

SIGNIFICANCE OF PET/CT IN EVALUATION OF MALIGNANT MELANOMA

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Malignant melanoma is the most aggressive cancer of the skin. The incidence of cutaneous malignant melanoma is increasing dramatically in persons with light-colored skin throughout the world.^{1,2}

Numerous studies have demonstrated that development and progression of melanoma are based on increasing levels of cutaneous solar exposure, particularly ultraviolet B radiation, in combination with the genotype, phenotype, and immunocompetence of the patient.³

Melanomas can be located anywhere on the body but most commonly occur on the lower extremities in women and on the black men. Malignant melanomas appear typically according to the "ABCD" rule with A being asymmetry of the lesion, B border irregularity, C color variation, and D diameter of more than 6 mm. Any pigmented lesion with a change in size, configuration, or color should be considered a potential melanoma, and an excisional biopsy should be performed.

Histologic verification and accurate microstaging of tumor thickness are essential for treatment decision and to predict the risk of metastases. For microstaging, two methods are currently used. The Clark method categorizes different levels of invasion that reflect increasing depth of penetration into the dermal layers and the subcutaneous fat. The Breslow method measures the microscopic vertical height of melanomas using an optical micrometer.

It has been demonstrated that the total vertical height of a melanoma (Breslow thickness) is the single most important prognostic factor in stage I and II melanoma.⁴ Lesions with a Breslow thickness of less than 0,76 mm have an excellent prognosis, not differing significantly from that of a general population, whereas those with more than 4 mm in thickness have a 10-year survival rate of less than 40 %.⁵

The high mortality rate of patients with melanoma is due to its early hematogenous spread.

The skin, subcutaneous tissue, and distant lymph nodes are the most common sites of distant metastases, but melanoma can metastasize to all organs. Because of the poor response to chemotherapy and immunotherapy, early detection and surgical excision are important in improving the prognosis. As soon as distant metastases are diagnosed, the prognosis is poor, with a median survival time of 4 to 6 months.⁶

STAGING OF MALIGNANT MELANOMA

Proper tumor staging is a key prerequisite for choosing the appropriate treatment strategy in melanoma. After resection of the primary melanoma, the Breslow analysis

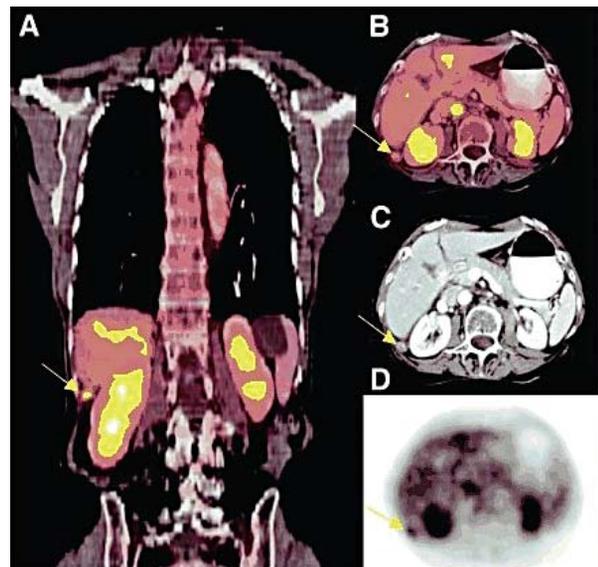


Figure 1: Coronal PET/CT (A) and axial PET/CT (B), CT (C), and PET (D) images acquired in patient with melanoma. Small focus of moderately increased 18F-FDG uptake corresponded to small soft-tissue nodule on CT (yellow arrows). Biopsy confirmed melanoma, and subsequent surgery for solitary metastasis was performed.

gives an immediate estimate of the statistical likelihood of regional lymph node metastases and distant metastases. In patients with thin melanomas (Breslow thickness of less than 0,75 mm), the likelihood of metastases is so small that staging with imaging modalities is not cost-effective.⁷

