Abstract

Systematic approaches have been used in surgery, anesthesia, and other industries to prevent human error. Interpretation of Positron Emission Tomography/Computed Tomography (PET/CT) exams is complex and spans traditional boundaries of nuclear medicine and cross-sectional imaging. This article describes a systematic approach to the interpretation of PET/CT exams that may be helpful for radiology residents and others learning to read this modality.

Keywords

Artifacts; PET/CT Interpretation; Systematic Approach

Introduction

Although radiology is often at the forefront of technologic advancement in medicine, the field has little experience with the science of performance improvement [1]. Structured mechanisms and checklists utilized in high-reliability fields, such as aviation and nuclear power, are practical models for the development of systematic approaches to safety and performance improvement in medicine [2]. For instance, the aviation industry has been transformed from a relatively high-risk endeavor during the mid-twentieth century into a low-risk enterprise due to a recognition of the underlying cause of human failures often being a systematic problem [3].

Surgeon and author, Atul Gawande, advocates for the use of checklists in medicine to reduce systematic errors, while also improving compliance with clinical standards and decreasing surgical complications [4]. For example, the World Health Organization’s 19-item Surgical Safety Checklist has reduced perioperative complications by more than one-third in urgent non-cardiac surgery [5]. Similarly, patient safety efforts within the field of anesthesiology have led to a 10- to 20-fold reduction in anesthesia-related mortality over the past several decades, serving as a model for other medical specialties [6-8].

Patient safety and quality initiatives within radiology are more limited with current systems such as RADPEERTM, a quality assessment and improvement product developed by the American College of Radiology, that emphasizes the retrospective peer review of individual error [9]. While knowledge of errors can improve performance through feedback and learning, there is little evidence correlating this knowledge with positive impacts on an individual radiologist’s performance [10]. Regardless of individual skill, all radiologists are human and mistakes are inevitable. The utilization of systematic approaches in radiology, such as checklists for interpreting exams, has the potential to reduce human error, as demonstrated by successful efforts in a variety of other disciplines [11].

One modality within the field of radiology that is amenable to the use of interpretation checklists is Positron Emission Tomography/Computed Tomography (PET/CT), which now considered a standard component of oncology diagnosis and staging. PET/CT permits accurate staging and restaging of most tumors and can alter therapeutic decisions, including avoiding unnecessary invasive procedures and toxic chemotherapy. However, scan interpretation is complex and spans the traditional boundaries of nuclear medicine and cross-sectional imaging. Even to the most experienced radiologist, the volume of information in each study can be intimidating due to large scan areas, high volume of image series available for review, and simultaneous interpretation of both metabolic and anatomic information. Additional factors contributing to the complexity of PET/CT include modality...
specific artifacts, normal physiologic variants that may simulate disease, and benign metabolically active disease processes. Many patients undergoing PET/CT examination also have a complex oncologic history with multiple prior therapies and surgical interventions. To alleviate some of these issues and increase radiologists’ diagnostic accuracy and efficiency, we recommend following a nine-step systematic approach (Table 1) to interpret PET/CT examinations.

1. Review Patient History.
2. Review Prior Imaging.
3. Evaluate PET Images with Varying Degrees of Intensity.
   a. 3D Maximum Intensity Projection Images (MIP).
   b. Brain and Bladder.
   c. Remaining Organ Systems.
4. Characterize Abnormality as High or Soft Tissue Density Using the Low-Dose Attenuation CT Images.
5. Further Characterize High Density Lesions with Non-Attenuation Corrected PET Images to Exclude High Attenuation Artifact.
6. Evaluate Non-Attenuation Corrected PET Images of the Entire Field of View.
7. Obtain Relevant Standardized Uptake Value (SUV) Measurements.
8. Evaluate Low-Dose Attenuation CT Images.

Table 1: Nine-Step Systematic Approach to Interpretation of PET/CT Examinations.

