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Assessing response to chemotherapy in metastatic melanoma with FDG PET: Early experience

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Objective **The management of metastatic melanoma remains challenging with only modest response rates to chemotherapy but the need to identify the best re-staging techniques remains paramount. This study evaluates our early experience in the use of FDG PET-CT in the assessment of early response to chemotherapy in metastatic melanoma.**

Methods **FDG PET-CT was performed at baseline and following two or three cycles of combination or single agent chemotherapy in seven patients. Response was assessed visually as complete, partial metabolic response or progressive disease.**

Results **There was intense FDG uptake in all metastases at baseline. Following two to three cycles of chemotherapy, there was a complete metabolic response (CMR) in one patient, partial metabolic response (PMR) in two patients and progressive metabolic disease (PMD) in the remaining three patients. Survival was 679 days in the single patient with a CMR, median of 206 and 129 days in the patients with PMR and PMD respectively.**

Conclusion **This pilot study demonstrates the potential use of FDG PET as a biomarker in early response assessment to chemotherapy in metastatic melanoma. PET-CT already plays in integral role in staging high risk melanoma patients and it may also have a promising role in assessing response to current and novel therapies. Further larger studies examining specific therapies and optimal timing are required.** ***Nucl Med Commun*** **28:902–906 © 2007 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

The incidence of cutaneous melanoma is increasing around the world with a crude incidence of approximately 10/100 000 per year in the European Union [1]. Advanced metastatic melanoma has a poor prognosis and chemotherapy is palliative with the aim of improving patient symptoms and quality of life. Despite the difficulty in treating patients with metastatic melanoma there is an urgent need to identify the best techniques to re-stage patients following treatment. Ideally, this should be performed as early as possible so as to avoid the adverse effects and costs of therapies that are ineffective.

The role of 2-[^{18}F]fluoro-2-deoxy-D-deoxyglucose (FDG) positron emission tomography (PET) is already firmly established in the staging of patients with melanoma, with the exception of early stage disease when sentinel node imaging is more useful [2,3]. As metabolic changes precede anatomic changes, functional imaging with FDG PET is better suited to this task than anatomical modalities such as computer tomography (CT). In other malignancies, the use of FDG PET as an imaging biomarker for early re-staging to assess chemotherapy response is proving valuable [4]. This study aims to evaluate and report our early experience in the use of serial FDG PET examinations in the assessment of response after two or three cycles of chemotherapy in the setting of palliation for metastatic melanoma.

Methods

Patients

From January 2004 to April 2006, all patients with metastatic melanoma who underwent a baseline PET study prior to chemotherapy and a repeat re-staging study after two to three cycles of chemotherapy were included in this retrospective analysis. The patients were managed by a multi-disciplinary team at a tertiary referral skin tumour unit (St John's Institute of Dermatology, St Thomas' Hospital). The study population comprised seven patients (age range 24–49 years). All patients were referred from a

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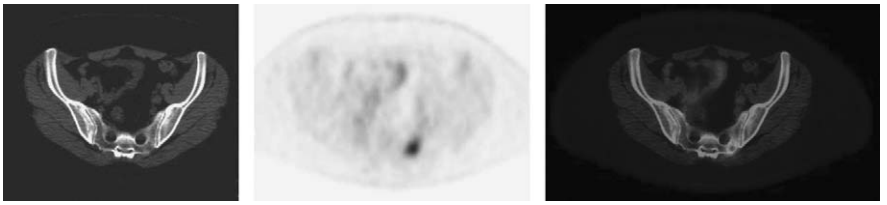
Table 1 Clinical characteristics of the patients in this study

Patient no.	Age†	Sex	Melanoma thickness (mm)	Melanoma type	Site of primary disease	Sentinel lymph node status	Interval between diagnosis and initial recurrence (years)	Initial site of recurrence
1	32	F	<1.0	Nodular	H&N	Not indicated	3	Distant node
2	58	F	0.37*	Acral lentigenous	LL	Not indicated	13	Regional node
3	24	F	0.7	Acral lentigenous	UL	Not indicated	5	Regional node
4	52	F	3.2	Superficial spreading	LL	Not performed	8	Regional node
5	49	M	1.26	Nodular	UL	Negative	4	In-transit
6	49	M	N/A	N/A	trunk	Not performed	2	Brain
7	46	M	0.6	Metastasis**	H&N	Not indicated	N/A	Liver, bone, subcutaneous, brain

UL upper limb, LL lower limb, H&N head and neck.
†Age at disease presentation.
*Vascular invasion present.
**Metastasis favoured rather than primary.