For staging of patients with increased risk for metastases of malignant melanoma (Breslow thickness of 1,5 mm or more), a variable combination of conventional imaging modalities have historically been used, such as chest x-ray, ultrasound of the abdomen and/or lymph nodes of the axilla, cervical region and groin, computed tomography (CT), and magnetic resonance imaging (MRI) of the body. The primary value of CT and MRI are the clear delineation of anatomic detail. However, these methods have generally been used to evaluate a specific region, rather than the entire body. Furthermore, specific identification of tumor tissue is difficult with these methods.⁸

Due to the limitations of morphologic imaging modalities, several radiopharmaceuticals have been used in nuclear medicine to visualize metastases of melanoma. However, these radiotracers did not offer any significance in diagnostic sensitivity in screening for

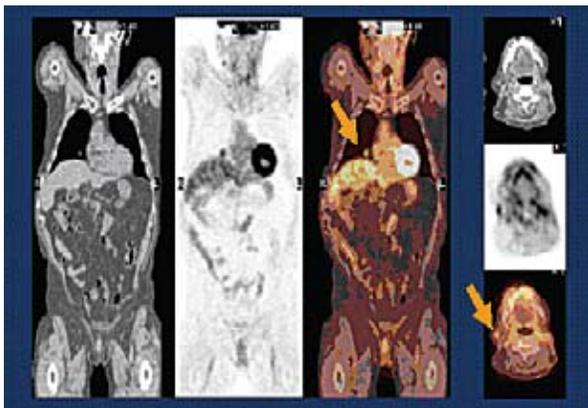


Figure 2: Preoperative PET maximum intensity projection (A) and preoperative cross sectional fused PET/CT images (B) of a patient with recurrent metastatic melanoma to the left thigh. The preoperative PET/CT scan revealed three hypermetabolic foci within the left thigh.

metastases of malignant melanoma. False-negative scan results were common because of poor sensitivity.

THE ROLE OF WHOLE –BODY FDG PET

Today, fluoro-2-deoxy-D-glucose (FDG) is the most widely used PET radiopharmaceutical for staging of malignant melanoma. In vitro and in vivo experiments with tumor cells demonstrated higher FDG uptake in melanoma than in other tumor types.¹⁰ FDG is a glucose analogue that is taken up by rapidly dividing cells. It is trapped in the first step of glucose utilization and accumulates in the cell. Whole-body positron emission tomography (PET) using FDG has been proven to be a highly effective and cost saving modality to screen for metastases of malignant melanoma throughout the body. With exception of the brain, whole-body FDG PET can largely replace the standard battery of imaging tests currently performed on high-risk patients (Fig. 1)

In 1993, Gritters et al. compared the accuracy of regional FDG PET with that of CT in 12 patients with known metastatic melanoma.¹¹ The sensitivity of PET was 100% for intra-abdominal visceral and lymph node metastases.

The excellent results in staging patients who have high-risk melanoma with whole-body FDG PET have been confirmed in larger patient studies in different PET centers worldwide.^{12,13,14} PET demonstrated high FDG uptake by nearly all untreated melanoma metastases

in the lymph nodes and viscera. An overall sensitivity of 90% (95% confidence level (CI), 86-94%) and an overall specificity of 87% (95% CI, 79-95%) were determined. (Fig. 2)

Holder et al. compared FDG PET with CT in 76 patients with metastatic melanoma.¹³ PET scanning for the detection of melanoma metastases had a sensitivity of 94,2 % compared with 55,3 % for CT scanning.

In an other study, sensitivity, specificity, and accuracy of PET/CT for the depiction of metastases based on FDG information were 85%, 96%, and 91%, respectively. Sensitivity, specificity, and accuracy of PET/CT for the depiction of metastases on the basis of the combination of FDG information and CT morphologic information were 98%, 94%, and 96%, respectively. The diagnostic performance of PET/CT with dedicated CT interpretation found significantly superior to that of PET/CT alone. The use of the CT portion of integrated PET/CT imaging for attenuation correction of emission PET images and for the precise localization of lesions with increased FDG uptake is known advantages of PET/CT imaging. Furthermore, coregistered PET and CT images can be used to improve the overall accuracy of the combined study (Fig.3). With the additional CT information, increased FDG uptake by physiologic tissues and benign variants, such as brown fatty tissue or muscle, can be identified with increased specificity. However, relying only on lesions with increased FDG uptake may result in a decreased overall sensitivity because of false-negative lesions. The additional dedicated interpretation of CT images may improve overall sensitivity by identifying metastases with a poor FDG uptake rate at PET.¹⁵

