
1357

Final Protocol to guide
the assessment of
 ^{18}F -FDG PET in proven
locally advanced,
suspected locally and
regionally recurrent, and
suspected metastatic
breast cancers.

June, 2014

TABLE OF CONTENTS

| | |
|--|-----------|
| MSAC and PASC | 4 |
| Purpose of this document..... | 4 |
| Purpose of application | 5 |
| Proposed MBS listing | 5 |
| Clinical claims..... | 6 |
| Background | 6 |
| Current arrangements for public reimbursement | 6 |
| Population | 7 |
| Patient groups for whom the intervention is to be considered..... | 7 |
| Intervention | 9 |
| Description | 9 |
| Regulatory status | 10 |
| Delivery of the intervention..... | 10 |
| Prerequisites | 12 |
| Co-administered and associated interventions..... | 13 |
| Comparator | 13 |
| Reference standard test..... | 16 |
| Clinical management algorithm..... | 16 |
| Outcomes for the evaluation of safety and effectiveness | 21 |
| Effectiveness..... | 21 |
| Safety 21 | |
| Economic considerations | 22 |
| Proposed MBS fee | 22 |
| Approach to the economic evaluation..... | 22 |
| Health care resources | 23 |
| Proposed structure of economic evaluation (decision-analytic) | 26 |
| Questions for public funding..... | 26 |
| APPENDICES | 27 |

| | |
|---|-----------|
| A.1. MBS Items For The Comparator | 27 |
| A.2. Breast Cancer Staging | 31 |
| REFERENCES | 32 |

FINAL

MSAC AND PASC

The Medical Services Advisory Committee (MSAC) is an independent expert committee appointed by the Australian Government Health Minister to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Commonwealth Minister for Health and Ageing on the evidence relating to the safety, effectiveness, and cost-effectiveness of new and existing medical technologies and procedures and under what circumstances public funding should be supported.

The Protocol Advisory Sub-Committee (PASC) is a standing sub-committee of MSAC. Its primary objective is the determination of protocols to guide clinical and economic assessments of medical interventions proposed for public funding.

Purpose of this document

NHMRC as part of its contract with the Department of Health and Ageing, has drafted this decision analytic protocol (DAP) to guide the assessment of the safety, effectiveness and cost-effectiveness of confirmatory diagnostic imaging for staging spread of disease for proven locally advanced, suspected locally and regionally recurrent and suspected metastatic breast cancer.

In order to inform MSAC's decision-making regarding public funding of the intervention. Draft protocols will be finalised after inviting relevant stakeholders to provide input. The final protocol will provide a framework within which the assessment of the intervention can take place.

The protocol guiding the assessment of the intervention has been developed using the widely accepted "PICO" approach. The PICO approach involves a clear articulation of the following aspects of the research question that the assessment is intended to answer:

- P**atients – specification of the characteristics of the patients in whom the intervention is to be considered for use;
- I**ntervention – specification of the proposed intervention;
- C**omparator – specification of the therapy most likely to be replaced by the proposed intervention; and
- O**utcomes – specification of the health outcomes and the healthcare resources likely to be affected by the introduction of the proposed intervention.

PURPOSE OF APPLICATION

An application requesting Medicare Benefits Schedule (MBS) listing of F-18 fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography (PET) for the evaluation and staging of spread of disease in proven locally advanced breast cancer, suspected locally and regionally recurrent, or suspected metastatic breast cancer was received from the Australasian Association of Nuclear Medicine Specialists by the Department of Health and Ageing in May 2013.

The purpose of the application is to assess the role of ¹⁸F-FDG PET in (i) staging potentially operable locally advanced breast cancer and (ii) in replacing the current practice of doing a confirmatory standard diagnostic imaging study (e.g. CT) with confirmatory ¹⁸F-FDG PET imaging to more accurately stage proven locally advanced, suspected locally and regionally recurrent, and suspected metastatic breast cancers.

It is noted that the USA National Comprehensive Cancer Network's (NCCN) 2014 Guidelines for breast cancer (Version 1.2014) state that "the use of PET or PET/CT is not indicated in the staging of clinical Stage 1, II or operable III breast cancer",¹ and the European Society for Medical Oncology (ESMO) 2013 Guidelines state "Current evidence does not support the use of FDG-PET/CT in the staging procedure of local/regional disease, due to limited specificity compared with the gold standard methods for axillary staging —SLNB and axillary lymph node dissection".² Factoring in these international recommendations, there needs to be agreement about whether to ask in this protocol if all or part of the locally advanced breast cancer population should have ¹⁸F-FDG PET imaging.

Proposed MBS listing

Table 1: Proposed MBS item descriptor for confirmatory ¹⁸F-FDG PET for proven locally advanced breast cancer

| Category 5 – DIAGNOSTIC IMAGING SERVICES |
|--|
| MBS [item number] Whole body ¹⁸ F-FDG PET study, performed for the staging of spread of disease in proven locally advanced breast cancer in patients considered potentially suitable for active therapy, where initial standard diagnostic imaging is equivocal or suspicious for spread of disease. Fee: \$? |

Table 2: Proposed MBS item descriptor for confirmatory ¹⁸F-FDG PET for suspected locally or regionally recurrent or suspected metastatic breast cancer

| Category 5 – DIAGNOSTIC IMAGING SERVICES |
|--|
| MBS [item number] Whole body ¹⁸ F-FDG PET study, performed for the confirmation and evaluation of suspected metastatic or suspected locally or regionally recurrent breast carcinoma in patients considered suitable for active therapy, where initial standard diagnostic imaging is equivocal or suspicious for spread of disease. Fee: \$? |

Clinical claims

(i) ^{18}F -FDG PET will more accurately assess the local extent of disease or disease stage for patients assessed with conventional diagnostic processes as having potentially operable locally advanced breast cancer. This may result in a change in how patients are managed.

(ii) After an equivocal result for spread of disease from initial standard diagnostic imaging studies, confirmatory diagnostic ^{18}F -FDG PET imaging will more accurately detect and stage / restage advanced breast cancers compared to the current practice of doing a confirmatory standard diagnostic imaging study. This may result in a change in how patients are managed.

BACKGROUND

Current arrangements for public reimbursement

Medicare rebates were previously restricted to specific PET indications performed at seven designated PET facilities nationally: the Royal Prince Alfred and Liverpool hospitals New South Wales, the Peter MacCallum Cancer Institute and Monash Medical Centre in Victoria, the Royal Adelaide Hospital in South Australia, the Wesley Hospital in Queensland and the Sir Charles Gairdner Hospital in Western Australia.³ In addition, the Australian Government had funded PET scans at the Austin Hospital, Melbourne, and Westmead Hospital, Sydney, through a grant arrangement,³ however this arrangement has now ceased. The 2011-2012 Budget recommended PET services to be added to the Health Insurance (Diagnostic Imaging Service Table) Regulations 2010, making Medicare rebates available at all Medicare-eligible PET facilities from 1st July 2011 [communication with Diagnostic Imaging Section, Primary Care, Diagnostics and Radiation Oncology Branch, Medical Benefits Division, Department of Health].

There is currently no Medical Benefits Schedule (MBS) funding nor interim funding arrangement for reimbursing whole-body ^{18}F -FDG-PET performed for the staging/restaging of proven locally advanced breast cancer, or suspected locally or regionally recurrent or suspected metastatic breast cancers. There is also no private health insurance rebate for PET services, so patients need to pay out of pocket for this service.

Under current Medicare eligibility for diagnostic PET services for other cancers (e.g. MBS #61529 for non-small cell lung cancer, MBS #61598 and #61604 for head and neck cancer, etc) there are a number of a number of criteria that are required to be satisfied for funding, including that the services be linked to a comprehensive cancer service. PET can be performed as either an inpatient or outpatient procedure.

In 2006, a report from the PET Data Collection Project run by the Australian and New Zealand Association of Physicians in Nuclear Medicine (Inc) summarised outcomes from non-Medicare PET services in oncology for a selected group of hospitals involved in the project.⁴ It reported that there were 384 breast cancer patients who used PET, with 339 using it for restaging. Out of these 339 patients, compared with conventional restaging methods (confirmatory diagnostic imaging and biopsy), 141 (41.6%) were unchanged, 33 (9.7%) were upstaged, 71 (20.9%) were down-staged, 8 (2.4%) were changed to equivocal, and 86 (25.4%) were changed from equivocal.

POPULATION

Patient groups for whom the intervention is to be considered

Proven locally advanced breast cancer:

Locally advanced breast cancer (LABC) is defined by one or more of the following features (American Joint Committee on Cancer [AJCC] Stage III, Appendix 2, Table 16):

- Primary tumour larger than 5cm.
- Spread to several lymph nodes in the axilla or other areas near the breast.
- Spread to other tissue around the breast such as skin, muscles, or ribs.

This protocol considers both women and men with proven locally advanced breast cancer. Patients may or may not have had prior treatment. This may be a new staging, or an upstaging from a lower level breast cancer stage for a patient.

