MOLECULAR IMAGING AND BIOLOGY

© Academy of Molecular Imaging 2005
Published Online: 23 July 2005

Mol Imaging Biol (2005) 7:304-308
DOI: 10.1007/s11307-005-0002-7

RESEARCH ARTICLE

Impact of 2-Deoxy-2[F-18]Fluoro-D-Glucose Positron Emission Tomography on the Management of Patients with Advanced Melanoma

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Abstract

Purpose: Accurate staging of patients with melanoma is vital to guide appropriate treatment. 2-Deoxy-2-[F-18]fluoro-D-glucose (FDG)-positron emission tomography (PET) has been reported to be a sensitive and specific technique for the staging of advanced melanoma, however, few studies provide information regarding its impact on patient management.

Procedures: We retrospectively reviewed the FDG-PET scan results of 92 patients with melanoma who had 126 scans performed over a six-year period. These patients were seen at the specialist melanoma clinic at our Institution, and 84 patients (92%) had stage III or IV disease. FDG-PET scan results were correlated with computed tomography (CT) scans and other imaging when available, and with clinical follow-up of a minimum of three to six months. The impact of FDG-PET scans on patient management was also assessed.

Results: On a lesion-by-lesion analysis, FDG-PET had a sensitivity of 92%, a specificity of 88%, and an accuracy of 91%. FDG-PET correctly affected the clinical decision-making process in 40 of 126 patient studies (32%), particularly assisting in the selection of patients for surgery.

Conclusion: FDG-PET has an important role in guiding the management of patients with advanced melanoma, particularly when surgery is contemplated.

Key words: Melanoma, Positron emission tomography, Clinical management

Introduction

Accurate disease staging of melanoma is important to guide the use of potentially curative surgery or radiotherapy in patients with stage III or IV disease. Conventional staging investigations have limited sensitivity and specificity for the detection of melanoma metastases [1]. The reported accuracy of 2-deoxy-2-[F-18]fluoro-D-glucose (FDG)-positron emission tomography (PET) in detecting melanoma metastases ranges from 80% to 100%, and FDG-PET has particular sensitivity and specificity in the detection of metastases in soft tissue and lymph nodes that are not assessable by clinical examination and have not been demonstrated by computed tomography (CT) [2–6]. However, FDG-PET was found to be an insensitive indicator of microscopic lymph node metastases compared with sentinel lymph node biopsy in patients with early stage disease because of the small tumor volumes involved [7, 8]. Information on the direct impact of FDG-PET on the clinical management of patients with melanoma is relatively limited. Retrospective studies of patients with predominantly stage III and IV disease suggested that the FDG-PET result influences the management of 22–49% of patients [4, 9, 10]. In two prospective studies, the FDG-PET result

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changed patient management 15% of the time in one series of 95 patients with stage III disease, and contributed to a change in therapy in 40% of a second series of 58 patients with suspected recurrent melanoma [11, 12]. We undertook to examine the accuracy of FDG-PET in the staging of patients with melanoma at our institution and to determine the impact of FDG-PET on the clinical management of patients with this disease.

Methods

Patients

Between February 1994 and November 2000, 278 FDG-PET scans were performed on patients with melanoma at our institution. Of this group, 92 patients who had 126 scans were selected for retrospective review as they had an adequate period of clinical follow-up, which was defined as three months, unless death from progressive metastatic melanoma occurred prior to this.

FDG-PET Scans

All PET images were acquired using a Siemens ECAT 951/31R whole body PET scanner (CTI PET Systems, Knoxville, TN, USA). This scanner produces a 31-slice image per bed position, with a slice thickness of 3.37 mm, pixel size of 2.26 × 2.26 mm, with an effective in-plane spatial resolution of 6.5 mm (full-width half-maximum). FDG was synthesized using fluorine-18 produced by an in-house medical 10 MeV cyclotron (Ion Beam Applications, Belgium). Samples of FDG were subjected to radiopharmaceutical quality control as specified by US Pharmacopoeia.

