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## LEARNING OBJECTIVES

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

- Appreciate the value of PET/CT and integrate equivocal results in the management of the oncology patient.
- Identify ways that the PET/CT interpreter and the medical oncologist can work together to reduce the ambiguities and maximize the value of PET/CT.
- Understand the value and perils of SUV analysis in PET/CT.
- Assess the confounding results of PET/CT that can be obtained in post-treatment scanning.

### Who will benefit:

Physicians, physician assistants, nurses, and radiologic technologists will benefit from the information in this educational activity and can receive Continuing Medical Education credit by completing the post test and evaluation provided.

## PET/CT for the Medical Oncologist

By Michael S. Roberts, M.D., Alison M. Irving, and Ronald L. Korn, M.D., Ph.D.

**P**ET/CT is a powerful tool in the evaluation of patients who are known to have or are suspected of harboring cancer. The many uses of PET/CT imaging in cancer management are still being discovered and reported. In the last decade, PET/CT has moved beyond the university environment and into routine community clinical practice.

In order to appropriately incorporate PET/CT data into the medical management of patients, the oncologist must be able to appreciate the many strengths and applications of this modality and its limitations. Sometimes the results of PET/CT might present a real challenge to patient care if these data conflict with or even contradict the results of other imaging or laboratory tests. With caution, the practicing clinician

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can navigate through the ambiguities of PET/CT to provide the best patient care.

### VALUE OF PET/CT

Clinical PET scanning is performed by injecting a patient with a radiolabeled tracer such as FDG, which allows the examiner to assess areas of high metabolic activity that can be indicative of malignancy. A PET/CT study is constructed through the coregistration of PET images with correlated CT images, typically via concurrent acquisition of both.

The use of PET/CT fusion offers the benefits of the metabolic information obtained from PET scans with anatomic localization from CT scans. The combined study provides added value in differentiating physiologic from pathologic uptake.<sup>1</sup> PET/CT can directly affect the choice of treatment regimen, ultimately providing the best possible care for the oncology patient. Abundant literature exploring the utility of FDG-PET/CT has recently been summarized by Czernin.<sup>2</sup>

Although the merits of a positive or negative PET/CT study cannot be overemphasized, no test is perfect. In general, PET/CT is at least as accurate as conventional imaging

