma.30,31 Primary malignant lymphoma of the spleen is defined as lymphoma involving the spleen with or without lymph nodes in the splenic hilum.32 Primary malignant lymphoma of the spleen is uncommon, yet it is the most common primary malignancy of the spleen.

Primary nonhematopoietic tumors of the spleen may be epithelial in origin (namely, angiosarcoma and hemangioendothelioma) or from connective tissue (such as fibrosarcoma). Of these extremely rare entities, angiosarcoma is the most common tumor to involve the spleen with fewer than 200 cases reported in the literature.33 Clinically, these tumors
may manifest with left upper quadrant abdominal pain, anemia, coagulopathy, and spontaneous rupture. Hematogenous metastases at diagnosis are common and overall prognosis is poor. Although there are no reports of 18F-FDG-PET in the diagnosis of primary splenic angiosarcoma, angiosarcoma of the pleura and chest wall has been shown to be FDG-avid.

**Conclusion**

Conventional imaging modalities (sonography, CT, and MRI) often discover incidental solid splenic masses. Frequently, these are difficult to definitively characterize on conventional imaging, as even hemangiomas, the most common solid lesion in the spleen, may have a complex appearance,
making differentiation from malignancy difficult. Splenic biopsy, although feasible, is associated with morbidity, especially for vascular lesions. 18F-FDG-PET/CT is a noninvasive imaging modality that appears to have a high negative-predictive value for malignancy in assessing solid splenic masses. The main differential diagnosis for FDG-avid splenic lesions is malignancy (primary or secondary), or granulomatous disease. Therefore, histological sampling is warranted for FDG-avid splenic masses.

References