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A Prospective Analysis of Positron Emission Tomography and Conventional Imaging for Detection of Stage IV Metastatic Melanoma in Patients Undergoing Metastasectomy

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Abstract

Background—Positron emission tomography with 2-deoxy-2-[¹⁸F]fluoro-D-glucose (FDG-PET) is available for evaluation of patients with melanoma. This study evaluates the potential of FDG-PET to improve on conventional imaging (CI) in patients with stage IV melanoma undergoing metastasectomy.

Methods—This was a prospective study comparing radiological evaluation of patients who underwent metastasectomy for palliation or cure. Patients underwent preoperative evaluation by physical examination, CI by computed tomography and/or magnetic resonance imaging, and FDG-PET. Independent observers performed three separate analyses of CI alone, FDG-PET alone, or FDG-PET read with knowledge of CI (FDG-PET + CI). Abnormalities were reported as benign or malignant and assessed by pathologic analysis or by clinical outcome determined by disease progression detected on serial evaluations.

Results—Ninety-four lesions were noted in 18 patients who underwent preoperative assessment, metastasectomy, and long-term follow up (median, 24 months). Lesion-by-lesion analysis for CI demonstrated a sensitivity of 76%, a specificity of 87%, a positive predictive value (PPV) of 86%, and a negative predictive value (NPV) of 76%. FDG-PET demonstrated a sensitivity of 79%, a specificity of 87%, a PPV of 86%, and an NPV of 80%. For FDG-PET + CI, the sensitivity was 88%, specificity was 91%, and PPV and NPV were 91% and 88%, respectively.

Conclusions—Combined use of FDG-PET and CI may be an accurate strategy to identify sites of disease in patients with stage IV melanoma being considered for metastasectomy. Interpreted independently, FDG-PET and CI seemed to be equivalent modalities. FDG-PET + CI had both the highest sensitivity on lesion-by-lesion analysis and the best accuracy on patient-by-patient analysis.

Keywords

Melanoma; Cancer; FDG-PET; Imaging; Metastasectomy; Surgery

The median survival for patients diagnosed with metastatic melanoma is 6 to 9 months, with an estimated 5-year survival of 5% to 10%.¹ Complete and durable regression of metastatic disease can be achieved in some patients (6%) with interleukin-2–based immunotherapy.² Chemotherapy has a higher overall response rate, but these responses tend not to be durable.² Retrospective single-institution series have been published to support surgical resection of metastatic melanoma for curative intent at sites other than brain; patients with limited disease (especially when confined to skin, subcutaneous, or nodal sites) that can be completely resected seem to be most likely to demonstrate a survival benefit from surgery.³ The complete and accurate identification of all sites of metastatic melanoma is therefore critical for optimal surgical management.

Positron emission tomography with 2-deoxy-2-[¹⁸F]fluoro-D-glucose (FDG-PET) is an imaging modality for evaluating patients with melanoma for local recurrences or metastatic disease. In 1999, the Health Care Financing Administration (now Centers for Medicare and Medicaid Services) approved the use of FDG-PET as a new modality for the evaluation of “recurrent melanoma prior to surgical intervention.”⁴ FDG-PET imaging is based on the pioneering work of the chemist Otto Warburg, who demonstrated that malignant transformation of cells is associated with an increased glycolytic rate. FDG-PET has thus been used for imaging a variety of cancers.⁵

Recent studies suggest that FDG-PET has a high degree of sensitivity and specificity for detection of stage I to III melanoma.^{6–20} Some studies suggest that FDG-PET may be more sensitive and specific than conventional diagnostic tests for detecting this disease.^{13,14,17,20} However, these studies have some important limitations, which include a lack of pathologic confirmation of suspected sites of metastatic disease and a relatively short clinical follow-up. In addition, most studies have determined specificity and sensitivity on the basis of a patient-by-patient analysis instead of a lesion-by-lesion analysis. Finally, most reports have evaluated the accuracy of FDG-PET imaging in patients at risk for developing metastatic disease instead of evaluating its accuracy in patients known to have metastatic disease. More recent reports have evaluated patients with metastatic disease, with more favorable results for FDG-PET than conventional imaging (CI).²⁰

The purpose of this study was to compare CI alone, FDG-PET alone, and the combination of PET and CI (FDG-PET + CI) in patients with stage IV melanoma undergoing resection of their disease. This unique patient population allowed for direct lesion-by-lesion comparison and pathologic evaluation of suspected lesions. In addition, extensive long-term follow-up was possible because these patients were concurrently monitored for other clinical trials.