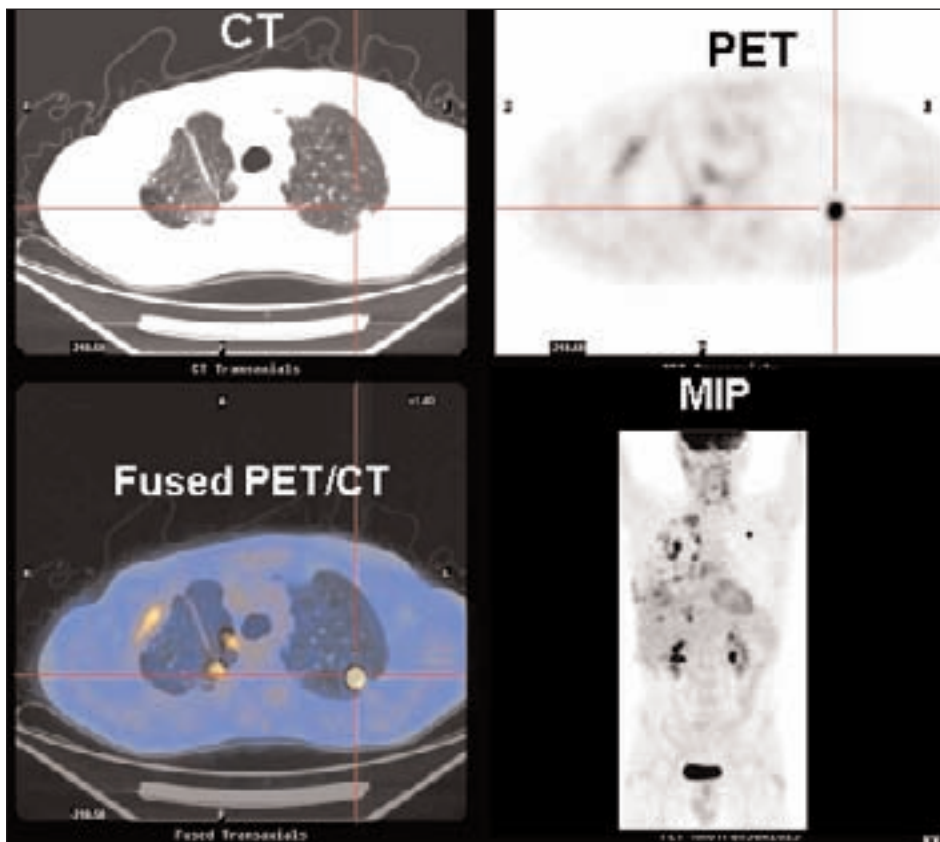


FIGURE 1. Clinical value of PET/CT information is apparent when a specific clinical question is addressed; in this example, staging of left upper lobe bronchogenic carcinoma (crosshairs on axial CT, PET, and fused images). Lack of left hilar or mediastinal activity (MIP image) suggests stage I disease. Widespread nodular activity in right pleural space is due to pleurodesis therapy. If the cancer had been located on the right lung, PET/CT scan would have been unhelpful for staging purposes.

in the various aspects of cancer detection and staging, and it can often change patient management by detecting more or less disease than was suspected on conventional imaging.

In our community practice, a clear-cut PET/CT result showing either increased hypermetabolic activity (typical standardized uptake values  $>4$ ) or no abnormal hypermetabolic activity (typical SUV  $<2.5$  to  $3$ ) can have high positive predictive and negative predictive values (65% to 99%). Many factors, such as tumor histology, lesion location, and previous or current treatment with chemoradiation or surgery, affect these values.

Clearly, false-positive and false-negative results can arise due to concurrent disease or treatments, including endemic community infections such as coccidioidomycosis in Central Arizona, prior

talc pleurodesis for malignant effusions, sarcoidosis, or uncontrolled diabetes. In these situations, we discourage the ordering of PET/CT while the concurrent diseases or conditions are active. Even so, PET/CT can provide important information to the clinician if the question being posed is focused and specific.

In Figure 1, PET/CT was ordered for a 42-year-old man with prior history of right talc pleurodesis for coccidioidomycosis empyema after a 1.5-cm spiculated lesion in the left upper lobe was shown to be bronchogenic carcinoma on chest CT.

The PET/CT scan showed the expected increased metabolic activity in the left upper lobe lesion and right pleural space. There was no evidence of abnormal metabolism in the left hilum or mediastinum. At surgery, the patient was

shown to have stage I lung cancer (T1N0M0). The results of the PET/CT, including the expected false-positive activity in the right pleural space, assisted the oncologist in treatment planning, which included only close observation. The patient remains disease-free after three years.

### EQUIVOCAL PET/CT RESULTS

An equivocal PET/CT result can be thought of as a focus, area, or region on the scan that demonstrates low-level, diffuse, or poorly defined hypermetabolic activity. Inadequate characterization of the focus in question on the CT portion of the PET/CT examination can also prevent the radiologist from confidently determining the presence or absence of tumor. When these types of results arise occasionally in daily practice, the options available to the medical oncologist include additional tests, follow-up PET/CTs, or tissue sampling, particularly if the results will change patient management.

Careful patient preparation, blood sugar control, image acquisition and optimization, and adequate knowledge of past medical history and tumor pathology can help reduce the number of equivocal studies. Good communication between the ordering physician and the PET/CT interpreter is vital for image interpretation. An area of low-level uptake in a lesion, for example, would more likely be related to malignancy in a patient who is at high risk for advanced stage disease or disease recurrence than in a patient who is at low risk for advanced stage disease (Figure 2).

### VALUE OF SUV

The SUV is a parameter specific for PET imaging that has been used in patient management. It is a measurement of the static amount of radiotracer present in a region of interest. SUV is defined as the tissue concentration of injected tracer divided by the injected dose per body weight. Many clinicians have come to rely upon SUVs to guide their treatment

