



Medical Services Advisory Committee Public Summary Document

Reference 35c – Positron Emission Tomography (PET) for Lymphoma

Applicant: (former) Diagnostics and Technology Branch
(now Diagnostics Services Branch) of the
Department of Health and Ageing

Date of MSAC consideration: 46th MSAC meeting, 11 September 2009,
Melbourne

1. Purpose of application

An application from the Department of Health and Ageing was made to the Medical Services Advisory Committee (MSAC) to review new evidence for whole body 2-[¹⁸F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) for lymphoma since the 2001 MSAC assessment. The latter assessment recommended interim funding until June 2010 for staging of patients with newly diagnosed or previously untreated Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) (MBS 61616), for the evaluation of a residual mass after treatment of HL and NHL (MBS 61622), and for restaging of suspected recurrent or residual HL and NHL (MBS 61628). The current assessment focuses on the assessment of PET performed for the evaluation of eight lymphoma indications.

2. Background

Dual-modality PET/CT, in which PET and x-ray computed tomography (CT) scanners are incorporated in a single device, has recently been developed in order to provide more accurate anatomic localisation of the distribution of FDG, and more efficient attenuation correction than is possible with 'stand-alone' PET scanners. Stand-alone PET scanners are no longer being produced and MSAC noted that in practical terms the purpose of the current submission relates to the funding of PET/CT. For simplicity, MSAC adopted the term PET to refer to either PET or PET/CT.

PET is a minimally invasive nuclear medicine imaging technique that uses short-lived radiopharmaceuticals to detect and assess perfusion and metabolic activity in various organ systems. It provides information about function and metabolism that is complementary to the structural information provided by anatomical imaging techniques such as CT.

The review considered by MSAC was restricted to an examination of PET conducted with the radiopharmaceutical ¹⁸F-FDG, which is a radio-labelled analogue of glucose. The primary advantage of FDG use in oncological applications relates to the increased uptake of glucose by many malignant tumours compared with normal surrounding tissue. However, heightened FDG uptake is not specific to malignant cells. Inflammatory cells and some benign tumours are also FDG avid, and thus inflammatory foci, sarcoidosis, and acute and chronic infections can be positive on PET imaging, and may contribute to false-positive results with respect to the index malignancy. The causes of increased uptake can only be differentiated by clinical assessment, further diagnostic investigation or repeat testing.

3. Clinical need

MSAC noted the complex classification and staging of the disease, as well as treatments requiring a variety of decisions. “Lymphoma” encompasses a heterogeneous group of lymphoproliferative malignancies which vary widely in their biological and clinical behaviour. Therapy for lymphoma is therefore highly individualised, depending upon histologic type, staging, and a variety of clinical and laboratory features which have been shown to have an impact on prognosis.

In order to undertake this assessment, considerable simplification of classification and management was necessary. The lymphomas were assessed in two broad groups: *classical Hodgkin and aggressive non-Hodgkin lymphomas*, which are relentlessly progressive and uniformly fatal if untreated but are potentially curable with chemotherapy +/- radiotherapy; and *indolent non-Hodgkin lymphomas*, which progress very slowly, are often asymptomatic, and at this point in time are considered incurable (with the exception of very early-stage disease).

PET has a potential role at multiple points in the management pathway. A number of changes in therapy have also occurred since the first report in 2000. PET has already become widely incorporated into the standard management of lymphoma, ahead of rigorous clinical trial data on its particular contribution to improving health outcomes for patients with the disease.

MSAC noted that:

- The first use of PET is to more accurately stage the disease (both indolent NHL and HL and aggressive NHL) at initial diagnosis.
- In HL and aggressive NHL, the following five other uses were also considered:
 - to determine the patient’s response to first-line treatment while treatment is underway, ie. is the patient’s disease resistant to the currently administered treatment?
 - to assess the response after first-line treatment is completed, ie. was the first treatment course successful?
 - to detect recurrent disease – this is where use has risen most rapidly.
 - to stage and re-assess the extent of disease in a patient with a confirmed relapse in order to establish a new baseline prior to second-line chemotherapy. This is analogous to its use in primary staging.
 - to assess the response to the second-line treatment prior to consideration of stem cell transplantation.

MSAC also considered other uses of PET in *indolent NHL*: to evaluate suspected relapse following initial treatment and to assess transformation to more aggressive disease.

4. Comparator

MSAC noted that this was the second report regarding a very complex issue and that, in contrast to the 2000 report it had been difficult to find comparative data with respect to gallium scanning as nowadays this type of imaging was only rarely used.. MSAC accepted that the comparator for PET across the management pathway was either as a replacement test to CT alone or as an additional investigation.

5. Safety

The safety of PET has been assessed and reported in previous MSAC reports. No known toxicity has been noted and PET is considered a safe procedure.