PATIENTS AND METHODS

Study Group

This prospective study included 18 patients who were referred, screened, and enrolled on institutional review board–approved melanoma immunotherapy protocols and who underwent surgical resection for either palliation or attempted cure between January 2000 and March 2001. To ensure adequate postoperative assessment, long-term follow-up evaluations continued for more than 2 years. All patients were known to have radiologically assessable and pathologically confirmed American Joint Committee on Cancer (AJCC) stage IV metastatic melanoma. Patients with brain metastases were excluded. Only patients scheduled to undergo metastasectomy were included. The median age of patients on study was 42 years. Eleven patients (61%) were male, and seven patients (39%) were female. All patients had an Eastern Cooperative Oncology Group performance status of 0 to 1. All patients had prior therapy: surgery, 18 patients (100%); immunotherapy, 14 patients (78%); chemotherapy, 7 patients (39%); radiotherapy, 3 patients (17%); and hormonal therapy, 1 patient (6%). Most

patients—16 (89%)—had received ≥ 2 prior therapies, and 6 patients (33%) had received ≥ 3 therapies. With respect to response to immunotherapy, three patients (21%) were deemed complete responders but had a suspected solitary site of recurrence, three patients (21%) were partial responders who developed disease progression, and eight patients were deemed to have not responded to interleukin-2–based immunotherapy.

Preoperative Radiological Evaluation

All radiological evaluations were performed within 2 weeks of the surgical procedure. CI was performed with a multidetector computed tomograph (CT; Lightspeed: General Electric Medical Systems, Waukesha, WI; MX 9000: Philips Medical Systems, Cleveland, OH) with 5-mm collimation before and after the administration of 130 mL of iopamidol (Isovue 300; Bracco, Princeton, NJ) except when this was contraindicated by the administration of interleukin-2 within the prior 30 days. Contrast was administered as a bolus infusion by using a mechanical pump at 2 mL/second (Medrad, Indianola, PA). Magnetic resonance imaging (MRI) scans were performed on a 1.5-T MRI unit (General Electric Medical Systems) by using axial T1-weighted spin echo (TR, 400 msec; TE, 12 msec); fat-suppressed T2-weighted fast spin echo (TR, 4000 msec; TE, 102 ms; echo train, 8); and axial and coronal breath-held T1-weighted gradient echo images after .1 mmol/kg of gadolinium diethylenetriamine pentaacetic acid (Magnevist; Berlex Inc., Wayne, NJ). Five- to 7-mm-thick sections were obtained.

FDG-PET scans were performed on all patients after they had fasted for at least 4 hours. Patients received an intravenous administration of ~ 15 mCi of commercially bought FDG if they weighed less than 200 lb, and they received 20 mCi if they weighed ≥ 200 lb (16.5 ± 2.3 mCi). The patients were scanned with a General Electric Advance PET scanner that produced 35 slices over an approximately 15-cm axial field of view. An emission scan was acquired from the base of the skull to the mid thigh, typically in six to seven bed positions at 8 minutes per bed position. Attenuation correction was performed with a 3-minute transmission scan obtained with a germanium-68/gallium-68 transmission source. Images were acquired in two-dimensional mode and reconstructed in a 256×256 array by using an iterative reconstruction algorithm with an in-plane and axial reconstructed resolution of ~ 7 -mm full width half maximum, with a slice separation of 4.25 mm. Patients with brain metastases were excluded, and FDG-PET images of the brain are not routinely obtained because these are believed to be less sensitive than MRI. FDG-PET images were analyzed interactively at a workstation by reviewing rotating three-dimensional images (maximal-intensity projections) and by using an orthogonal viewer that allowed review of transaxial, coronal, and sagittal planes.

