

Clinical applications of fluorodeoxyglucose—positron emission tomography in the management of malignant melanoma

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Purpose of review

Malignant melanoma is the seventh most common newly diagnosed cancer among Americans. In most cases, melanoma is curable by means of surgical excision if diagnosed in early stages of the disease. The prognosis is linked directly to the initial stage at the time of diagnosis. Early diagnosis and accurate disease staging is important for appropriate treatment planning. This review focuses on clinical applications of positron emission tomography (PET) using ¹⁸F-fluorodeoxyglucose (FDG) in the management of patients with malignant melanoma.

Recent findings

Many investigators have studied the role of FDG-PET in the management of malignant melanoma. PET has been shown to have a strong role in detection of metastatic disease. FDG-PET can highlight metastases at unusual sites that are easily missed with conventional imaging modalities. It is more sensitive than computed tomography (CT) for detection of metastatic lesions in skin, lymph nodes, and abdomen. Despite the overall superiority of FDG-PET in the detection of melanoma metastases, it has limitations in detection of early-stage disease (stage I–II), small lung nodules, and brain metastases. Most of the false-negative FDG-PET results are due to micrometastases and lesions small than 10 mm. False-positive FDG-PET results are due to postsurgical inflammation, other inflammatory lesions, and some benign tumors.

Summary

FDG-PET is a metabolic, noninvasive imaging modality for detecting distant metastatic and recurrent melanoma. FDG-PET is of limited use in patients with early-stage disease and cannot replace sentinel node biopsy, which is much more sensitive in detecting microscopic lymph node metastases.

Keywords

fluorodeoxyglucose—positron emission tomography, malignant melanoma, oncology, sentinel lymph node

Introduction

Malignant melanoma is diagnosed in more than 40 000 patients annually in the United States. A projected 55 100 individuals will be diagnosed with the disease during 2004 [1]. It is the seventh most common newly diagnosed cancer among Americans and most common cause of deaths from cutaneous malignancies. The incidence of malignant melanoma is increasing as compared with other malignancies. This rise in incidence may be partially related to improved screening programs and detection of disease in early stages and thin lesions. In most cases, melanoma is curable by means of surgical excision if diagnosed in early stages of the disease. However, even patients with thin melanomas (less than 1 mm) have a 15% chance of developing metastases [2]. About 6 to 10% of patients show detectable metastases at the time of diagnosis, and 16% of patients develop metastases over time [2,3]. Unfortunately, few therapies exist that have a significant impact on survival in patients with regional or distant metastatic disease. The prognosis is linked directly to the initial stage at diagnosis. The patients who present with locally advanced or metastatic disease at the time of diagnosis have a poor prognosis; the multidisciplinary treatment approach, however, can improve the prognosis. The 10-year survival after lymphadenectomy for palpable regional lymph node metastasis is 24% [3]. Therefore, early diagnosis and treatment of local lymph node and distant metastases improve the prognosis in patients with malignant melanoma. Medicare guidelines approve positron emission computed tomography (PET) using ¹⁸F-fluorodeoxyglucose (FDG) for diagnosis, staging (excluding regional lymph nodes), and restaging of melanoma. The present work will review the current literature regarding the use of PET in the diagnosis, initial staging, and restaging of patients with cutaneous melanoma.

Principles of positron emission tomography

PET is an advanced diagnostic imaging technique that is used for diagnosis, staging, and restaging after treatment or recurrence of various cancers including melanoma. This technique exploits the increased metabolism of glucose in malignant viable cells. FDG is one of the most commonly used radioisotopes, which is an analogue of glucose and detects the difference in glucose metabolism. Like glucose, FDG is transported into tumor cells, by means of glucose transporter protein, and subsequently it is phosphorylated by an enzyme hexokinase to FDG-6-phosphate. FDG-6-phosphate is not a substrate for glucose-6-phosphate isomerase; thus, it is biochemically trapped within the cell. There is a many-fold increase in glucose

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metabolism in malignant tumors as compared with normal; therefore, it is easy to detect this difference in metabolism using PET.