6. Clinical effectiveness

The available evidence base for all indications is poor. MSAC noted slides which showed examples of PET in lymphoma, both before and after treatment. Whilst PET techniques showed consistently improved sensitivity and specificity and better prognostic information when used in the management of lymphoma, there have been no prospective outcome data showing that the diagnostic use of PET delivers better health outcomes compared to CT alone.

- **Hodgkin lymphoma (HL) and aggressive non-Hodgkin lymphoma (NHL)**

It was anticipated that the metabolic signal provided by the FDG avidity of active HL and aggressive NHL should provide a more sensitive marker of disease extent, disease response to therapy, and disease recurrence than anatomical indices (CT), thereby permitting more timely and appropriate clinical decision-making and improving patient outcomes.

MSAC agreed that an initial staging PET scan does not commonly alter how patients are managed, but its main purpose is to obtain baseline data against which to assess future response. The use of PET may occasionally improve the formulation of a management plan for initial staging of HL or, even less commonly aggressive NHL. MSAC noted however that the health impact of use of PET in this setting has not been quantified.

Using PET to determine the patient's response to first-line therapy while treatment is underway ("interim response assessment") is the subject of six current clinical trials, so it is premature to consider this indication further until these studies are completed.

There is weak evidence to support the conclusion that PET assessment within three months of completing definitive first line treatment is beneficial. The rationale for such an assessment is that early detection of failed first-line treatment will lead to the administration of effective salvage therapy. MSAC noted that it would be illogical to provide reimbursement for a post-treatment scan if reimbursement for a baseline scan is not supported.

MSAC considered that the evidence provided no support for the use of PET as surveillance for recurrent disease. In this context, PET was usually being used for reassurance rather than to determine further management. MSAC noted that there was an important distinction between routine surveillance and the investigation and staging of a true relapse of lymphoma. MSAC considered PET performed in the setting of confirmed relapse represents a new baseline staging test. In the setting of suspected, as opposed to confirmed recurrent disease, MSAC found no evidence that PET led to improved health outcomes.

There is no comparative evidence of diagnostic accuracy, impact on patient management, or change in health outcome in using PET to assess response to the second-line treatment prior to stem cell transplant. The available evidence base compares outcomes of stem cell transplant according to whether the patient was previously PET-positive or PET-negative.

- **Indolent non-Hodgkin lymphoma (NHL)**

Indolent NHL tends, by its nature, to be less metabolically active and is therefore less often FDG-avid than aggressive NHL. However, in FDG-avid indolent disease, it is anticipated that PET should permit more accurate initial staging in patients with early stage (I/II) disease where radiation is being proposed as definitive therapy. There is insufficient evidence of benefit in using PET for the evaluation of suspected relapse. PET should also be a more sensitive marker of transformation to aggressive NHL than conventional methods, but the clinical impact of this use could not be established.

7. Cost-effectiveness

MSAC noted that the available evidence base for all indications is poor, so that the economic evaluation presented is based on a series of assumptions and extrapolations which were considered plausible by the clinical experts on the Advisory Panel. Consequences in the economic evaluation rely on modelled effects to provide estimates. In this analysis, the impact on health outcomes flow from improved targeting of therapy with either more or less aggressive therapy resulting in either improved survival or reduced complications and improved quality of life. Given the limitations of the evidence, reliable estimates in terms of health outcomes were not able to be determined. However the assessment overall is reasonably suggestive of clinical benefit without incurring a large incremental cost.

In the setting of aggressive HL/NHL the cost-consequence analysis estimated that there would be cost savings of dual modality PET/CT compared with CT without PET in which 14/100 patients would correctly avoid escalated therapy, and 9/100 would be correctly redirected to escalated therapy. The overall conclusion from the analysis is that cost savings depend on the proportion of patients who subsequently undergo stem cell transplant. Sensitivity analyses indicated that PET continued to be cost-saving unless the proportion of patients undergoing stem cell transplantation for relapsed aggressive NHL (following “salvage” or second-line chemotherapy) was set at a lower value (0.5 rather than 0.75). In the setting of indolent NHL the use of baseline PET/CT for suspected early stage disease would result in 19/100 patients avoiding the complications of radiotherapy at an incremental cost of \$66,900/100 patients.

8. Financial/budget impacts

If PET were reimbursed in Australia using the current MBS fee for a standard whole-body PET scan (\$953), the potential annual total cost to the MBS could range, depending on utilisation, between \$208,707 and \$291,618 for indolent lymphoma; between \$1,413,299 and \$2,616,173 for initial staging and assessment of first-line treatment in patients with HL and aggressive NHL, and between \$598,484 and \$801,473 for assessment of second-line treatment.

The net financial cost across HL and aggressive and indolent NHL is negative, representing cost savings.

