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Cost-effectiveness analysis of PET/CT surveillance imaging to detect systemic recurrence in resected stage III melanoma: study protocol

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ABSTRACT

Introduction In the new era of effective systemic therapies for advanced melanoma, early detection of lower volume recurrent disease using surveillance imaging can improve survival. However, intensive imaging follow-up strategies are likely to increase costs to health systems and may pose risks to patients. The objective of this study is to estimate from the Australian health system perspective the cost-effectiveness of four follow-up strategies in resected stage III melanoma over a 5-year period following surgical treatment with curative intent.

Methods and analysis A decision-analytic model will be built to estimate the costs and benefits of (1) 12 monthly, (2) 6 monthly, (3) 3–4 monthly positron emission tomography/CT imaging for 5 years, compared with (4) no imaging follow-up. The model will be populated with probabilities of disease recurrence, test performance measures using data from >1000 consecutive resected stage III melanoma patients from Melanoma Institute Australia diagnosed between 2000 and 2017. Healthcare resource use, including surveillance imaging, doctor's visits, subsequent tests and procedures to investigate suspicious findings, will be quantified from detailed patient records and valued using Australian reference pricing. Economic outcomes include cost per new distant melanoma recurrence detected and cost per diagnostic error avoided, for no imaging compared with the other strategies.

Deterministic sensitivity analyses will examine the robustness of model results.

Ethics and dissemination This study was approved by the Sydney Local Health District, Sydney Local Health District Ethics Review Committee (RPAH Zone), AU/1/830638 and the Australian Institute of Health and Welfare (EO2019-1-454). The results of this study will be published in peer-reviewed medical and health economics journals and will inform melanoma management guidelines.

Strengths and limitations of this study

- The analysis will be based on test accuracy and prevalence data from a cohort study of over 1000 patients with stage III melanoma.
- The model structure accounts for clinical and policy-relevant outcomes including test accuracy.
- The comparison of the three imaging schedules was not based on data from randomised trials and some selection bias might be introduced.
- Treatment cost data will be obtained from the published literature.

INTRODUCTION

Melanoma

In Australia, melanoma is the third most common cancer in both men and women, accounting for 10% of all new cases (13 280: 7850 women and 5440 men) and 3.8% of cancer deaths (1775: 545 women and 1230 men) in 2016.[1] Its incidence is continuing to rise slowly in both sexes, and while mortality and 5-year survival (95%) after melanoma diagnosis are stable, the disease remains a leading cause of cancer death in young adults aged under 40.

Stage III melanoma is defined as the presence of metastatic disease in regional lymph nodes and/or the presence of intransit/satellite/microsatellite metastasis.[2 3] The dissemination of melanoma to regional nodes and visceral organs, such as the lung, liver or brain, implies a poor prognosis. The risk of recurrence is highest in the first 3 years after diagnosis,[4] but patients have a life long risk of relapse. Appropriate surveillance can identify disease recurrence and enable early individualised treatment.[5] However, there is no randomised trial evidence that early recognition and treatment of systemic recurrence improve survival outcomes.[3]

Follow-up strategies

In melanoma clinics, after treatment for initial stage III disease, patients are routinely followed up for at least 5 years[3 6] with clinical

examination and various imaging tests. CT, positron emission tomography (PET) or PET/CT specifically assess for evidence of systemic recurrence. CT is a medical imaging modality that uses ionising radiation and computer processing to generate detailed anatomical scans of the body. Whole-body CT including chest, abdomen and pelvis±the brain can detect cancer metastases as small as 2–4 mm.[7] Reported CT detection rates range from as high as 72% of distant metastases in asymptomatic patients in one study using clinical follow-up as reference standard[8] to 15%–28% in another study with whole-body MRI as reference standard.[9] Drawbacks to CT are its limited soft tissue contrast, cost and radiation exposure, with an effective dose of up to 20 mSv per test.[10]