Indications of fluorodeoxyglucose–positron emission tomography imaging

The potential indications of FDG-PET imaging in patients with melanoma are the following: detection of regional and distant metastases at the time of initial diagnosis, surveillance in patients with a high risk for distant metastases based on extent of locoregional disease, patients with findings that are suspect for distant metastases, individuals with known distant tumor deposits who still stand to benefit from customized therapies if new lesions are discovered or treated lesions regress, patients at high risk for systemic relapse who are considering aggressive medical therapy, and evaluation of response to chemotherapy or immunotherapy.

Initial staging of melanoma

Melanoma staging is now based on the following factors: depth of invasion of the primary lesion; ulceration upstages patients in each T stage subgroup; the number of lymph nodes in N staging is significant; and stage IV metastatic disease is subclassified based on anatomic site and elevated serum lactate dehydrogenase.

Stage I disease is now defined as lesions that are less than 1.0 mm thick and ulcerated or less than 2.0 mm thick and not ulcerated.

Stage II disease includes localized lesions greater than 1 mm thick that are ulcerated and all lesions greater than 2.0 mm thick.

Stage III disease is now defined by the presence of any type of regional metastasis, including in-transit metastases, satellite cutaneous metastases, and any type of regional lymph node metastasis.

Stage IV disease is defined as any distant metastases (any thickness with or without ulceration).

There is no single modality that is highly sensitive and specific for the detection of all types of local or distant lesions of metastatic melanoma. Most of the staging information in these patients is usually obtained from computed tomography (CT) imaging. Despite this important role, CT imaging has limitations. Lymph node size is a main diagnostic criterion of malignancy, but a CT scan only defines anatomy and it is insufficient for the depiction of small volumes of tumor in normal-sized structures [4]. Unlike CT, FDG-PET imaging is based on increased glucose metabolism in malignant lesions. In 1991, Wahl *et al.* [5] independently demonstrated that radiolabeled glucose analogs were preferentially taken up in murine melanomas xenografts, setting forth the rationale for the potential use of FDG in patients with melanoma.

Primary tumors

FDG-PET is rarely required for primary tumor staging of malignant melanoma because it is easy to detect atypical pigmented lesions on physical examination. The diagnosis can be made easily by punch biopsy or surgical excision, which almost always occurs before the FDG-PET scanning. Moreover, FDG-PET has no or very little influence on staging of primary tumor because the highest stage (4 mm = T4) is beyond the practical spatial resolution of current PET scanners.

Regional lymph node metastasis

The presence or absence of metastatic involvement of local–regional lymph nodes is an important prognostic criterion in patients with malignant melanoma. Assessment of the lymph node involvement is very important, in particular for intermediate and high-risk lesions greater than 1 mm in thickness where the probability of malignant spread is increased. In recent times, full lymph node dissection has largely been replaced by sentinel lymph node (SLN) biopsy [6]. SLN biopsy has been established as a safe and accurate procedure for determination of presence or absence of metastases in the regional lymph node basin [7•]. However, this technique does not provide any information about the possible distant metastases.

Table 1 shows the sensitivity and specificity of FDG-PET for the detection of regional lymph node metastases in patients with primary malignant melanoma. Early studies, which have reported good accuracy of FDG-PET in evaluating regional lymph node status, were obtained in patients with clinical or imaging results suspect for lymph node metastatic involvement [8–12]. Recent reports have suggested that sensitivity of FDG-PET is much lower than initially reported [13–16,17•]. This big variation in the sensitivity of FDG-PET is caused by introduction of step sectioning and immunohistochemical staining, which detect micrometastasis. FDG-PET and any other imaging modalities are expected to have more false-negative rates than SLN biopsy and histologic examination of tissues. In contrast to variable sensitivity of FDG-PET, almost all studies have shown specificities of higher than 90% and some approaching 100% for determining the status of regional lymph nodes [8–12]. The high specificity of FDG-PET warrants use of preoperative staging of patients with malignant melanoma, especially in patients with clinical suspicion of nodal involvement.