**Step 1: Review patient history**

Improved survival rates due to advances in oncology have led to a diverse and increasingly complex patient population. However, an accurate and thorough patient history can improve a radiologist’s diagnostic accuracy [12]. In PET/CT interpretations, this includes information about the patient’s primary tumor (e.g., location, staging, and pathology), current medications, and treatments, including dates of ongoing or previous chemotherapy, radiation therapy, and surgeries [13].

Information about tumor cell type can assist radiologists in determining whether or not a particular malignancy is reliably detected with fluorine-18 Fluorodeoxyglucose (FDG) PET imaging (Table 2) [14]. Additionally, development of intense metabolic activity in a patient with known low-grade indolent lymphoma or another low-grade cell type may represent transformation to a higher grade tumor or the existence of a second primary neoplasm, requiring a change in patient care. PET/CT can also help guide biopsy in these patients [15].

- Small Tumor Size (e.g., pulmonary nodules and nodal metastatic disease)
- Highly Necrotic or Cystic Neoplasms (e.g., head and neck cancer and pancreatic/ovarian carcinoma, respectively)
- Tumors with Minimal FDG Avidity (e.g., low-grade lymphoma, some renal cell carcinomas, prostate cancer, lobular breast cancer, carcinoid, adenocarcinoma in-situ and other predominately mucinous neoplasms, such as mucinous colon carcinoma)
- Tumors Obscured Due to Intense Background Activity (e.g., brain metastases and transitional cell urothelial carcinoma)

Table 2: Malignant Processes Not Reliably Detected on FDG PET Examinations.

Modern clinical PET scanners have a resolution limit of 4 mm, corresponding to the detection of tumors with a volume of 0.2 ml (7 mm diameter) in 5:1 Tumor/Background ratio. However, the limits of detectability of tumors under clinical conditions depend upon numerous parameters, including: tumor-to-background ratio, imaging isotope, tumor depth and location, total image counts, gamma camera properties, and image processing [16].

Medication lists may also provide insight into the relevance of PET/CT scan findings. For example, various treatments for diabetes, such as metformin, can result in increased FDG uptake in the colon and, to a lesser extent, in the small intestine [17,18]. This effect can be mitigated by discontinuing these medications at least two days prior to performing a PET examination whenever possible [19].

Prior treatment information can help distinguish benign causes of FDG uptake from active tumor involvement, including bone marrow and splenic reactivation, post-radiation inflammation, and other post-therapeutic causes of FDG uptake. Bone marrow and splenic reactivation occurring after chemotherapy or secondary to bone marrow stimulating agents causes diffuse homogenous FDG uptake due to hematopoietic expansion and bone marrow stimulation [13,20]. These findings are usually diffuse, persist for at least two months post-chemotherapy, and are difficult to differentiate from neoplastic infiltration unless an adequate history is obtained (Figure 1). Furthermore, the timing of a PET/CT examination in relation to radiation therapy can be helpful in determining the significance of particular findings with an average recommended waiting time of 3-4 months [21]. Recent surgical intervention may also cause an inflammatory response with elevated FDG uptake, which is typically diffuse and decreases on subsequent examinations, but may persist beyond a year in a substantial number of patients [22].

![Figure 1: Bone marrow and splenic reactivation due to hematopoietic expansion two weeks after cessation of a chemotherapy regimen for the treatment of lymphoma.](image-url)
Step 2: Review prior imaging

Reviewing pertinent prior radiologic examinations, including the most recent PET/CT scan and all other pertinent examinations performed in the interim, is important given the complexity of the patient population, multiple treatments, and the possibility of rapid tumor changes between studies. Comparison should be made to the most recent study regardless of modality or location, as it has been shown to reduce error rates [23]. Fortunately, the widespread use of digital radiography and Picture Archiving and Communication Systems (PACS), as well transfer of images via the cloud, allows for more convenient access to images from multiple modalities and geographically disparate locations.