Interpretation of Radiographical Studies

For CI, patients underwent preoperative evaluation with CI alone to determine sites of disease. CI included chest, abdomen, and pelvic CT in all patients, and MRI of the liver/abdomen was additionally obtained in three patients to evaluate eight lesions. A radiologist together with a surgeon familiar with the patient's history reviewed the CI. The reviewers of CI had access to the prior studies for all patients. With respect to CI, the lesion location, size, and index of suspicion for malignancy were interpreted and recorded. Lesions were considered malignant if they showed abnormal patterns of enhancement that could not be explained by normal structures on CT.

For FDG-PET, a nuclear medicine physician read the scans alone, blinded with respect to any additional imaging; this physician was not informed about the specifics of any patients' individual history except that all patients were known to have a history of metastatic melanoma. The location and index of suspicion for malignancy for each lesion were interpreted and recorded.

For FDG-PET + CI, FDG-PET scans were reviewed by a nuclear medicine physician together with a surgeon familiar with the patient's clinical history. The reviewers of FDG-PET + CI had access to the prior studies (including CI) for all patients. There were no prior FDG-PET scans for comparison. The size, location, and index of suspicion for malignancy were interpreted and recorded for each lesion observed on these scans. Lesions were considered malignant on the basis of visual interpretation of the FDG-PET scan when a focal area of increased accumulation was present and could not be attributed to physiologic tracer distribution as recognized from the PET scan or from CI.

Data Analysis

Groups (CI, FDG-PET, and FDG-PET + CI) were interpreted blinded to one another's readings, and suspected lesions were deemed most likely benign or malignant. Lesions noted by each group were rated on a scale of 1 to 5 (1, benign; 2, probably benign; 3, equivocal; 4, probably malignant; and 5, malignant). On the basis of this rating system, lesions rated 4 or 5 were considered to be malignant, and lesions rated ≤ 3 were considered to be benign.

Preoperative radiological assessment of individual lesions was compared with the operative findings and pathologic analysis. This was achieved for most lesions. Any additional sites of metastasis were included as lesions. If histological or intraoperative confirmation of a specific lesion was inappropriate or not confirmed, serial CT and/or MRI scans performed at 3-month intervals were used to follow up patients for evidence of disease progression. To ensure adequate postoperative assessment, long-term follow-up evaluations continued for more than 2 years (median follow-up, 24 months).

The sensitivity [$TP/(TP + FN)$, where TP indicates true positive and FN indicates true negative], specificity [$TN/(TN + FP)$, where FP indicates false positive], and positive (PPV) and negative predictive value (NPV) for the preoperative detection of stage IV metastatic melanoma were determined. TP occurred when a lesion was rated as 4 (probably malignant) or 5 (malignant) and the lesion was found to be malignant by surgical pathology (in most cases) or by long-term follow-up. TN occurred when a lesion was rated as 1 (benign), 2 (probably benign), or 3 (equivocal) and was found to be benign on pathology or failed to show evidence of disease progression on subsequent CT/MRI evaluation. False negative (FN) occurred either when one of the modalities failed to detect a lesion or when a lesion was inappropriately rated as 1 (benign), 2 (probably benign), or 3 (equivocal) and the lesion was found to be malignant at operation or by subsequent evidence of disease progression at that site on serial radiographical evaluation. Finally, FP occurred when a modality rated a lesion as 4 (probably malignant) or 5 (malignant) and the lesion was found to be benign on histology or by lack of disease progression on serial imaging.

RESULTS

Conventional Imaging

Ninety-four lesions were assessable in 18 patients who underwent preoperative assessment, metastasectomy, and follow-up (median, 24 months; Table 1). Twenty operations were performed. All patients diagnosed with a solitary lesion ($n = 14$) went on to have a complete resection (Fig. 1). Six patients had multiple lesions noted before surgery, and only one of these patients had a complete resection of all metastatic disease.