Blessing *et al.* [8] reported a sensitivity of 74% and a specificity of 93% in 20 patients with clinically palpable lymph nodes. In another study, Wagner *et al.* studied 11 patients who had both palpable and nonpalpable regional lymph nodes and who underwent elective or therapeutic lymphadenectomy on 14 regional nodal basins. FDG-PET correctly predicted nodal metastases in seven of seven histologically positive nodal basins (sensitivity 100%)

Table 1. Studies showing sensitivity and specificity of fluorodeoxyglucose-positron emission tomography and sentinel lymph node biopsy in detecting lymph node metastases in patients with melanoma

Authors	No. of patients	Sensitivity (%)	Sensitivity (%)
Blessing 1995 [8]	20	74	93
Wagner 1997 [9]	11	100	100
Macfarlane 1998 [10]	22	85	92
Wagner 1999 [11]	70	17	96
Crippa 2000 [12]	38	95	84
Acland 2001 [13]	50	0	—
Havenga 2003 [14]	53	15	88
Longo 2003 [15]	25	22	—
Fink 2004 [16]	48	13	—
Hafner 2004 [17**]	100	8	100

and correctly excluded nodal disease in seven of seven histologically negative nodal basins (specificity 100%) [9]. In a similar study of 22 patients, with clinically suspected or pathologically proved lymph node metastases, FDG-PET showed sensitivity of 85% and specificity of 92% [10]. Wagner *et al.* [11] reported data from a large prospective trial with 70 patients with primary thick melanomas (>1.0 mm) and 4 patients with recurrent melanoma in or adjacent to the surgical scar; these patients underwent PET and SLN biopsy. Using the biopsy results as a gold standard for regional lymph node metastases, the authors reported a sensitivity of 17% and specificity of 96% with FDG-PET. Crippa *et al.* [12] correctly identified regional lymph node metastases in 35 of 37 patients (95%). All the patients in this study, however, had clinical suggestion of lymph node metastases by physical examination, CT, or ultrasonography. Interestingly, when results were analyzed for individual lymph nodes, FDG-PET had significantly lower sensitivity of 66%. In one study of 17 patients with primary cutaneous melanoma by Klein *et al.*, PET had an accuracy of 94%, as compared with findings from SLN mapping [18]. It has been shown that for PET to demonstrate disease in regional lymph nodes with 90% sensitivity, a 78-mm³ volume of tumor must be present [19].

In recent studies, FDG-PET was found to have poor sensitivity in patients who had no clinical evidence of nodal spread of the disease [14–16,17**]. Wagner *et al.* [11] studied 89 patients with stage I, II, or III cutaneous melanoma and reported a sensitivity of 17% with PET as compared with that of SLN biopsy and surgical exploration. Acland *et al.* [13] found that FDG-PET failed to identify all 14 positive SLNs found in 50 patients who underwent SLN biopsy for primary melanomas that were histopathologically greater than 1 mm in thickness or invading lymphatics. Havenga *et al.* [14] reported the value of SLN biopsy and FDG-PET in 55 patients with primary cutaneous melanoma larger than 1.0 mm and clinically negative nodes for metastases. FDG-PET could detect metastases only in 2 of the 13 patients with SLN metastases. In a recent study, Fink *et al.* [16] compared FDG-PET with his-

topathological results of SNL biopsy to determine the value of FDG-PET in predicting regional lymph node involvement in patients with primary malignant melanoma stage I and II. PET was positive in only one of eight patients with a positive SNB, yielding a sensitivity of 13%. Similarly, Hafner *et al.* studied the sensitivity and specificity of ultrasound, FDG-PET, and SLN biopsy in the early detection of regional lymph node metastases or distant metastases [17**]. SLN biopsy was positive in 26 patients, whereas ultrasound and PET detected 2 of 26 histologically tumor-positive sentinel nodes (sensitivity 8%). The conclusion from these studies is that FDG-PET has lower sensitivity as compared with SLN biopsy and cannot replace SLN biopsy for regional lymph node staging.

