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PET and PET/CT in the Diagnosis and Treatment of Melanoma

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LEARNING OBJECTIVES

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

- Describe the staging and prognosis of the different stages of melanoma.
- Explain basic principles and techniques of PET/CT.
- Outline the stages for which PET or PET/CT will be useful.
- Summarize the pitfalls of PET or PET/CT in the evaluation of melanoma.

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Melanoma, the leading cause of death from cutaneous malignancies, has a propensity to spread to unusual sites. In 2004, melanoma was estimated by the American Cancer Society to be the fifth and the seventh most common newly diagnosed tumor in men and women, respectively, in the U.S.¹ The incidence of malignant melanoma is increasing, but this increase may be partly attributable to improved screening programs. Melanoma accounts for 7910 deaths per year (1% to 2% of all cancer deaths).¹

A noninvasive method of evaluating the entire patient for metastases is critical in the initial staging and subsequent follow-up. PET and PET/CT imaging can play a role in the evaluation of patients with different stages of melanoma. Accurate pretreatment staging is crucial not only in assessing extent of disease involvement but also in assessing therapeutic options and prognosis.

The American Joint Committee on Cancer proposed a revised staging system in 2002.² This staging system incorporated prognostic factors including primary tumor thickness, presence/absence of ulceration, the number of regional nodes, the site(s) of distant metastases, and presence/absence of elevated serum lactate dehydrogenase (LDH).²

Stages I and II refer to localized melanoma. Stage III melanoma includes patients with regional metastases, either in the regional lymph nodes or as intralymphatic metastases manifest-

ing as satellite or in-transit metastases. Stage III is subdivided by clinical and pathologic stages. Stage IV melanoma includes patients with distant metastases. This stage is further divided based on the site of metastases and the serum LDH level.

In localized melanoma, surgery can be curative in around 85% of the patients.³ Surgery is also beneficial in patients with regional lymph node metastases for local control, but the assessment of regional node involvement has been a subject of controversy. The new staging system has defined separate clinical and pathologic stagings, so as to incorporate the results of sentinel node biopsy or elective lymphadenectomy into the staging for the regional lymph node metastases.

Morton et al⁴ were the first to describe the use of surgical identification of the sentinel node draining the site of the primary cutaneous melanoma. Excision and detailed pathologic and immunohistochemical analysis of the sentinel nodes are able to identify clinically occult melanoma metastases in regional lymph nodes.⁵ The advantages of lymphatic mapping and sentinel lymph node biopsy include possible upstaging of patients with clinically occult disease and positive sentinel nodes, change in prognosis, access to regional lymphadenectomy in these patients, and the ability to consider adjuvant therapy.

Patients with a negative sentinel node are over six times more likely to survive than those

with a positive sentinel node. In patients with a positive sentinel node, regional lymphadenectomy has shown a positive rate of additional nonsentinel nodes between 7% and 33%.⁶⁻⁸ Currently, lymphatic mapping and sentinel lymph node biopsy are considered standard of care.

The prognosis for stage IV melanoma continues to remain poor.⁹ Five-year survival rates range from 7% to 19%, depending on the site of involvement. Patients with soft-tissue, nodal, and isolated lung metastasis have a slightly better prognosis than those with other visceral metastasis and/or elevated LDH levels. However, survival beyond one year occurs in only a minority of stage IV patients. Systemic chemotherapy is usually used as the first line of therapy, despite poor response.

Recurrent melanoma can occur locally or involve distant organs. Among the patients who develop recurrence, 70% show initial local recurrence as compared with 30% who progress to distant metastases.¹⁰ Local recurrence can involve the primary excision site, in-transit metastases, or regional nodes. Depending on the location of the recurrence, the number of lesions, and the size of the largest lesion, isolated limb perfusion has been used in these patients instead of surgery. Overall response rates between 80% and 90% and complete response rates between 55% and 65% can be obtained using this approach. A subgroup of complete responders makes up 20% to 25% of the total patient population.¹⁰

Recurrent melanoma involving distant organs has poor prognosis and limited therapeutic options, including systemic chemotherapy and bioimmunotherapy. The role of imaging in recurrent melanoma is to identify patients with local recurrence versus those with distant recurrence and to assess response to treatment.

RADIOLOGICAL EVALUATION

PET imaging is increasingly being used in staging and post-treatment follow-up in a variety of malignancies.

