Which Kinds of Lymph Node Metastases Can FDG PET Detect? A Clinical Study in Melanoma

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The purposes of this study were to establish the diagnostic accuracy of FDG PET for lymph node metastases and to determine the smallest detectable volume of disease. **Methods:** Using FDG PET, we preoperatively studied 56 lymph node basins in 38 patients with a clinical or instrumental diagnosis of lymph node metastases from melanoma. All lymph node basins underwent node dissection. The FDG PET results were compared with the postoperative histopathology results. PET images were obtained using a GE 4096 WB scanner, after injection of a mean activity of 496 MBq (range, 366–699 MBq) of FDG. **Results:** The efficacy of FDG PET in the diagnosis of involved lymph node basins was good. Sensitivity was 95% (35/37); specificity, 84% (16/19); accuracy, 91% (51/56); positive predictive value, 92% (35/38); and negative predicative value, 89% (16/18). Metastases were shown histologically in 114 of 647 surgically removed lymph nodes. FDG PET detected 100% of metastases ≥ 10 mm, 83% of metastases 6–10 mm, and 23% of metastases ≤ 5 mm. Moreover, FDG PET had high sensitivity (≥ 93%) only for metastases with more than 50% lymph node involvement or with capsular infiltration. **Conclusion:** Our study shows that FDG PET has a reasonable sensitivity and specificity for detecting the presence or absence of lymph node metastases in patients with melanoma. However, even if able to detect small volumes of subclinical macroscopic disease, FDG PET cannot detect subclinical microscopic disease with acceptable sensitivity. The specificity of FDG PET is good, but some false-positive results may occur.

Key Words: melanoma; lymph node metastases; FDG PET

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Accurate detection of nodal metastases is a key step in the evaluation of patients with malignant melanoma (*1*). Conventional noninvasive diagnostic modalities such as sonography, CT, and MRI are sensitive to morphologic changes in lymph nodes, but normally sized lymph nodes may contain metastatic cells, and enlarged lymph nodes are not necessarily malignant (*2*). Among the nuclear medicine techniques for the detection of lymph node metastases is radiocolloid lymphoscintigraphy, which may be combined with intraoperative probe detection of the sentinel node (*3,4*). FDG PET is a noninvasive high-technology approach that is currently being proposed for the detection of nodal metastases. Melanoma avidly accumulates FDG with a high tumor-to-background ratio, allowing excellent clinical imaging of lesions by means of PET (*5*). In patients with melanoma, FDG PET has also been shown to be sensitive for assessing metastases in normal-sized lymph nodes (*6,7*) and for detecting occult distant metastases (*8–16*).

The purposes of the study were to establish the accuracy of FDG PET in the diagnosis of lymph node metastases and to determine the smallest volume of disease detectable with FDG PET. The detectability of lymph node metastases depends on the performance of the diagnostic instrument, which for this study was a scanner considered representative of an average PET scanner in the field today—the GE 4096 Plus (Scanditronix-GE PET Systems, Uppsala, Sweden).

MATERIALS AND METHODS

Patients

We studied 38 patients (age range, 19–75 y; mean age, 47 y) who had previously undergone surgery for cutaneous melanoma and had a current clinical diagnosis (through physical examination, sonography, or CT) of nodal metastases in at least 1 lymph node basin. The total number of lymph node basins under investigation was 56, with the following distribution: 2 parotid, 7 cervical, 12 axillary, 13 pelvic (external or common iliac), 21 inguinal, and 1 popliteal. All these sites underwent node dissection.

Histopathology

Surgical samples were fixed with 10% buffered formalin and embedded in paraffin. One hematoxylin-eosin–stained section of each lymph node was examined. The number and size of both normal and metastatic lymph nodes were evaluated. Size was assessed by histologic examination using a dedicated instrument (Laborlux D; Leitz, Oberkochen, Germany). In addition, the metastases were classified as massive (nodal involvement > 75%), subtotal (50%–75%), or partial (<50%). Metastases confined to the lymph sinuses were classified as embolic or pluriembolic, and capsular infiltration was evaluated.

FDG PET

PET studies were performed 1–3 d before surgery. Before the PET examination, patients fasted for at least 5 h. The mean blood glucose level measured before PET was 84 mg/dL (range, 64–108

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mg/dL). The patients were positioned with the arms along the body during the examination. A mean activity of 496 MBq (range, 366–699 MBq) FDG was injected. For axillary or inguinal lymph node examinations, FDG was injected into the arm contralateral to the site of the suspected lesion.