PET registers metabolic and biochemical activity, however, the images produced lack fine anatomical detail. Images from both modalities (CT and PET) can be taken sequentially, combined and superimposed to create one functional and detailed imaging sequence. This PET/CT combines functional imaging from the PET scan with specific anatomical images from the CT; if any areas of tumour activity are detected, the superimposed CT scan pinpoints the location. High accuracy of PET/CT has been reported by recent studies assessing the ability of PET/CT to detect distant metastases. Danielsen *et al*[5] pooled the findings for seven studies that investigated PET/CT in follow-up of cutaneous malignant melanoma and found a pooled sensitivity and negative predictive value of 96% and 95%. Another systematic review by Rodriguez *et al*[11] reported an overall sensitivity of 89.4% and a specificity of 88.8% in detecting metastases in stage III melanoma patients.

Surveillance imaging during follow-up for resected stage III melanoma patients at risk of systemic recurrence remains controversial.[12 13] Potential benefits include early detection of distant disease that induces a change in management (eg, treatment with surgery, systemic therapies, radiotherapy or enrolment in clinical trials of new treatments), which may lead to better survival outcomes than if patients were diagnosed and treated once symptomatic (with higher disease burden).[14] Patients also report feeling reassured by regular imaging.[15] The disadvantages include exposure to radiation that can increase the risk of cancer in the future[16 17]; incidental findings that are later found to be harmless, causing unnecessary investigations and anxiety[18]; added downstream tests including both image-guided biopsies and short-term additional cross-sectional imaging follow-up as a result of equivocal findings, to prove or rule out melanoma metastasis[19] and possible complications of these tests, such as bleeding from biopsy of a suspected visceral metastasis. However, not all incidental findings will later be found to be harmless. Some will be treated and the patient will get better, and it is only by looking at population-level mortality data that we are able to ascertain that some of these cancers must have harmless.

Current guidelines

International guidelines for follow-up after treatment of stage III melanoma vary considerably with respect to surveillance imaging, illustrating the paucity of high-level evidence. The German guidelines recommend CT or PET/CT every 6 months for the first 3 years for resected stage III patients[20]; The US guidelines recommend imaging every 4–12 months for the first 5 years,[21] while the UK National Institute for Health and Care Excellence guidelines recommend surveillance imaging only if there is a clinical trial investigating the value of regular imaging or a local policy with specific funding for 6 monthly imaging for 3 years.[22] The Australian Melanoma Guidelines (2018) state CT of the chest, abdomen and pelvis or PET may be performed prior to definitive therapy where the detection of metastatic disease would influence management.[3] Ultrasound assessment can detect locoregional recurrence, but it is not applicable for detection of systemic recurrence, and not recommended by Australian guidelines. Currently there is no high-level evidence that early detection and management of recurrence from surveillance imaging improves patient outcomes.

Cost-effectiveness of surveillance imaging

Few research studies have investigated the cost-effectiveness of a surveillance imaging strategy in resected stage III melanoma patients.[23–25] Mostly the published studies have reported costs and benefits of one-off (baseline) imaging prior to surgery or imaging to assess treatment response in the management of distant (stage IV) disease as well as exploring whether annual imaging to detect systemic recurrence for resected stage III melanoma patients is more effective than no annual imaging, there is a need to investigate and establish its relative cost-effectiveness for the identification of melanoma recurrence.

The follow-up strategies in current practice were developed before potentially effective systemic therapies that were available to treat advanced melanoma and also before patients with stage III melanoma received adjuvant therapy (where different adjuvant treatments have different recurrence risks, particularly in the first 1–2 years). These new therapies have significant benefits for patients, and in the metastatic setting, the potential to be most efficacious in patients with lower disease burden.[26] Therefore, it might be beneficial to identify recurrence earlier for patients who might benefit more from earlier systemic treatment. This study aims to investigate the 'opportunity cost' of surveillance imaging by exploring the cost-effectiveness of four surveillance strategies (see table 1) for the diagnosis and treatment of distant melanoma recurrence by modelling the relative costs and benefits accrued from (a) no- scheduled imaging follow-up compared with: (b) 12 monthly imaging: one PET/CT scan per year for 5 years, (c) 6monthly imaging: two PET/CT scans per year for 5 years, (d) 3–4 monthly PET/CT imaging for 5 years: (involves routine imaging