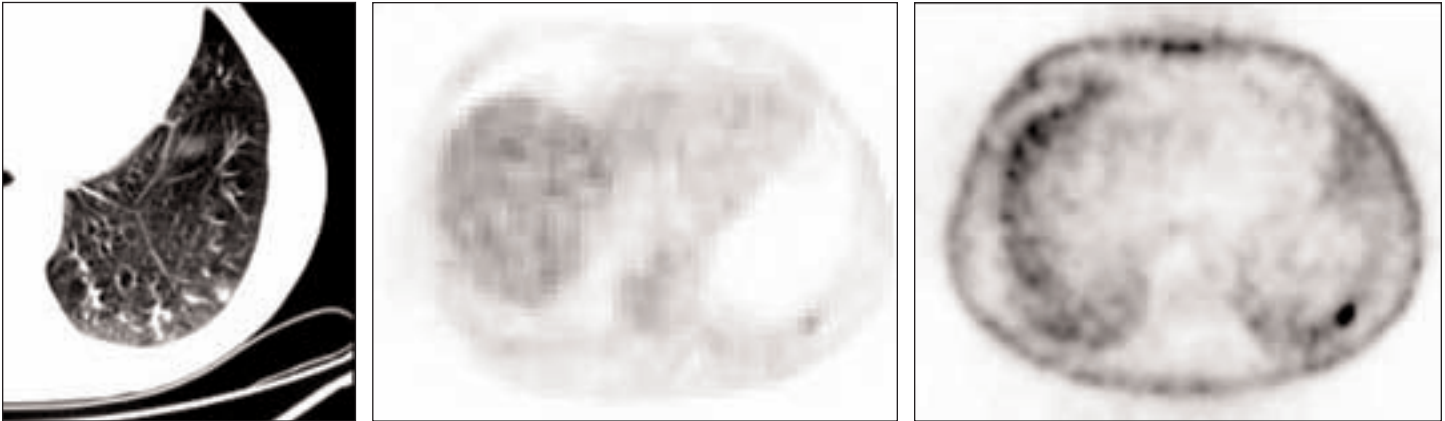


FIGURE 2. New 6-mm left lower lobe pulmonary nodule (left) is seen in 50-year-old man with stage III truncal melanoma. Attenuation-corrected image (middle) reveals low-level activity (SUV 1.8). Focus is more conspicuous on non-attenuation-corrected images (right). This was interpreted as consistent with metastatic disease due to high-risk staging of patient. The oncologist recommended tissue sampling to confirm diagnosis, then switched therapeutic regimens based on pathology showing metastatic melanoma.

approach since these measurements are easily obtained and reproducible.

Such reliance on SUVs is undoubtedly fraught with error, since SUVs can be affected by image reconstruction and attenuation parameters, region of interest size, the reporting of mean versus maximum values, the time that elapses between injection of FDG and image acquisition, and blood glucose levels between studies.<sup>3</sup> Some clinicians, especially pulmonologists, have focused incorrectly on absolute cutoff values for SUVs of 2.5 in solitary pulmonary nodules to distinguish benign from malignant uptake.

When PET/CT scans are performed for treatment follow-up, the SUV change between scans needed to declare a treatment response (or lack thereof) is un-

known. Multiple studies have reported different SUVs depending on tumor type and site. Indeed, there is even disagreement between different investigators regarding the same tumor type. In an attempt to standardize the use of SUVs in measuring treatment response, the European Organization for Research and Treatment of Cancer (EORTC) recommended the classification scheme outlined in the table.<sup>4</sup>

In our practice, SUVs are used as an adjunct to visual interpretation, while the EORTC recommendations function as guidelines for overall tumor burden assessment. When multiple malignant lesions are present, we evaluate treatment response by estimating the overall lesion burden and selecting only representative tumor lesions for SUV analysis.

**FLARE RESPONSE**

Although a general decline in SUVs from baseline to post-treatment scans can be a hopeful sign of tumor response, occasionally the worsening of hypermetabolic activity on follow-up scans can also be a sign of treatment efficacy due to a flare response. Dehdashti et al showed that in women with breast cancer treated for seven to 10 days with tamoxifen therapy, a metabolic flare response could be seen in responders, based on an increase in SUVs, but not in nonresponders.<sup>5</sup> Interestingly, none of the responders showed worsening of clinical symptoms.

A larger series confirmed these results, noting that SUVs in responders increased by 28.4% ± 23.3% (mean ± SD), compared with no significant change in nonresponders.<sup>6</sup> Distinguishing a flare response from progressive disease is difficult from a single imaging timepoint. Obviously, the onset of new lesions would be a sign of progressive disease. Short-term follow-up PET/CT scans would be critical to differentiate between progressive disease and flare response. The ideal timing interval has yet to be determined.

