

High-Risk Melanoma: Accuracy of FDG PET/CT with Added CT Morphologic Information for Detection of Metastases¹

Klaus Strobel, MD
Reinhard Dummer, MD
Daniela B. Husarik, MD
Marisol Pérez Lago, MD
Thomas F. Hany, MD
Hans C. Steinert, MD

Purpose:

To prospectively determine the accuracy of positron emission tomography (PET)/computed tomography (CT) with added CT morphologic information for depiction of metastases in patients with high-risk melanoma and negative findings for metastases at PET, by using histologic findings or additional imaging and/or follow-up findings as reference standard.

Materials and Methods:

Institutional review board approval was obtained. Informed consent was obtained from patients. One hundred twenty-four consecutive high-risk melanoma patients (65 female, 59 male; mean age, 54.4 years; range, 15–82 years) were included. Fluorine 18 fluorodeoxyglucose (FDG) PET/CT was performed. First, PET/CT scans were evaluated for presence of metastases with increased FDG uptake; CT anatomic location was determined. Lesions were considered metastases if there was focal uptake higher than that of background tissue. Second, coregistered CT images of combined PET/CT scans were evaluated for presence of lesions without FDG uptake. Findings were compared with reference standard findings to determine the accuracy of each evaluation. McNemar test was used to assess statistical differences in accuracy.

Results:

In 53 of 124 patients, metastases were found. In 46 of 53 patients with metastases, lesions had increased FDG uptake. In seven patients with metastatic disease, metastases did not have increased FDG uptake (maximum standard uptake value [SUV], <1.5; $n = 5$) or had faint FDG uptake (maximum SUV, 2.5 and 2.9; $n = 2$)—findings that were inconclusive with PET alone. These lesions were interpreted as metastases only with coregistered CT images. Lesions missed with PET were located in the lungs, iliac lymph nodes, subcutis, and psoas muscle. Sensitivity, specificity, and accuracy, respectively, of PET/CT for depiction of metastases were 85%, 96%, and 91%, and those of PET/CT with dedicated CT interpretation were 98%, 94%, and 96% ($P = .016$).

Conclusion:

Dedicated analysis of coregistered CT images significantly improves the accuracy of integrated PET/CT for depiction of metastases in patients with high-risk melanoma.

© RSNA, 2007

¹ From the Division of Nuclear Medicine, Department of Medical Radiology (K.S., D.B.H., M.P.L., T.F.H., H.C.S.), and Department of Dermatology (R.D.), University Hospital Zurich, Raemistr 100, 8091 Zurich, Switzerland. Received June 26, 2006; revision requested August 30; revision received September 15; accepted October 25; final version accepted December 11. Supported in part by the Bonizzi-Theler Foundation. Address correspondence to K.S. (e-mail: klaus.strobel@usz.ch).

Whole-body fluorine 18 fluorodeoxyglucose (FDG) positron emission tomographic (PET) imaging has been shown to be superior to conventional imaging methods in patients with high-risk melanoma (1–6). However, limitations of FDG PET imaging have been recognized. FDG is not tumor specific and is also taken up by muscles and inflammatory cells (7–11). Sensitivity of FDG PET in the depiction of tumor spread to the sentinel lymph node is poor (12–15). FDG accumulation in nodal metastases depends on the size of the metastases and on nodal tumor involvement of more than 50% or capsular infiltration (15). Because of their small tumor volume, cutaneous and subcutaneous lesions in particular can be missed at FDG PET imaging.

In the assessment of pulmonary metastases of melanoma, FDG PET has a higher specificity but a lower sensitivity than computed tomography (CT) (16, 17). In a previously published study (16), sensitivity of CT and PET in the evaluation of lung nodules were 93% and 57%, respectively. Because of the physiologic uptake of FDG by the brain, FDG PET imaging is of limited value in screening for brain metastases.

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 are known advantages of PET/CT imaging. Furthermore, coregistered PET and CT images can be used to improve the overall

accuracy of the combined study. With the additional CT information, increased FDG uptake by physiologic tissues and benign variants, such as brown fatty tissue (18) or muscle (19), 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. Thus, the purpose of our study was to prospectively determine the accuracy of PET/CT with added CT morphologic information in the depiction of metastases that were not detected at PET in patients with high-risk melanoma, by using histologic or additional imaging and/or follow-up findings as the reference standard.

Materials and Methods

We received approval from our institutional review board to undertake this study. Written informed consent was given by all patients.

Patients

One hundred twenty-seven consecutive patients with melanoma referred for PET/CT imaging between August 2004 and April 2005 were prospectively enrolled in the study. Three patients were excluded because they underwent chemotherapy before the first PET/CT examination, because metastases after systemic therapy may be completely without FDG uptake but still morphologically visible. This resulted in a study population of 124 patients (65 female patients, 59 male patients; mean age, 54.4 years; age range, 15–82 years).

Implications for Patient Care

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

Our institution is a teaching and tertiary care hospital and a major referral site for patients with malignant melanoma. In all patients, PET/CT imaging was performed for depiction or exclusion of metastases in patients with high-risk melanoma (Breslow tumor thickness, >4 mm; Clark level, III or IV; or known metastases).

PET/CT Imaging

All data were acquired with a combined PET/CT in-line system (Discovery LS or Discovery ST; GE Health Systems, Milwaukee, Wis).

Patients fasted for at least 4 hours before scanning, which started 45–60 minutes after the injection of 350–400 MBq of FDG. All patients were tested for a normal glucose level (range, 80–120 mg/dL [4.4–6.7 mmol/L]) before scanning. Patients with elevated glucose levels had their examinations rescheduled and were scanned when their glucose levels were normal. Oral CT contrast agent (Micropaque Scanner; Guerbet, Aulnay-sous-Bois, France) was given 15 minutes before the injection of FDG. Patients were examined while in the supine position. No intravenous contrast agent was given. CT scans initially were acquired starting from the level of the head by using the following parameters: 40 mAs; 140 kV; tube rotation time, 0.5 second; section thickness, 4.25 mm; scan length, 867 mm; data acquisition time, 22.5 seconds. CT scans were acquired during breath

Advances in Knowledge

- In 13% of patients with metastatic melanoma, metastases, especially lung metastases, were detected only by using coregistered CT.
- Sensitivity, specificity, and accuracy of PET/CT for depiction of distant metastases were 85%, 96%, and 91%; those of PET/CT with dedicated CT interpretation were 98%, 94%, and 96% ($P = .016$).
- CT information improves the overall accuracy of integrated PET/CT for the detection of melanoma metastases with negative findings at PET.