PET images were obtained with the GE 4096 Plus scanner, which has an axial field of view of approximately 10 cm and produces 15 simultaneous contiguous axial slices with a slice thickness of 6.5 mm. Positioning of the lymph node regions in the field of view was checked by a built-in laser guide. Before FDG injection, up to 3 10-min transmission scans (according to the number of lymph node regions under evaluation) were acquired with a rotating ^{68}Ge rod source for correction of attenuation of the body regions. Forty-five to sixty minutes after FDG injection, 20-min static emission images were acquired at the transmission positions. Repositioning of the patient was facilitated by the use of skin markers before the transmission scan.

The PET results were analyzed on attenuation-corrected emission images, which were reconstructed by filtered backprojection using 2-mm pixels in a 256 × 256 matrix and a 4.2-mm Hanning filter. The average reconstructed transaxial and axial resolutions were 7.3 and 5.3 mm, respectively, full width at half maximum, corresponding to a volumetric resolution of 0.28 cm^3. This reconstructed resolution was measured using needle sources of different sizes placed in a phantom filled with water. This parameter should be considered the reference resolution of our clinical working conditions.

All PET images were initially evaluated without knowledge of the histopathologic findings at surgery, and any lymph node basins having at least 1 focus of FDG uptake were considered positive for melanoma. The interpretation was based on visual evaluation of uptake relative to the surrounding background and required the consensus of 2 nuclear medicine physicians with wide experience in PET examinations. Subsequently, the PET results were compared with the histopathologic results. All PET images and histopathologic samples were then retrospectively reanalyzed to compare, for each lymph node basin, the number of foci of FDG uptake with the number and type of metastases found by histopathology.

RESULTS

Of the 56 lymph node basins, histology found lymph node metastases in 37 and PET found at least 1 focus of FDG uptake in 35 (Fig. 1). FDG PET findings were correctly negative for 16 of the 19 lymph node basins with negative postoperative histology findings (Table 1). The 2 false-negative FDG PET results showed very limited metastatic involvement at histopathology, with only 1 embolic metastasis of 0.09 mm in 1 inguinal lymph node (patient 8) and pluriembolic metastases (the largest measuring 0.04 mm) in 1 pelvic lymph node (patient 10). FDG PET gave false-positive results for 3 patients in whom histopathology findings were negative for 5 removed lymph nodes. We found no histopathologic features (e.g., lymph node hyperplasia) to explain the false-positive uptake observed in 5 nodes. Conversely, FDG PET results were correctly negative for 16 patients who had a total of 528 removed lymph nodes with negative histopathology findings. The mean size of the smaller negative lymph nodes removed in each lymph node basin was 8.3 mm, with a range of 1–35 mm.

To study the potential of FDG PET in the detection of metastases, we compared the number of foci of FDG uptake in each lymph node basin with the corresponding number and type of metastases found by histology. A total of 647 lymph nodes were surgically removed, and metastases were histologically found in 114 of them. The metastatic lymph nodes had a mean size of 19 mm (range, 1–90 mm) and contained metastases with a mean size of 11.4 mm (range, 0.3–45 mm). Table 2 summarizes the FDG PET results according to metastasis size. FDG PET revealed 100% of the metastases > 10 mm, 83% of the metastases ranging in size from 6 to 10 mm, and 23% of the metastases ≤ 5 mm. FDG PET showed a high sensitivity (93%–100%) in the detection of metastatic nodes with tumor involvement of more than 50% or capsular infiltration (Table 3).

TABLE 1
Overall Diagnostic Performance

Index	No. of metastatic basins found	
	Histologically	By FDG PET (%)
Sensitivity	37	35 (95)
Specificity	19	16 (84)
Accuracy	56	51 (91)
Positive predictive value	38	35 (92)
Negative predictive value	18	16 (89)

FIGURE 1. Coronal PET slice shows abnormal FDG uptake (arrows) on left side of neck in patient with bilateral palpable cervical lymph nodes and positive test for toxoplasmosis. Patient underwent bilateral dissection of cervical lymph nodes, and histology showed metastases only in left nodes.

TABLE 2
Size of Metastases

Size of metastases (mm)	No. of metastases found	
	Histologically	By FDG PET (%)
≤5	44	10 (23)
6–10	29	24 (83)
11–15	13	13 (100)
16–20	15	15 (100)
21–25	9	9 (100)
>25	4	4 (100)
Total	114	75 (66)

TABLE 3
Lymph Node Involvement

Type of metastases	No. of lymph nodes involved	
	Histologically	By FDG PET (%)
Embolic or pluriembolic*	11	3 (27)
Partial	48	18 (37.5)
Subtotal	15	14 (93)
Massive	21	21 (100)
Perinodal infiltration	19	19 (100)
Total	114	75 (66)

*Based on size of largest metastasis.