Forty-three lesions were thought to be melanoma by preoperative CI. After assessment of lesion status, 37 lesions were classified as TP. Most TP lesions (30 of 37) were confirmed by pathologic analysis. Six abnormalities detected by CI were FP findings; three lesions were lung lesions <1 cm in diameter (two of the three lung lesions showed no evidence of progression,

and one was pathologically confirmed to be a granuloma). Another FP abnormality was a 12-mm retroperitoneal lymph node rated 4 (probably malignant), which remained stable. The remaining two FP lesions were a 15-mm splenic lesion and a 4-cm axillary node, both rated 4 (probably malignant), in a patient who had responded to high-dose interleukin-2. Pathologic analysis determined that the splenic lesion was a granuloma and that the axillary lesion showed only fibrosis. The location of these FP lesions and comparison of the various modalities can be seen in Figure 2.

There were 51 lesions deemed to be benign by preoperative CI. Thirty-nine lesions were determined to be TNs, and 12 were FNs. These FN lesions included two intraperitoneal metastases, two subcutaneous metastases, two intramuscular metastases, two axillary lymph nodes, two mediastinal lymph nodes, a right cervical lymph node, and one lung lesion. All of the FN lesions were >1 cm except for a mediastinal lymph node and a 2-mm lung nodule that was seen on CT only in retrospect. The location of these FN lesions and comparison of the various modalities can be seen in Figure 3.

Thus, the sensitivity and specificity for CI were 76% and 87%, respectively. In addition, the PPV and NPV were 86% and 76%, respectively (Table 1).

Positron Emission Tomography With 2-Deoxy-2-[¹⁸F]Fluoro-D-glucose

Forty-four lesions were considered to be melanoma by FDG-PET; 38 were determined to be TP, and 31 were confirmed pathologically after resection. The six FPs included a mesenteric lymph node rated 4 (probably malignant), a hilar lymph node rated 4 (probably malignant), a supraclavicular lymph node rated 4 (probably malignant), an axillary lymph node rated 4 (probably malignant), an intraperitoneal lesion rated 4 (probably malignant), and a visceral splenic lesion rated 5 (malignant) that pathology reported to be a granuloma. Of note, all the FP lesions were >1 cm (Fig. 2).

Fifty lesions were deemed to be benign by preoperative FDG-PET. With respect to these lesions, 40 were TNs, and 10 were FNs. The FNs included five visceral lung lesions, a retroperitoneal lymph node, a right cervical lymph node, a mesenteric lymph node, an intramuscular psoas lesion, and a subcutaneous breast lesion. With respect to these FN lesions, 9 of the 10 had no evidence of metabolic activity, and only 1 lesion (subcutaneous breast lesion) was visualized and inappropriately rated as benign (3, equivocal). Finally, 6 of 10 FN lesions were <1 cm; however, 3 of the 5 lung lesions and the mesenteric lymph node were >1 cm (Fig. 3).

Thus, the sensitivity and specificity for CI were 79% and 87%, respectively. In addition, the PPV and NPV were 86% and 80%, respectively (Table 1).

Positron Emission Tomography With 2-Deoxy-2-[¹⁸F]Fluoro-D-glucose Plus Conventional Imaging

Forty-six lesions were deemed to be melanoma by preoperative FDG-PET + CI. Of these lesions, there were 42 TPs and 4 FPs. More than 80% of lesions were confirmed pathologically by metastasectomy. The FPs included three axillary lesions and the splenic lesion described previously. Two of the three axillary findings were <1 cm; pathologically, these were found to be benign lymph nodes. The location of these FP lesions and comparison of the various modalities can be seen in Figure 2.

There were 48 lesions deemed to be benign by preoperative FDG-PET + CI. With respect to these lesions, 42 were TNs, and 6 were FNs. The six FNs included three visceral lung lesions, a retroperitoneal lymph node, a right cervical lymph node, and a subcutaneous breast lesion. Five of these six FN lesions (83%) were <1 cm, and only one visceral lung lesion was >1 cm.

No metabolic activity was visible on the FDG-PET scans for these six FN lesions, emphasizing that these missed lesions were not due to incorrect rating by the reviewers. Of note, several FNs by FDG-PET alone were correctly rated as malignant (TP) by FDG-PET + CI; two visceral lung lesions were correctly rated as 4 (probably malignant) on FDG-PET + CI; a 15-mm mesenteric lymph node was correctly rated as malignant (4, probably); and a 15-mm intramuscular psoas lesion missed by PET was correctly rated as 5 (malignant) on FDG-PET + CI (Fig. 3). Finally, the subcutaneous breast lesion rated as 3 (equivocal) by PET was not appreciated by the reviewers of FDG-PET + CI (Fig. 3).