Table 1 Follow-up strategy description

	Follow-up strategy	Description
Intervention	No imaging follow-up	No further routine imaging during follow-up. Clinical visit every 4 months for the first 3 years, every 6 months in years 4–5. Patients receive imaging if either the patient or doctor identifies signs/symptoms suggesting recurrence
Comparators	Intensive surveillance imaging	Patients given routine imaging every 3–4 months during the first 3 years, every 6 months in years 4–5. Clinical visit with a melanoma specialist at the time of each scan
	Routine 6-monthly imaging	Two PET/CT scans per year for 5 years. Clinical visit with a melanoma specialist at the time of each scan +every 3 months in between
	Routine 12-monthly imaging	One PET/CT scan per year for 5 years. Clinical visit with a melanoma specialist at the time of the scan

PET, positron emission tomography.

every 3 months during the first 3 years, every 6 months in years 4–5).

METHODS AND ANALYSIS

Patients and data source

This prospective cohort study identified consecutive resected stage III melanoma patients with American Joint Cancer Committee eighth edition stage III disease,[2] treated at Melanoma Institute Australia (MIA) between the years 2000 and 2017 and entered into the research database at MIA. We included stage IIIA–D melanoma patients who had received surgical treatment with curative intent had no evidence of further disease postoperatively and were followed-up clinically at MIA to assess for recurrence. Many patients underwent repeated surveillance imaging as a part of their scheduled follow-up. We also identified a cohort of patients with standard clinical follow-up that did not include surveillance imaging.

Patientand public involvement

No patient involved.

Model structure

To assess the cost-effectiveness of a no-imaging follow-up strategy compared with 12 monthly, 6 monthly and 3–4 monthly imaging, a decision tree will be built in TreeAge software (TreeAge Software, Williamstown, Massachusetts, USA). The model will start with patients receiving one of four follow-up strategies: (1) routine 12 monthly imaging, (2) routine 6 monthly imaging, (3) 3–4 monthly imaging or (4) follow-up without imaging (see figure 1). Each branch of the decision tree will represent a follow-up strategy under assessment and will be parameterised with data on diagnostic accuracy, costs and recurrence obtained from our prospective cohort and from published literature over a time horizon of 5 years. Two economic outcomes will be assessed: cost per case of distant recurrence appropriately identified and cost per diagnosis error avoided.

Model assumption

The model assumptions include:

a. Surveillance imaging is primarily used to identify systemic recurrence. Locoregional melanoma recurrence is often identified by physical examination in contrast to distant disease, which is difficult to detect by physical examinations. Thus PET/CT imaging surveillance is predominantly undertaken to identify distant metastatic disease.[27]
b. Systemic recurrence occurs only once for patients who progress. Therefore, the model will simulate the costs and benefits up to the first (initial) systemic recurrence.
c. In the absence of histopathology, disease status after 6 months of clinical follow-up will be used as a reference standard for PET/CT imaging.
d. Based on Australian guidelines,[3] patients with positive imaging test results will undergo confirmatory investigations: fine-needle aspiration biopsy, core biopsy, serum lactate dehydrogenase, whole body PET/CT, MRI of the brain and gene mutation testing.
e. The costs for unresectable stage III or stage IV melanoma treatments included standard imaging, medical appointments, genetic testing and pharmacotherapies where relevant as well as costs for grades 3 and 4 adverse events for pharmacotherapies (eg, colitis).
f. Costs of palliative and end of life care will be excluded. As the main outcomes, the effectiveness end point applied was the detection and treatment of distant recurrence, the costs of end of life care were not included in the economic analysis.

IMAGING SURVEILLANCE STRATEGIES

We will evaluate the ability of the four surveillance strategies to detect systemic recurrence for each patient in the respective cohort. Table 1 describes the different follow-up strategies.