- *Principles.* PET imaging is based on detection of the photons that are released at the time of annihilation of a positron (from a positron-emitting radionuclide) and an electron.¹¹ The photons thus released have

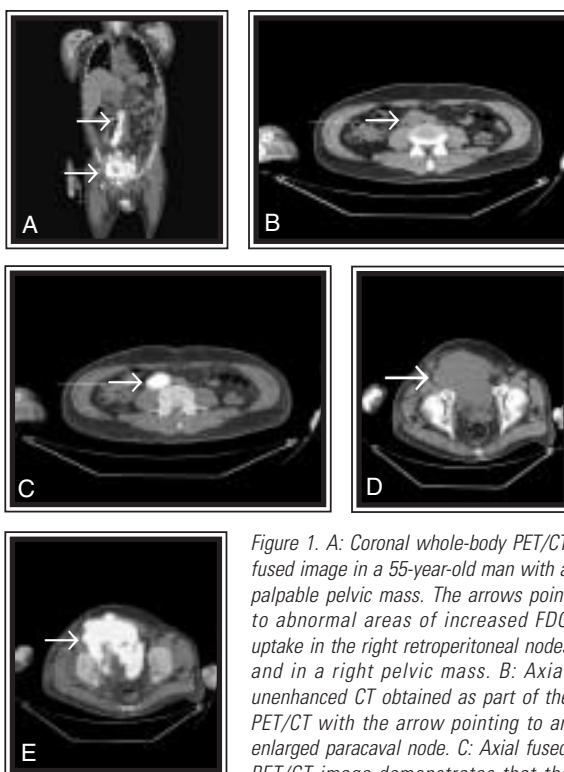


Figure 1. A: Coronal whole-body PET/CT fused image in a 55-year-old man with a palpable pelvic mass. The arrows point to abnormal areas of increased FDG uptake in the right retroperitoneal nodes and in a right pelvic mass. B: Axial unenhanced CT obtained as part of the PET/CT with the arrow pointing to an enlarged paracaval node. C: Axial fused PET/CT image demonstrates that the enlarged paracaval node has significant FDG uptake, consistent with metastases. D: Axial unenhanced CT obtained as part of the PET/CT with the arrow pointing to an anterior right pelvic mass, which involves the anterior right pelvic musculature. E: Axial fused PET/CT image demonstrates that the right pelvic mass has markedly increased FDG uptake consistent with a metastatic lesion.

energies of 511 keV and are detected by coincidence imaging as they strike scintillation crystals.

The radionuclide most commonly used for PET is fluoro-2-deoxyglucose, an F-18-labeled analog of glucose to study glucose metabolism. In vivo, FDG behaves like glucose, providing an accurate means of quantifying intracellular glucose metabolism. The metabolite of FDG following phosphorylation by hexokinase, unlike the metabolite of glucose, is not a substrate for glycolytic enzymes. Therefore, the radiolabeled metabolite of FDG is trapped in the cell, allowing subsequent imaging and quantification.

The principle of PET and PET/CT imaging differs from that of conventional imaging in that PET provides functional information by assessing glucose metabolism. The combination of PET with CT has proved useful in fusing and using both functional and anatomic information.

- *Technique.* At our institution, we scan melanoma patients using combined

PET/CT imaging. All patients undergo imaging after fasting for at least six hours. Scanning is started 60 minutes after injection of FDG (average dose, 12 to 20 mCi). Images are obtained by an integrated PET/CT scanner (Discovery ST-8, GE Healthcare). PET scans are acquired with the 2D mode for three minutes per bed position and reconstructed using standard vendor-provided algorithms. Emission data are corrected for scatter, random events, and dead-time losses using the manufacturer's software, and images are reconstructed both with and without attenuation correction, which is performed by CT. Nonenhanced CT images are acquired in helical mode (13.5 mm per rotation), performed from the base of the skull to the feet for melanoma patients, using a 3.75-mm section thickness, 140 kVp, and 120 mA.

PET AND PET/CT IN MELANOMA

Wahl et al¹² showed that radiolabeled glucose analogs were preferentially taken up in murine melanomas. Gritters et al¹³ imaged patients with melanoma and found a 100% sensitivity and specificity in the detection of lymph node and visceral metastases. There is no role for PET imaging in the initial diagnosis of melanoma, however, given the poor spatial resolution of PET imaging and the size of most primary cutaneous melanoma lesions.¹⁴