Suspected locally or regionally recurrent or suspected metastatic breast cancer:

Locally or regionally recurrent breast cancer is defined by the (re)development of cancer in the same breast (local) or ipsilateral (usually axillary) lymph nodes (regional) after an apparently disease-free interval following treatment.^{5, 6} Metastatic (secondary) breast cancer (stage 4 breast cancer) is defined by spread to other parts of the body, either at the first diagnosis of breast cancer, or as a recurrence of a previously treated breast cancer. This protocol considers both women and men with suspected locally or regionally recurrent or suspected metastatic breast cancer. .

Presentation for diagnostic imaging for staging / restaging:

A suspicious breast mass may be identified through a formal breast screening programme, or via presentation to a general practitioner by a patient.^{5, 7} The breast/s and axillary areas are investigated clinically through palpation and mammography or ultrasound, and MRI in high risk groups, and the presence of malignant tumour confirmed by biopsy.^{5, 7} Breast cancer is staged, or classified, to determine the severity of the disease. Staging classification is determined by the American Joint Committee on Cancer's breast cancer staging TNM system.⁸ Staging of the disease depends on tumour size ("T"), the number of involved lymph nodes ("N"), and the presence or absence of distant metastases ("M"). Tumour size and axillary metastases can be estimated by clinical examination and imaging techniques, but definitive status/staging is achieved through surgery and histology.⁷

Following and during initial treatment, breast cancer patients continue to have regular examinations and tests to evaluate treatment response and to detect recurrence or metastatic spread. In Australia, from QLD registry data, at initial diagnosis approximately 47% of patients have Stage I and 45% of patients have Stage II-IV disease and unknown in 8% of cases (see Appendices for explanation of stages).⁹ There are two scenarios (based on US National Comprehensive Cancer Network (NCCN) and

European Society Medical Oncology (ESMO) clinical practice guidelines) where PET/CT may have a role in the assessment of breast cancer patients^{10, 11}:

- Proven locally advanced breast cancer
- Suspected locally or regionally recurrent or suspected metastatic breast cancer, particularly when conventional imaging tests are equivocal for spread of disease.

Funding for PET/CT in the US from the Centres for Medicare & Medicaid Services is available for patients with breast cancer as follows¹²:

- “Breast: Non-covered for diagnosis and/or initial staging of axillary lymph nodes. Covered for initial staging of metastatic disease.”
- For the “subsequent treatment strategy” (formerly “restaging” and “monitoring response to treatment when a change in treatment is anticipated”).

Expected numbers for proven locally advanced breast cancer:

The application proposes that confirmatory imaging using ¹⁸F-FDG PET be used in patients who have proven locally advanced disease, where prior diagnostic imaging does not provide sufficient information to determine if appropriate treatment for disease up-staging or spread is required. The data here will be primarily for women, but we will include men in the final assumptions, as they will likely contribute a small proportion to the data. In 2008, 13,567 new breast cancers were diagnosed in women.¹³ The AIHW estimates that 14,940 women will be diagnosed with breast cancer in 2013 and 15,270 women in 2014.¹³ Cancer Australia states that between 10 to 20% of new breast cancer diagnoses each year have locally advanced disease.¹⁴ This means approximately 1,500 to 3,000 women using 2013 numbers will have locally advanced breast cancer. According to clinicians involved in the Austin Report⁴ and HESP clinicians, of these patients, 30% will have inconclusive conventional imaging staging studies for spread of disease and would therefore be suitable for PET evaluation. Based on these assumptions, approximately 450 to 900 patients (women and men) per year with locally advanced breast cancer would be eligible for ¹⁸F-FDG PET imaging.

Expected numbers for suspected locally or regionally recurrent or suspected metastatic breast cancer:

The population that would be targeted for confirmatory imaging using ¹⁸F-FDG PET are those where locally or regionally recurrent or metastatic disease is suspected and for whom active therapy is likely to be pursued.

There are complexities in estimating incidence and prevalence of recurrent or metastatic breast cancer. The prevalence of the disease is influenced by the incidence of the initial disease, survival from the initial disease, and the age at which people were diagnosed with the initial disease, type of treatment taken, and site of recurrence or metastasis. Unfortunately, the incidence and prevalence of recurrences and metastases of any type are not notifiable in any jurisdiction, so there is no reliable national data on this [correspondence with HESP, AIHW's Cancer Screening Unit, and state and territory cancer registries].

The data here will be drawn primarily from women, as men contribute a small amount to the data. At the end of 2008, almost 160,000 Australian women alive had been diagnosed with breast cancer in

the previous 27 years, including about 57,000 diagnosed in the previous 5 years.^{13, 15} Of these women, recurrence may occur. There are only a few studies estimating recurrence in Australian breast cancer patients. Two Australian studies from 1995 on women who had been treated for early breast cancer found that 6-8% of women had recurrent ipsilateral breast cancer and 14-16% had metastatic disease at relapse.¹⁶⁻¹⁸ A 2012 study using 2001-2002 data from NSW found that 5% with localised node-negative disease and 17% with regional disease at initial diagnosis developed metastatic breast cancer within 5 years.¹⁹ This study highlights the different statistics that occurs depending on factors such as initial diagnosis. A 2012 Australian study supports a view that the annual rate at which metastatic breast cancer is diagnosed peaks at 2 years after initial treatment.¹⁹

Based on these data 5% to 15% of all patients (women and men) with breast carcinoma would undergo restaging for suspected local or regional recurrence (closer to 5%) or suspected metastatic disease (closer to 15%) annually [based on HESP and applicant advice]. Extrapolating to the breast cancer population, this means that 5% to 15% of 160,000 patients (AIHW 2008 estimate for all patients diagnosed with breast cancer), or 8,000 to 24,000 patients, diagnosed with breast cancer and alive up to 2008 could undergo restaging for suspected local or regional recurrence or suspected metastatic disease. According to clinicians involved in the Austin Report⁴ and HESP clinicians, of these patients, 30% would have equivocal conventional imaging studies and be suitable for PET evaluation (i.e. 2,400 patients for suspected locally or regionally advanced breast cancer and 7,200 patients for suspected metastatic breast cancer). However, since this is an estimate from clinical experience, it is unclear exactly how accurate this number is.

INTERVENTION

Description

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 x-ray computed tomography (CT).²⁰

This review is restricted to the radiopharmaceutical ¹⁸F-FDG (2-[¹⁸F]fluoro-2-deoxy-D-glucose, FDG), a radiolabelled analogue of glucose, which has greater uptake by many malignant tumours compared to normal surrounding tissue.²⁰ ¹⁸F-FDG is phosphorylated and becomes trapped intracellularly in the target cells where it remains essentially unmetabolised and accumulates.²¹ This accumulation is seen as a 'hot spot' on PET imaging assessed visually or semiquantitatively by the standardised uptake value (SUV). SUV estimates the uptake of ¹⁸F-FDG in the volume of interest relative to the mean uptake in the rest of the body (usually normalised to body weight), with higher values (typically >2.5) being associated with an increased likelihood of malignancy.²⁰ SUV is also affected by a large number of other variables beyond just the malignancy itself.

In this protocol the term 'PET' is used to refer to either PET or PET/CT. The term 'PET/CT' is used where specific reference to this modality is made. Current and future practice will relate to the use of PET/CT machines, as all PET machines sold now in Australia are PET/CT machines. A more detailed

description of PET and PET/CT is provided in the previous MSAC reviews of PET for various cancers.³
20

Regulatory status

PET machines:

There are 3 registered ARTG PET machine types. Please note that there are many more machines available in Australia than listed here. The ARTG database only listed the few machines reported here. These few are meant to encompass a product range or family of medical devices rather than a specific device. [Correspondence with the Medical Devices Information Unit, TGA]

The listed PET machines are GE Healthcare Australia Pty Ltd's ARTG #156649 and ARTG #114476m, and Phillips Electronics Australia Pty's ARTG #147067. There are three registered PET/CT machine types. These are Siemens Ltd's ARTG #144218, Philips Electronics Australia Ltd's ARTG #118077, and Regional Health Care Group #181317. There are two registered PET/MRI machine types. These are Siemens Ltd's ARTG #188470, and Philips Electronics Australia Ltd's ARTG #193622. There are also four registered PET imaging softwares available. These are Siemens Ltd's ARTG #181848 and ARTG #178420, and GE Healthcare Australia Pty Ltd's ARTG #154936 and ARTG #153390.

¹⁸F-FDG:

There are two registered entries for 2-deoxy-2-[¹⁸F]fluoro-D-glucose (¹⁸F-FDG). One is by Austin Health, in Melbourne, with ARTG #54251. The other is by PETNET Australia Pty Ltd, with ARTG #78935. The requested MBS listing for ¹⁸F-FDG PET is consistent with the regulatory body approved indication.

Delivery of the intervention

Delivery of ¹⁸F-FDG PET:

Delivery of ¹⁸F-FDG PET scanning can be broken down into 3 "phases". These are (1) ¹⁸F-FDG preparation, (2) PET scanning, and (3) image reconstruction and interpretation.