All patients fasted for four hours before the FDG-PET study and any patient with elevated blood glucose levels (i.e., >12–15 mmol/l) did proceed with an FDG-PET scan. Emission scans (eight to 10 bed positions, 7–9 min per position) were acquired 45 min after intravenous administration of 370 MBq (10 mCi) of FDG (normalized to 70 kg body weight). The majority of patients had whole-body scans acquired without attenuation correction, which did not involve routine brain imaging as part of the acquisition protocol. Only four patients had a focused FDG-PET scan of the brain performed. All images were reconstructed using a standard filtered back projection algorithm (Hamming filter with a cutoff frequency of 0.3 cycles/pixel).

FDG-PET Image Analysis

FDG-PET scans were reported as part of routine diagnostic imaging performed in the nuclear medicine department of the hospital. Reconstructed FDG-PET images were qualitatively analyzed by experienced PET nuclear physicians who had access to the patient's clinical history and CT scans when these were available for correlation. The FDG uptake within the lesion relative to comparable normal tissue was the basis of analysis. Images were viewed on a computer workstation with the capability of multiple color scales and image orientations, including 3D rotational whole-body views. The reporting physicians paid special attention to the intensity of FDG accumulation within each lesion relative to normal background, the relative distribution of FDG within the defined lesion and the general extent of the regions of abnormal FDG uptake. Abnormal foci of FDG uptake were classified as being involved by melanoma if reported as definitely, probably, or possibly involved, but not if reported as being equivocal.

FDG-PET reports were compared with clinical examination findings over the follow-up period in which patients were followed by medical oncologists in the melanoma clinic at our institution. FDG-PET reports were also compared with CT reports as well as a limited number of plain X-rays, bone scans, and magnetic resonance imaging (MRI) scan reports if these were performed within six weeks of the FDG-PET scan. The conventional diagnostic imaging tests were all performed and reported as part of a standard assessment under normal clinical circumstances. In most cases, this consisted of a CT scan of the chest, abdomen, and pelvis with or without a CT scan of the brain. In our Melanoma Unit all patients with stage III and stage IV melanoma have a cerebral CT scan performed as part of routine staging. A CT scan was performed within six weeks of the FDG-PET for 116 of the 126 scans. False positive and negative FDG-PET scans were reviewed by a single reviewer (AMS) to verify the FDG-PET result. Eight FDG-PET reports were amended after review.

Analysis of FDG-PET Results

FDG-PET results were described on a lesion by lesion basis as follows:

True positive (TP): if the lesion seen on FDG-PET was shown to be metastatic melanoma or another tumor (benign or malignant) by standard imaging, clinical examination, or tissue biopsy during the three-month follow-up period.
True negative (TN): if the lesion was seen on standard imaging, negative on FDG-PET, and shown to be neither a benign or a malignant tumor by biopsy, serial imaging, or clinical examination over the three-month follow-up period.
False positive (FP): if the lesion was seen on FDG-PET and reported to be a benign or malignant tumor but was not apparent on targeted imaging performed at a minimum of three months post-FDG-PET.
False negative (FN): if a benign or malignant tumor was not identified by FDG-PET but was identified on standard imaging performed ≤ six weeks before or after FDG-PET (with growth seen during serial assessments or biopsy) or apparent on clinical examination within two months of the FDG-PET scan.
Indeterminate (I): if follow-up was inconclusive such that the nature of a lesion identified by FDG-PET or standard imaging was unable to be satisfactorily identified at the end of the follow-up period.

One lesion was defined per organ. For example, the detection of multiple liver lesions or subcutaneous deposits was recorded as one disease site/lesion each. Where there was discordance within an organ, such as one lung metastasis detected and another missed by FDG-PET, one lesion was deemed true positive and one lesion deemed false negative. This definition was adopted as several patients had multiple lesions of skin, soft tissues, liver, or lungs.

Analysis of CT Scan Results

Standard imaging and CT scan results were not independently analyzed as some CT scans were not performed within six weeks of the FDG-PET scans and some scans were not available for

retrospective review. Lesions were identified from the standard reports, with the criteria of one lesion per organ (as defined for FDG-PET above).