Thus, the sensitivity and specificity for FDG-PET + CI were 88% and 91%, respectively. The PPV and NPV were 91% and 88%, respectively (Table 1).

Patient-by-Patient Analysis

On the basis of the lesion-by-lesion analysis, we examined whether using FDG-PET improved on standard CI for each patient with stage IV melanoma undergoing metastasectomy for palliation or cure. FDG-PET had a higher accuracy than CI in 3 patients, the same accuracy in 10 patients, and less accuracy in 5 patients. FDG-PET + CI had a higher accuracy in 5 patients, the same accuracy in 11 patients, and less accuracy in 2 patients as compared with CI.

DISCUSSION

FDG-PET is increasingly used as an imaging modality for patients with melanoma. The utility and accuracy of FDG-PET scans for patients with stage I to III melanoma have been extensively studied.^{6–22} The sensitivity of FDG-PET to detect metastatic disease in this patient population has been reported to be 87% to 100%.^{13,14,18,21} The specificity of FDG-PET for patients with no radiological evidence of metastatic disease was noted to be 78% to 96%.^{13,14,18,21} Analysis of anatomical regions with no radiological evidence of metastatic disease revealed the specificity of FDG-PET to be 44% to 94%. FN findings for this group of patients were most likely to occur when lesions were <1 cm. FP findings were most often due to FDG-PET uptake in surgical wounds, inflammatory sites, and benign tumors.^{6–18}

Several recent reports have suggested that FDG-PET may be superior to CI for the identification of metastases; some have suggested that FDG-PET may be able to replace CI as a screening modality for these patients.^{13,14,20} In a prospective study of 100 patients with AJCC stage I to III melanoma, Rinne et al.¹³ directly compared the sensitivity and specificity FDG-PET with those of CI. In this study, FDG-PET was found to be 92% sensitive and 94% specific for the detection of metastases, whereas CI had a sensitivity of only 58% and a specificity of only 45%. In another prospective study of 76 patients with AJCC stage II to IV melanoma, Holder et al.¹⁴ reported that FDG-PET scans had a sensitivity of 94%, compared with a sensitivity of 55% with CI. These authors noted that the specificity of FDG-PET (83%) and CI (84%) were similar. In a third study, Tyler et al.¹⁷ noted that FDG-PET augmented the findings of CI for patients with stage III disease; in some patients, FDG-PET not only confirmed the findings of CT, but also identified sites of disease that were missed by CI. In other patients, solitary lesions on CT that were suspected to represent metastatic disease showed no metabolic activity on FDG-PET and were subsequently found to be benign. Finally, in some patients, CT demonstrated numerous lesions consistent with widespread systemic disease, whereas FDG-PET identified a solitary site that was resected. In contrast to these results, Wagner et al.¹¹ and Acland et al.¹⁶ evaluated stage I and II patients with blinded interpretations plus histological confirmation of nodal disease and showed poor performance of FDG-PET.

Whereas these prior studies have focused on patients diagnosed with AJCC stage I, II, or III melanoma,^{6–20} very few studies have specifically addressed FDG-PET imaging in patients with advanced stage IV disease. Because improved preoperative detection of stage IV

metastatic lesions in patients undergoing metastasectomy may be of benefit, this study was undertaken to determine whether a new (and approved) imaging modality improves on our standard preoperative assessment. Indeed, metastasectomy is often considered as an option for potential cure or, more frequently, for palliation in this group of patients. Thus, this study prospectively assessed our conventional preoperative approach (CI) compared with FDG-PET alone and with the combination of both modalities in patients being evaluated for resection of metastatic melanoma. Although a limitation of this study is that all patients did not undergo histological confirmation of all lesions, we attempted to minimize the limitations of previous studies by including pathologic confirmation of suspected sites of metastatic disease, by allowing for both direct lesion-by-lesion and patient-by-patient comparison, and by establishing a long clinical follow-up (median, >2 years), which allowed for serial CT and MRI imaging to determine the stability or growth of all lesions that were not pathologically defined.

