**CLINICAL TRIAL PROTOCOL**

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**Type of project**

Single-armed prospective cohort study

**Clinical meeting review**

This protocol is reviewed by Melanoma Institute Australia Research Committee

**Title**

Does staging with $^{18}$F-FDG PET/**C**T and brain MRI alter the initial treatment proposal in melanoma patients wit**h** s**a**tellite or i**n**-transit metastases as a first recurrence or at time of dia**g**nosis? A prosp**e**ctive study. (The CHANGE study)

**Brief background and rationale**

In cutaneous melanoma, staging provides prognostic information and is important in determining subsequent management. Five-year survival rates within AJCC stage III melanoma has been shown to vary between 78% for patients with stage IIIA, 59% for stage IIIB and 40% for stage IIIC.[1] This large range illustrates the importance of accurate staging. Still there is no consensus on the diagnostic approach in stage III melanoma patients[2-5]. Some clinicians refrain from proper staging because they feel that a lymph node or in-transit metastasis needs to be removed whether or not there is distant disease. Others routinely perform a range of imaging techniques and blood tests.
Recently the benefit of staging in melanoma patients with palpable lymph nodes has been demonstrated. Staging using whole-body $^{18}$F-fluorodeoxyglucose PET/CT and brain MRI led to

a change in management in 37%.[6] PET was found to have a sensitivity of 87% and a specificity of 98% in the detection of other metastases.[6] We wondered whether this would also be the case in patients with satellite or in-transit metastases. The purposes of this study are to determine the implications of PET/CT and brain MRI for subsequent management of patients with satellite or in-transit metastases as a first recurrence or at time of initial diagnosis and to establish the diagnostic accuracy of PET/CT and MRI in this population.

Current management of patients with in-transit metastases includes a variety of local methods: complete excision, carbon dioxide laser therapy, cryotherapy, local application or intralesional injection of drugs or immunomodulants. More extensive disease in a limb can be treated with isolated limb perfusion (ILP) or isolated limb infusion (ILI). In specific cases radiotherapy may be useful.[2-5, 7] Also, lymphatic mapping and sentinel lymph node biopsy (SNLB) have been suggested to maintain regional control.[8] Evidence of distant metastases could change management into more extensive surgery with curative intent or into systemic treatment, or palliation, the latter guarding patients from potentially morbid treatment options.

In this study, suspicious lesions identified with PET/CT or MRI are confirmed by pathology examination or, if not possible, by six-month follow-up imaging or physical examination as a gold standard. To be considered true positive, imaging would reveal metastasis confirmed by pathology, six-month repeat imaging or clinical signs. Imaging is classified as false positive if suspicious lesions are confirmed to be something other than melanoma. Absence of lesions on imaging is regarded true negative if during six-month follow-up patients remain without metastases. Imaging is considered false negative if evidence of metastasis is established within six-month follow-up despite imaging initially being reviewed as negative.


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2. Coit DT, Andtbacka R, Anker CJ, Bichakjian CK, Carson WE 3rd, Daud A. et al. Melanoma, version 2.2013: featured updates to the NCCN guidelines. *J Natl Compr Canc Netw* 2013; 11(4):395-407.
3. Australian Cancer Network, New Zealand Guidelines Group, Cancer Council Australia, New Zealand. Ministry of Health. Clinical practice guidelines for the management of melanoma in Australia and New Zealand: evidence-based best practice guidelines. Sydney, N.S.W.: Australian Cancer Network; 2008.
4. Melanoma Guideline. Dutch melanoma working group. 2012. http://www.oncoline.nl. Accesed on October 28, 2013.
5. Marsden JR, Newton-Bishop JA, Burrows L, Cook M, Corrie PG, Cox NH et al. Revised U.K. guidelines for the management of cutaneous melanoma 2010. *Br J Dermatol* 2010; 163(2):238-56.
6. Aukema TS, Valdés Olmos RA, Wouters MWJM, Klop WMC, Kroon BBR, Vogel WV et al. Utility of preoperative 18F-FDG PET/CT and brain MRI in melanoma patients with palpable lymph node metastases. *Ann Surg Oncol* 2010; 17:2773-2778
7. Hayes AJ, Clark MA, Harries M, Thomas JM. Management of in-transit metastases from cutaneous melanoma. *Br J Surg* 2004; 91:673-682.
8. Yao KA, Hsueh EC, Essner R, Foshag LJ, Wanek LA, Morton DL. Is sentinel lymph node mapping indicated for isolated local and in-transit recurrent melanoma? *Ann Surg* 2003; 238(5):743-747.