**INTERPRETATION FOLLOWING TREATMENT**

Not all cancers show immediate response to treatment, so repeating PET/CT shortly after initiating therapy may not be

**EORTC RECOMMENDATIONS FOR ASSESSING RESPONSE TO TREATMENT**

TUMOR RESPONSE	DEFINITION
Progressive disease	Increase in FDG SUV >25% compared with baseline, visible increase in size of FDG uptake, or appearance of new metastatic lesions
Stable metabolic disease	Increase in FDG SUV <25% or decrease >15% and no increase in size of FDG uptake
Partial metabolic response	Reduction in FDG SUV of at least 15% to 25% compared with baseline measurement after one cycle of chemotherapy or reduction by >25% after two cycles
Complete metabolic response	No FDG uptake

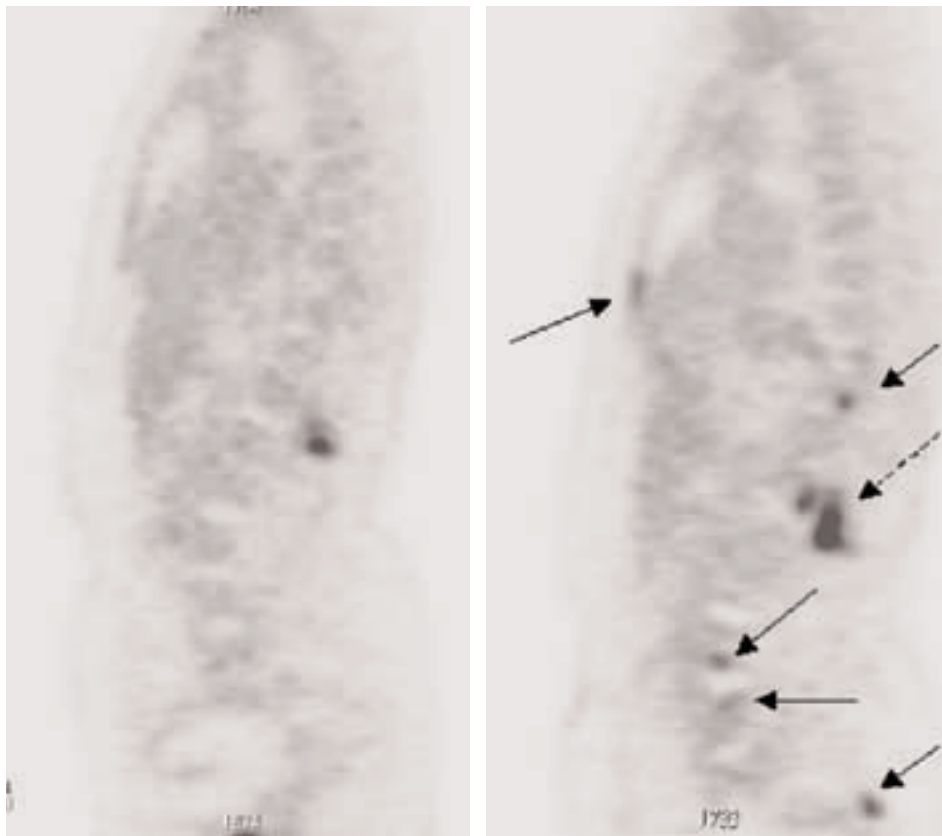


FIGURE 3. New lesions are shown in osseous structures (solid arrows) on sagittal PET image, with worsening of activity in previous T12 vertebral body metastasis (broken arrow) following a change in chemotherapy regimen. PET/CT helped to show that change in treatment was not effective.

beneficial; however, some cancers can show rapid response to therapy, and PET/CT scans performed shortly after treatment initiation may give an indication of whether a patient will respond. Knowing right away whether a treatment will work gives the oncologist the opportunity to change the treatment plan. Breast cancers, lymphomas, lung cancers, and gastrointestinal stromal tumors have been demonstrated to show rapid responses to therapy, and evidence is mounting that other cancers may also show early responses. Currently, only breast cancer is covered by the Centers for Medicare and Medicaid Services for PET/CT study for early treatment monitoring.

Although early scanning has a place in some cancers, PET/CT scans acquired during or immediately after a treatment course can produce confounding results. Sometimes results can show persistent or

increased activity in the diseased area, which can be falsely interpreted as positive. Other times, early PET/CT scans may show a suppression of activity that can produce false-negative results, particularly in patients with head and neck cancers.

Questions regarding the presence or absence of recurrent cancer most frequently arise when the patient has undergone radiation therapy.<sup>7</sup> PET/CT scans following radiation therapy can demonstrate low-level increased glucose metabolism conforming to the radiation port that can last for several years. Unusual patterns of FDG activity can cause image misinterpretation, and the activity at times may be difficult to distinguish from infection or tumor.