Fig. 1



Axial slice through pelvis demonstrate focus of intense tracer uptake (centre), without abnormality of correlative CT with bony windows (left). Fusion PET/CT (right) accurately localizes abnormality to the left sacrum adjacent to the sacroiliac joint (patient 3).

single physician (M.H.). Table 1 summarizes the clinical characteristics of the patients studied. All studies were performed as part of routine clinical management. All patients had a baseline PET study prior to initiation of chemotherapy. A further PET study was performed 2–6 weeks after completion of two or three cycles of chemotherapy. The study was registered with the institutional clinical audit committee and informed consent was obtained from patients regarding use of their images.

PET-CT data acquisition

PET scans were performed from base of skull to upper thighs after a 6 h fast. Arms were raised above shoulders unless the primary disease was on the upper limb. An additional series of the lower limbs was obtained if the primary site of disease was on either leg. A dedicated head and neck series was also performed for disease in this region. Emission data were acquired for 5 min per bed position starting 90 min after intravenous injection of 350 MBq ^{18}F-FDG. All patients were examined with a dual-modality PET-CT scanner (General Electric Discovery ST, Wisconsin, USA), which consists of a four-row spiral CT and a full-ring bismuth germanate PET. Images were acquired in two-dimensional mode. CT was performed for attenuation correction and image fusion/anatomical localization. Images were reconstructed with an iterative technique using an ordered subset expectation-maximization (OSEM) algorithm.

PET image interpretation and patient follow-up

Two experienced nuclear medicine physicians read all scans. Response was assessed visually. A complete metabolic response was defined as complete absence of metabolically active disease. Progressive metabolic response indicated new lesions and/or increase in intensity or size of existing lesions. A partial metabolic response indicated fewer lesions and/or decrease intensity or size of lesions but without a complete response. Stable metabolic disease indicated no change in intensity of number of lesions. Standardized uptake values (SUVs) were calculated by measuring the maximum SUV of each lesion and selecting the lesion with the highest SUV but this was not used directly in response assessment.

Follow-up was obtained retrospectively from histology where available, review of correlative imaging and patient medical records. Follow-up was obtained until death in five patients. One patient was lost to complete follow-up after commencement of palliative care, and one patient remained alive 11 months post-initiation of chemotherapy.

Results

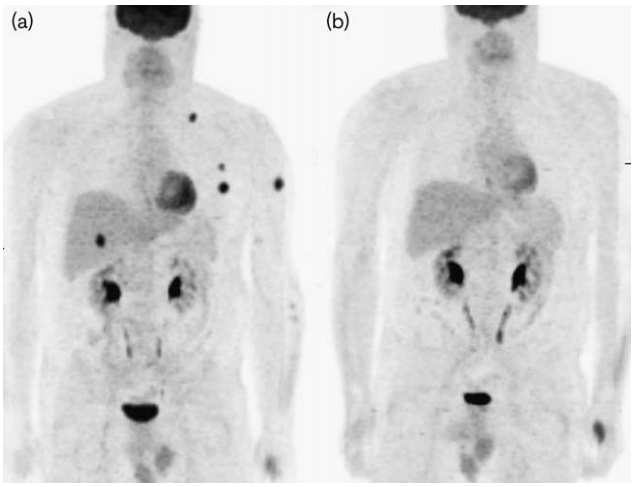
At baseline, there was intense FDG uptake in all metastases (Fig. 1). The number of metastatic lesions ranged from five to greater than 20. Four patients had combination chemotherapy with CVD regimen and three patients had single agent DTIC chemotherapy (Table 2).

Table 2 PET response after two or three cycles of chemotherapy

Patient no.	Sites prior to chemotherapy	Prior treatment	Chemotherapy	No of cycles	PET response	Days until death*	Management after PET and subsequent follow-up
1	Nodal, brain	WBI	CVD	2	PMR	215	Further 2 cycles given. Deterioration in CNS symptoms with mixed response on MRI. Changed dacarbazine to temozolamide and further 2 cycles given. Progressive CNS disease
2	Liver, adrenal	Nodal dissection	DTIC	3	PMD	Lost to follow-up**	Palliative care
3	Nodal, bone	Nodal dissection	CVD	3	PMD	Alive	Palliative care
4	Nodal, liver, lung	Nodal dissection	DTIC	3	PMD	115	Palliative care
5	Liver, lung, nodal, subcutaneous	Nodal dissection	CVD	3	CMR	679	3 further cycles chemoRx. Further PET study sustained CMR. 13 months post initial chemoRx CNS symptoms with brain mets on MRI. Palliative radiotherapy
6	Lung, nodal, liver, colon, muscle, brain	Brain radiotherapy	DTIC	3	PMR	198	Further 3 cycles of chemoRx with further PMR on repeat PET. Developed increasing left leg weakness from brain met, therefore chemoRx withheld
7	Liver, bone, subcutaneous, brain	nil	CVD	3	PMD	143	Palliative care