Published online

10.1148/radiol.2442061099

Radiology 2007; 244:566–574

Abbreviations:

FDG = fluorine 18 fluorodeoxyglucose
SUV = standard uptake value

Author contributions:

Guarantors of integrity of entire study, K.S., H.C.S.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; literature research, K.S., M.P.L.; clinical studies, K.S., R.D., D.B.H.; statistical analysis, K.S.; and manuscript editing, all authors

Authors stated no financial relationship to disclose.

Figure 1

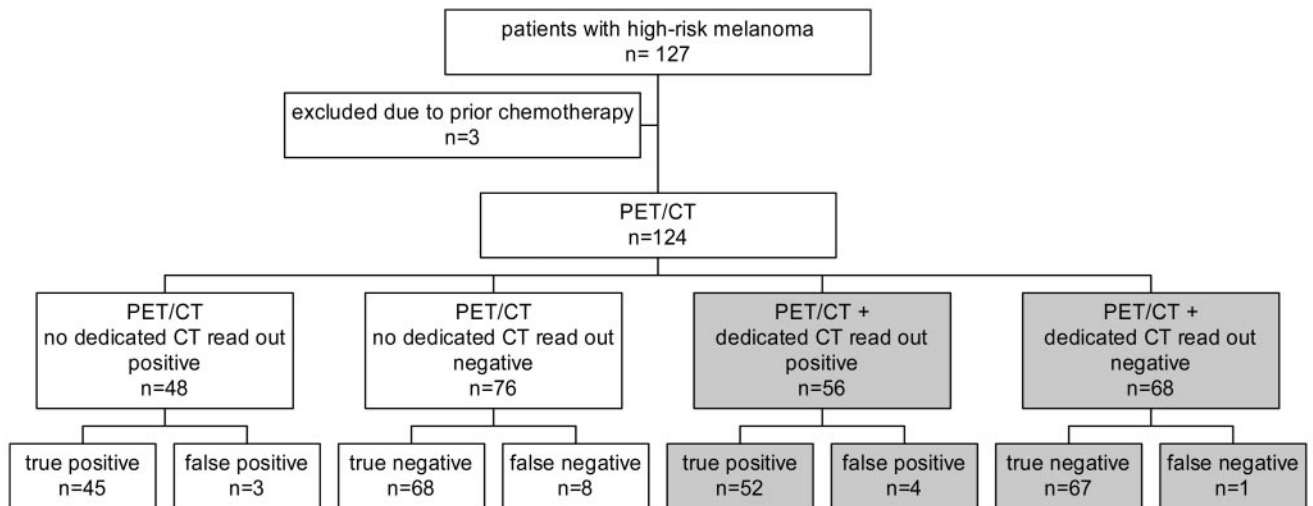


Figure 1: Flow diagram of study patients.

holding in normal expiration. In patients with primary tumors in the lower extremities, scanning of the lower legs was performed.

Immediately after CT scan acquisition, PET emission scans were acquired with an acquisition time of 3 minutes per table position, with a one-section overlap in two-dimensional mode (matrix, 128×128). The eight to nine table positions, starting from the head and continuing to the knees, resulted in an acquisition time of approximately 24–27 minutes. In patients with primary tumors of the lower extremities, scanning of the lower legs was performed. CT data were used for attenuation correction, and images were reconstructed by using a standard iterative algorithm (ordered-subset expectation maximization). The acquired images were viewed with software that provided multiplanar reformatted images of PET data alone, CT data alone, and fused PET/CT data, with linked cursors (Xeleris workstation; GE Health Systems). PET/CT imaging was performed according to the recently published “Procedure Guideline for Tumor Imaging with ^{18}F -FDG PET/CT 1.0” (20).

PET/CT Interpretation

Images were analyzed by two nuclear radiology physicians (H.C.S., 13 years of experience; K.S., 7 years of experi-

Figure 2

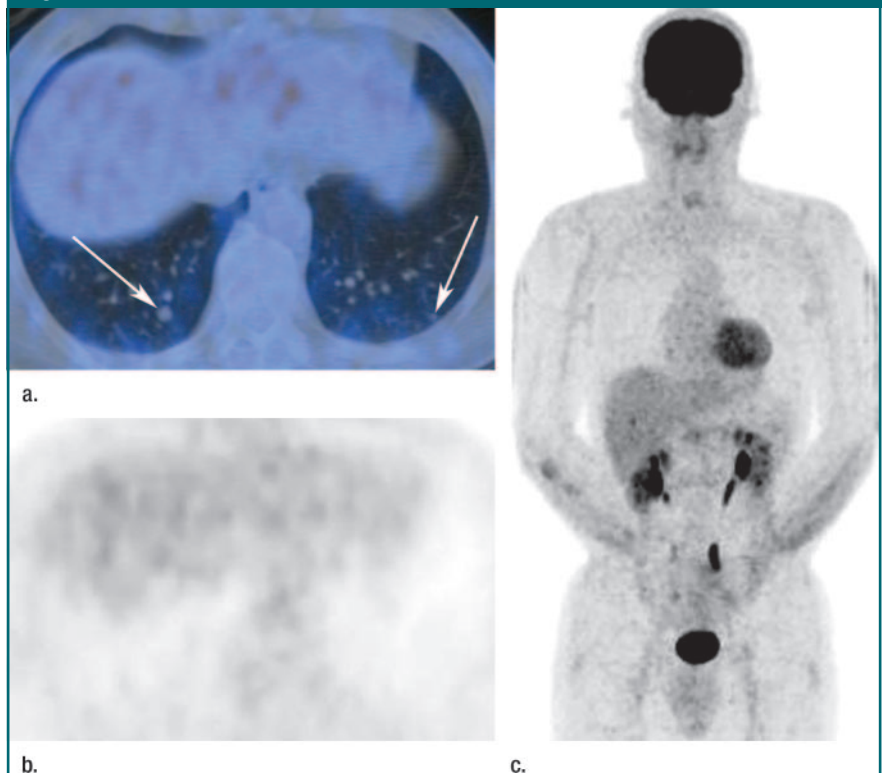


Figure 2: (a–c) Images in 50-year-old man. PET/CT was performed 7 months after resection of an ulcerating nodular malignant melanoma of scalp (Breslow thickness, 5.0 mm; Clark level, IV or V); there were negative findings at sentinel node biopsy. (a) Transverse fused PET/CT image shows two pulmonary nodules (arrows) in lower lobes. (b) Corresponding transverse PET image and (c) coronal maximum intensity projection show no FDG uptake. MR imaging (results not shown) was performed 3 days after brain metastases were detected at initial PET/CT; palliative radiation therapy was started (Fig 2 continues).

ence) without knowledge of the results of other imaging studies. PET images were analyzed for the presence of focal lesions with an increased FDG uptake. For all of the patients, attenuation-corrected PET images were used. Lesions were interpreted as metastases if the uptake was higher than the uptake of the surrounding background tissue and thus a focal lesion was clearly depicted. FDG uptake by physiologic tissues or benign variants, such as muscles or pulmonary infiltration, was excluded from the analysis. If a focal lesion with increased FDG uptake was detected, the exact anatomic location was determined on the fused PET/CT images.