Paying close attention to the nondiagnostic CT information from PET/CT can be helpful, however, in distinguishing tumor from other processes. In lung

cancers, the supporting findings of traction bronchiectasis, volume loss, and consolidation of the lung on CT can be helpful signs of radiation pneumonitis. Although no standard time has been set for when to image patients following radiation therapy, most sites advise a three to six-month waiting period before performing PET/CT. In some instances, tissue sampling will be necessary to further investigate areas of focal activity that persist or enlarge on serial PET/CT examination.

In cases in which patients are treated with neoadjuvant therapy, PET/CT is often used to restage disease. Follow-up PET/CT shows an improvement in activity in many cases, but the metabolic activity is still present. In esophageal cancer, Weber et al<sup>8</sup> have shown that a decrease in SUV greater than 35% compared with baseline suggests a response to therapy, meaning the patient might be a candidate for surgery. Others, however, have noted that even a complete lack of activity following neoadjuvant therapy cannot guarantee sterilization of the tumor field.

A positive PET/CT does not mean that there is viable tumor in the treatment field, since inflammation and infection can mimic malignant type metabolism. Nevertheless, we use a drop in SUV values of greater than 30% to 50% following completion of neoadjuvant therapy as a harbinger of response to therapy and a good prognostic sign in predicting favorable outcomes.

#### FOLLOWING PATIENTS ON MAINTENANCE THERAPY

Certain cancers may require patients to undergo maintenance hormonal or chemotherapy once their malignancy has stabilized. PET/CT scans can be performed at periodic intervals or in cases of rising tumor markers to monitor disease activity. Maintenance therapies can be quite effective in limiting the growth of the tumor but can also lead to unwanted side effects. When this occurs, the oncologist must contemplate a change in ther-