**Aim**

To evaluate the influence of whole body $^{18}$F-FDG PET/CT and brain MRI on management of stage III melanoma patients with satellite or in-transit metastases as a first recurrence or at time of diagnosis.

To determine the diagnostic accuracy of $^{18}$F-FDG PET/CT and MRI of the brain in stage III melanoma patients with satellite or in-transit metastases as a first recurrence or at time of diagnosis.

**Objectives**

To assess how often stage of the disease is altered.
To assess how often management of the disease is altered.
To calculate sensitivity of $^{18}$F-FDG PET/CT and brain MRI.
To calculate specificity of $^{18}$F-FDG PET/CT and brain MRI.

**Hypotheses**

Staging using $^{18}$F-FDG PET/CT and brain MRI in patients with satellite or in-transit metastases as a first recurrence or at time of diagnosis will alter the stage and subsequent management of disease in a substantial fraction of the patients (at least 10%).

**Population and setting**

Inclusion criteria
- Men or women, age 18 years or older able to give informed consent.
- Clinically or pathologically confirmed satellite or in-transit metastasis (N2c) without clinical evidence of metastases elsewhere (stage IIIB, C).
- Able to undergo $^{18}$FDG PET/CT (no uncontrolled diabetes mellitus or severe claustrophobia).
- Performance Status: ECOG 02 (Appendix A).
- Life Expectancy: At least 6 months in respect to the required 6 month follow up.
- Patient medically able to undergo a surgical procedure performed under general anesthetics at time of enrolment.

Exclusion criteria
- True local recurrences (melanoma recurrences in contact with a skin graft or scar of the primary melanoma excision).
- Clinical evidence of nodal or distant metastasis at time of enrolment.
- Concurrent or intercurrent illness:
• Subjects with significant concurrent or intercurrent (including cardiovascular, respiratory or immunological) illness, psychiatric disorders, or alcohol or chemical dependence that would, in the opinion of the investigator, compromise their safety or compliance or interfere with interpretation of study results.
- Pregnancy:
• Female subjects who are pregnant.
• Fertile subjects who are not using effective contraception.
- Other contraindications regarding nuclear imaging or MRI (contrast agent allergy, insulin-dependent diabetes, compromised kidney function, claustrophobia, intracranial aneurysm clips or cardiac implantable devices) should be assessed by a radiology specialist

**Interventions (if applicable)**

Whole body $^{18}$F-FDG PET/CT and brain MRI.
If imaging is positive, pathology confirmation will be pursued.