Many earlier publications on PET imaging in the assessment of regional nodes demonstrated high sensitivity and specificity,^{15,16} but the patient populations in these studies were small and mixed, containing patients with both palpable and nonpalpable nodes and pathologically proven negative nodes. A more recent study by Wagner et al⁵ evaluated 70 patients with primary melanoma (>1 mm thickness) and four patients with locally recurrent melanoma. None had palpable regional lymphadenopathy. This study showed that PET had a sensitivity of 11% and a specificity of 100% in detecting regional node metastases when compared with biopsy. This paper has been followed by others¹⁷⁻¹⁹ that also demonstrate that PET imaging is not as sensitive as sentinel lymph node biopsy in the initial evaluation of patients with no palpable region-

al lymphadenopathy. Lymphatic mapping with sentinel node biopsy is a safe and accurate method to assess for regional node metastases in this group of patients, where there is no palpable regional lymphadenopathy and no suspicion of distant metastatic disease.

Tyler et al²⁰ evaluated 95 patients with either palpable regional lymphadenopathy or in-transit melanoma. PET imaging was shown to have a sensitivity of 87% in this group. The lesions missed by PET imaging were mainly foci less than 1 cm in size. PET imaging demonstrated unsuspected sites of metastases in 19.7% of the scans, leading to a change in management in these patients. Crippa et al²¹ evaluated 38 patients with a preoperative diagnosis of regional node metastasis by biopsy or on clinical examination. They showed that PET imaging had a sensitivity of 95% and a specificity of 84%. In this study, FDG-PET detected 100% of metastases greater than or equal to 1 cm, 83% of metastases between 0.6 and 1 cm, and 23% of metastases less than or equal to 0.5 cm.

These studies suggest that PET imaging is clinically useful and potentially could change management in patients with abnormal regional lymph nodes (either biopsy-proven or palpable lymphadenopathy) or in-transit metastases.

PET imaging has a definite role in evaluation of patients with aggressive primary melanoma with suspected distant metastases, in follow-up of high-risk patients with previously excised melanoma, and in the restaging of patients with known distant metastases to evaluate for treatment response. Several studies have compared PET with CT in the detection of distant metastatic disease.

Rinne et al¹⁶ evaluated a total of 100 patients with both PET and CT: 52 were imaged at initial diagnosis and 48 at follow-up. All patients had a high-risk primary melanoma. The investigators demonstrated a high accuracy of PET (92.1%) compared with CT (55.7%). The two sites where CT was superior were in the detection of lung nodules and the evaluation of brain metastases.

Other studies have also confirmed the superiority of PET over CT in the evaluation of melanoma metastases. A recent study by Finkelstein et al²² assessed 94 lesions in 18 patients. While the sensitivity and specificity of PET and CT alone were

comparable in this study, the use of combined PET/CT increased both sensitivity and specificity. Lung and brain metastases continue to be better evaluated with CT than PET. The advantage of PET/CT imaging in these patients is the evaluation of small lung nodules not detected by PET.

PET imaging appears to have a role in the follow-up of high-risk patients with

methods. This included both locoregional and distant metastases. PET results led to a change in the clinical management of 36% of patients in this study. The sensitivity of CT was superior (93%) to PET (57%) in the evaluation of lung nodules.

Swetter et al²⁵ evaluated a mixed group of patients with primary and recurrent melanoma and compared PET with CT.