After reviewing PET images for metastases with increased FDG uptake, the reviewers interpreted the CT images alone with the knowledge of the

lesions with increased FDG uptake at PET. All morphologic lesions that were not considered suspicious for metastases in the prior reading were recorded. All solid pulmonary nodules without calcifications or fatty tissue constituents were interpreted as lung metastases. In cases of discrepancy between the two reviewers, consensus was reached by discussing the findings. Metastases were diagnosed if a lesion detected by one or both reviewers fulfilled the described criteria.

Semiquantitative analysis of FDG uptake in the lesions, additionally seen at CT, was performed by measuring the maximum standard uptake value (SUV). A personal scale (Tanita, model 2001; Tanita, Tokyo, Japan) with an integrated foot-to-foot bioelectric impedance analyzer was used to determine

the lean body mass (LBM) of the patients. The manufacturer-supplied equations for this model incorporate sex, mass, height, and a measured impedance value to determine the percentage of body fat and to calculate LBM. By using attenuation-corrected PET data, maximum SUV (SUV_{max}) was calculated with the following equation by creating a freehand region of interest over the complete visible lesion on the fused PET/CT image: $SUV_{max(lbm)} = (LBM - C_{FDG})/D$, where LBM is measured in grams, C_{FDG} is the concentration of FDG in becquerels per milliliter, and D is the injected dose measured in becquerels. Lesions that were not detected with PET alone and had a maximum SUV of less than 1.5 were classified as not having FDG uptake, and lesions that were not detected with PET alone and had a maximum SUV between 1.5 and 3.0 were classified as having faint FDG uptake. The size of every lesion without uptake was measured on CT images.

Reference Standard

Every lesion suspicious for a metastasis was confirmed with findings from histologic examination, other imaging modalities (such as magnetic resonance [MR] imaging and/or PET/CT follow-up), and/or clinical follow-up for a minimum of 6 months (range, 6–18 months). Clinical follow-up included measurement of the tumor marker S 100B (S 100B values $> 0.2 \mu\text{g/L}$ indicated metastasis) (21).

A false-negative diagnosis at PET/CT was determined if findings from another imaging method (superior to PET/CT for the investigated region, such as brain MR imaging) showed metastases or if clinical findings (increasing tumor marker value) raised the suspicion of metastases, which were proved with histologic findings or further follow-up findings (progressive FDG uptake and/or increasing size of the lesions without evidence of other malignancies and/or increasing tumor marker value). A false-positive diagnosis at PET/CT was determined if histologic findings of the lesion and/or clinical and PET/CT follow-up findings (complete disappearance of focal lesion with increased FDG uptake) ruled

Figure 2 (continued)

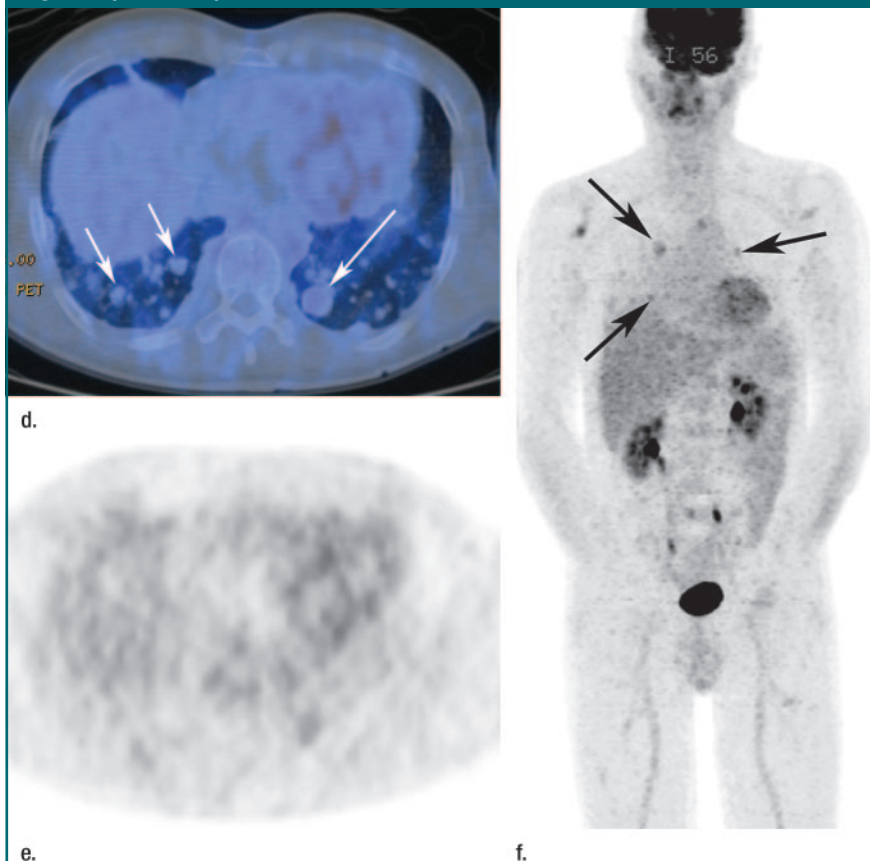


Figure 2 (continued): (d–f) Images obtained 6 months later. (d) Transverse fused PET/CT image shows progression of pulmonary nodules (arrows) in size and number. (e) Corresponding transverse PET image and (f) coronal maximum intensity projection show increased FDG uptake in several lung nodules (arrows).

out metastases. Diagnosis of noncalcified nodules without FDG uptake (eg, in the lung) was determined to be a false-positive finding if there was no change in number or size at follow-up PET/CT examination and no clinical suspicion for metastases.

Statistical Analysis

Recorded data were entered into a worksheet (Excel; Microsoft, Redmond, Wash). Sensitivity, specificity, and accuracy of the integrated PET/CT images with FDG accumulation alone were compared with those of the integrated PET/CT in combination with the dedicated CT interpretation. Data analysis was on a per-patient basis. The McNemar test was used to assess statistical differences in accuracy of the diagnoses. $P < .05$ was considered to indicate a significant difference. Software (SPSS, version 11, 2002; SPSS, Chicago, Ill) was used for statistical analysis.