¹⁸F-FDG preparation and administration:

¹⁸F-FDG can be produced either in-house in facilities with a cyclotron and radiopharmacy capability, or sourced from a commercial supplier. Patients must fast for 4 to 6 hours prior to ¹⁸F-FDG administration. ¹⁸F-FDG is administered intravenously 60 minutes prior to scanning. European Association of Nuclear Medicine (EANM) and Society of Nuclear Medicine and Molecular Imaging (SNMMI) clinical practice guidelines state that the activity of ¹⁸F-FDG will vary according to body mass and PET machine parameters used, but is approximately 180 to 260 MBq for a 75kg patient,²² but can be as high as 740 MBq in some circumstances,²³ and is adjusted accordingly for body weight at around 5 MBq per kilogram of body weight.^{22, 23} The activity required is becoming lower with newer advanced machines (e.g. time-of-flight PET scanners would typically require an activity of less than 250 MBq in a small woman according to clinical experts from HESP and the applicant). During the 60

minutes prior to scanning, patients are rest quietly in a dimly lit room. Following this uptake period, patients are taken to the PET suite and positioned on the scanning bed.

PET scanning:

PET scanning is done using a standard protocol which usually includes low-dose computed tomography (CT) for attenuation correction and anatomical correlation. In some cases, when the referring clinician deems necessary, a diagnostic CT may be done at the time of the PET study, using oral and/or intravenous contrast material (this would be a PET/CT diagnostic study). The field-of-view for PET scans is determined by the clinical indication, but usually extends from the base of the skull to the upper thighs. Typical PET study acquisition times with current scanners are less than 30 minutes, but are determined by performance characteristics of the PET scanner, the field-of-view, and the administered activity of FDG. For attenuation correction and anatomical correlation, an additional CT scanning time of 1 to 2 minutes is added.

PET scanning radiation dose:

In terms of radiation dose delivered, nuclear medicine and PET services abide by the ALARA principle ("as low as reasonably achievable") with consideration of the clinical situation. The International Commission on Radiological Protection (2008) states that the effective radiation dose for FDG is 0.019 mSv/MBq ; the typical effective dose for low-dose CT (for attenuation correction and anatomic correlation) is 2 – 3 mSv.²⁴

PET image reconstruction and interpretation:

PET images are usually reconstructed using the PET scanner manufacturer's recommended reconstruction protocols and software. The nuclear medicine specialist interprets the images (including correlated imaging where available) and generates a clinical report. This report is provided to the requesting clinician. Electronic copies of the PET images are provided to the requesting clinician as appropriate.

Potential utilisation for proven locally advanced breast cancer:

As mentioned previously, based on these assumptions, approximately 450 to 900 patients per year with proven locally advanced breast cancer would be eligible for ¹⁸F-FDG PET imaging to confirm or exclude spread of disease. The role of ¹⁸F-FDG PET would be to identify patients with involvement of internal mammary and mediastinal lymph node stations that are currently not routinely sampled, as well as to detect occult distant metastases [applicant correspondence]. In terms of utilisation per patient, patients with locally advanced breast cancer will undergo 1 confirmatory ¹⁸F-FDG PET study per year.

Potential utilisation for suspected locally and regionally recurrent and suspected metastatic breast cancer:

As mentioned previously, after standard diagnostic imaging studies, about 2,400 patients for suspected locally or regionally advanced breast cancer and 7,200 patients for suspected metastatic breast cancer would have equivocal findings, and these patients would then go on to have ¹⁸F-FDG

PET imaging. It is expected that patients with suspected locally or regionally recurrent or suspected metastatic breast cancer would undergo 1 ¹⁸F-FDG PET study per year.

Prerequisites

Initial diagnostic imaging testing (prior testing):

The main modality for an initial diagnostic imaging test for diagnosing and staging breast cancers is usually CT.

For suspected metastatic breast cancer, or for suspected locally or regionally recurrent breast cancer, standard diagnostic imaging will consist of CT, MRI and bone scintigraphy.

Personnel and Facilities:

Diagnostic imaging studies require the following clinicians and staff:

- MRI, CT, ultrasound: radiologists, radiographers, and clerical staff.
- Nuclear medicine (including FDG PET): nuclear medicine specialists, nuclear medicine technologists, clerical staff.

Inpatient services would require other staff such as nurses and orderlies.

Nuclear medicine specialists include both dual trained radiologists and nuclear medicine physicians.

Like the regulations on the MBS for delivering PET services for other diseases (i.e. "Note DIN Group I4 – Nuclear Medicine Imaging" for MBS Items 61523 to 61646), it is envisioned that PET services for breast cancer patients must be, quoting the MBS descriptor:

1. Performed by a:
 - a) specialist or consultant physician credentialled under the Joint Nuclear Medicine Specialist Credentialling Program for the Recognition of the Credentials of Nuclear Medicine Specialists for Positron Emission Tomography overseen by the Joint Nuclear Medicine Credentialling and Accreditation Committee of the RACP and RANZCR; or
 - b) practitioner who is a Fellow of either RACP or RANZCR, and who, prior to 1 November 2011, reported 400 or more studies forming part of PET services for which a Medicare benefit was payable, and who holds a current licence from the relevant State radiation licensing body to prescribe and administer the intended PET radiopharmaceuticals to humans;
2. Provided in a comprehensive facility that can provide a full range of diagnostic imaging services (including PET, CT, XRay and diagnostic ultrasound) and cancer treatment services (including chemotherapy, radiation oncology and surgical oncology) at the one site;
3. Provided using equipment that meets:
 - a) The Requirements for PET Accreditation (Instrumentation & Radiation Safety) dated 4 May 2007 and issued by the Australian and New Zealand Society of Nuclear Medicine; and

b) NEMA NU 2207 Standard published by the National Electrical Manufacturers Association (USA).

4. Only provided following referral from a recognised specialist or consultant physician.

Machines currently approved by the TGA and sold in the Australian market are combination PET/CT machines, so any facilities having these machines will not need to purchase additional capital equipment. Facilities with separate CT and PET machines will upgrade to PET/CT machines in the future.

On top of these requirements, PET facilities need to be in shielded scanning rooms, have an external supply chain for PET tracers (usually from commercial providers) or have an on-site cyclotron or on-site radiopharmacy (where generators are used in-house to produce PET radiopharmaceuticals).

Co-administered and associated interventions

There are no co-administered or associated diagnostic tests or treatments with ¹⁸F-FDG PET.

COMPARATOR

Prior tests:

The initial diagnostic imaging testing regime for the comparator is the same as described in the Prerequisites section above.

Standard confirmatory diagnostic imaging is the comparator test:

Initial diagnostic imaging tests for diagnosing and staging breast cancers is CT. MRI may also be used to confirm brain and spine tumour involvement and spread. For radiography, diagnostic mammography and CT can be used to evaluate the primary lesion in the breast and search for spread to the lungs and other chest tissues. Ultrasound can be used to characterise breast lesions, where it can be used to differentiate between cysts and solid masses such as a tumour. The more complex diagnostic techniques (i.e. MRI, CT, bone scintigraphy) are discussed below.

MRI^{3, 20}:

MRI is used for various imaging purposes, including for oncological investigations. There are MBS items for MRI for breast cancer investigations (MBS #63457 and #63458), brain investigations (MBS #63001 and #63491), and spinal investigations (MBS #63154 and #63491). MRI uses the physical properties of unpaired hydrogen ions (protons) in different chemical, structural and magnetic environments to produce images of tissues. Unlike PET and CT, it does not use ionising radiation. The effectiveness of a given MRI examination is highly dependent on the imaging parameters (pulse sequences) selected. Furthermore, MRI may be conducted with the use of contrast agents, typically intravenous gadolinium attached to a chelating agent such as DTPA (diethylene triamine penta-acetic acid).

CT^{3, 20}:

CT is used for various imaging purposes, including for oncological investigations. Most patients will have CT of their chest, abdomen, and pelvis (MBS #56807). Some patients may rarely have CT on their chest only (MBS #56307). Some patients may additionally have brain CT (MBS #56007). CT is a non-invasive imaging modality that involves measuring the x-ray attenuation coefficient of the anatomical part examined. Radiopaque intravenous and oral contrast material is usually given during the examination.

Bone scintigraphy:

Bone scintigraphy is a diagnostic study used to evaluate the distribution of active bone formation in the body²⁵. The MBS item is #61425. Radiopharmaceuticals are injected intravenously into the patient to allow clinicians to detect how much radiotracer collects in the bones. These radiolabelled bisphosphonates bind to hydroxyapatite at sites of osteogenesis²⁶. To evaluate metastatic bone disease, images are taken 2 - 3 hours after radiotracer injection. There are a few options for using bone scintigraphy. These are:

1. Whole-body bone scintigraphy produces planar images of the skeleton.
2. Bone single-photon emission computed tomography (SPECT) produces a tomographic image of a portion of the skeleton.
3. Multiphase bone scintigraphy usually includes blood flow images, immediate images, and delayed images.

Personnel and Facilities:

Diagnostic imaging studies require the following staff:

- Radiology staff (for CT, ultrasound, and MRI): radiographers, radiologists and clerical staff.
- Nuclear medicine staff (for bone scintigraphy): nuclear medicine technologists, nuclear medicine specialists, and clerical staff.