DISCUSSION

A common nuclear medicine technique that has been used for the diagnosis of metastatic lymph nodes is radiocolloid lymphoscintigraphy (*17*). Clinical evidence shows that lymphoscintigraphy associated with intraoperative γ-probe detection of the sentinel node improves diagnostic accuracy by allowing insight into the existence and topography of lymph node involvement (*18,19*). However, that technique is relatively demanding, involves minimally invasive procedures, and can be applied only in association with surgery. ^{201}Tl scintigraphy was also recently proposed as a way to detect melanoma metastases (*20*). This technique, when used in patients with metastatic melanoma confirmed by histology, showed a diagnostic sensitivity of 78% (28/36); 8 patients had false-negative findings, and 5 had lymph nodes larger than 1.5 cm.

FDG PET is a noninvasive technique that can be applied at any stage of disease management, is highly standardized, and has had an accuracy of more than 90% in the detection of lymph node metastases, including cases in which the nodes were of normal size (*6,7*). Blessing et al. (*21*) reported less encouraging results, with comparable sensitivity and specificity for FDG PET and sonography (74% and 95%, respectively). Such studies are usually flawed by the heterogeneity of patient characteristics and the methods used to determine the real nodal status. In fact, histology has not always been used as the gold standard; FDG PET has been compared with conventional imaging techniques or with clinical follow-up. Therefore, the true false-positive and false-negative rates for FDG PET of lymph node metastases are often not well defined, and the lower limit of resolution of the technique for detection of disease in lymph nodes has not been determined.

We evaluated, by comparison with postoperative histologic findings, the ability of FDG PET to detect metastases in lymph node basins in which metastases were diagnosed clinically (through palpable nodes) or with instruments (through positive sonography or CT findings). Our purpose was to establish the diagnostic accuracy of FDG PET and to determine the smallest detectable volume of disease. For the first issue, we studied the number of nodal basins with disease; for the second, we compared the number of foci of FDG uptake with the number and type of metastases found by histopathology in each lymph node basin.

In our series of patients, FDG PET showed good accuracy (91%). Two false-negative results occurred in 2 lymph node basins with very limited metastatic involvement (embolic or pluriembolic involvement of 1 lymph node only). False-positive FDG PET findings have been reported in reactive lymph nodes and areas of infection (*22*). In our study, despite exclusion of patients who, through clinical examination, sonography, or CT, were found to be free of regional lymphadenopathy, we obtained 3 false-positive regional FDG PET results without any clinical or histologic explanation. However, we had true-negative FDG PET studies in 16 lymph node basins with a total of 528 removed nodes.

In determining the smallest volume of disease detectable by FDG PET, our approach has a limitation in that the real number of foci of uptake may be underestimated on images with several contiguous foci. However, this problem was present in only 5 (14%) of the 37 lymph node basins with metastases documented by histopathology. The results of the comparison between FDG PET and histopathology showed that FDG PET had a good sensitivity (83%) for metastases ≥ 5 mm and a better sensitivity (100%) for metastases ≥ 10 mm. By contrast, the sensitivity was poor (23%) for metastases ≤ 5 mm. Considering the resolution of our scanner, we were even pleasantly surprised by these results (Fig. 2). In determining the extent of metastatic infiltration into lymph nodes, FDG PET showed good sensitivity (≥ 93%) for metastases with an infiltration of more than 50% or capsular infiltration.

CONCLUSION

Our study shows that FDG PET is a diagnostic modality with an interesting sensitivity and specificity for detecting lymph node metastases in patients with melanoma. However, even if FDG PET can detect small subclinical macroscopic lesions, it has no acceptable sensitivity in the detection of subclinical microscopic disease. Our results encourage the use of FDG PET in melanoma patients with doubtful lymph node involvement. The limitations in diagnostic sensitivity for very small lesions can be partially overcome using later generation scanners. The resolution of our GE 4096 Plus scanner in air with a ramp filter is 5.9

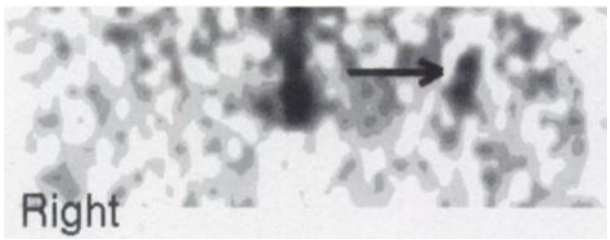

FIGURE 2. Coronal PET slice shows abnormal FDG uptake (arrow) on left side of inguinal region. Palpable 24-mm lymph node was removed and showed pluriembolic metastases (largest measuring 0.9 mm).

mm, slightly lower than that at the center of the field of view for the more recent Advance scanner (5.0-mm resolution; General Electric Medical Systems) and HR Plus scanner (4.5-mm resolution; Siemens Medical Systems, Inc., Hoffman Estates, IL) (*23–25*). Therefore, dedicated PET scanners with a higher resolution than ours may increase the potential to detect metastatic lymph node disease in patients with melanoma.

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