Results

Reference Standard Results

According to the reference standard, 53 patients had melanoma metastases and 71 did not. Metastases were confirmed

Figure 3

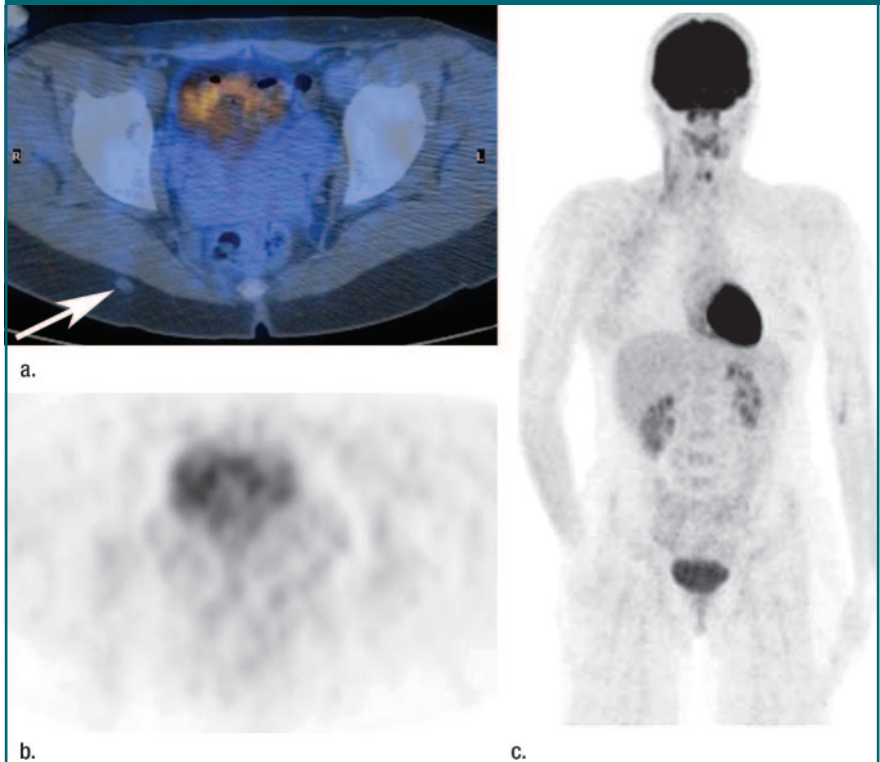


Figure 3: (a–c) Images in 36-year-old woman 6 years after resection of malignant melanoma on abdominal wall (Breslow thickness, 1.0 mm; Clark level, IV). After resection and radiation therapy of axillary and supraclavicular lymph node metastases on right side 1 year before, PET/CT follow-up was performed. (a) Transverse fused PET/CT image shows small lesion (arrow) in gluteal subcutaneous fatty tissue on right side. (b) Corresponding transverse PET and (c) coronal maximum intensity projection show no FDG uptake by this lesion (*Fig 3 continues*).

Table 1

Patients with Melanoma Metastases Detected Only at Dedicated CT Interpretation

Patient No.	Sex	Age (y)	Location of Primary Tumor	Location of Metastases	Size of Metastases (mm)	Maximum SUV	Clinical Follow-up Findings
1	M	50	Scalp	Lung	4	<1.5	Increase in tumor marker value, brain metastases detected 3 months later, progression of lung metastases
2	F	66	Back	Lung	10	<1.5	Increase in tumor marker value, progression of lung metastases
3	F	36	Abdomen	Subcutaneous node in gluteal soft tissue	12	<1.5	Disease progression with death of patient 4 months later secondary to bleeding brain metastases; autopsy results confirmed multiple metastases (brain, heart, ovary, gluteal soft tissue)
4	M	59	Leg	Iliac lymph nodes	11	2.4	Resection
5	M	73	Forehead	Lung	4–19	<1.5	Increase in tumor marker value, progression of lung metastases
6	M	57	Toe	Psoas muscle (centrally necrotic)	40	2.9	Increase in tumor marker value, progression of metastases
7	F	67	Knee	Lung	4	<1.5	Increase in tumor marker value, progression of lung metastases

Figure 3 (continued)

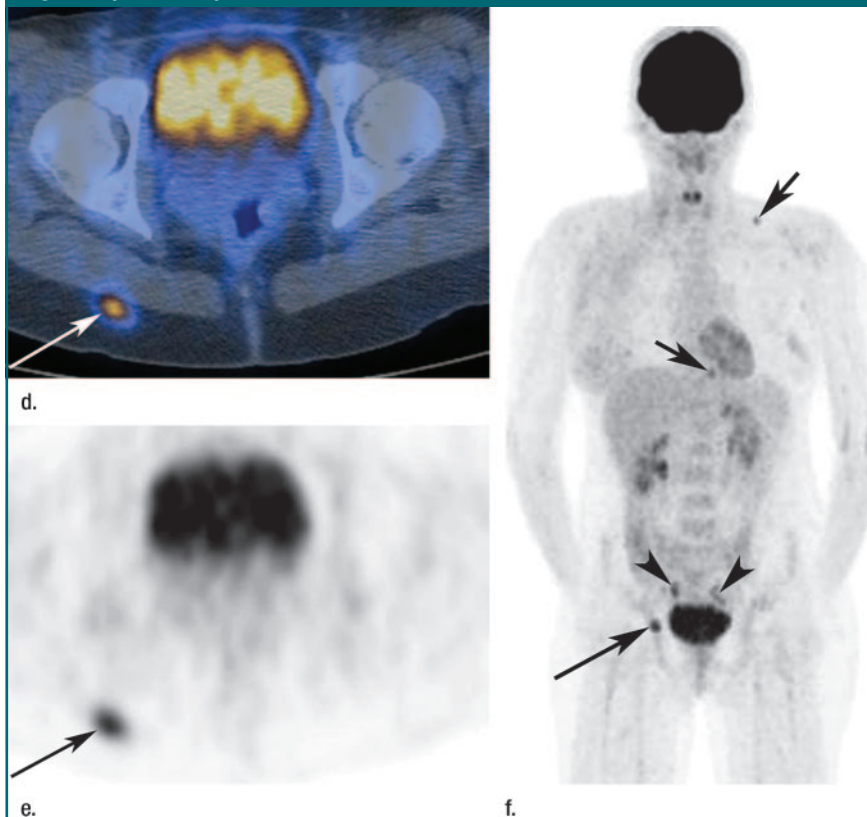


Figure 3 (continued): (d–f) Images obtained 3 months later. (d) Transverse PET/CT fused image shows growth of subcutaneous lesion (arrow). (e) Transverse PET image shows pathologic focal FDG uptake by lesion (arrow). (f) Coronal PET image shows, in addition to gluteal metastasis (long arrow), two new focal lesions: supraclavicular lymph node (upper short arrow) and paraaortal lymph node (lower short arrow). Note physiologic FDG uptake in ovaries (arrowheads). Patient died of bleeding brain metastasis 2 weeks after follow-up PET/CT scan.