For delivering diagnostic imaging services using nuclear medicine services, (i.e. "Note DIN Group I4 – Nuclear Medicine Imaging"), the MBS states that "Benefits for a nuclear scanning service are only payable when the service is performed by a specialist or consultant physician, or by a person acting on behalf of the specialist and the final report of the service is compiled by the specialist or consultant physician who performed the preliminary examination of the patient and the estimation and administration of the dosage." MBS "Note DIL Group I2 – Computed Tomography (CT)" also states that appropriately credentialed staff can deliver CT services, including PET/CT and SPECT/CT machines.

Nuclear medicine specialists or consultant physicians must be credentialed by the Joint Nuclear Medicine Credentialing and Accreditation Committee of the Royal Australasian College of Physicians (RACP) and the Royal Australian and New Zealand College of Radiologists (RANZCR).

Under Note DIL for Group I2 – Computed Tomography (CT), there are also personnel specifications for using only the CT function on hybrid PET/CT or SPECT/CT machines. The rules say:

Diagnostic CT scans rendered on hybrid Positron Emission Tomography / CT (PET/CT) or hybrid Single Photon Emission Computed Tomography / CT (SPECT/CT) units are eligible for a Medicare benefit provided [quoting the MBS descriptor]:

- the CT scan is not solely used for the purposes of attenuation correction and anatomical correlation of any associated PET or SPECT scan; and
- the CT scan is rendered under the same conditions as those applying to services rendered on stand-alone CT equipment. For example, the service would need to be properly requested and performed under the professional supervision of a specialist radiologist, including specialist radiologists with dual nuclear medicine qualifications.

Clinical experts vary in their assessment of how often this occurs, but it is agreed that it is increasing in frequency in Australia. However, it is noted from PASC that the performance of a “diagnostic” CT scan with PET/CT will add substantially to the cost of PET/CT (the “intervention”), so the actual frequency with which this is being performed needs to be established.

MBS items for the comparator:

The MBS items listed below are the most commonly used ones, but other MBS items may be used at times but not routinely. See the Appendices for the full tables containing descriptions of the comparator devices and services. A quick description of the services used is provided here.

Table 3. Summary of MBS items for the comparator of confirmatory diagnostic imaging.

| MBS Item Number | Description | Fee |
|-----------------|--|----------|
| 56807 | Computed tomography (chest, abdomen, and pelvis) | \$560.00 |
| 56307 | Computed tomography (chest) | \$400 |
| 56007 | Computed tomography (brain) | \$250 |
| 63457 | MRI (breasts) | \$345.00 |
| 63458 | MRI (breasts – follow-up) | \$345.00 |
| 63001 | MRI (brain) | \$403.20 |
| 63491 | MRI (brain – contrast medium) | \$44.90 |
| 63154 | MRI (spine) | \$358.40 |
| 63491 | MRI (spine – contrast medium) | \$44.80 |
| 61505 (?) | CT (with SPECT, for localisation / correction) | \$100.00 |
| 61719 (?) | CT (with SPECT, for localisation / correction) | \$50.00 |
| 61425 | Bone study (for bone scintigraphy) | \$600.70 |
| 55059 | Breast ultrasound | \$49.15 |
| 55061 | Breast ultrasound | \$54.55 |

Utilisation of confirmatory standard diagnostic imaging for proven locally advanced breast cancer:

As per the “Intervention” utilisation calculations of this Protocol, the estimated utilisation per patient is for patients to undergo 1 “confirmatory standard diagnostic imaging” study per year.

Utilisation of confirmatory standard diagnostic imaging for suspected locally and regionally recurrent and suspected metastatic breast cancer:

As stated previously in the “Intervention” section of this Protocol, in terms of utilisation per patient, patients undergo 1 “confirmatory standard diagnostic imaging” study per year.

Reference standard test

Reference standard test is pathology (biopsy):

The reference standard to identify breast cancer is a biopsy. Cells from the area of concern are removed so they can be studied in the laboratory. There are several types of biopsies that can be performed.⁵ For breast biopsies, these are:

- Fine needle aspiration (FNA) biopsy. This is the easiest type of biopsy to have, but it doesn't always give a clear answer.
- Core needle biopsy. It is used to remove one or more cores (pieces) of tissue. Because more tissue is removed, a core needle biopsy is more likely than an FNA to provide a clear result.
- Vacuum-assisted biopsies. These can be done with various commercial systems under the guidance of a mammogram or MRI. The skin is numbed, a small cut (incision) is made, then a hollow probe is put through the cut into the breast tissue, and a piece of tissue is sucked out. Several samples can be taken from the same cut. This method usually removes more tissue than core biopsies.
- Surgical (open) biopsy: Most often, breast cancer can be found using the other types of biopsy. Surgery is rarely needed to remove all or part of a lump so it can be looked at under a microscope. The whole lump as well as some normal tissue around it may be taken out.

A lymph node biopsy may also need to be done for suspected advanced, metastatic and recurrent breast cancers⁵. Tissue removed during biopsy is analysed by the laboratory, which will report on the breast cancer grade, hormone receptor status (i.e. oestrogen and progesterone), HER2 / neu status, and in some cases gene patterns.

Clinical management algorithm

Three clinical management algorithms are presented – each shows current and proposed algorithms for proven locally advanced breast cancer, suspected locally and regionally recurrent breast cancer, and suspected metastatic breast cancer. Please note that these Protocols present the common pathways, as there are always unique circumstances where variations in practice may occur (e.g. no biopsy after clearly positive findings on initial and confirmatory diagnostic imaging studies). The Protocols do not show the pathways for positive or negative results after initial standard diagnostic imaging, as we are only interested in comparing the pathway options for an equivocal result after initial standard diagnostic imaging study.

The treatment options for spread of disease in proven locally advanced breast cancer include:

- Local treatment for treatable disease after a negative biopsy result: Any combination of surgery, radiotherapy, chemotherapy, and/or hormonal therapy.
- Altered local treatment +/- systemic therapy for treatable disease after a positive biopsy result: Any combination of surgery, radiotherapy, chemotherapy, and/or biologic therapy.
- Palliation for incurable disease.

The treatment options for spread of disease in metastatic breast cancer include:

- Observation.
- Further therapy for treatable disease after a positive biopsy: Treatment is based on number of sites, organs involved, and hormonal/HER2+ status of tumour. This would be surgery +/- radiotherapy, hormonal therapy, and/or biologic therapy.
- Palliation for incurable disseminated disease.

The treatment options for spread of disease in locally and regionally recurrent breast cancer include:

- Further therapy for treatable disease after a positive biopsy: Treatment is based on number of sites, organs involved, and hormonal/HER2+ status of tumour. This would be surgery +/- radiotherapy, hormonal therapy, and /or biologic therapy.
- Palliation for incurable disseminated disease.

Figure 1: Clinical management algorithm for proven locally advanced breast cancer. Confirmatory standard diagnostic imaging vs confirmatory ¹⁸F-FDG PET.

