Australian Government

Department of Health

Application 1485:

Sentinel Lymph Node Biopsy for Intermediate Thickness Melanoma

DRAFT

PICO Confirmation

(to guide a new application to MSAC)

(Version 1.0)

This PICO Confirmation Template is to be completed to guide a new request for public funding for new or amended medical service(s) (including, but not limited to the Medicare Benefits Schedule (MBS)). It is relevant to proposals for both therapeutic and investigative medical services.

Please complete all questions that are applicable to the proposed service, providing relevant information only.

Should you require any further assistance, departmental staff are available through the Health Technology Assessment (HTA Team) on the contact number and email below to discuss the application form, or any other component of the Medical Services Advisory Committee process.

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Version Control

Document History

Version Number	Date Changed	Author	Reason for Change
0.1	10 March 2016	MSAC Reforms	Final for Publication
0.2	19 May 2016	MSAC WEB	Accessibility compliance

Document Approval

Version Number	Date Changed	Author	Reason for Change
1.0	19 May 2016	MSAC Web	Document released for Online publication

Summary of PICO/PPICO criteria

Table 1 describes the PICO/PPICO criteria to define the question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC).

Table 1 Summary of PICO/PPICO criteria

Component	Description
Patients	Patients with intermediate thickness malignant cutaneous melanoma (depth >1.0mm to 4mm)
Prior tests	Excision biopsy of melanoma
Intervention	Sentinel lymph node biopsy (SLNBx) with excision of lymph node(s) identified by a combination of blue dye (lymphotropic dye injection) and lymphoscintigraphy/gamma probe
Comparator	Clinical surveillance of the regional lymph nodes (by GP, 1-2 per year); or SLNBx under existing MBS items
Outcomes	Efficacy/effectiveness • Overall survival • Melanoma-specific survival • Disease-free survival • Time to progression • Cumulative rate of nonsentinel-node metastasis • (Hazard) rate of local recurrence • Time to recurrence • Change in patient management (e.g. complete lymph node dissection, close surveillance, adjuvant treatment) • Quality of life Safety • Frequency of adverse reactions (e.g. lymphoedema, nerve injury, infection) • Patient-reported adverse reactions (e.g. reassurance, anxiety) Cost-effectiveness • Cost per life year gained • Cost per QALY gained

Component	Description
	Healthcare resources • Cost of lymphoscintigraphy and lymphotropic dye injection • Cost of nuclear medicine services for lymphoscintigraphy • Cost of removing sentinel lymph node(s) • Cost associated with changes in clinical management (e.g. increased follow-up) Total Australian Government Healthcare costs • Total cost to the Medical Benefits Schedule (MBS) • Total cost to the Pharmaceutical Benefits Scheme (PBS)Total cost to other healthcare services

PICO or PPICO rationale for therapeutic and investigative medical services only

Population

The intervention is proposed in Australia for the use in patients undergoing wide excision of intermediate thickness malignant cutaneous melanoma.

Melanoma is a malignancy of skin pigment cells (melanocytes). The lifetime risk for melanoma in Australia is 1 in 24 for males and 1 in 35 for females. There are more than 12,000 new cases diagnosed in Australia each year, and more than 1,500 people die each year from the disease.

A commonly used classification scheme for melanoma staging is based on Breslow tumour depth analysis, which describes lesions as thin (<1 mm), intermediate thickness (1–4 mm), or thick (>4 mm). Most cases are diagnosed at an early stage (<1.0mm thickness) where 5-year survival is >95%. With increasing depth, there is a stepwise decline in survival.

In addition to tumour depth, the presence or absence of nodal disease impacts on long term survival. Lymph node positive patients may subsequently be considered for a nodal clearance for local disease control. There are also a number of medical treatments with survival benefits for stage IV patients (distant metastases) that are currently being trialled in stage III patients (lymph node positive). Preliminary evidence of these trials suggests that sentinel lymph node positive patients may be eligible for adjuvant treatment in the future that could provide survival benefits.

Rationale

Sentinel node status is the most significant prognostic indicator in patients with intermediate thickness melanoma. Patients with intermediate thickness melanoma (greater than 1.0mm depth) have an increased risk of lymph node involvement and hence poorer survival.

SLNBx is increasingly being performed in Australia, but this procedure is not coded in the MBS and alternative item numbers do not accurately reflect its use or procedural requirements.