Step 3: Evaluate PET images with varying degrees of intensity

a. Evaluate 3D Maximum Intensity Projection (MIP) images

Evaluation of 3D MIP images provides broader patient context and allows detection of hypermetabolic lesions that can be easily compared to the adjacent background and normal blood pool activity [24]. Intensity of the PET data can be easily adjusted for evaluation of all organs in the MIP image. Furthermore, 3D MIP images help an interpreter recognize truncation artifact from a discrepancy between the Fields of View (FOVs) in a PET/CT scanner, as the PET FOV extends beyond the CT FOV (Figure 2) [25]. This artifact results in an underestimation of metabolic activity in the periphery of PET images that are without corresponding CT attenuation correction data. The missing CT data for attenuation correction can be extrapolated using the fact that the total attenuation of the slice should be the same in all parallel beam projections [25-27]. In addition to evaluating the MIP images first, the authors also recommend taking a “time out” immediately prior to signing the case to closely review the MIP images one final time.

b. Evaluate brain and bladder

Cross-sectional PET images should be reviewed in isolation to avoid missing subtle areas of increased FDG uptake due to overlaying CT images and to avoid truncation artifact. Adjusting the intensity of PET data is important to ensure proper evaluation of all organ systems, similar to CT “windows” for soft tissue, lung, bone, brain, and liver. The intensity of PET images should be adjusted lower to evaluate regions with fairly intense physiologic activity, such as the brain, which utilizes glucose as its primary substrate, and the bladder, given the renal clearance and subsequent accumulation of FDG in urine [13].

If the intensity of the images is not properly adjusted, significant findings, such as brain metastasis or a bladder transitional cell carcinoma, can be obscured by the normal high physiologic activity within these regions (Figures 3 and 4, respectively). When evaluating the bladder, the reader should be aware of occasional posterior bladder layering of FDG, which usually occurs in patients who are unable to completely empty their bladder prior to the scan (Figure 5) [28]. The presumed physiologic mechanism is more delayed and gradual accumulation of FDG within a distended urinary bladder, which occurs in approximately 4% of patients [28].
Step 4: Characterize abnormality as high or soft tissue density using the low-dose attenuation CT images

Hypermetabolic lesions with soft tissue density represent one of three possibilities:

1. Normal variation in physiologic uptake,
2. A benign process simulating malignancy, or
3. A true malignant lesion.

Familiarity with normal variants of increased FDG uptake, such as brown fat, ovarian/endometrial uptake in menstruating women, and normal muscle and bowel activity, is necessary to avoid misinterpretation of tumor involvement. The innumerable normal variants of increased FDG uptake are beyond the scope of this article, but are further described in the scientific literature [31]. Additionally, it is equally important to recognize benign processes that may masquerade as malignant pathology, including a broad spectrum of inflammatory/infectious processes, rebound thymic hyperplasia, and bone marrow/splenic reactivation.

Step 5: Further characterize high density lesions with non-attenuation corrected PET images to exclude high attenuation artifact

High attenuation artifact is generated by an inappropriately large amount of attenuation correction from high-density structures on low dose CT images that artificially elevate the corresponding PET values [32]. However, high attenuation artifact is easily discerned because it resolves on the non-attenuation corrected PET images and no further evaluation is warranted (Figures 7 and 8). Common causes of high attenuation artifact include oral contrast, chemotherapy ports, dental implants, orthopedic devices, vertebroplasty cement, and calcified lymph nodes (Table 3) [33].

<table>
<thead>
<tr>
<th>Common Causes of High Attenuation Correction Artifact</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Oral Contrast</td>
</tr>
<tr>
<td>• Chemotherapy Ports</td>
</tr>
<tr>
<td>• Dental Implants</td>
</tr>
<tr>
<td>• Orthopedic Hardware (including vertebroplasty cement)</td>
</tr>
<tr>
<td>• Calcified Lymph Nodes</td>
</tr>
</tbody>
</table>

Table 3: Common Causes of High Attenuation Correction Artifact.
A high attenuation abnormality that persists on the non-attenuation corrected PET images represents one of the following:

1. Partially calcified tumor,
2. Tumor adjacent to high-density material, such as calcium or metal (e.g., surgical clip) (Figure 9), or
3. An inflammatory process with associated high density as seen with talc pleurodesis (Figure 10), granulomatous disease, or inflammation adjacent to a high-density process.