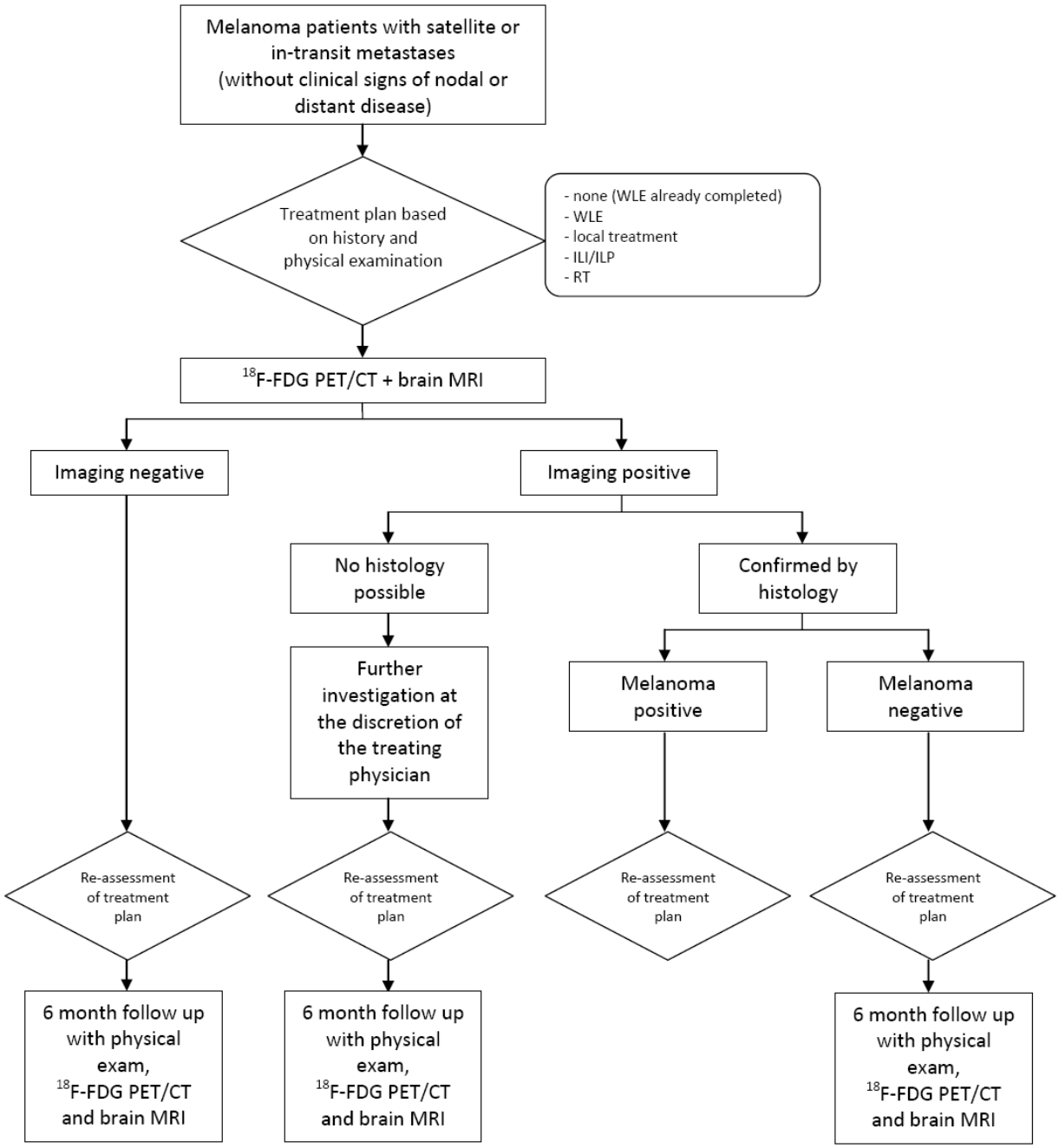
**Outcomes and measures**
**Primary outcome**

Percentage of patients with change of disease management.

**Secondary outcomes**

Change of AJCC stage.
$^{18}$F-FDG PET/CT and brain MRI sensitivity and specificity.
Subgroup analysis on the effect of the number of in transit metastases or satellites on change of management

**Study design and procedure – outline only**



**Statistical considerations/sample size/data collection**

A feasibility estimate was conducted based on incidence in the previous five years at Melanoma Institute Australia. The eligible number of patients is estimated to be 85 annually: 27 patients with (micro) satellites, 13 with primary melanoma and in-transit metastasis and 45 with first in-transit recurrence.

A sample size calculation was conducted based on the assumption that a change in management in 10% of the study population is clinically relevant. A sample size of 34 from a population of 2000 achieves 90% power to detect a difference (P1-P0) of 0.1000 using a one-sided binomial test. The target significance level is 0.0500. The actual significance level achieved by this test is 0.0440. These results assume that the population proportion under the null hypothesis is 0.0100.

Data will be collected and securely stored at Melanoma Institute Australia.

**Timeline**

Oct 2013 – Jan 2014 Ethics application
Jan 2014 – Jul 2014 patient recruitment Sydney
Aug 2014 – Jan 2015 second half patient recruitment Sydney
Feb –March 2015 first data analysis
Mai 2015 – Mai 2016 roll out other centres
June 2016 inclusion closed
December 2016 final analysis multicenter trial

**External/Internal funding sources**

If the six month repeat scans will not be covered by Medicare we would seek external/internal funding sources. Another possibility is an agreement between the surgeons of MIA to decide that the six month scans are considered standard of care, so that Medicare will cover them.

**Recruitment**

Pilot study of six months with patient recruitment at MIA affiliated centres (Mater Hospital and Royal Prince Alfred Hospital) and subsequently enrolment of external centres.

**Clinical trial feasibility**

Not required.

**Ethics approval process**

Ethics approval will be sought from the Royal Prince Alfred Ethics Committee.

**Proposed date of commencement**

Once ethics approval has come through, estimated Jan 2014

**Proposed date of completion**

Patient inclusion is closed in June 2016

## Appendix A: ECOG performance status

| Grade | Definition |
|---|---|
| 0 | Able to carry out all normal activity without restriction. |
| 1 | Restricted in physically strenuous activity but ambulatory and able to do light work. |
| 2 | Ambulatory and capable of all self-care but unable to carry out any work. Up and about more than 50% of waking hours. |
| 3 | Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. |
| 4 | Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair. |
| 5 | Dead |