The diagnosis of no metastases was confirmed with histologic findings (resection or biopsy of FDG-active lesions) in three of 71 patients and with cytologic findings in three patients. In four patients, MR imaging was performed to exclude metastases, and in the remaining 61 patients, PET/CT follow-up and/or clinical follow-up findings excluded metastases.

PET/CT Findings without Dedicated CT Readout

Without dedicated CT readout, metastases were detected in 48 patients, and no metastases were detected in 76 patients (Fig 1). According to the reference standard, there were 45 true-positive findings, three false-positive findings, 68 true-negative findings, and eight false-negative findings. The biopsy-proved false-positive lesions at PET/CT were pigmented villonodular synovitis of the knee, renal cyst, and inflammatory mediastinal lymph nodes.

PET/CT Findings with Dedicated CT Readout

With dedicated CT readout, metastases were detected in 56 patients, and no metastases were detected in 68 patients. According to the reference standard, there were 52 true-positive findings, four false-positive findings, 67 true-negative findings, and one false-negative finding.

Metastases were missed without dedicated CT readout in seven of 53 patients; these metastases were detected with dedicated CT readout (Table 1). In these seven cases, the lesions were either without FDG uptake (five patients) or had faint FDG uptake (two patients). All of these lesions were clearly visible and were suspicious for metastases on the coregistered CT images. The locations of metastases missed at PET included the lungs (four patients), the iliac lymph nodes, the gluteal subcutaneous tissue (Fig 2), and the psoas muscle. The mean size of these lesions was 11 mm (range, 4–40 mm). Metastases in the lungs (Fig 3) in four patients and in the gluteal soft tissue in one patient showed no visible FDG uptake. Metastases in lymph nodes and

Table 2

Overall Patient-based Accuracy of PET/CT and PET/CT plus Dedicated CT Interpretation

Parameter	PET/CT	PET/CT plus Dedicated CT Interpretation
Sensitivity	85 (45/53)	98 (52/53)
Specificity	96 (68/71)	94 (67/71)
Positive predictive value	94 (45/48)	93 (52/56)
Negative predictive value	89 (68/76)	99 (67/68)
Accuracy	91 (113/124)	96 (119/124)

Note.—Data are percentages of patients. Numbers used to calculate the percentages are in parentheses.

with histologic findings (resection or biopsy) in 17 patients and with cytologic findings (fine-needle aspiration) in 18 patients. The remaining 18 patients had no histologic or cytologic findings avail-

able, and PET/CT and clinical follow-up findings were used as the reference standard. Ten of 53 patients with metastases underwent MR imaging to confirm the metastases.

psoas muscle in two patients showed low FDG uptake (maximum SUV, 2.5 and 2.9), which was inconclusive at PET alone.

One case of a patient (with a true-negative finding without dedicated CT readout and a false-positive finding with dedicated CT readout) with noncalcified pulmonary nodules (<10 mm) without FDG uptake at CT was misinterpreted. Noncalcified and solid pulmonary nodules initially were considered malignant. However, PET/CT follow-up findings after 3 and 6 months ruled out metastases. The pulmonary nodules did not show any progression in size or FDG accumulation.

Without dedicated CT interpretation, there were eight false-negative cases. After dedicated CT interpretation, one false-negative case remained. This was a patient without any morphologically obvious lesion or uptake at PET/CT but with an increasing tumor marker value. MR imaging of the brain, performed 4 weeks later, depicted a brain metastasis, which was resected and histologically proved. In six of the 45 patients with metastases with increased FDG uptake, additional lung metastases without uptake (maximum SUV, <1.5) were detected with CT. In all of these patients, the intrapulmonary lesions were smaller than 10 mm and did not change the therapy.

Accuracy

Sensitivity, specificity, and accuracy of PET/CT for the depiction of metastases on the basis of 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 (Table 2). The diagnostic performance of PET/CT with dedicated CT interpretation was significantly superior to that of PET/CT alone ($P = .016$).

Discussion

The results suggest that the added CT information improves the overall accuracy of integrated PET/CT for depiction

of melanoma metastases not detected at PET. In 13% of patients with metastatic melanoma, metastases were detected only by using coregistered CT. Particularly, metastases in the lung with no FDG accumulation were diagnosed by using coregistered CT. However, the combined use of functional and morphologic information resulted in a slight decrease in the overall specificity of the PET/CT study. Metastases with no or only weak FDG accumulation can occur (22), which limits the overall accuracy of FDG PET imaging.

A known limitation of PET imaging is the identification of brain metastases and small melanoma metastases, especially in the lung. In a study by Gulec et al (5), all (29 of 29) lesions larger than 1 cm had FDG uptake, whereas only two (13%) of 15 lesions smaller than 1 cm were detected with PET alone. The usefulness of PET/CT imaging for the assessment of pulmonary metastases was demonstrated with 438 metastases of different primary malignancies, including melanoma (23). PET depicted only 39.7% of all lung metastases, and sensitivity in depicting metastases decreased rapidly if the nodule was smaller than 10 mm. Our results confirm these findings and demonstrate a high sensitivity in the detection of even small metastases by using nonenhanced CT images. In four patients, small metastases of the lung were detected only by using coregistered CT. The smallest lung metastasis was 4 mm. A careful interpretation of the lung windows of coregistered CT images is essential for the early detection of small lung metastases. The negative results in the lung at PET might be because of motion-related degradation of spatial resolution on PET images. Because emission time is rather long, breath-hold acquisition is not possible.

In our institution, an uptake time of 45–60 minutes and an emission scanning time of 3 minutes per bed position are routinely used for PET scanning. Our review of the literature did not result in data that indicated that a longer uptake time or longer emission scanning time increases the sensitivity of PET for the depiction of melanoma metastases. Lowe et al (24) performed dynamic PET

in pulmonary lesions and found no advantage in beginning emission data acquisition later than 50 minutes. In our study, the uptake time in the seven patients with metastases without FDG uptake did not differ from the uptake time of patients with metastases detected at PET.