Step 6: Evaluate non-attenuation corrected PET images using entire field of view

A complete evaluation of the non-attenuation corrected PET images should be performed on a routine basis. These images are useful for the evaluation of small pulmonary nodules (Figure 13), superficial lesions, and skin lesions, which may appear more...
prominent than on the attenuation corrected images [38,39]. Additionally, non-attenuation corrected PET images enable recognition of misregistration artifact due to patient motion between the CT and PET images, as well as enhance the reader’s ability to further characterize high-density lesions and exclude high attenuation artifact.

**Figure 13:** Small pulmonary metastasis within the right middle lobe is more conspicuous on non-attenuation corrected image (far right).

**Step 7:** Obtain relevant Standardized Uptake Value (SUV) measurements

Standardized Uptake Values (SUVs) are relative measurements of FDG accumulation within a user-specific Region of Interest (ROI) at a single time point. An SUV is a semi-quantitative index defined as tissue tracer activity (microcuries per gram) divided by the product of injected radiotracer (microcuries) and patient weight (kilograms) [40]. Calculations can be made for the most intense pixel (SUVmax) or an average of pixel values within an ROI (SUVmean). SUVmax is more commonly used since it is not affected by partial volume averaging that occurs with SUVmean measurements. Following visual detection, relevant SUV measurements can be obtained from different Regions of Interest (ROIs). As a three-dimensional volume of tissue, ROIs should be visualized in all three planes to ensure the lesion of interest is truly the most hypermetabolic structure within the ROI. This is particularly important in lesions adjacent to normal structures with high FDG activity, such as the brain, kidneys, and bladder. As shown in table 4, numerous factors can influence the biodistribution of FDG and corresponding SUVs [14].

- Blood glucose/insulin resistance
- End organ dysfunction (including delayed clearance of FDG with renal failure)
- Patient weight
- FDG dose (including residual at injection site or in-catheter tubing)
- Uptake time
- Technical aspects (e.g., dose/scanner calibration)

**Table 4: Determinants of FDG Biodistribution.**

Because these factors can influence FDG biodistribution, SUVs obtained at different time points may vary widely. This is particularly important when comparing current images to prior PET/CT scans. SUVmax measurements vary by approximately 10% in highly controlled test-retest studies, with a predicted actual variability of 15-20% in everyday practice, despite being less affected by tumor inhomogeneity and volume than SUVmean measurements [41]. The variability of SUV measurements can be mitigated by comparing the target lesion FDG activity to the “normal” activity within a particular reference tissue, such as the Mediastinal Blood Pool (MBP), liver, lung, and cerebellum [42,43]. In particular, the MBP may be the most valuable reference, as Perry et al., (2008) found it to have the least variance among patients when compared to other reference tissues [42]. In our practice, lesion/MBP ratios and lesion/liver ratios are used in select cases to help determine whether or not a change in the SUVmax is clinically significant, particularly when visual assessment appears similar, but SUVs are substantially different (Figure 14).

**Figure 14:** Example of reference tissue utility in determining significance of an increase or decrease in SUVmax of a target lesion. The metabolic activity of a mediastinal lymph node is decreased on a three-month follow-up PET/CT (left column) from 6.0 to 3.7. Blood pool (middle column) and hepatic SUVmean values (right column) have decreased by nearly the same ratio, suggesting there has been no significant change between the two examinations.

When evaluating primary soft tissue tumors, additional quantitative PET indices may also be useful to predict prognosis. Initial staging of most solid tumors utilizes the Tumor-Node-Metastases (TNM) staging system to predict prognosis [44]. Recent advances in PET/CT software allow for automated Volume of Interest (VOI) assessments. Volume-based metabolic parameters have surfaced as additional quantitative PET indices, such as Metabolic Tumor Volume (MTV) (volume of voxels exceeding a certain threshold SUV or volume of voxels exceeding a certain percentage of lesion SUVmax) and Total Lesion Glycolysis (TLG) (product of MTV and mean MTV and SUV) [45]. MTV and TLG are more indicative of the total tumor volume and FDG uptake than single-pixel values, such as SUVmax.