True positive and true negative CT results were defined by the presence or absence of lesions on CT scans. Apparent CT false positive and false negative results were defined as:

False positive: if the lesion was reported to be present on CT but not on FDG-PET, and neither a benign or malignant tumor was identified on tissue biopsy, serial CT, alternative imaging (MRI, ultrasound), or clinical examination over the follow-up period.
False negative: If the lesion was seen on FDG-PET but not reported to be present on CT performed within six weeks of FDG-PET, and was confirmed to be a benign or malignant tumor by tissue biopsy, later detection by CT, or clinical examination within two months of the CT scan.

Impact of FDG-PET on Patient Management

Only those patients with adequate clinical follow-up were included in this study. This was defined as a three-month minimum follow-up unless patient death occurred prior to three months because of progressive metastatic melanoma. All 92 patient records were reviewed by a single reviewer (MTH) to determine the impact of the FDG-PET scan result on patient management. A rigorous approach to impact on clinical management was taken, such that the FDG-PET scan was deemed not to have affected decision making if it confirmed the CT or clinical impression of multiple metastatic sites even if showing extra disease sites (unless the site was of particular clinical significance), or if it confirmed the CT and clinical impression of no active disease.

Results

Patients

Of the 92 patients, 60 were male. The age range was 21–77 years with a median of 54 years. As determined clinically and by conventional imaging, three patients had stage I disease, five had stage II disease, 29 stage III disease, and 55 stage IV disease (92% of patients had stage III or IV disease).

The FDG-PET scans were requested by medical oncologists in our melanoma clinic. The indications for FDG-PET scanning were for staging for 107 scans, and assessment of response to investigational treatment (a monoclonal antibody) for 19 scans [13]. A total of 126 FDG-PET scans were performed in 92 patients. The median number of FDG-PET scans was one with a range of 1–7.

Clinical follow-up was obtained for a six-month minimum after 92 scans, a three- to six-month follow-up after 26 scans (15 due to patient deaths), and less than three months follow-up after eight scans (all due to patient deaths).

FDG-PET Scan Results

The FDG-PET results by individual lesions were: TP 222, FP 2, TN 15, FN 20, and Indeterminate 31. False positives were attributable to a retrosternal goitre and a case of mediastinal sarcoidosis (see Table 1). Analysis of FDG-PET results showed no evidence of false positive results in scans performed after investigational treatment. False negative sites included: lung 6, liver 8, brain 2, skin 3, and orbit 1. Fifteen false negative lesions were less than 1 cm in size and five lesions were 1, 1.5, 1.8, 2, and 4 cm each. No patients with false negative FDG-PET scans had received chemotherapy or radiotherapy within six weeks of the FDG-PET scan. Indeterminate lesions were excluded from subsequent analysis.

Other tumors identified by FDG-PET ($n = 7$) included a case each of non-Hodgkin's lymphoma, multiple myeloma, bowel cancer, breast cancer, pancreatic cancer, thyroid adenoma, and a neurofibroma. The overall FDG-PET sensitivity was 92%, specificity 88%, and accuracy 91%.

CT Scan Results

Fourteen CT false positive sites were identified, and included: liver 5, brain 2, mediastinal lymph nodes 3, ovary 2, lung 1, and axillary lymph node 1. The two false positive brain lesions were confirmed as small infarcts on MRI. Eighteen CT false negative sites were identified, and included: pancreas 3, liver 1, small bowel/omentum 4, abdominal nodes 3, skin nodules 4, adrenal 1, axillary nodes 1, and groin nodes 1.