From results of CT screening studies (25–27) in smokers, a high prevalence of noncalcified small pulmonary nodules (up to 51%) is known. Most of these nodules are benign. The guidelines for the management of small pulmonary nodules detected on CT scans are still controversial (28). However, the screening population is not comparable to patients with high-risk melanoma. Reduction of radiation exposure is important, especially in young patients. Therefore, we believe that a low-dose CT protocol with 40 mAs for integrated PET/CT imaging is a good compromise between low radiation exposure and sufficient sensitivity for detecting initial lung metastases (29). This protocol is used in many institutions (30–33). In our study, one case of a patient with noncalcified pulmonary nodules (<10 mm) with no FDG uptake at CT was misinterpreted. The pulmonary nodules initially were considered malignant. However, on follow-up PET/CT scans after 3 and 6 months, neither progression of the known lung nodules nor increased FDG accumulation in the lung was found. The follow-up findings excluded metastatic spread of melanoma. Thus, we recommend follow-up CT of the thorax after 3 months in every patient with melanoma for newly CT-depicted pulmonary nodules without FDG uptake.

Depiction of necrotic lymph node metastases is another limitation of PET imaging. In one patient, a 40-mm mass in the psoas muscle was detected by using integrated PET/CT, which showed in some parts mildly increased FDG accumulation (maximum SUV, 2.9). CT images revealed a large, centrally hypodense area most likely due to a central necrosis of the metastasis. The extent of necrosis in a metastasis can obviously reduce FDG uptake. Further, detectability of faint FDG uptake by me-

tastases can be difficult with PET alone if they are embedded in background tissue with relatively high FDG uptake.

To our knowledge, ours is the first study to describe the value of added CT morphologic information in patients with high-risk melanoma. A recently published study (34) compared FDG PET/CT imaging with PET alone and CT alone for N and M staging of 250 consecutive patients with melanoma. Similar to our results, the accuracy of PET/CT for M staging was significantly higher than that of PET alone and CT alone (98% vs 93% and 84%, respectively). A change of treatment according to PET/CT findings occurred in 121 (48.4%) patients. Interestingly, the authors pointed out that the most important advantage of PET/CT in comparison to the single modalities PET and CT was observed in the detection of visceral metastases.

The results of our study suggest that dedicated CT interpretation can overcome some false-negative findings at FDG PET. Our results are in accordance with those of other studies. The additional value of dedicated CT information with integrated PET/CT imaging in staging disease in patients with colorectal cancer has been demonstrated (35). As in our study, unenhanced CT images were used to localize lesions with FDG uptake at PET. In addition, dedicated CT information improved sensitivity, specificity, and accuracy in staging patients with colorectal cancer at integrated PET/CT imaging.

Our study had limitations. Histologic findings were not available for all patients because we could not ethically justify obtaining histologic proof of the diagnosis for all lesions identified. Nevertheless, we have done our best to establish the reference standard by using histologic confirmation of lesions without increased FDG uptake whenever possible (two of seven patients) or by using the confirmation of findings from other imaging modalities in addition to PET/CT findings and/or with PET/CT and clinical follow-up findings. In some patients, a follow-up period of only 6 months was achievable. In our experience, this time interval is sufficient, and

potentially missed melanoma metastases should be evident clinically or with imaging after this period.

The reviewers analyzed PET images and fused PET/CT images first for the detection of FDG-accumulating lesions and their anatomic locations at CT. CT images were then read for the detection of additional lesions with the knowledge of PET findings. This approach was chosen because it represents the standard practice of combined reading of PET and CT images. Experienced PET/CT readers review PET data first. If a lesion with a positive finding is found, the lesion can be localized on the fused image. For the detection of additional findings, the CT images should be examined separately (31). In this study, we did not compare CT images with PET images for the detection of melanoma metastases. We used CT images in addition to PET images for the detection of additional lesions.

On the basis of the cases of four patients in our study with false-positive findings at PET/CT, we strongly recommend histologic confirmation of suspected metastases. The results may affect the treatment of these patients. In our study, the results changed the overall patient-based sensitivity significantly.

In conclusion, our results indicate that a dedicated analysis of coregistered CT data significantly improves the performance of integrated PET/CT imaging for the depiction of metastases in patients with high-risk melanoma. In 13% of patients with metastatic disease, metastases were detected only by using coregistered CT data and not by using an increased accumulation of FDG at PET alone.

References

- Eigtved A, Andersson AP, Dahlstrom K, et al. Use of fluorine-18 fluorodeoxyglucose positron emission tomography in the detection of silent metastases from malignant melanoma. *Eur J Nucl Med* 2000;27:70–75.
- Gritters LS, Francis IR, Zasadny KR, Wahl RL. Initial assessment of positron emission tomography using 2-fluorine-18-fluoro-2-deoxy-D-glucose in the imaging of malignant melanoma. *J Nucl Med* 1993;34:1420–1427.
- Schwimmer J, Essner R, Patel A, et al. A review of the literature for whole-body FDG PET in the management of patients with melanoma. *Q J Nucl Med* 2000;44:153–167.
- Steinert HC, Huch Boni RA, Buck A, et al. Malignant melanoma: staging with whole-body positron emission tomography and 2-[F-18]-fluoro-2-deoxy-D-glucose. *Radiology* 1995;195:705–709.
- Gulec SA, Faries MB, Lee CC, et al. The role of fluorine-18 deoxyglucose positron emission tomography in the management of patients with metastatic melanoma: impact on surgical decision making. *Clin Nucl Med* 2003;28:961–965.
- Swetter SM, Carroll LA, Johnson DL, Segall GM. Positron emission tomography is superior to computed tomography for metastatic detection in melanoma patients. *Ann Surg Oncol* 2002;9:646–653.
- Engel H, Steinert H, Buck A, Berthold T, Huch Boni RA, von Schulthess GK. Whole-body PET: physiological and artifactual fluorodeoxyglucose accumulations. *J Nucl Med* 1996;37:441–446.
- Strauss LG. Fluorine-18 deoxyglucose and false-positive results: a major problem in the diagnostics of oncological patients. *Eur J Nucl Med* 1996;23:1409–1415.
- Cook GJ, Maisey MN, Fogelman I. Normal variants, artefacts and interpretative pitfalls in PET imaging with 18-fluoro-2-deoxyglucose and carbon-11 methionine. *Eur J Nucl Med* 1999;26:1363–1378.
- Cook GJ, Fogelman I, Maisey MN. Normal physiological and benign pathological variants of 18-fluoro-2-deoxyglucose positron emission tomography scanning: potential for error in interpretation. *Semin Nucl Med* 1996;26:308–314.
- Shreve PD, Anzai Y, Wahl RL. Pitfalls in oncologic diagnosis with FDG PET imaging: physiologic and benign variants. *RadioGraphics* 1999;19:61–77.
- Hafner J, Schmid MH, Kempf W, et al. Baseline staging in cutaneous malignant melanoma. *Br J Dermatol* 2004;150:677–686.
- Crippa F, Leutner M, Belli F, et al. Which kinds of lymph node metastases can FDG PET detect? a clinical study in melanoma. *J Nucl Med* 2000;41:1491–1494.
- Acland KM, Healy C, Calonje E, et al. Comparison of positron emission tomography scanning and sentinel node biopsy in the detection of micrometastases of primary cutaneous malignant melanoma. *J Clin Oncol* 2001;19:2674–2678.
- Wagner JD, Schauwecker DS, Davidson D, Wenck S, Jung SH, Hutchins G. FDG-PET sensitivity for melanoma lymph node metas-