Therefore, TLG may be an ideal metabolic parameter of initial primary tumor burden, as it is a combination of SUV and MTV that simultaneously represents the degree of FDG uptake and size of metabolically active tumor [46]. Recent studies suggest that primary tumor TLG may have more prognostic value than SUVmax for initial staging of some oncologic patients and may be a valuable tool for risk stratification and treatment guidance.

Step 8: Evaluate low-dose attenuation CT images

The typical ‘low-dose’ CT images obtained for PET attenuation correction should be thoroughly evaluated independent of the PET images. The CT images are not solely for anatomical localization purposes, in fact, these images should be considered an ‘exam within an exam’ [41]. The low-dose CT images require evaluation with the same systematic approach employed to interpret non-contrast CT examinations of the neck, chest, abdomen, pelvis, and musculoskeletal structures.

The interpreter should give special attention to the pulmonary parenchyma, kidneys, and other vital organs, such as the heart and aorta. Renal cell carcinomas are notorious for their variable avidity for glucose and inconspicuous appearance on interpretation of PET images even after fusion with CT data [48]. Other pathologic entities, such as non-FDG avid blastic bone metastases necrotic lymph nodes or tumors, are easily missed if the CT images are not evaluated independent of PET data on the appropriate window settings. Finally, if evaluating head and neck malignancies, the interpreter should have expertise in body imaging, as well as head and neck anatomy and pathology. If not, a multidisciplinary approach to interpretation incorporating a neuroradiologist should occur.

Step 9: Generate report and impressions

The report generated by a radiologist or nuclear medicine specialist is the sole proclamation of that individual’s expertise after years of training and experience. It is often radiologist’s only interaction with referring physicians and directly affects the management of oncology patients.

The mental checklist used for evaluating PET/CT cases described in this article can be reinforced using standardized or formatted reports [49]. Structured reporting can lead to more consistent and thorough reports. Additionally, given the potential for multiple significant findings, it is also hoped that formatted reports will help prevent “satisfaction of search errors,” which occur when lesions remain undetected after detection of an initial lesion [50,51].

In this author’s experience teaching residents how to read PET/CT exams, it has been helpful to separate pertinent positive and negative PET/CT findings into anatomic regions within the body of the report. A separate paragraph is used for reporting non-attenuation corrected PET image findings to ensure they are independently evaluated. CT findings are also described in a separate paragraph to reinforce the notion that the low-dose CT should be treated as a separate exam. The impression is then dictated in a disease-based approach, which summarizes and prioritizes findings based on clinical importance.

Conclusion

The field of radiology has much to learn from the aviation industry and other medical specialties, such as surgery and anesthesiology, where structured mechanisms and checklists have demonstrated improved outcomes. Given the complexity of PET/CT exam interpretation, which combines both metabolic and anatomic information throughout the body, as well as its unique artifacts, normal variations, and multitude of benign causes of increased uptake, a structured and systematic approach to reading exams will likely reduce mistakes and result in more accurate interpretations. While the exact order of each step described in this article can be adjusted, it is most important to ensure each step is completed to prevent misdiagnosis or delayed diagnosis. Radiology’s acknowledgment of the impact of systematic failures that are not attributable to the individual interpreter has the potential to improve both diagnostic accuracy and efficiency. Despite our inability to eliminate human error entirely, utilizing tools such as systematic checklists can reduce errors and translate into higher quality patient care.

“No matter what measures are taken, doctors will sometimes falter, and it isn't reasonable to ask that we achieve perfection. What is reasonable is to ask that we never cease to aim for it” [52]. - Atul Gawande

References


NorCal Open Access Publications
Radiology 259: 626-632.