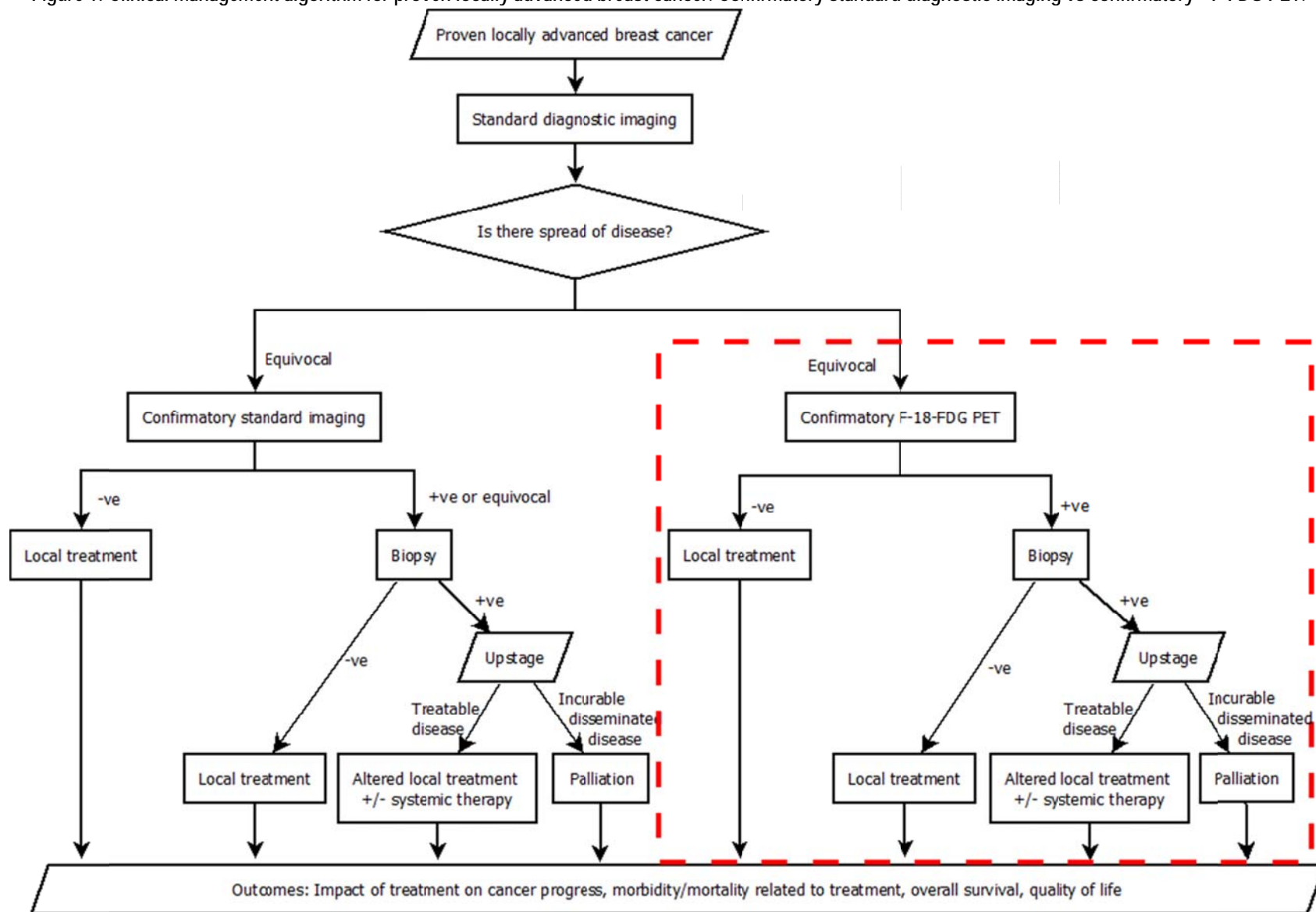


Figure 2: Clinical management algorithm for suspected locally and regionally recurrent breast cancer. Confirmatory standard diagnostic imaging vs confirmatory ¹⁸F-FDG PET.

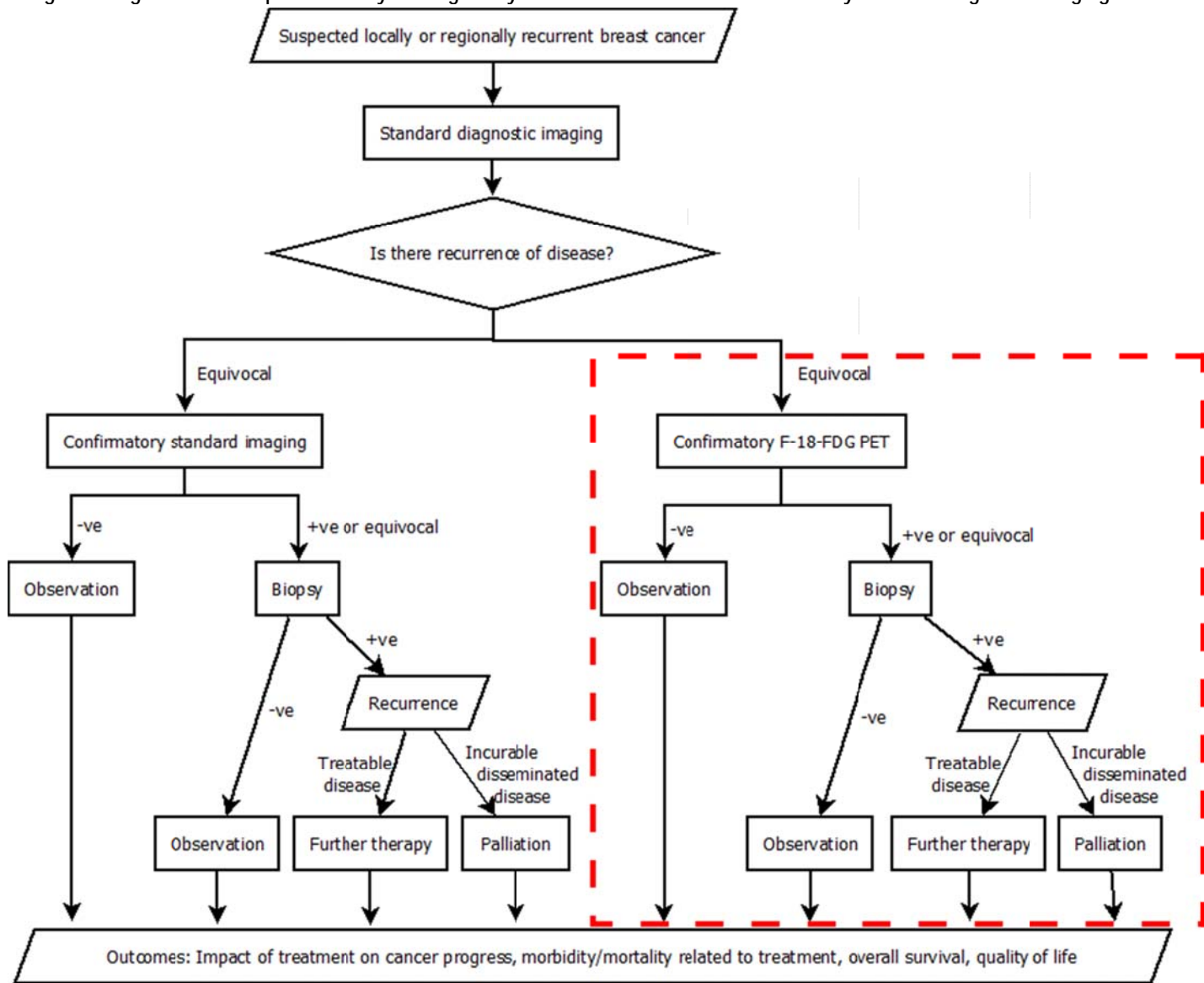
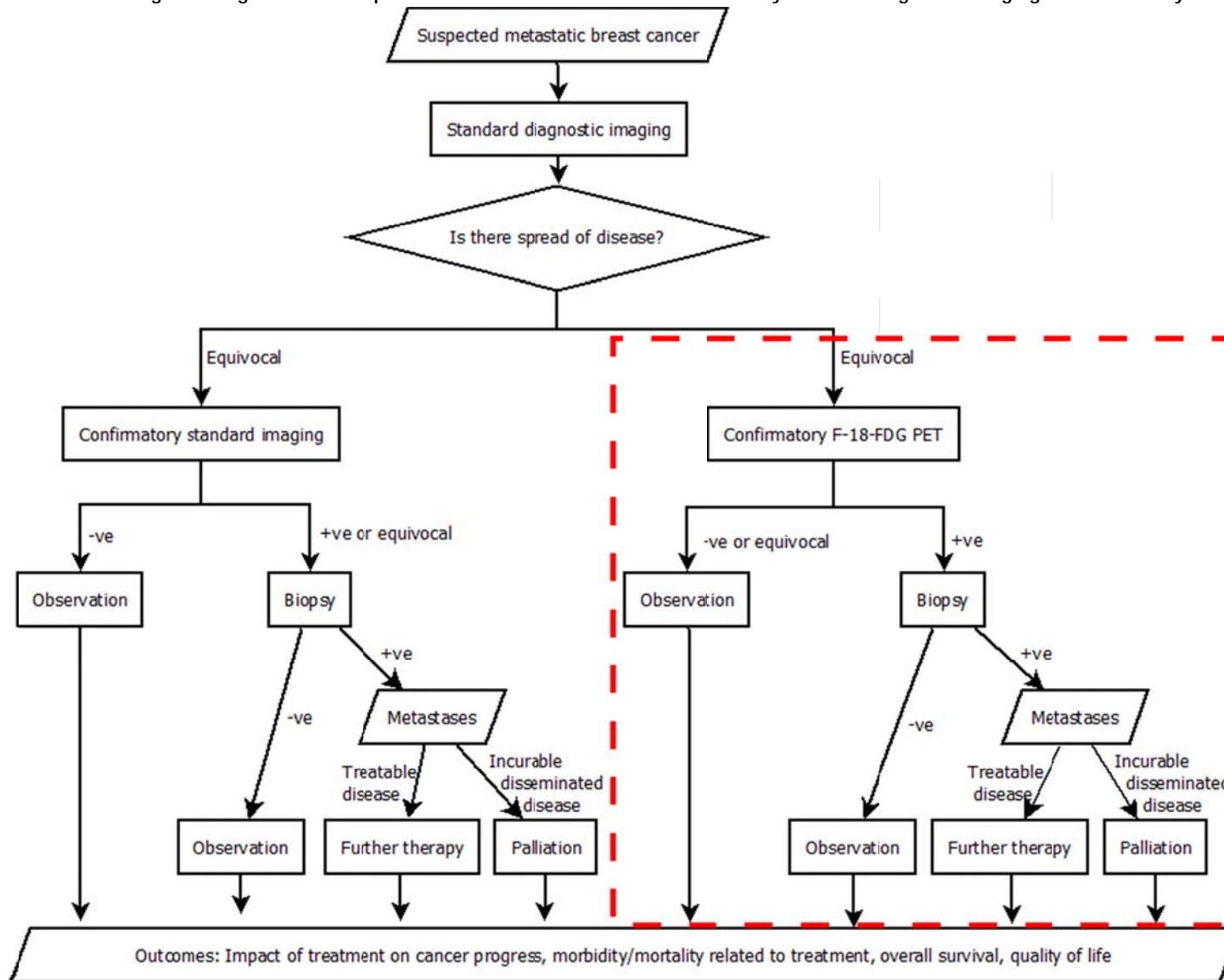


Figure 3: Clinical management algorithm for suspected metastatic breast cancer. Confirmatory standard diagnostic imaging vs confirmatory ¹⁸F-FDG PET.