Impact of FDG-PET on Patient Management

FDG-PET affected the clinical decision making process after 43 out of 126 patient studies (34%). This influence was correct in 40 out of 43 of these clinical decisions (32% of total patient studies) as determined by observation during the period of clinical follow-up. The principal impact of FDG-PET was in determining suitability of patients for surgery (Figs. 1 and 2). The cases where FDG-PET scan result correctly impacted on the clinical management of patients are summarized in Table 2. The FDG-PET scan

Table 1. False positives (FP) and false negatives (FN) FDG-PET and CT scans

FDG-PET FP ($n = 2$)	FDG-PET FN ($n = 20$)	CT FP ($n = 14$)	CT FN ($n = 18$)
Retrosternal goitre (1)	Lung (6)	Liver (5)	Pancreas (3)
Mediastinal sarcoidosis (1)	Liver (8)	Brain (2)	Liver (1)
	Brain (2)	Mediastinal nodes (3)	Small bowel/ omentum (4)
	Skin (3)	Ovary (2)	Abdominal nodes (3)
	Orbit (1)	Lung (1)	Skin (4)
		Axillary nodes (1)	Adrenal gland (1)
			Axillary nodes (1)
			Groin nodes (1)

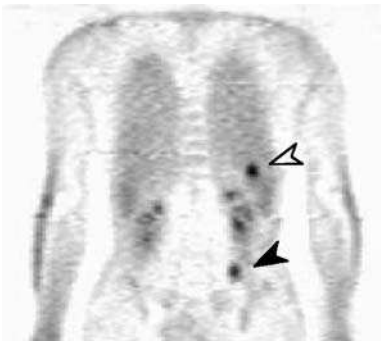


Fig. 1. Coronal FDG-PET image of a patient with a known melanoma lesion in the left lung base. FDG-PET showed the left lung lesion (open arrow), and in addition an unsuspected metastasis in the left side of the abdomen (black arrow) was also identified and subsequently confirmed histologically to be a small bowel metastasis. Surgery for resection of the left lung lesion did not proceed on the basis of the FDG-PET scan result.

result did not affect the clinical decision making process for any patient with stage I or II disease.

The three scans where FDG-PET incorrectly guided management included a case where cancer was thought to be localized to lymph nodes in a man who presented a few weeks after the scan with clinical symptoms from multiple small (<0.5 cm) brain metastases (shown by MRI but not by FDG-PET). These developed before we could proceed to node dissection. In two other cases, FDG-PET falsely reassured that lesions of uncertain significance were not malignant; however, subsequent follow-up identified progressive disease at these sites. In neither case was patient management adversely affected.

Surgery undertaken after FDG-PET scanning in 22 patients included neurosurgery (n = 1), major abdominal surgery (n = 5) (which included hepatic resections, pancreatectomy, porta hepatis, and a small bowel resection), as well as lymph node dissections of different sites (n = 16). Surgery was performed on 12 patients with stage III disease and nine patients with stage IV disease; one other patient with a past history of melanoma had multiple myeloma discovered on pathology following surgery to remove what was thought to have been a metastatic deposit in a rib. Six patients progressed within six months of the surgery and four of these subsequently underwent resections for stage IV disease.

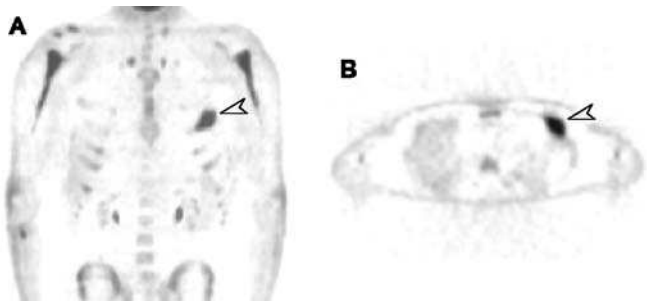


Fig. 2. (**A**) 3D coronal FDG-PET image of a patient with a history of melanoma and a new solitary rib lesion believed to be a metastasis. FDG-PET showed increased uptake in a left anterior rib (arrow) [also seen in (**B**), transaxial image], but with no other focal metastases identified. Increased FDG uptake in humeri, ribs and pelvis was also evident. On the basis of the FDG-PET scan result, the rib lesion was resected and found to be a plasmacytoma. The patient subsequently received treatment for multiple myeloma.