- tases is dependent on tumor volume. *J Surg Oncol* 2001;77:237–242.
16. Rinne D, Baum RP, Hor G, Kaufmann R. Primary staging and follow-up of high risk melanoma patients with whole-body 18F-fluorodeoxyglucose positron emission tomography: results of a prospective study of 100 patients. *Cancer* 1998;82:1664–1671.
 17. Nguyen AT, Akhurst T, Larson SM, Coit DG, Brady MS. PET scanning with (18)F 2-fluoro-2-deoxy-D-glucose (FDG) in patients with melanoma: benefits and limitations. *Clin Positron Imaging* 1999;2:93–98.
 18. Hany TF, Gharehpapagh E, Kamel EM, Buck A, Himms-Hagen J, von Schulthess GK. Brown adipose tissue: a factor to consider in symmetrical tracer uptake in the neck and upper chest region. *Eur J Nucl Med Mol Imaging* 2002;29:1393–1398.
 19. Kamel EM, Goerres GW, Burger C, von Schulthess GK, Steinert HC. Recurrent laryngeal nerve palsy in patients with lung cancer: detection with PET-CT image fusion—report of six cases. *Radiology* 2002;224:153–156.
 20. Delbeke D, Coleman RE, Guiberteau MJ, et al. Procedure guideline for tumor imaging with 18F-FDG PET/CT 1.0. *J Nucl Med* 2006;47:885–895.
 21. Jury CS, McAllister EJ, MacKie RM. Rising levels of serum S100 protein precede other evidence of disease progression in patients with malignant melanoma. *Br J Dermatol* 2000;143:269–274.
 22. Aquino SL, Kuester LB, Muse VV, Halpern EF, Fischman AJ. Accuracy of transmission CT and FDG-PET in the detection of small pulmonary nodules with integrated PET/CT. *Eur J Nucl Med Mol Imaging* 2006;33:692–696.
 23. Reinhardt MJ, Wiethoelter N, Matthies A, et al. PET recognition of pulmonary metastases on PET/CT imaging: impact of attenuation-corrected and non-attenuation-corrected PET images. *Eur J Nucl Med Mol Imaging* 2006;33:134–139.
 24. Lowe VJ, DeLong DM, Hoffman JM, Coleman RE. Optimum scanning protocol for FDG-PET evaluation of pulmonary malignancy. *J Nucl Med* 1995;36:883–887.
 25. Henschke CI, Yankelevitz DF, Naidich DP, et al. CT screening for lung cancer: suspiciousness of nodules according to size on baseline scans. *Radiology* 2004;231:164–168.
 26. Aberle DR, Gamsu G, Henschke CI, Naidich DP, Swensen SJ. A consensus statement of the Society of Thoracic Radiology: screening for lung cancer with helical computed tomography. *J Thorac Imaging* 2001;16:65–68.
 27. Swensen SJ, Silverstein MD, Ilstrup DM, Schleck CD, Edell ES. The probability of malignancy in solitary pulmonary nodules: application to small radiologically indeterminate nodules. *Arch Intern Med* 1997;157:849–855.
 28. MacMahon H, Austin JH, Gamsu G, et al. Guidelines for management of small pulmonary nodules detected on CT scans: a statement from the Fleischner Society. *Radiology* 2005;237:395–400.
 29. Hany TF, Steinert HC, Goerres GW, Buck A, von Schulthess GK. PET diagnostic accuracy: improvement with in-line PET-CT system—initial results. *Radiology* 2002;225:575–581.
 30. Gearhart SL, Frassica D, Rosen R, Choti M, Schulick R, Wahl R. Improved staging with pretreatment positron emission tomography/computed tomography in low rectal cancer. *Ann Surg Oncol* 2006;13:397–404.
 31. Osman MM, Cohade C, Fishman EK, Wahl RL. Clinically significant incidental findings on the unenhanced CT portion of PET/CT studies: frequency in 250 patients. *J Nucl Med* 2005;46:1352–1355.
 32. Schoder H, Yeung HW, Larson SM. CT in PET/CT: essential features of interpretation. *J Nucl Med* 2005;46:1249–1251.
 33. Yeung HW, Schoder H, Smith A, Gonen M, Larson SM. Clinical value of combined positron emission tomography/computed tomography imaging in the interpretation of 2-deoxy-2-[F-18]fluoro-D-glucose-positron emission tomography studies in cancer patients. *Mol Imaging Biol* 2005;7:229–235.
 34. Reinhardt MJ, Joe AY, Jaeger U, et al. Diagnostic performance of whole body dual modality 18F-FDG PET/CT imaging for N- and M-staging of malignant melanoma: experience with 250 consecutive patients. *J Clin Oncol* 2006;24:1178–1187.
 35. Kamel IR, Cohade C, Neyman E, Fishman EK, Wahl RL. Incremental value of CT in PET/CT of patients with colorectal carcinoma. *Abdom Imaging* 2004;29:663–668.

Radiology 2007

This is your reprint order form or pro forma invoice

(Please keep a copy of this document for your records.)

Reprint order forms and purchase orders or prepayments must be received 72 hours after receipt of form either by mail or by fax at 410-820-9765. It is the policy of Cadmus Reprints to issue one invoice per order.

Please print clearly.

Author Name _____
Title of Article _____
Issue of Journal _____ Reprint # _____ Publication Date _____
Number of Pages _____ KB # _____ Symbol Radiology
Color in Article? Yes / No (Please Circle)

Please include the journal name and reprint number or manuscript number on your purchase order or other correspondence.

Order and Shipping Information

Reprint Costs (Please see page 2 of 2 for reprint costs/fees.)

_____ Number of reprints ordered \$ _____
_____ Number of color reprints ordered \$ _____
_____ Number of covers ordered \$ _____
Subtotal \$ _____
Taxes \$ _____

(Add appropriate sales tax for Virginia, Maryland, Pennsylvania, and the District of Columbia or Canadian GST to the reprints if your order is to be shipped to these locations.)