OUTCOMES FOR THE EVALUATION OF SAFETY AND EFFECTIVENESS

The health outcomes, upon which the comparative clinical performance of confirmatory ¹⁸F-FDG PET vs confirmatory standard diagnostic imaging in patients with proven locally advanced, suspected locally and regionally recurrent, or suspected metastatic breast cancers will be measured are:

Effectiveness

Diagnostic accuracy:

- Sensitivity.
- Specificity.
- Additional true positive (TP) and false positive (FP), receiver operator characteristic (ROC) area under the curve (AUC), Cochran Q statistic for testing heterogeneity, diagnostic odds ratios (DOR).

Change in management:

- Definitive treatment avoided.
- Investigations avoided.
- Definitive treatment instigated.
- Overall change.
- Type of change occurring.

Patient outcomes:

- Morbidity.
- Mortality.
- Overall survival.
- Cancer-specific mortality.
- Cancer progression.
- Treatment morbidity.
- Adverse events.
- Quality of life.

Safety

¹⁸F-FDG PET is considered a safe procedure. A previous MSAC report discussed relevant safety issues on PET for recurrent colorectal cancer.³ Patients undergoing ¹⁸F-FDG PET will be exposed to additional radiation on top of the radiation from CT during the initial diagnostic imaging tests, but doses from PET are typically lower than with diagnostic CT.²⁰ The potential long-term effects of exposure to diagnostic levels of radiation are unlikely to be a relevant consideration for patients with proven locally advanced, suspected locally or regionally recurrent or suspected metastatic breast cancers. This is due to their likely exposure to radiotherapy and/or chemotherapy either in the past or in the future of their treatments.²⁰

ECONOMIC CONSIDERATIONS

Proposed MBS fee

The applicant has not provided a MBS fee estimate as “the level of funding remains contentious, as it does not provide a capital component for depreciation and replacement of equipment”.

However, from another MBS items for diagnostic ¹⁸F-FDG PET service for various cancers, the MBS fee is \$953 (for MBS items 61529 for non-small cell lung cancer, 61598 for head and neck cancer, 61604 for head and neck cancer, 61523 for pulmonary nodule, 61538 for brain tumour, 61541 for colorectal carcinoma, 61565 for ovarian carcinoma, 61571 and 61575 for carcinoma of the uterine cervix, 61610 for squamous cell carcinoma involving cervical nodes, 61616 for indolent non-Hodgkin’s lymphoma, and 61620, 61622, 61628, and 61632 for Hodgkin’s or non-Hodgkin’s lymphoma).

Approach to the economic evaluation

The clinical claim is that confirmatory ¹⁸F-FDG PET imaging is superior to confirmatory standard diagnostic imaging. The claim will be that ¹⁸F-FDG PET is more effective (for the outcomes listed previously) than standard diagnostic imaging, and it is superior to confirmatory standard imaging for safety. The reason for claiming superior safety is that clinical experts from HESP and the applicant suggest that standard diagnostic tests (e.g. CT) have a higher risk of adverse events (e.g. allergic reactions) than ¹⁸F-FDG PET.

Provided that sufficient clinical data are available to support the claim of superiority, an appropriate type of economic analysis would be a cost-effectiveness or cost-utility analysis (Table 4). The final structure of the economic analysis will be dependent on the available clinical data.

Table 4: Classification of an intervention for determination of economic evaluation to be presented

| | | Comparative effectiveness versus comparator | | | | |
|--------------------------------------|--------------|---|----------|--------------|----------------------|----------|
| | | Superior | | Non-inferior | Inferior | |
| Comparative safety versus comparator | Superior | CEA/CUA | | CEA/CUA | Net clinical benefit | CEA/CUA |
| | | | | | Neutral benefit | CEA/CUA* |
| | | | | | Net harms | None^ |
| | Non-inferior | CEA/CUA | | CEA/CUA* | None^ | |
| | Inferior | Net clinical benefit | CEA/CUA | None^ | None^ | |
| | | Neutral benefit | CEA/CUA* | | | |
| Net harms | | None^ | | | | |

Abbreviations: CEA = cost-effectiveness analysis; CUA = cost-utility analysis

* May be reduced to cost-minimisation analysis. Cost-minimisation analysis should only be presented when the proposed service has been indisputably demonstrated to be no worse than its main comparator(s) in terms of both effectiveness and safety, so the difference between the service and the appropriate comparator can be reduced to a comparison of costs. In most cases, there will be some uncertainty around such a conclusion (i.e., the conclusion is often not indisputable). Therefore, when an assessment concludes that an intervention was no worse than a comparator, an assessment of the uncertainty around this conclusion should be provided by presentation of cost-effectiveness and/or cost-utility analyses.

^ No economic evaluation needs to be presented; MSAC is unlikely to recommend government subsidy of this intervention

Health care resources

Table 5: List of resources to be considered for the diagnostic index tests in the economic analysis

| Resource | Provider of resource | Setting in which resource is provided | Unit cost | Source (MBS/PBS) |
|---|-----------------------------|---------------------------------------|-----------|------------------|
| Resources to deliver proposed diagnostic test (i.e. ¹⁸F-FDG PET) | | | | |
| PET/CT machine | Nuclear Medicine Specialist | Outpatient | | |
| 2- ^{[18} F]fluoro-2-deoxy-D-glucose (¹⁸ F-FDG) | Specialist | Outpatient | | |
| Intravenous infusion of ¹⁸ F-FDG | Specialist | Outpatient | | |
| Specialist consultation? | Specialist | Outpatient | | |
| Resources used in association with ¹⁸F-FDG PET (e.g., co-administered interventions, resources used to manage adverse events) | | | | |
| Resources to deliver the comparator diagnostic test (i.e. confirmatory standard diagnostic imaging) | | | | |
| Specialist consultation? | Specialist | | | |
| Computed tomography (chest, abdomen, and pelvis) | Radiologist | Outpatient | \$560.00 | MBS 56807 |
| Computed tomography (chest) | Radiologist | Outpatient | \$400 | MBS 56307 |
| Computed tomography (brain) | Radiologist | Outpatient | \$250 | MBS 56007 |
| MRI (breasts) | Radiologist | Outpatient | \$345.00 | MBS 63457 |
| MRI (breasts – follow-up) | Radiologist | Outpatient | \$345.00 | MBS 63458 |
| MRI (brain) | Radiologist | Outpatient | \$403.20 | MBS 63001 |
| MRI (brain – contrast medium) | Radiologist | Outpatient | \$44.90 | MBS 63491 |
| MRI (spine) | Radiologist | Outpatient | \$358.40 | MBS 63154 |
| MRI (spine – contrast medium) | Radiologist | Outpatient | \$44.80 | MBS 63491 |
| CT (with SPECT, for localisation/correction) | Radiologist | Outpatient | \$100.00 | MBS 61505 (?) |
| CT (with SPECT, for localisation/correction) | Radiologist | Outpatient | \$50.00 | MBS 61719 (?) |
| Bone study (for bone scintigraphy) | Nuclear Medicine Specialist | Outpatient | 600.70 | MBS 61425 |
| Breast ultrasound | Specialist | Outpatient | 49.15 | MBS 55059 |
| Breast ultrasound | Specialist | Outpatient | 54.55 | MBS 55061 |

Table 6: List of resources to be considered for the reference standard test in the economic analysis

| Resource | Provider of resource | Setting in which resource is provided | Unit cost | Source (MBS/PBS) |
|--|----------------------|---------------------------------------|-----------|------------------|
| Resources used to deliver the reference standard test (i.e. pathology / biopsy) | | | | |
| CT in conjunction with a surgical procedure | Radiologist | Outpatient | \$470.00 | MBS 57341 |
| Diagnostic percutaneous aspiration biopsy | Specialist | Outpatient | \$185.85 | MBS 30094 |
| Examination of complexity level 3 biopsy material with 1 or more tissue blocks | Specialist | Outpatient | \$97.45 | MBS 72817 |
| Specialist consultation? | Specialist | | | |
| Resources association with the reference standard test (e.g., co-administered interventions, resources used to manage adverse events) | | | | |
| Wound management? | | | | |
| Antibiotics for infection? | | | | |