A number of factors may interfere with the accuracy of PET scanning for metastases. FDG is not tumor specific and is also taken up by muscles and inflammatory cells. Sensitivity of FDG PET in the depiction of tumor spread to the sentinel lymph node is poor. FDG accumulation in nodal metastases depends on the size of the metastases and on nodal tumor involvement of more than 50% or capsular infiltration. Because of their small tumor volume, cutaneous and subcutaneous lesions in particular can be missed at FDG PET imaging.¹⁶

False-positive results may be caused by an increased FDG uptake in inflammatory lesions or postoperative changes (17,18). False-negative results may occur in patients with slow growing tumors with a large necrotic component. Micrometastatic disease cannot be detected

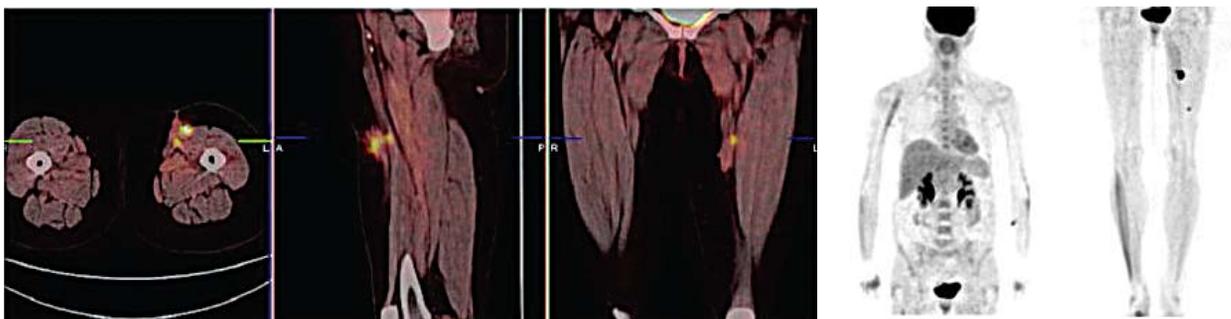


Figure 3: 82 Y/O male with history of 1.6 cm melanoma lesion on right side of head resected 2 years prior. No chemotherapy or radiation. Now presents with swelling in right parotid area. CT shows 2.3 cm lesion in right parotid gland with no other suspicious findings. PET/CT was performed to rule out metastatic recurrence. Abnormal FDG uptake in: Right parotid region and local lymph nodes, right hilum, left humeral head and shaft, left iliac bone and multiple ribs, left ear tissue. Findings consistent with metastatic, recurrent melanoma.

with any imaging modality.

PET\CT changes the treatment in 20% of patients with high-risk melanoma.¹⁹ Other groups reported an even higher influence of FDG PET on the diagnostic and therapeutic management of patients. In one study, PET resulted in a change in surgical management in 16 (36%) of 45 patients. The addition of FDG PET to the diagnostic algorithm resulted in a savings-to-cost ratio of 2:1 because of the avoidance of unnecessary procedures.²⁰

The results of these studies have shown that whole-body PET\CT is an excellent imaging method to screen for metastases of malignant melanoma in patients at risk. Contrary to the morphologic cross-sectional imaging modalities, PET permits, in essence, an "at-a-glance" diagnosis. PET, with the high FDG accumulation in tumor sites, has a high sensitivity for the identification of metastases. The procedure takes less than 1 hour of

scanning time and is virtually noninvasive.

In conclusion, whole-body PET\CT is a very effective imaging modality to screen for tumor metastases in patients with metastatic melanoma.

Patients with melanoma should be imaged with PET/CT, if available, and not with PET alone. Patients with melanoma should be imaged and interpreted both with PET\CT and coregistered CT images together. Dedicated analysis of coregistered CT data significantly improves the accuracy of integrated PET/CT for depiction of metastases in patients with high-risk melanoma.

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