Prior test (investigative services only - if prior tests are to be included)

Excision biopsy of the primary melanoma is performed to identify patients with intermediate thickness melanoma.

If the biopsy is incomplete/partial, a complete biopsy is considered to gauge depth (according to NHMRC guidelines).

Intervention

The intervention is sentinel lymph node biopsy with excision of lymph node(s) identified by a combination of blue dye (lymphotropic dye injection) and lymphoscintigraphy/gamma probe, ideally performed at the time of the primary melanoma wide excision (although this is not always possible). The admission duration is usually shorter than 24 hours.

Eligible patients are identified by excision biopsy, and informed consent is obtained from these patients for the proposed SLNBx.

Pre-operative lymphoscintigraphy is then performed to identify the nodal basin: Lymphoscintigraphy requires an injection of technetium antimony sulphur colloid prepared by a nuclear physician, injected into the site of the primary melanoma with a needle and syringe.

During melanoma excision surgery, Patent Blue V 1ml is injected subcutaneously around the site of the primary melanoma by the surgeon. Using a combination of a hand-held gamma probe and visualisation of blue lymphatics, the sentinel lymph node is identified, removed and referred for histopathology. The reusable hand-held gamma probe (same as that used in breast cancer surgery) is covered with a disposable sterile plastic sleeve for the procedure.

The primary melanoma is cleared based on NHMRC guidelines. The wound for the SLNBx is closed with the same suture material as the primary melanoma site.

Rationale

It is possible to perform SLNBx with blue dye (lymphotropic dye injection) alone, although identification rates are lower.

The best results are achieved with the proposed combination of lymphoscintigraphy and blue dye (greater than 95% identification) (Vidal, Vidal-Sicart et al. 2012).

Comparator

Currently patients with intermediate thickness melanoma either have clinical surveillance of the regional lymph nodes by the General Practitioner (1-2 per year) or SLNBx depending on patient wishes, after an informed discussion with their general practitioner, dermatologist, or surgeon.

Hence, SLNBx for melanoma is already being performed within the MBS but cannot be identified from other indications for lymph node biopsy (MBS items 30075, 30329, 30332, 31420, 31423). Details on these existing MBS items are listed in the Appendix.

If patients in the observation only group develop clinical or radiological evidence of nodal disease during follow-up (about 20%) then a therapeutic lymph node dissection is offered to those patients, provided no distant metastases are detected.

Rationale

A new MBS item number is proposed to replace existing non-specific item numbers, which encompass a broad range of indications, of which SLNBx for melanoma is just one.

Outcomes

Patient relevant

It is claimed that SLNBx provides important prognostic information, allowing for improved local disease control and more effective treatment selection in patients with intermediate thickness melanoma. In sentinel lymph node positive patients, complete lymph node dissection may be considered/avoided, and adjuvant molecular and immune therapies may be introduced in the future. This may result in improved overall survival, melanoma-free survival and disease-free survival; and health-related quality of life may be improved.

Safety outcomes to be considered include the frequency of adverse reactions (e.g. lymphoedema, nerve injury, infection) and patient-reported adverse reactions (e.g. reassurance, anxiety).

Healthcare system

The management of patients with a positive sentinel lymph node changes in that close specialist follow-up will be performed, potentially avoiding a complete lymph node dissection, which may be necessary if nodal disease develops during general surveillance. More accurate prognosis, treatment and management plans may result in savings to the health system as fewer procedures are needed due to better risk stratification, lower progression rates, longer time to progression and lower rates of and longer time to recurrence. However, future costs could rise if effective adjuvant therapy were to become available for node positive patients.

About 30% of new cutaneous melanoma cases detected in Australia are staged as intermediate thickness melanoma. In these 2,500 - 3,000 patients (including patients treated within the public health sector), SLNBx could be utilised. As mentioned above, SLNBx is already widely performed in Australia, but its use is not quantifiable. It is unclear whether the number of SLNBx will increase or whether the interventions will just be coded differently under a specific MBS item number. A SLNBx specific item number would enable accurate documentation of the prevalence of this procedure.