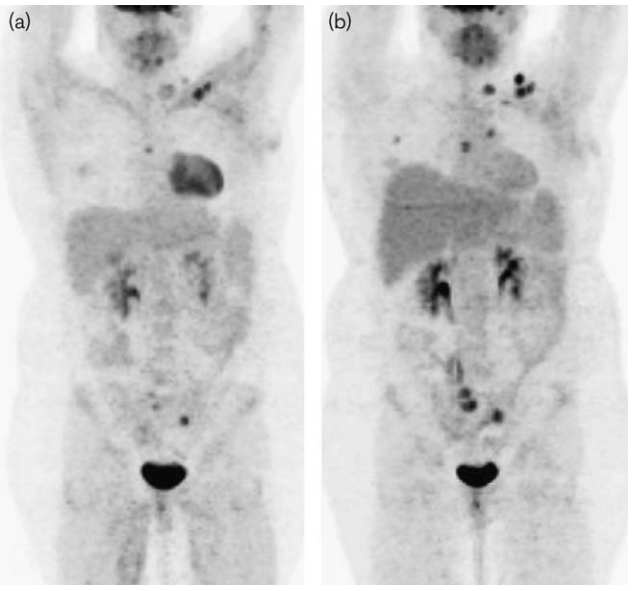
ChemoRx, chemotherapy; WBI, whole brain radiation; CMR, complete metabolic response; PMR, partial metabolic response; PMD, progressive metabolic disease; CVD, cisplatin, vinblastine/vindesine, dacarbazine; DTIC, dacarbazine.
*Days from commencement of initial chemotherapy until patient death.
**Approximately 3 months after initial chemotherapy in setting of terminal palliative care.

Fig. 2



Complete metabolic response. Initial FDG PET study maximum image projection (MIP) image (a) demonstrates one liver metastasis, two left axillary nodal metastases, left clavicle and soft tissue deposit in left upper arm. Repeat study (b) after three cycles of CVD chemotherapy demonstrates no abnormality (patient 5).

Fig. 3

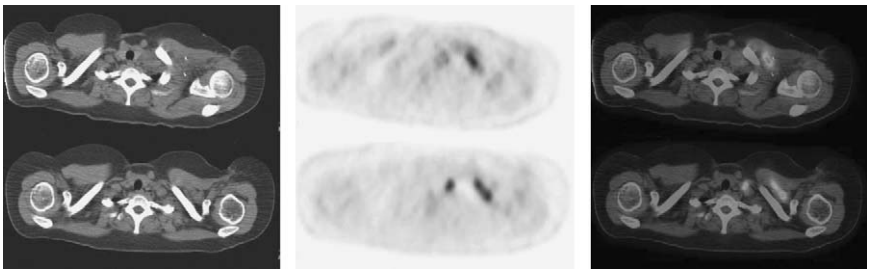


Maximum image projection (MIP) image at baseline demonstrates nodal disease in the left axilla and anterior mediastinum, bony metastasis in right 5th rib and sacrum. Re-staging study (b) demonstrates progressive metabolic disease (patient 3).

Re-staging was performed after three cycles in six patients, and after two cycles in one. There was a complete metabolic response (CMR) in one patient (Fig. 2), which was maintained on two further PET scans, performed at completion of a further three cycles of chemotherapy, and repeated 3 months after this. A partial metabolic response (PMR) was observed in two patients, and progressive metabolic disease (PMD) occurred in four patients (Figs 3 and 4).

Survival was 679 days in the single patient with a complete metabolic response, a median of 206 days in the patients with partial metabolic response and a median of 129 days in the patients with progressive disease. One patient with a progressive metabolic disease was still alive

Fig. 4



CT (top panel, left) at baseline demonstrates subtle abnormal soft tissue in the left axilla at the site previous surgical intervention (clips) which cannot be distinguishing between post-surgical fibrosis or residual/recurrent disease. PET (top, middle) and fusion (top, right) images demonstrate intense metabolic activity consistent with malignancy. PET/CT re-staging after three cycles chemotherapy (lower panel) demonstrates progressive disease with more extensive disease in the left axilla and new metastasis in a subcentimetre supraclavicular node (patient 3).

Table 3 Number of lesions and SUV_{max} before and after chemotherapy

	Baseline study		After chemotherapy	
Patient no.	Number of PET-avid lesions	SUV_{max}	Number of PET-avid lesions	SUV_{max}
1	>20	19.3	3	9.1
2	5	19.0	7	21.6
3	3	9.1	>20	20
4	5	21.8	10	22.5
5	5	14.2	0	0
6	6	13.0	4	4.3
7	4	4	6	13.0

11 months after initial chemotherapy. One patient was lost to follow-up after commencement of palliative therapy in the setting of progressive disease.