In this study we found that FDG-PET scans, when interpreted without knowledge of CT or MRI findings, were both sensitive (79%) and specific (87%) for the identification of metastases in patients with a history of stage IV melanoma. These results for FDG-PET alone were good despite the slight bias against the blinded reader of the FDG-PET who had no additional clinical information. CI with CT and MRI scans demonstrated a sensitivity (76%) and specificity (87%) comparable to those of FDG-PET in the same patient cohort. When FDG-PET and CI were read together, both the sensitivity and specificity of diagnostic imaging seemed to improve. FN findings for each imaging modality were most likely to occur when the lesion in question was <1 cm. FP findings in this patient population were associated with reactive lymph nodes or granulomas. When this information was considered on a patient-by-patient basis, FDG-PET had a higher accuracy than CI in 4 patients, equivalent accuracy in 10 patients, and less accuracy in 4 patients. FDG-PET + CI had a higher accuracy in 5 patients, was equivalent in 11 patients, and was less accurate in 2 patients when compared with CI.

CT and MRI scans play important roles for the preoperative evaluation of patients being considered for metastasectomy. At our institution, CI may have an advantage because many patients have serial scans for clinical protocols that date over months or years. This allows for more accurate interpretations and may explain why our reported sensitivity and specificity for CI is higher than in most other reports. Although FDG-PET scans provide little anatomical information, it is our experience that these scans can draw attention to very subtle findings on CT or MRI scans that would otherwise be overlooked. It is equally important to note that CI does not generally include a full view of the extremities or neck, whereas total-body FDG-PET scans do screen the neck and the extremities.

CONCLUSIONS

This prospective study suggests that the combined use of FDG-PET scanning and CI with CT and/or MRI imaging may be an accurate strategy to help identify sites of metastasis in patients with stage IV melanoma who are being considered for complete surgical resection. The accurate identification of all sites of metastatic disease is critical when surgeons are considering metastasectomy in patients with stage IV melanoma; only patients made completely free of disease are likely to show any survival benefit from surgery. It remains our clinical practice to obtain both CI with CT or MRI scanning and FDG-PET scans for patients with stage IV melanoma who are being considered for complete surgical resection.²³

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FIG. 1. Metastatic melanoma detected by conventional imaging and positron emission tomography with 2-deoxy-2- ^{18}F fluoro-D-glucose. Preoperative and postoperative findings in a patient with a right buttock lesion are shown.

FIG. 2. Location and size of false-positive lesions by conventional imaging (CI; blue), positron emission tomography with 2-deoxy-2- ^{18}F fluoro-D-glucose (FDG-PET; red), and FDG-PET + CI (black). Large circles represent lesions >1 cm; small circles represent lesions <1 cm.

FIG. 3. Location and size-false negative lesions by conventional imaging (CI; blue), positron emission tomography with 2-deoxy-2- ^{18}F fluoro-D-glucose (FDG-PET; red), and FDG-PET + CI (black). Large circles represent lesions >1 cm; small circles represent lesions <1 cm.

Lesion-by-lesion analysis of CI, FDG-PET, and FDG-PET + CI in patients with AJCC stage IV melanoma undergoing metastasectomy for palliation or cure

TABLE 1

Group	Preoperative diagnosis (n = 94) ^a				
	Melanoma	Benign			
CI	TP 37 (30) FP 6 (3)	TN 39 (1) FN 12 (6)			
FDG-PET	TP 38 (31) FP 6 (4)	TN 40 (0) FN 10 (5)			
FDG-PET + CI	TP 42 (33) FP 4 (4)	TN 42 (0) FN 6 (3)			
			Sensitivity	Specificity	PPV
			76%	87%	86%
			79%	87%	86%
			88%	91%	91%
					NPV
					76%
					80%
					88%

PPV, positive predictive value; NPV, negative predictive value; CI, conventional imaging; TP, true positive; TN, true negative; FP, false positive; FN, false negative; FDG-PET, positron emission tomography with 2-deoxy-2-[¹⁸F]fluoro-D-glucose; AJCC, American Joint Committee on Cancer.

^aIn parentheses is the number of lesions histologically confirmed.