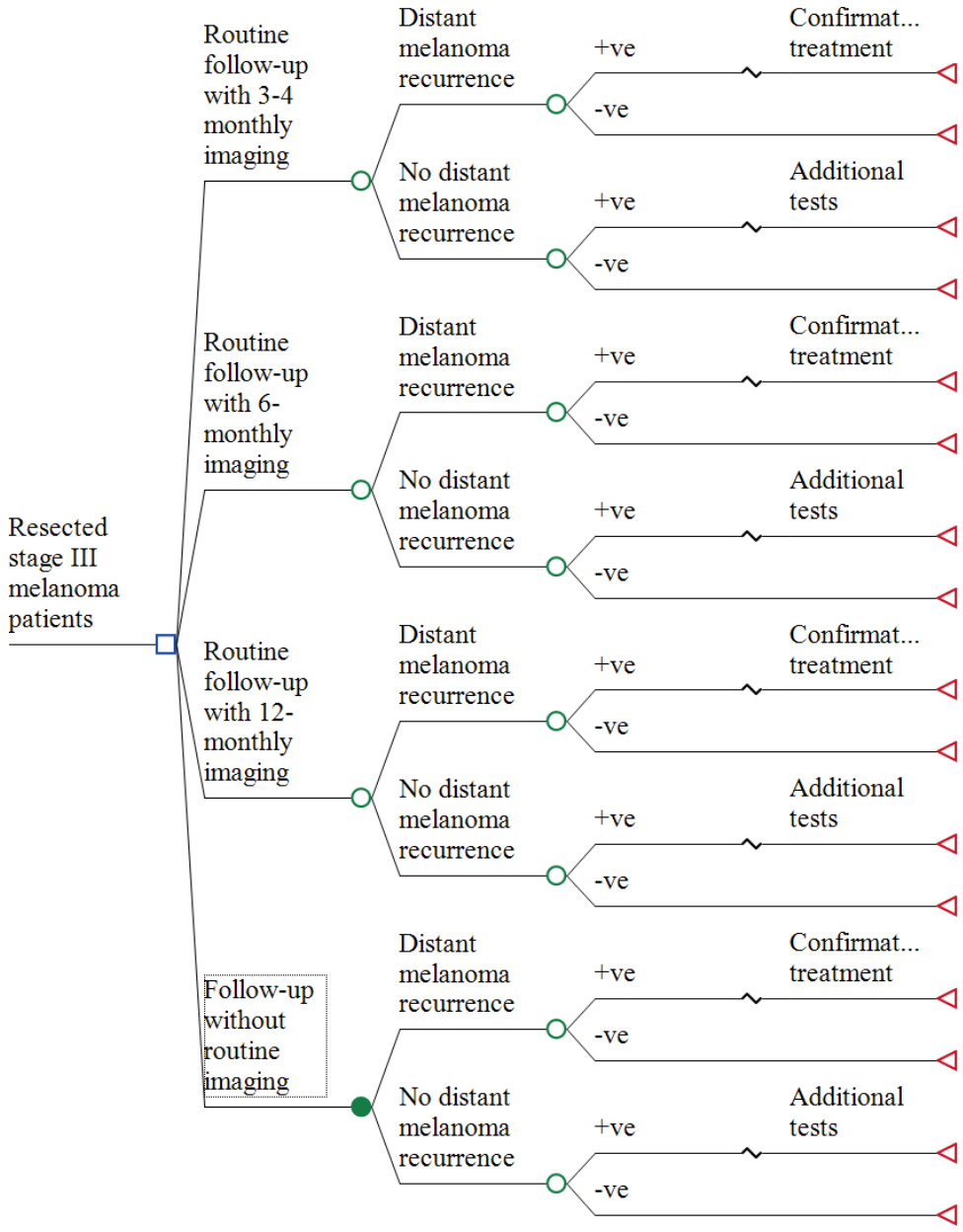

Figure 1 Decision model structure. PET, positron emission tomography.

DATA REQUIRED FOR THE MODEL

Prevalence data

We will populate the decision model with the prevalence of distant melanoma recurrence from our MIA cohort. For each follow-up strategy, the prevalence of systemic recurrence will be calculated.