A significant proportion of cutaneous melanomas are treated in General Practice. For SLNBx to be performed, referral to appropriately trained specialists is required. Lymphoscintigraphy requires nuclear medicine services. SLNBx can be performed by a surgeon trained in the technique (including General Surgeon, Plastic and Reconstructive Surgeon, ENT, procedural dermatologist). Similar to surgeon training in SLNBx in breast cancer, it is suggested that the first 20 cases be supervised. Surgeons already performing SLNBx in the management of breast cancer will not need additional training.

The projected costs are commensurate with SLNBx for breast cancer (30299-30303), i.e. between the costs of lymph node biopsy (30075) and lymph node clearance (30330, 30335, 30336, 31426, 31429, 31438, 35551).

Rationale

The evidence provided in the application reports the following results:

Biopsy based staging versus nodal observation

The staging of intermediate-thickness primary melanomas according to the results of sentinel-node biopsy provides important prognostic information and identifies patients with nodal metastases whose survival can be prolonged by immediate lymphadenectomy (Morton, Thompson et al. 2006).

Biopsy-based management prolongs disease-free survival for all patients and prolongs distant disease–free survival and melanoma-specific survival for patients with nodal metastases from intermediate-thickness melanomas (Morton, Thompson et al. 2014).

Complete lymph node dissection

Two recent trials investigated the efficacy of complete lymph node dissection versus no dissection in patients with sentinel lymph node biopsy positive melanoma. The DeCOG-SLT trial found no difference in survival in patients treated with complete lymph node dissection compared with observation only (Leiter, Stadler et al. 2016), although this trial did not achieve the required number of events, leading to the trial being underpowered.

The second Multicenter Selective Lymphadenectomy Trial (MSLT-II) showed that immediate completion lymph node dissection increased the rate of regional disease control and provided prognostic information but did not increase melanoma-specific survival among patients with melanoma and sentinel-node metastases (Faries, Thompson et al. 2017).

Adjuvant treatment of intermediate thickness melanoma

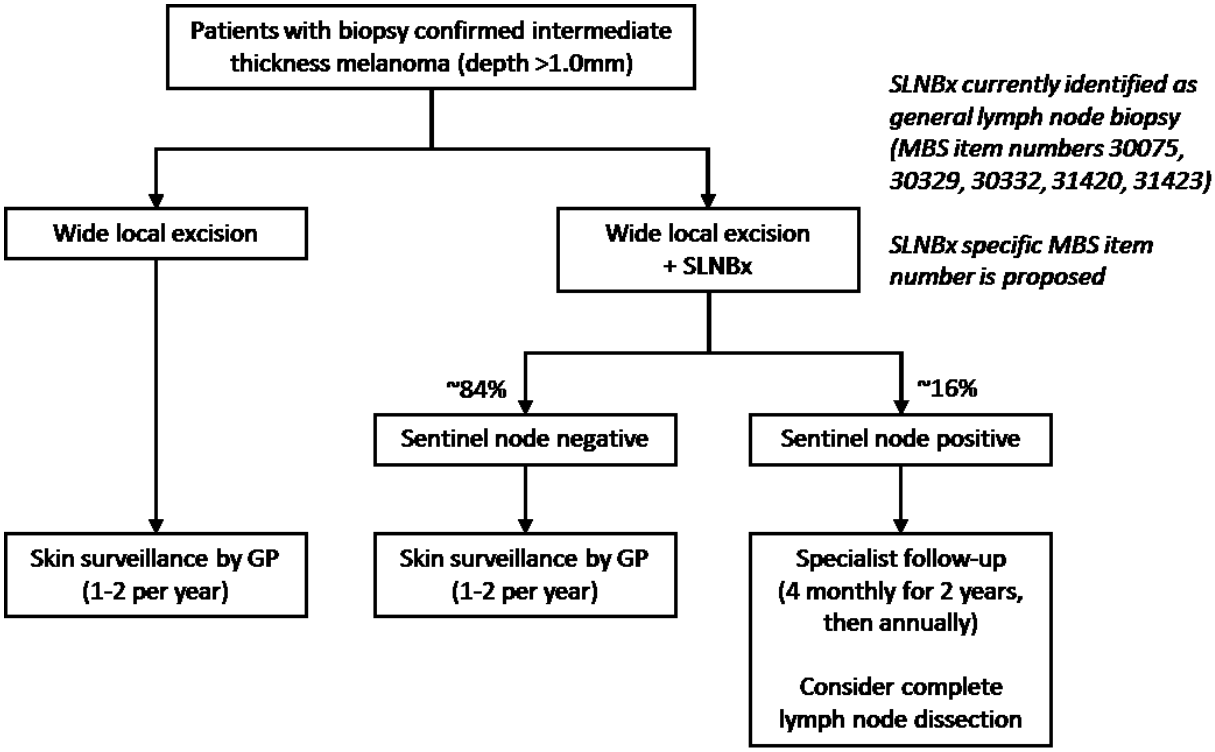
The European Organisation for Research and Treatment of Cancer (EORTC) 18071 trial assessed ipilimumab as adjuvant therapy for patients with completely resected stage III melanoma at high risk of recurrence. It reported that adjuvant ipilimumab significantly improved recurrence-free survival for patients with completely resected high-risk stage III melanoma. The adverse event profile was consistent with that observed in advanced melanoma, but at higher incidences in particular for endocrinopathies. According to the authors the risk–benefi t ratio of adjuvant ipilimumab at this dose and schedule requires additional assessment based on distant metastasis-free survival and overall survival endpoints to defi ne its defi nitive value (Eggermont, Chiarion-Sileni et al. 2015).