Distant metastasis

FDG-PET is most commonly used for suspected or known distant metastases in patients with melanoma. Melanoma can metastasize widely, which includes the skin, muscles, bones, bowel, omentum, mesentery, and so on. FDG-PET has been shown to be more accurate than conventional modalities (CM) such as CT, magnetic resonance imaging, ultrasound, and physical examination for determination of the presence and extent of metastatic disease. Schwimmer *et al.* [20] reviewed the literature and reported that PET has been found to be 92% sensitive and 90% specific for metastases. When PET is added to CT in evaluation of patients undergoing initial staging of high-risk primary melanoma, a change in patient care occurs in up to 90% of cases because unsuspected sites of disease are detected [18]. To the best of our knowledge and literature review, there is only one study that reported detection of a greater number of lesions with CT as compared with FDG-PET [21]. The histopathological diagnosis, however, was not obtained in most of the cases. CT has also been reported to be more sensitive than PET in lung metastases [22]. However, superiority of CT in pulmonary lesions compared with FDG-PET is not unexpected because CT has high resolution and contrast.

There are many studies that compared sensitivity and specificity of FDG-PET to CM in evaluating regional and distant metastases (Table 2). The sensitivity of FDG-PET for metastatic lesions or abnormal regions ranged from 78% to 100%. Gritters *et al.* [22] reported the utility of FDG-PET in detecting metastatic disease in 12 patients of varying stage. FDG-PET identified 15 of 15 intraabdominal visceral and lymph node metastases that were 0.5 to 8.0 cm in diameter [22]. Five of these lesions were not seen on initial CT imaging, although retrospective review found three, and follow-up CT identified the lesions within 2 to 6 months. PET also identified two biopsy-proven skin metastases and two soft-tissue lesions in the musculature of the back that were only seen on retrospective review of the CT. In another study of 33

Table 2. Studies showing sensitivity and specificity of fluorodeoxyglucose-positron emission tomography (PET) and conventional modalities (CM) for detecting metastatic disease in patients with melanoma

Author	No. of patients	Sensitivity PET (%)	Sensitivity CM (%)	Sensitivity PET (%)	Specificity CM (%)
Gritters 1993 [22]	12	100			
Steinert 1995 [23]	33	92	—	77	—
Damian 1996 [24]	100	93			
Rinne 1998 [25]	100	100	85	96	68
Holder 1998 [26]	76	94	55	83	84
Eigtved 2000 [27]	38	97	62	56	22
Tyler 2000 [28]	95	87	—	44	—
Acland 2000 [29]	44	78	—	87	—
Swetter 2002 [30]	104	84	58	97	70
Finkelstein 2004 [31*]	18	79	76	87	87

patients with suspected metastases, the sensitivity of FDG-PET was 92%, whereas specificity was 77% (without clinical information) and 100% (with clinical information) [23]. Initial reports of 100 patients by Damian *et al.* [24] suggest that FDG-PET may offer greater diagnostic accuracy and versatility than CM in staging patients with metastatic melanoma. FDG-PET showed a sensitivity of 93% in evaluation of metastatic lesions. In addition, PET detected 24 metastases up to 6 months earlier than conventional imaging or physical examination in 20 patients. Rinne *et al.* demonstrated the sensitivity of 100% and the specificity was 94% with PET, whereas CM demonstrated a lower specificity of 80% [25]. Holder *et al.* [26] reported a significantly higher sensitivity of 94.2% and a specificity of 83.3% for PET scanning compared with 55.3% and 84.4%, respectively, for CT scanning for the detection of melanoma metastases. Eigtved *et al.* [27] also demonstrated the lower sensitivity and specificity of CM as compared with FDG-PET in 38 patients. Tyler *et al.* [28] reported the identification of 144 of the 165 (87.3%) metastatic lesions using FDG-PET. Acland *et al.* [29] reported a lower sensitivity with FDG-PET, especially in patients with stage I and stage II. PET scanning had an overall sensitivity of 78% and specificity of 87%. In a retrospective cohort review of 104 patients with primary or recurrent melanoma, PET demonstrated sensitivity of 84% and specificity of 97%, whereas CT showed sensitivity of 58% and specificity of 70% [30]. In a recent study, Finkelstein *et al.* demonstrated a sensitivity of 76% and a specificity of 87% with CM, and a sensitivity of 79% and a specificity of 87% with FDG-PET [31*]. The sensitivity was 88%, specificity was 91%, and positive predictive value (PPV) and negative predictive value (NPV) were 91% and 88%, respectively, for combined FDG-PET and CM.