Test accuracy data

PET/CT sensitivity and specificity over a 5-year period will be derived from a cohort study we conducted among 332 resected stage III melanoma patients (median follow-up 61 months). This analysis has provided data regarding the diagnostic accuracy of PET/CT at each 3, 6 and 12 monthly follow-up time points. (table 2). The result of PET/CT imaging will be classified as true positive (TP), if metastatic disease was detected by the surveillance imaging. PET/CT findings will be defined as true negative (TN), if the scan was negative and no distant disease was detected during further follow-up. PET/CT results will be defined as false negative (FN), if the scan was negative, but recurrent disease was detected during 6-month follow-up by other tests or physical examination in clinical follow-up. PET/CT findings will be defined as false positive (FP), if the scan indicated melanoma or suspicion for melanoma, but the reference standard confirmed there was no melanoma.

Healthcare resource use and costs

Healthcare resources will include all imaging, confirmatory tests and blood tests, medical appointments and subsequent treatment, following the initial surgical management of stage III melanoma (table 3). Healthcare use incurred to diagnose stage III disease or to treat it surgically will be excluded. To account for the cost of

Table 2 Test performance of PET/CT surveillance imaging

Investigation	Sensitivity (95% CI)	Specificity (95% CI)	Reference
3–4 monthly imaging	79% (70% to 86%)	88.6% (86.4 to 90.5)	32
12-monthly imaging	79% (70% to 86%)	88.6% (86.4 to 90.5)	32
6-monthly imaging	79% (70% to 86%)	88.6% (86.4 to 90.5)	32
No imaging follow-up	71.4% (55.4–84.3)	99.6% (99.2 to 99.8)	33

PET, positron emission tomography.

incidental findings, our model will include the costs of further investigations (eg, extra scans, diagnostic biopsies) following an FP result resource use will be identified from each patient's detailed medical records at MIA.

The costs of resource utilisation will be estimated from the perspective of the Australian health system. Resource use will be valued using unit costs from the Medicare Benefits Schedule for diagnostic tests and outpatient care and Australian Refined Diagnosis Related Groups for hospital admissions.[28] Treatment costs following a melanoma recurrence or stage IV diagnosis will be derived from published Australian study.[29] All costs will be adjusted to 2020 prices and 5% discounting per annum will be applied.[30]

Outcomes

We will report two different effectiveness/outcome measures from an Australian health system perspective: the cost per new distant melanoma recurrence detected and treated, and the cost per diagnostic error avoided.

Outcome for recurrent melanoma appropriately diagnosed

For distant recurrent melanoma appropriately diagnosed and treated, we will use the difference between the TP and FN value from our cohort study. We will give a value of 1 to TP and 0 to FN. For convenience, we will give the value 1 for FP and TN, therefore, we will only give the value of 0 for an erroneous identification.

Outcome for diagnostic error avoided

For the outcome of diagnostic error avoided, no effectiveness data are required. The TP and TN cases will be given the value of 1. TPs and FNs will be given the value of 0.

Table 3 Cost inputs for the model, 2019 Australian dollars

Test	Site	Base case costs (AUD)	Sensitivity analysis range (AUD)	Source
Whole body PET/CT	Whole body	1397		MBS #57007, MBS #61 553
Ultrasound	Regional lymph node	93		MBS #55 812
MRI	Brain and head	343		MBS #63 001
X-ray	Chest and abdomen	81		MBS # 58903, MBS # 58 503
FNAB	Solid tissue or tissues from two or more sites	188		MBS # 73 066
Bone scan	Whole body	408		MBS # 61 421
Clinical follow-up (Specialist)		66		MBS #116
Mutation analysis	Stage III/IV tumour tissue	196		MBS # 73 336
Core biopsy	Lymph node, muscle or other deep tissue or organ	129	135–997	MBS #30075, AR-DRG
Serum lactate dehydrogenase (LDH)		8		MBS # 66 500
Cost of treatment: 12-month cost—stage III unresectable/IV		115 072	1 05 208–1 25 573	29
Cost of treatment: 36-month cost—stage III unresectable/IV		187 599	1 75 520–2 00 130	29

AUD, Australian dollar; FNAB, fine needle aspiration biopsy.