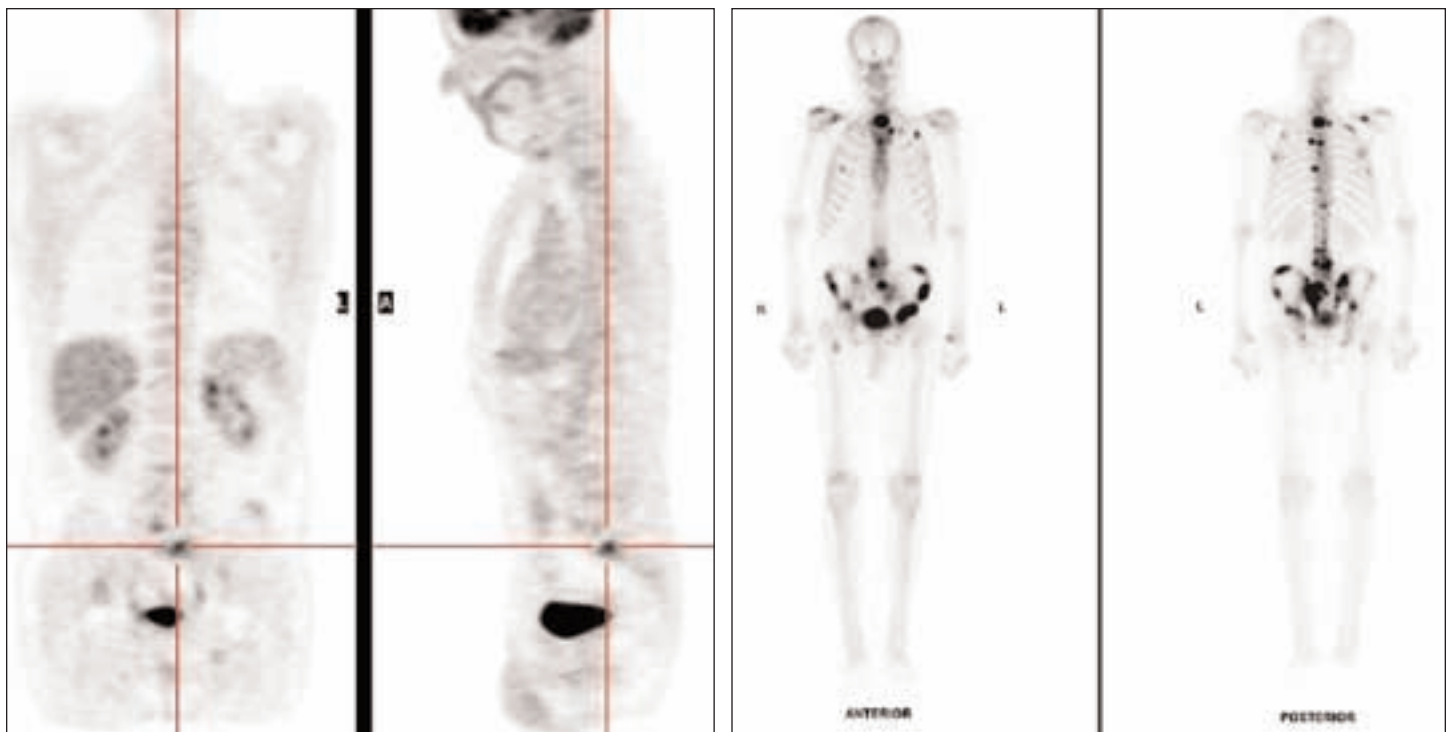


FIGURE 4. Relative lack of FDG uptake in the osseous structures on PET/CT exam (left two panels) is compared with Tc-99m MDP bone scans (right two panels).

apy or alteration in the drug(s), dosage, or delivery.

PET/CT scans can be quite useful for assessing whether the change in therapy or drug dosage is effective in prohibiting tumor growth and spread. Figure 3 shows a 55-year-old woman with breast cancer metastatic to bone who was treated with maintenance chemotherapy for two years. She developed gastrointestinal toxicity to the therapy, requiring a reduction in the dosage of the drug. Follow-up PET/CT on lower dose maintenance chemotherapy resulted in a recrudescence of the bone metastases. In this example, the results of the PET/CT study greatly assisted the medical oncologist in switching to a different treatment regimen.

#### DISCORDANT STUDIES

Discordant results from radiologic studies can further complicate the clinical picture. In evaluating a patient's disease status, it is likely that more than one diagnostic modality will be employed. Cross-sectional imaging (CT and MRI) is commonly used in conjunction with

PET/CT, and other modalities such as ultrasound and bone scan can also be performed when clinically warranted. When PET/CT data conflict with results obtained on other imaging modalities, all pieces of the picture must be taken into account in making clinical decisions.

A typical example of discordant results is illustrated in Figure 4. This 75-year-old patient with adenocarcinoma of unknown primary underwent PET/CT to find the primary lesion. The scan revealed bone metastasis limited to the lumbar sacral spine without identification of the primary malignancy. Technetium-99m medronate bone scans performed within a few weeks of each other prior to any therapy showed extensive bone metastases, above and beyond the PET/CT scan. Diffuse osseous metastasis was confirmed on MRI (not shown).

The significance of discordant results in the context of bone metastasis has yet to be elucidated. Possible explanations include a greater sensitivity of FDG metabolism for the detection of osteolytic lesions compared with osteoblastic lesions, but considerable overlap occurs.

In the setting of concurrent or prior chemoradiation where the PET/CT underestimates bone involvement compared with bone scan, it has been suggested that the PET/CT scan provides an estimate of viable tumor burden in the marrow space. Tc-99m MDP bone scans provide nonspecific information, measuring increased turnover due to bony repair and local trabecular remodeling.

Occasionally, biopsy is the only remaining option to confirm the presence of viable tumor when the results of multiple studies are in conflict with one another and when a definitive answer will greatly affect clinical decision making. In these situations, PET/CT scans can help direct biopsy. Until the significance of discordant studies is fully elucidated, the medical oncologist should consider all exams as providing complementary information.

#### CONCLUSION

Clinical decision making is a complex task for the medical oncologist, and an awareness of the strengths and limitations of the available tools is essential in

providing the best clinical care for patients. The wealth of metabolic and anatomic information supplied by PET/CT imaging can augment the clinician's understanding of a patient's disease state and can affect clinical decisions.

When PET/CT data are integrated with other radiologic information and clinical context, they can be a powerful tool in patient care. Both the medical oncologist and the PET interpreting physician must always be aware of the pitfalls and limitations of PET/CT scanning to avoid erroneous conclusions that

can adversely affect treatment decisions. Close communication between the PET/CT interpreting physician and the oncologist regarding the information sought from the PET/CT scan and knowledge of the patient's medical and surgical history are of paramount importance to the successful application of this modality to patient care. ■

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