Restaging of melanoma

FDG-PET is highly sensitive and specific for detection of metastatic melanoma. Therefore, FDG-PET can be used for surveillance after treatment in patients with high-risk stage III and IV melanoma. In patients with known recurrence of melanoma, the FDG-PET has been shown to de-

tect additional unsuspected sites of disease and to result in alteration of treatment planning in up to 20% of cases [20]. Stas *et al.* [32] analyzed consecutive 100 PET scans performed on 84 melanoma patients with regional or distant recurrence according to conventional modalities. FDG-PET scan showed a sensitivity of 85%, specificity of 90%, and accuracy of 88%. The similar values for CM were 81%, 87%, and 84%, respectively. Mijnhout *et al.* [33] assessed the reproducibility and clinical impact of FDG-PET and concluded that FDG-PET had considerable impact on diagnostic understanding and management. Fuster *et al.* [34**] compared the accuracy of FDG-PET and standard CM in detecting recurrent melanoma in 156 patients. The sensitivity and specificity of PET for detecting lesions on an individual-patient basis were 74% and 86%, respectively, compared with respective values of 58% and 45% for CM alone. The overall accuracy for PET was 81%, compared with 52% for other methods. PET was more accurate (91% versus 67%) than CT in detecting locoregional disease and distant metastases (85% versus 55%).

Impact on patient management

FDG-PET can affect therapeutic planning of treatment for melanoma in many ways. Damian *et al.* [24] reported influence of therapy by PET findings in 22% (22/100) patients. In addition, PET was used to clarify another 12 cases where CT was inconclusive [24]. Similarly, Tyler *et al.* [28] and Acland *et al.* [29] reported the change in management in 15% and 28% of patients with FDG-PET. Jadvar *et al.* [35] reported that CT underestimated the disease in 5 of 38 (13%) patients. In a retrospective study of 100 scans, PET showed an additional value over and above CM by upstaging in 10 cases, downstaging in 24 cases, and depiction of more lesions within the same stage of disease in 15 cases [32]. Wong *et al.* [36] studied the impact of FDG-PET on patient stage and management from the referring physician's perspective. FDG-PET changed the clinical stage in 15 of 51 (29%) patients (two thirds were upstaged and one third were downstaged). The PET findings resulted in intermodality management changes in 15 of 51 patients (29%) and

intramodality management change in 9 patients (18%). Mijnhout *et al.* [33] assessed the clinical impact of FDG-PET in 58 consecutive patients with suspected recurrent melanoma. Diagnostic understanding and therapy choice by referring physicians were evaluated before, directly after, and 6 months after PET. FDG-PET improved diagnostic understanding in 33 cases (57%). In six patients (10%), diagnostic understanding was solely based on PET information. PET contributed to a positive change of planned treatment in 23 patients (40%) and increased confidence in the chosen treatment in 23 (40%). Gulec *et al.* [37] reported treatment changes in 49% (24/49) of patients with FDG-PET.

Conclusion

FDG-PET is a metabolic, noninvasive imaging modality for detecting distant metastatic and recurrent melanoma. FDG-PET is more sensitive than CT for detection of metastatic lesions in skin, lymph nodes, and abdomen, but CT is equivalent to or more sensitive than FDG-PET for detecting small pulmonary lesions. There are no data suggesting the utility of FDG-PET in the initial diagnosis of melanoma. FDG PET is of limited use in patients with early-stage disease and cannot replace sentinel node biopsy, which is much more sensitive in detecting microscopic lymph node metastases.

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