At baseline, the average SUV_{max} of the most intense focus of uptake in the patient cohort was 17.2 (Table 3). In patients with PMR there was a 60% mean reduction in SUV_{max} compared with a 47% increase in SUV_{max} in those with PMD.

Discussion

^{18}F-FDG PET/CT is rapidly evolving as a key imaging modality for the assessment of patients with advanced metastatic melanoma. Numerous studies and meta-analyses have reported higher sensitivity and specificity of PET compared with conventional imaging [5–9]. In particular, the sensitivity of PET for detecting metastatic disease is substantially higher than CT. The development of combined PET/CT scanners allowing integrated assessment of functional (PET) and anatomical (CT) images has been shown to decrease false positives by increasing specificity for distant lymph node metastases and visceral metastasis, and to increase sensitivity mainly by detecting PET-negative pulmonary lesions [10]. Nevertheless, PET-CT remains complementary to other conventional investigations as MRI is superior for brain metastases, and small liver lesions may be missed without contrast-enhanced CT. PET and PET/CT have also importantly been shown to result in change of management ranging from 15 to 48% [10,11].

The treatment of localized or regionally disseminated melanoma remains primarily surgical. Chemotherapy options for patients with widespread disease are limited. Dacarbazine, a methylating agent, is currently the first-line treatment either as a single agent or in combination with other chemotherapeutic or immunological agents [12,13]. Dacarbazine is generally well tolerated with modest response rates in the range 5–20%. Other combinations including vinblastine/vincristine and platinum analogues or paclitaxel and platinum analogues have been used as second-line treatment with generally disappointing results and more significant toxicities. However, a number of innovative treatments are currently being tested in phase I and II trials, include monoclonal antibodies (anti-CTLA 4), anti-integrin RAF kinase inhibitors (Sorafenib), anti-angiogenetic agents (thalidomide) and novel chemotherapy combinations [14].

Chemotherapy in stage III and IV disease is given with a palliative intent and rarely before the patient becomes symptomatic. Physical examination and conventional imaging have been used to assess the extent of the disease (baseline) prior to chemotherapy as well as the response to chemotherapy (interim and post chemotherapy). Conventional re-staging with CT using RECIST (response evaluation criteria in solid tumours) criteria have multiple disadvantages including difficulty in measuring tumours with irregular or diffuse boundaries, differences related to timing of contrast injection and reporter reproducibility [15]. The use of FDG PET in early assessment of chemotherapy response has been studied in a variety of malignancies, including lymphoma, oesophageal, breast, head and neck, lung, and gastrointestinal stromal tumours (GIST) tumours with

favourable results compared to conventional modalities [16]. PET has the chief advantage of assessing changes in metabolic activity that precede anatomical changes, allowing earlier assessment of therapeutic response. Moreover, in patients where PET has detected early metastatic disease not evident on other modalities (see Fig. 3), it is clearly not feasible to use these modalities to assess response.

To our knowledge there are no other published data on the use of FDG PET in the setting of palliative chemotherapy for metastatic melanoma. Mercier *et al.* [17] reviewed nine patients with locally advanced melanoma selected for isolated limb perfusion of which three patients had re-staging 34–43 days after treatment. All post-therapy FDG PET scans showed a reduction in the number of visualized limb lesions but also demonstrated diffuse uptake through the limb correlating with post-therapy limb inflammation. Despite either complete or partial response 4 weeks after therapy, all patients had recurrent disease by 11 months after treatment. In our study there was one dramatic responder and two partial responders and the rest showed progressive disease. The responders had a longer survival than the patients with progressive disease. The difficulty with interpreting this data is that each had differing treatment and different primary volumes of disease. Even so, response could be identified and raises the question as to whether this can be evaluated at earlier time points.

The optimal time to differentiate between responders and non-responders with FDG PET is unknown. In this study, imaging was performed after two or three cycles of chemotherapy. In the setting of palliative chemotherapy, with the ultimate aim of symptoms control and relief, earlier re-staging, perhaps as early as after one cycle of chemotherapy, may be beneficial to avoid potential side effects of ineffective chemotherapy. Early re-staging may also be cost-effective by avoiding expensive therapies.

Conclusion

This study demonstrates the potential use of PET and PET/CT to assess response to chemotherapy in patients with malignant melanoma. Metabolic imaging may improve the palliation of patients receiving chemotherapy for metastatic melanoma by identifying patients unlikely to respond and thereby avoiding ineffective chemotherapy. As newer therapies for melanoma become available, FDG PET may be useful as an imaging biomarker that can be used in place of classic endpoints in evaluating treatment response. In this study there does appear to be a correlation of survival with demonstrable response but this is not generalizable due to the heterogeneous patient population and small number of patients. The timing of the FDG scan and the role of other PET tracers need to be explored further. Prospective studies evaluating specific treatments need to be performed.

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