Table 7: List of resources for active curative treatments to be considered in the economic analysis

| Resource | Provider of resource | Setting in which resource is provided | Unit cost | Source (MBS/PBS) |
|---|----------------------|---------------------------------------|--------------------------------------|---|
| Resources association with therapeutic treatment (i.e. for local treatment and altered local treatments of possibly curable disease) | | | | |
| Surgery | | | | |
| Major procedure against malignant breast condition | Specialist | Inpatient | \$7,982.00 | ARDRG J06A |
| Specialist consultation These patients will have multiple medical consultations, including with surgeon, medical oncologist, radiation oncologist | Specialist | | \$43.00; \$88.55; \$263.90; \$150.90 | MBS 132 or 110 for physicians; MBS 104, 105 for surgeons, radiation oncologists |
| Follow-up consultation | Specialist | Outpatient | \$75.50 | MBS 116 |
| Chemotherapy | | | | |
| Chemotherapy agent x? | Specialist | Outpatient | Variable | Various |
| Administration of chemotherapy | Specialist | Outpatient | \$65.05 | MBS 13915 |
| Intravenous infusion of <1hr (x6) | Specialist | Outpatient | \$63.85 | MBS 13915 |
| Specialist consultation (x6) | Specialist | Outpatient | \$74.10 | MBS 116 |
| Follow-up consultation | Specialist | Outpatient | \$42.20 | MBS 119 |
| Radiotherapy | | | | |
| Radiotherapy agent at x Gy? | Specialist | Outpatient | Variable | Various |
| Dosimetry for 3D conformal radiotherapy | Specialist | Outpatient | \$1,099.85 | MBS 15562 |
| Simulation for 3D conformal radiotherapy | Specialist | Outpatient | \$646.30 | MBS 15550 |
| Radiation oncology treatment (1 field) (x25) | Specialist | Outpatient | \$58.55 | MBS 15254 |
| Radiation oncology treatment (fields 2-4) (at \$37.25 per field) (x25) | Specialist | Outpatient | \$74.50 | MBS 15269 |
| Treatment verification (x5) | Specialist | Outpatient | \$137.50 | MBS 15700 |
| Specialist consultation | Specialist | Outpatient | \$74.10 | MBS 116 |
| Follow-up consultation | Specialist | Outpatient | \$42.20 | MBS 119 |
| Biologic therapy | | | | |
| Trastuzumab injection 500mg (x4) | Specialist | Outpatient | \$3,543.33 | PBS 4623T |
| Treatment verification (x5) | Specialist | Outpatient | \$137.85 | MBS 15700 |
| Specialist consultation (x5) | Specialist | Outpatient | \$74.10 | MBS 116 |
| Follow-up consultation | Specialist | Outpatient | \$42.20 | MBS 119 |
| Hormonal therapy | | | | |
| Tamoxifen citrate – 20mg x 60 tablets (x30) | Specialist | Outpatient | \$61.30 | PBS 1880Y |
| Treatment verification (x10) | Specialist | Outpatient | \$137.85 | MBS 15700 |
| Specialist consultation (x5) | Specialist | Outpatient | \$74.10 | MBS 116 |
| Follow-up consultation | Specialist | Outpatient | \$42.20 | MBS 119 |

Table 8: List of resources for palliative treatment to be considered in the economic analysis

| Resource | Provider of resource | Setting in which resource is provided | Unit cost | Source (MBS/PBS) |
|---|----------------------|---------------------------------------|---------------|------------------|
| Resources association with palliative treatment (i.e. for incurable disseminated disease) | | | | |
| Supportive care | | | | |
| Morphine | | | \$14 to \$164 | PBS various |
| Prednisone | | | \$10 to \$13 | PBS various |
| Specialist consultation | Specialist | | | |
| Palliative radiotherapy | | | | |
| Radiotherapy (x Gy?) | Specialist | Outpatient | Variable | Various |
| Dosimetry for 3D conformal radiotherapy | Specialist | Outpatient | \$1,099.85 | MBS 15562 |
| Simulation for 3D conformal radiotherapy | Specialist | Outpatient | \$646.30 | MBS 15550 |
| Radiation oncology treatment (1 field) | Specialist | Outpatient | | |
| Radiation oncology treatment (more fields?) | Specialist | Outpatient | | |
| Treatment verification | Specialist | Outpatient | | |
| Specialist consultation | Specialist | | | |
| Palliative chemotherapy | | | | |
| Chemotherapy drug/s x? | | Outpatient | Variable | Various |
| Administration of chemotherapy | Specialist | Outpatient | \$65.05 | MBS 13915 |
| Intravenous infusion of <1hr | Specialist | Outpatient | \$63.85 | MBS 13915 |
| Specialist consultation | Specialist | | | |
| Resources association with observation (i.e. for no sign of spread or cancer in suspected locally or regionally recurrent or suspected metastatic cancers) | | | | |
| Follow-up consultation | Specialist | Outpatient | | |

PROPOSED STRUCTURE OF ECONOMIC EVALUATION (DECISION-ANALYTIC)

Table 9: PICO criteria for confirmatory ¹⁸F-FDG PET for proven locally advanced, suspected metastatic, or suspected locally and regionally recurrent breast cancer.

| Patients | Intervention | Comparator | (For the assessment of diagnostic tests only) Reference or evidentiary standard and prior tests. | Outcomes to be assessed |
|--|--------------------------------------|---|--|---|
| Patients with either (1) proven locally advanced, (2) suspected metastatic, or (3) suspected locally or regionally recurrent breast cancers. | Confirmatory ¹⁸ F-FDG PET | Confirmatory standard diagnostic imaging studies (i.e. mainly CT) | Reference standard: Pathology (i.e. biopsies) Prior tests: Standard diagnostic imaging studies (i.e. mainly CT) | <p>Diagnostic accuracy: Sensitivity. Specificity. Additional true positive (TP) & false positive (FP), receiver operative characteristic area under the curve (ROC AUC), Cochrane Q statistic for testing heterogeneity, diagnostic odds ratio (DOR).</p> <p>Change in management: Definitive treatment avoided. Investigations avoided. Definitive treatment instigated. Overall change. Type of change occurring</p> <p>Patient outcomes: Morbidity. Mortality. Overall survival. Cancer-specific mortality. Cancer progression. Treatment morbidity. Adverse events. Quality of life.</p> |

Questions for public funding

What is the safety, effectiveness and cost-effectiveness of confirmatory ¹⁸F-FDG PET scanning in comparison to confirmatory standard diagnostic imaging for the evaluation of spread of breast cancer in patients who have (1) proven locally advanced, (2) suspected metastatic, or (3) suspected locally or regionally recurrent breast cancer where initial standard diagnostic imaging does not provide sufficient information to determine appropriate treatment?

APPENDICES

A.1. MBS Items For The Comparator

MBS items for the comparator:

Table 10: MBS item descriptor for (confirmatory) standard diagnostic imaging techniques - CT.

| Category 5 – Diagnostic imaging services |
|--|
| <p>MBS 56807</p> <p>COMPUTED TOMOGRAPHY - scan of chest, abdomen and pelvis with or without scans of soft tissues of neck with intravenous contrast medium and with any scans of chest, abdomen and pelvis with or without scans of soft tissue of neck prior to intravenous contrast injection, when undertaken, not including a study performed to exclude coronary artery calcification or image the coronary arteries (R) (K) (Anaes.)</p> <p>Fee: \$560.00</p> |
| <p>MBS 56307</p> <p>COMPUTED TOMOGRAPHY - scan of chest, including lungs, mediastinum, chest wall and pleura, with or without scans of the upper abdomen, with intravenous contrast medium and with any scans of the chest including lungs, mediastinum, chest wall or pleura and upper abdomen prior to intravenous contrast injection, when undertaken, not being a service to which item 56807 or 57007 applies and not including a study performed to exclude coronary artery calcification or image the coronary arteries (R) (K) (Anaes.)</p> <p>Fee: \$400.00</p> |

Table 11: MBS item descriptor for confirmatory standard diagnostic imaging techniques - CT. Items for imaging metastases (brain).

| Category 5 – Diagnostic imaging services |
|--|
| <p>MBS 56007</p> <p>COMPUTED TOMOGRAPHY - scan of brain with intravenous contrast medium and with any scans of the brain prior to intravenous contrast injection, when undertaken, not being a service to which item 57007 applies (R) (K) (Anaes.)</p> <p>Fee: \$250.00</p> |

Table 12: MBS item descriptor for (confirmatory) standard diagnostic imaging techniques - MRI.