Analysis

The model will estimate the mean cost for each follow-up strategy and patients entering the model will be aged 18 years or older. The results of the cost-effectiveness analysis will be presented in incremental cost-effectiveness ratios (ICERs). The economic outcomes will be the cost per new distant melanoma recurrence appropriately detected and treated and cost per diagnostic error avoided, for the three strategies when compared with no imaging. A deterministic analysis will be carried out for the base-case results for the different outcome measures.

Sensitivity analysis

A number of sensitivity analyses will be carried out as summarised below:

1. Deterministic sensitivity analyses will be undertaken to explore the effect of differences in test performance and costs of surveillance imaging in terms of the ICERs. A range of sensitivity and specificity values as well as costs will be sourced from the published literature.
2. A deterministic sensitivity analysis will be carried out on the extreme values for the range of prevalence of systemic recurrence found in the published trials and registry studies.
3. Probabilistic sensitivity analysis will be undertaken to determine the uncertainty of the model input parameters of sensitivity and specificity, prevalence and treatment costs. Each model parameter will be assigned a distribution reflecting the amount and pattern of its variation, and cost-effectiveness results will be calculated by simultaneously selecting random values from each distribution. The process will be repeated 10 000 times in a Monte Carlo simulation of the model to give an indication of how variation in the model parameters leads to variation in the ICERs for a given imaging strategy. We will place a normal distribution for the data on test accuracy. Treatment costs point estimates will be derived from the literature.[29] For costs we will place a Gamma distributionand a beta distribution for sensitivity, specificity and prevalence.

Reporting of the study design, methods and results will follow the Consolidated Health Economic Evaluation Reporting Standards.[31]

Ethics and dissemination

This study was approved by the Institutional Review Board's ethics committee (MIA2016/182), the Australian Institute of Health and Welfare (EO2019-1-454) and the Royal Prince Alfred Hospital Ethics Committee X18-0144, LNR/18/RPAH/206.

The results of this study will inform the Cancer Council Australia's melanoma guidelines Wiki.[3] Additionally, the results of this study will be published in high-impact peer-reviewed medical and economic journals. A lay summary written in collaboration with consumers from Melanoma Patients Australia will be disseminated through social media channels.

DISCUSSION

After treatment of stage III melanoma, patients have regular follow-up with their treating doctors. Imaging techniques such as CT, PET or PET/CT for detection of distant disease are used alongside these visits. Routine surveillance aims to support and reassure patients and to detect systemic recurrence early so that appropriate treatment can be given in an optimal time frame. Furthermore, with new effective therapies for stage IV disease, robust evidence regarding the most cost-effective approach for follow-up of stage III melanoma patients is needed. There is a lack of consensus and evidence-based guidelines regarding the optimal imaging modalities or the frequency of schedules to best identify asymptomatic systemic melanoma recurrences.

This study will provide a framework for estimating the cost-effectiveness of four follow-up strategies in resected stage III melanoma over a 5-year time frame following curative-intent surgical treatment.

Strengths and limitations: this is one of the first studies to estimate the cost-effectiveness of three follow-up regimens compared with no imaging follow-up in melanoma. Furthermore, the analysis will be based on test accuracy data from a large cohort study of over 1000 patients with stage III and value of Information analysis will estimate the expected value of conducting a prospective randomised controlled trial of imaging surveillance to reduce decision uncertainty. Finally, the model structure accounts for clinical and policy-relevant outcomes including test accuracy.

There are some limitations to this study. First, the comparison of the three imaging schedules was not based on data from randomised trials and some selection bias might be introduced. The model structure was limited in the pathways for which data were unavailable, therefore, we had to make many assumptions. Second, the treatment cost and utility data will be obtained from the published literature. Furthermore, the comparison of the three imaging schedules was not based on data from randomised trials and some selection bias might be introduced.

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Competing interests RS received honoraria from Novartis and MSD for an advisory capacity.

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