First address included, add \$32 for
each additional shipping address \$ _____

TOTAL \$ _____

Shipping Address (cannot ship to a P.O. Box) Please Print Clearly

Name _____
Institution _____
Street _____
City _____ State _____ Zip _____
Country _____
Quantity _____ Fax _____
Phone: Day _____ Evening _____
E-mail Address _____

Additional Shipping Address* (cannot ship to a P.O. Box)

Name _____
Institution _____
Street _____
City _____ State _____ Zip _____
Country _____
Quantity _____ Fax _____
Phone: Day _____ Evening _____
E-mail Address _____

* Add \$32 for each additional shipping address

Payment and Credit Card Details

Enclosed: Personal Check _____
Credit Card Payment Details _____

Checks must be paid in U.S. dollars and drawn on a U.S. Bank.

Credit Card: VISA Am. Exp. MasterCard
Card Number _____

Expiration Date _____

Signature: _____

Please send your order form and prepayment made payable to:

Cadmus Reprints

P.O. Box 751903

Charlotte, NC 28275-1903

Note: Do not send express packages to this location, PO Box.
FEIN #: 541274108

Signature _____

Date _____

Signature is required. By signing this form, the author agrees to accept the responsibility for the payment of reprints and/or all charges described in this document.

Invoice or Credit Card Information

Invoice Address Please Print Clearly

Please complete Invoice address as it appears on credit card statement

Name _____
Institution _____
Department _____
Street _____
City _____ State _____ Zip _____
Country _____
Phone _____ Fax _____
E-mail Address _____

Cadmus will process credit cards and Cadmus Journal Services will appear on the credit card statement.

If you don't mail your order form, you may fax it to 410-820-9765 with your credit card information.

Radiology 2007

Black and White Reprint Prices

Domestic (USA only)						
# of Pages	50	100	200	300	400	500
1-4	\$213	\$228	\$260	\$278	\$295	\$313
5-8	\$338	\$373	\$420	\$453	\$495	\$530
9-12	\$450	\$500	\$575	\$635	\$693	\$755
13-16	\$555	\$623	\$728	\$805	\$888	\$965
17-20	\$673	\$753	\$883	\$990	\$1,085	\$1,185
21-24	\$785	\$880	\$1,040	\$1,165	\$1,285	\$1,413
25-28	\$895	\$1,010	\$1,208	\$1,350	\$1,498	\$1,638
29-32	\$1,008	\$1,143	\$1,363	\$1,525	\$1,698	\$1,865
Covers	\$95	\$118	\$218	\$320	\$428	\$530

Color Reprint Prices

Domestic (USA only)						
# of Pages	50	100	200	300	400	500
1-4	\$218	\$233	\$343	\$460	\$579	\$697
5-8	\$343	\$388	\$584	\$825	\$1,069	\$1,311
9-12	\$471	\$503	\$828	\$1,196	\$1,563	\$1,935
13-16	\$601	\$633	\$1,073	\$1,562	\$2,058	\$2,547
17-20	\$738	\$767	\$1,319	\$1,940	\$2,550	\$3,164
21-24	\$872	\$899	\$1,564	\$2,308	\$3,045	\$3,790
25-28	\$1,004	\$1,035	\$1,820	\$2,678	\$3,545	\$4,403
29-32	\$1,140	\$1,173	\$2,063	\$3,048	\$4,040	\$5,028
Covers	\$95	\$118	\$218	\$320	\$428	\$530

International (includes Canada and Mexico)						
# of Pages	50	100	200	300	400	500
1-4	\$263	\$275	\$330	\$385	\$430	\$485
5-8	\$415	\$443	\$555	\$650	\$753	\$850
9-12	\$563	\$608	\$773	\$930	\$1,070	\$1,228
13-16	\$698	\$760	\$988	\$1,185	\$1,388	\$1,585
17-20	\$848	\$925	\$1,203	\$1,463	\$1,705	\$1,950
21-24	\$985	\$1,080	\$1,420	\$1,725	\$2,025	\$2,325
25-28	\$1,135	\$1,248	\$1,640	\$1,990	\$2,350	\$2,698
29-32	\$1,273	\$1,403	\$1,863	\$2,265	\$2,673	\$3,075
Covers	\$148	\$168	\$308	\$463	\$615	\$768

International (includes Canada and Mexico)						
# of Pages	50	100	200	300	400	500
1-4	\$268	\$280	\$412	\$568	\$715	\$871
5-8	\$419	\$457	\$720	\$1,022	\$1,328	\$1,633
9-12	\$583	\$610	\$1,025	\$1,492	\$1,941	\$2,407
13-16	\$742	\$770	\$1,333	\$1,943	\$2,556	\$3,167
17-20	\$913	\$941	\$1,641	\$2,412	\$3,169	\$3,929
21-24	\$1,072	\$1,100	\$1,946	\$2,867	\$3,785	\$4,703
25-28	\$1,246	\$1,274	\$2,254	\$3,318	\$4,398	\$5,463
29-32	\$1,405	\$1,433	\$2,561	\$3,788	\$5,014	\$6,237
Covers	\$148	\$168	\$308	\$463	\$615	\$768

Minimum order is 50 copies. For orders larger than 500 copies, please consult Cadmus Reprints at 800-407-9190.

Reprint Cover

Cover prices are listed above. The cover will include the publication title, article title, and author name in black.

Shipping

Shipping costs are included in the reprint prices. Domestic orders are shipped via UPS Ground service. Foreign orders are shipped via a proof of delivery air service.

Multiple Shipments

Orders can be shipped to more than one location. Please be aware that it will cost \$32 for each additional location.

Delivery

Your order will be shipped within 2 weeks of the journal print date. Allow extra time for delivery.

Tax Due

Residents of Virginia, Maryland, Pennsylvania, and the District of Columbia are required to add the appropriate sales tax to each reprint order. For orders shipped to Canada, please add 7% Canadian GST unless exemption is claimed.

Ordering

Reprint order forms and purchase order or prepayment is required to process your order. Please reference journal name and reprint number or manuscript number on any correspondence. You may use the reverse side of this form as a proforma invoice. Please return your order form and prepayment to:

Cadmus Reprints

P.O. Box 751903
Charlotte, NC 28275-1903

Note: Do not send express packages to this location, PO Box. FEIN #: 541274108

Please direct all inquiries to:

Rose A. Baynard
800-407-9190 (toll free number)
410-819-3966 (direct number)
410-820-9765 (FAX number)
baynardr@cadmus.com (e-mail)

Reprint Order Forms and purchase order or prepayments must be received 72 hours after receipt of form.