Current clinical management algorithm for identified population

As the intervention is already widely used, the clinical management algorithm is the same for both current management and proposed management below. The only difference proposed is that there would be a new specific MBS item number for SLNBx for melanoma, to distinguish it from other indications for lymph node biopsy (currently MBS items 30075, 30329, 30332, 31420, 31423).

Proposed clinical management algorithm for identified population

Figure 1 Proposed clinical management algorithm for identified population



Proposed economic evaluation

The clinical claim is that SLNBx is non-inferior in safety and superior in clinical effectiveness to standard skin surveillance. According to the *Technical Guidelines for preparing assessment reports for the Medical Services Advisory Committee: Investigative* the required economic analysis is therefore a cost-utility or a cost-effectiveness analysis.

Proposed item descriptor

Table 2 Proposed item descriptor

Category 3 – THERAPEUTIC PROCEDURES
SENTINEL LYMPH NODE BIOPSY OR BIOPSIES for cutaneous melanoma, where the primary lesion is 1.0mm or greater in depth, and appropriate excision of the primary melanoma has occurred, using preoperative lymphoscintigraphy and lymphotropic dye injection (Anaes.) (Assist.) Fee: $637.45

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Appendix – MBS items for lymph node biopsy

Table 3 MBS item 30075

Category 3 – THERAPEUTIC PROCEDURES
Group T8 – SURGICAL OPERATIONS Subgorup 1 – GENERAL DIAGNOSTIC BIOPSY OF LYMPH GLAND, MUSCLE OR OTHER DEEP TISSUE OR ORGAN, as an independent procedure, where the biopsy specimen is sent for pathological examination (Anaes.) Fee: $149.75 Benefit: 75% = $112.35 85% = $127.30

Table 4 MBS item 30329

Category 3 – THERAPEUTIC PROCEDURES
Group T8 – SURGICAL OPERATIONS Subgorup 1 – GENERAL LYMPH GLANDS of GROIN, limited excision of (Anaes.) Fee: $246.95 Benefit: 75% = $185.25 85% = $209.95

Table 5 MBS item 30332

Category 3 – THERAPEUTIC PROCEDURES
Group T8 – SURGICAL OPERATIONS Subgorup 1 – GENERAL LYMPH NODES of AXILLA, limited excision of (sampling) (Anaes.) (Assist.) Fee: $346.75 Benefit: 75% = $260.10

Table 6 MBS item 31420

Category 3 – THERAPEUTIC PROCEDURES

Group T8 – SURGICAL OPERATIONS
Subgorup 1 – GENERAL

LYMPH NODE OF NECK, biopsy of

(Anaes.)

Fee: $183.90 Benefit: 75% = $137.95 85% = $156.35

Table 7 MBS item 31423

Category 3 – THERAPEUTIC PROCEDURES
Group T8 – SURGICAL OPERATIONS Subgorup 1 – GENERAL LYMPH NODES OF NECK, selective dissection of 1 or 2 lymph node levels involving removal of soft tissue and lymph nodes from one side of the neck, on a person 10 years of age or over (Anaes.) (Assist.) Fee: $401.75 Benefit: 75% = $301.35 85% = $341.50