MSAC also noted that PET scans (without prescriptive limitations) avoid the need for separate CTs of chest, abdomen, pelvis and other body sites. This would have considerable benefits for patients, noting that multiple diagnostic CTs incur comparable costs to one PET (with a higher total radiation dose).

9. Other relevant factors

MSAC noted equity issues related to access to PET and in particular public access, as well as workforce capacity to perform and interpret PET scans. MSAC also noted the variety of funding models currently in place for PET reimbursement and considered that this may need to be reconsidered to ensure equity of access to this form of imaging.

MSAC noted that the generalisability of the findings and assumptions is limited to high-level PET services within comprehensive multidisciplinary oncology settings (including access to stem cell transplantation).

10. MSAC's advice to the Minister

Members supported public funding for indolent NHL, HL and aggressive NHL in the specific circumstances outlined below.

- **Indolent NHL**

Based on the evidence in terms of diagnostic accuracy, changes in patient management, and hence probable improvements in health outcomes, MSAC advised that public funding should continue for a single dual modality PET/CT per patient in the initial staging of indolent NHL where clinic-pathological and anatomical imaging indicated that the stage was I or IIA and where the proposed management plan was to administer definitive radiotherapy with curative intent.

- **HL and aggressive NHL**

Based on similar considerations, MSAC advised that public funding should continue for patients who have HL and aggressive NHL as:

- a single dual modality PET/CT whole body scan per patient at baseline for staging newly diagnosed or previously untreated disease;
- a single dual modality PET/CT whole body scan per patient (as an alternative to CT) to assess response to first-line therapy either during treatment or within three months of completing definitive first-line treatment;
- a single dual modality PET/CT whole body scan per patient (as an alternative to CT) to establish a new baseline following confirmed recurrence of disease; and
- a single dual modality PET/CT whole body scan per patient (as an alternative to CT) to assess response to second-line chemotherapy prior to consideration of stem cell transplantation.

MSAC does not support the public funding of dual modality PET/CT for surveillance and also notes concern at the use of any diagnostic imaging modality for surveillance, and suggests that the cost-effectiveness of this practice should be investigated further.

MSAC advises that arrangements should be made to ensure that dual modality PET/CT scanning for HL and aggressive NHL is used in place of (rather than in addition to) conventional CT scanning as above.

MSAC advises that funding of PET for suspected (as opposed to confirmed) recurrent disease should no longer be supported (currently MBS item number 61628).

11. Summary of consideration and rationale for MSAC's advice

MSAC determined that, under the limited circumstances discussed above, there is sufficient evidence that PET used for indolent NHL, HL and aggressive NHL will improve diagnostic accuracy; favourably change clinical management and produce worthwhile improvements in health outcomes. The information available suggests that these results can be achieved without incurring disproportionate increases in costs (and in some scenarios results in cost savings).

MSAC considered it was important to limit the assessment of response to chemotherapy in HL and aggressive NHL to one PET/CT scan only. Having agreed on this limitation, it became less important to specify whether this should be conducted during chemotherapy or after completion of a definitive chemotherapy course. MSAC noted that given the current evidence, "interim response assessment" should only be undertaken in the context of a clinical trial and for this reason it was expected that most PET/CT would be done at the completion of definitive treatment.

MSAC further agreed that in the setting of proven HL and aggressive NHL a second baseline PET scan would be needed prior to commencement of further systemic treatment so that response to therapy could be subsequently assessed.

Members also agreed that it was important to cease public funding of multiple PET scans undertaken for the purposes of reassurance and surveillance of patients whilst in remission. MSAC also agreed that the descriptor of the MSAC items needed to minimise this possibility.

MSAC considered whether continued funding of PET for suspected recurrent disease should be supported. In the absence of any outcome data for this indication, or of any identifiable ongoing clinical trials which address this question, MSAC advised that funding of PET for suspected (as opposed to confirmed) recurrent disease should no longer be supported.

MSAC also formed the view that a crucial component of continued public funding of PET required a reduction in the frequency of PET scanning in situations where the clinical evidence did not support the benefit of scanning. This raised a much broader issue of the frequency of use of diagnostic imaging in routine surveillance. A predictable response to any implementation of advice to minimise use of PET for surveillance may be to increase use of other diagnostic imaging services (such as CT alone). This would need to be managed.

12. Context for decision

This advice was made under the MSAC Terms of Reference:

- Advise the Minister for Health and Ageing on the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported.
- Advise the Minister for Health and Ageing on which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness.
- Advise the Minister for Health and Ageing on references related either to new and/or existing medical technologies and procedures.
- Undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC) and report its findings to the AHMAC.

13. Linkages to other documents

MSAC's processes are detailed on the MSAC Website at: www.msac.gov.au.

The MSAC Assessment Report is available at
<http://www.msac.gov.au/internet/msac/publishing.nsf/Content/Completed-References1-40>