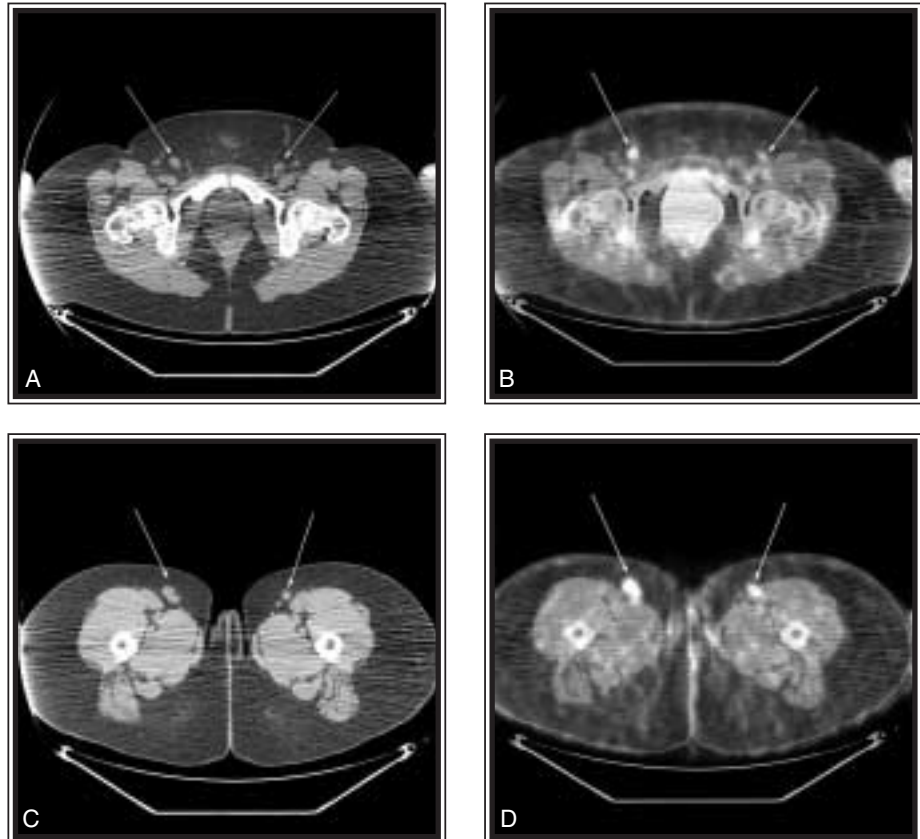


Figure 2. A: Axial unenhanced CT obtained as part of the PET/CT in a 36-year-old woman with a past history of melanoma in the right lower extremity. The arrows point to slightly prominent bilateral inguinal nodes. B: Axial fused PET/CT image demonstrates that these inguinal nodes have increased FDG uptake. C: Axial unenhanced CT obtained as part of the PET/CT with the arrows pointing to slightly prominent bilateral infrainguinal nodes. D: Axial fused PET/CT image demonstrates that these infrainguinal nodes have increased FDG uptake. This PET/CT was read as being concerning for the inguinal and infrainguinal node uptake. An ultrasound-guided biopsy of one of the infrainguinal nodes demonstrated results consistent with a reactive node. A follow-up PET/CT in three months demonstrated decreased FDG uptake in these regions. This is an example of a false-positive result on PET imaging.

previously excised melanoma and in the evaluation of patients with recurrence. Stas et al²³ analyzed 100 PET scans of 84 patients with regional or distant recurrence demonstrated or suspected on conventional imaging methods. They found a higher sensitivity and specificity with PET. In a recent study by Fuster et al,²⁴ 156 patients with recurrent melanoma were evaluated by both PET and CT. The overall accuracy for PET was 81% compared with 52% for other

They showed that PET is more sensitive and specific than CT for detection of melanoma metastasis and should be considered the primary staging study for recurrent disease. The combination of PET and CT in these patients should improve the sensitivity and specificity of detection of recurrent sites.

PITFALLS OF PET AND PET/CT

PET alone and PET used with CT have limitations, however.

• *False positives.* Increased FDG uptake can be seen in a variety of benign conditions, which can complicate image assessment. In many instances, the correlation of PET with CT can help minimize the false-positive findings seen on imaging. FDG uptake can be seen physiologically in normal structures, related to muscular contraction in muscles, tissues, or lymph nodes if there is injection leakage; in inflammatory conditions; postsurgery or post-radiation therapy; and with therapies such as granulocyte colony-stimulating factor (G-CSF).

Normal FDG uptake can be seen in the bowel, renal collecting systems, ureters, bladder, and thymus, especially in younger patients.²⁶ Anti-inflammatory cells, such as activated macrophages or

granulation tissue present in areas of inflammation, have been shown to actively take up FDG. The postsurgical setting involves localized inflammation with recruitment of leucocytes, which can increase FDG uptake.

The accumulation of FDG in tumor cells may be enhanced following radiation therapy, leading to increased uptake in these regions. G-CSF is a glycoprotein hormone that is being used increasingly to correct chemotherapy-induced neutropenia. Increased FDG uptake is often observed in bone marrow and spleen during and after G-CSF therapy.

• *False negatives.* One of the major limiting factors in PET imaging is its spatial resolution. Despite the intense FDG uptake by melanoma, when the size of the

tumor is less than 1 cm, there may be low or no uptake noted, leading to false-negative findings.

CONCLUSION

PET imaging has been shown to be of clinical use in patients with high-risk primary melanoma with palpable regional lymphadenopathy or biopsy-proven metastatic adenopathy, high-risk primary melanoma with suspected or confirmed distant metastases, and distant metastatic disease and unknown primary site. It is useful in follow-up of high-risk patients with excised primary melanoma and patients with suspected or known local or distant recurrence, and in restaging patients with known distant metastatic disease to assess tumor response.

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