Table 2. Patients where FDG-PET had direct impact on the clinical management of patients

Scan result	Number of patients	Clinical management outcome (n)
Confirmed limited disease	27	Surgery (22) Radiotherapy (2) Observation (3)
Confirmed metastatic disease	4	Surgery cancelled (4)
Confirmed nonmalignant lesion	4	No treatment or further investigation required (4)
Confirmed malignant lesion	3	Palliative chemotherapy (1) or palliative radiotherapy (2)
New primary identified requiring treatment	1	Surgery immediately performed (1)
Identified tumor response to therapy	1	Treatment continued (1)

Discussion

Our results show the accuracy of FDG-PET in the staging of advanced melanoma and confirm the conclusions of earlier studies. Our study also represents the largest series of patients with stage IV melanoma studied with FDG-PET where rigorous criteria for assessing management change resulting from FDG-PET scans have been applied. Most FDG-PET false negatives were less than 1 cm in diameter, and were mainly pulmonary and hepatic in location. The majority of these false negatives were detected by CT scanning, indicating that FDG-PET should complement rather than replace CT scanning in this group of patients. Twelve of eighteen CT false negatives were located in the abdomen, suggesting that FDG-PET can especially assist in the staging of this region. The advent of routine attenuation correction in whole-body FDG-PET scans and recent developments in PET/CT scanners should improve this false negative rate [6]. Our FDG-PET false positive rate was low, quite possibly due to the lack of clinical or imaging follow-up for all lesions, which in turn increased the number of lesions in the indeterminate category. In addition, an assessment of FDG-PET sensitivity for detection of cerebral metastases was not possible as most patients did not have a focused FDG-PET scan of the brain performed. Previous studies suggest that FDG-PET may be insensitive in the detection of small metastases in the cerebral cortex [14].

The use of standard imaging (mainly CT scanning), as well as clinical examination and biopsy as the method of validation of disease presence, biased the results against FDG-PET scanning. In addition, the definition of one lesion being any number of metastatic deposits within an organ also removed the inherent advantage of FDG-PET in detecting additional sites of disease at various sites, which was observed in our study and has been reported by other groups. Nevertheless, the sensitivity, specificity, and accuracy of FDG-PET in our series was high and comparable to the best results in the literature [2–6, 15–17]. The requirement for adequate clinical follow-up in the patient population to confirm the presence or absence of disease increased the accuracy of the data in our series. It is also noteworthy that seven other tumor types were detected by FDG-PET in this patient group (Fig. 2), emphasizing the importance of considering differential diagnoses and obtaining a tissue diagnosis particularly at the time of the first relapse.

By comparison, conventional diagnostic procedures (CT chest, abdomen, brain MRI with or without bone scan) have been estimated in studies of patients with stage II–IV melanoma to have a sensitivity of 57–81% and a specificity of 45–87%, respectively, on the basis of single melanoma lesions [2–4]. In a further study of 347 patients with clinical stage III melanoma, CT scans identified twice as many false positives as true positive melanoma lesions [1].

Importantly, in our study FDG-PET had an impact on clinical decision making in one of three patient studies. Its most important role was to assist in the appropriate selection of patients for surgery. Surgery can be curative for stage III disease and is the only therapy that influences survival in patients with stage IV disease [18]. Up to one quarter of patients with metastatic disease are candidates for potentially curative surgical resection and 20% of patients who achieve a curative resection become long-term survivors [19]. However, FDG-PET can miss small volume disease and/or micrometastatic disease, as evidenced by our false negative rate and by the number of patients who relapsed soon after surgery. As such, FDG-PET can help to guide the appropriate use of surgery in this patient population, but may not guarantee a long-term favorable outcome postoperatively.

Conclusion

We conclude that FDG-PET is accurate in staging advanced melanoma and complements the results provided by CT scanning. This is particularly the case in patients with stage III and stage IV disease, and for the assessment of nodal, omental, and cutaneous lesions. FDG-PET has a role to play in the clinical management of melanoma patients, particularly by guiding the appropriate use of surgery.

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