| Category 5 – Diagnostic imaging services |
|--|
| <p>MBS 63457</p> <p>MAGNETIC RESONANCE IMAGING performed under the professional supervision of an eligible provider at an eligible location where the patient is referred by a specialist or by a consultant physician and where:</p> <ol style="list-style-type: none"> a) a dedicated breast coil is used; and b) the request for scan identifies that the person is asymptomatic and is less than 50 years of age; and c) the request for scan identifies either: <ol style="list-style-type: none"> (i) that the patient is at high risk of developing breast cancer, due to 1 of the following: <ol style="list-style-type: none"> A. 3 or more first or second degree relatives on the same side of the family diagnosed with breast or ovarian cancer; B. 2 or more first or second degree relatives on the same side of the family diagnosed with breast or ovarian cancer, if any of the following applies to at least 1 of the relatives: <ul style="list-style-type: none"> • has been diagnosed with bilateral breast cancer; • had onset of breast cancer before the age of 40 years; • had onset of ovarian cancer before the age of 50 years; • has been diagnosed with breast and ovarian cancer, at the same time or at different times; |

| |
|--|
| <ul style="list-style-type: none"> • has Ashkenazi Jewish ancestry; • is a male relative who has been diagnosed with breast cancer; <p>C.1 first or second degree relative diagnosed with breast cancer at age 45 years or younger, plus another first or second degree relative on the same side of the family with bone or soft tissue sarcoma at age 45 years or younger; or</p> <p>(ii) that genetic testing has identified the presence of a high risk breast cancer gene mutation.</p> <p>Scan of both breasts for:</p> <ul style="list-style-type: none"> • detection of cancer (R) <p>NOTE: Benefits are payable on one occasion only in any 12 month period. (NK) (Anaes.)</p> <p>Fee: \$345.00</p> |
| <p>MBS 63458</p> <p>MAGNETIC RESONANCE IMAGING performed under the professional supervision of an eligible provider at an eligible location where the patient is referred by a specialist or by a consultant physician and where:</p> <ul style="list-style-type: none"> a) dedicated breast coil is used; and b) the person has had an abnormality detected as a result of a service described in item 63464 or 63457 performed in the previous 12 months <p>Scan of both breasts for:</p> <ul style="list-style-type: none"> • detection of cancer (R) <p>NOTE 1: Benefits are payable on one occasion only in any 12 month period</p> <p>NOTE 2: This item is intended for follow-up imaging of abnormalities diagnosed on a scan described by item 63464 or 63457</p> <p>(NK) (Anaes.)</p> <p>Fee: \$345.00</p> |

Table 13: MBS item descriptor for (confirmatory) standard diagnostic imaging techniques - MRI. Items for imaging metastases (brain and spine).

| Category 5 – Diagnostic imaging services | |
|--|---|
| MBS 63001 | <p>MAGNETIC RESONANCE IMAGING (including Magnetic Resonance Angiography if performed), performed under the professional supervision of an eligible provider at an eligible location where the patient is referred by a specialist or by a consultant physician - scan of head for:</p> <p>- tumour of the brain or meninges (R) (Contrast)</p> <p>Fee: \$403.20</p> |
| MBS 63491 | <p>NOTE: Benefits in Subgroup 22 are only payable for modifying items where claimed simultaneously with MRI services. Modifiers for sedation and anaesthesia may not be claimed for the same service.</p> <p>Modifying items for use with MAGNETIC RESONANCE IMAGING or MAGNETIC RESONANCE ANGIOGRAPHY performed under the professional supervision of an eligible provider at an eligible location where the service requested by a medical practitioner. Scan performed:</p> <p>- involves the use of contrast agent for eligible Magnetic Resonance Imaging items (Note: (Contrast) denotes an item eligible for use with this item)</p> <p>Fee: \$44.80</p> |
| MBS 63154 | <p>- tumour (R) (Contrast)</p> |

| |
|---|
| (Anaes.) Fee: \$358.40 |
| MBS 63491 NOTE: Benefits in Subgroup 22 are only payable for modifying items where claimed simultaneously with MRI services. Modifiers for sedation and anaesthesia may not be claimed for the same service. Modifying items for use with MAGNETIC RESONANCE IMAGING or MAGNETIC RESONANCE ANGIOGRAPHY performed under the professional supervision of an eligible provider at an eligible location where the service requested by a medical practitioner. Scan performed: - involves the use of contrast agent for eligible Magnetic Resonance Imaging items (Note: (Contrast) denotes an item eligible for use with this item) Fee: \$44.80 |

Table 14: MBS item descriptor for (confirmatory) standard diagnostic imaging techniques - CT. Items for localisation / correction.

| |
|--|
| Category 5 – Diagnostic imaging services |
| MBS 61505 CT scan performed at the same time and covering the same body area as single photon emission tomography for the purpose of anatomic localisation or attenuation correction where no separate diagnostic CT report is issued and only in association with items 61302 - 61650 (R) Fee: \$100.00 |
| MBS 61719 CT scan performed at the same time and covering the same body area as single photon emission tomography for the purpose of anatomic localisation or attenuation correction where no separate diagnostic CT report is issued and only in association with items 61302 - 61729 (R) (NK) Fee: \$50.00 |

Table 15: MBS item descriptor for (confirmatory) standard diagnostic imaging techniques – bone scintigraphy.

| |
|---|
| Category 5 – Diagnostic imaging services |
| MBS 61425 BONE STUDY - whole body and single photon emission tomography, with, when undertaken, blood flow, blood pool and delayed imaging on a separate occasion (R) Fee: \$600.70 |

Table 16: MBS item descriptor for (confirmatory) standard diagnostic imaging techniques – ultrasound.

| |
|--|
| Category 5 – Diagnostic imaging services |
| MBS 55059 BREAST, one, ultrasound scan of, where: (a) the patient is referred by a medical practitioner; and (b) the service is not associated with a service to which an item in Subgroup 2 or 3 of this group applies; and (c) the referring medical practitioner is not a member of a group of practitioners of which the providing practitioner is a member (R) (NK) Fee: \$49.15 |

MBS 55061

BREASTS, both, ultrasound scan of, where:

(a) the patient is referred by a medical practitioner; and

(b) the service is not associated with a service to which an item in Subgroup 2 or 3 of this group applies; and

(c) the referring medical practitioner is not a member of a group of practitioners of which the providing practitioner is a member (R) (NK)

Fee: \$54.55

FINAL

A.2. Breast Cancer Staging

Anatomic stage / prognostic groups for breast cancer based on the American Joint Committee on Cancer (AJCC) TNM staging system for breast cancer. Please refer to the 2013 NCCN guideline for breast cancer and the AJCC for full details on staging, definitions and treatments^{8, 10}.

Table 17: AJCC TNM staging system for breast cancer.

| General cancer category (NCCN Guideline V 3.2013) | Anatomic stage / prognostic group | T (primary tumour) | N (regional lymph nodes) | M (distant metastases) | |
|---|-----------------------------------|--|--------------------------|------------------------|----|
| Pure non-invasive carcinomas | Stage 0 | Tis | N0 | M0 | |
| Early breast cancer | Stage 1A | T1* | N0 | M0 | |
| | Stage 1B | T0 | N1mi | M0 | |
| | | T1* | N1mi | M0 | |
| | Stage 2A | T0 | N1** | M0 | |
| | | T1* | N1** | M0 | |
| | | T2 | N0 | M0 | |
| | Stage 2B | T2 | N1 | M0 | |
| | | T3 | N0 | M0 | |
| | | Locally or regionally advanced breast cancer | Stage 3A | T0 | N2 |
| | | | T1* | N2 | M0 |
| T2 | | | N2 | M0 | |
| T3 | | | N1 | M0 | |
| T3 | | | N2 | M0 | |
| Stage 3B | T4 | | N0 | M0 | |
| | T4 | | N1 | M0 | |
| | T4 | N2 | M0 | | |
| | Stage 3C | Any T | N3 | M0 | |
| Metastatic | Stage 4 | Any T | Any N | M1 | |

* T1 includes T1mi

** T0 and T1 tumours with nodal micrometastases only are excluded from Stage 2A and are classified Stage 1B.

REFERENCES

1. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Breast Cancer. Version 1.2014. USA: National Comprehensive Cancer Network,, 2014.
2. Senkus E, Kyriakides S, Penault-Llorca F, et al. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO* 2013; **24 Suppl 6**: vi7-23.
3. Medical Services Advisory Committee (MSAC). Positron Emission Tomography for recurrent colorectal cancer. Ref 35a. In: Department of Health and Ageing, editor. Canberra, Australia: Commonwealth of Australia; 2007.
4. Australian and New Zealand Association of Physicians in Nuclear Medicine (Inc). PET data collection project. Report of the demographic data collection. 1 March 2003 to 15 April 2005. Report to the Commonwealth of Australia represented by the Department of Health and Ageing. Balmain, Australia.: Australian and New Zealand Association of Physicians in Nuclear Medicine (Inc),, 2006.
5. American Cancer Society. American Cancer Society: Breast cancer detailed guide2013. <http://www.cancer.org/cancer/breastcancer/detailedguide/breast-cancer-detailed-guide-toc> (accessed).
6. National Cancer Institute. Breast cancer treatment (PDQ). 22/8/2013 2013. <http://www.cancer.gov/cancertopics/pdq/treatment/breast/healthprofessional/page4/AllPages> (accessed 22nd April 2013).
7. Cooper K, Meng Y, Harnan S, et al. Positron emission tomography (PET) and magnetic resonance imaging (MRI) for the assessment of axillary lymph node metastases in early breast cancer: systematic review and economic evaluation. UK: UK NICE, 2011.
8. American Joint Committee on Cancer. Breast cancer staging. 7th edition.2009, 2009. <http://cancerstaging.org/references-tools/quickreferences/Pages/default.aspx> (accessed).
9. Australian Institute of Health and Welfare, National Breast and Ovarian Cancer Centre. Breast Cancer in Australia: An overview, 2009. Canberra: Australian Institute of Health and Welfare, 2009.
10. National Comprehensive Cancer Network. NCCN guidelines: Breast cancer. Version 1. 2012. USA: National Comprehensive Cancer Network, 2012.
11. Cardoso F, Fallowfield L, Costa A, Castiglione M, Senkus E. Locally recurrent of metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology* 2011; **22**(Suppl 6): vi25-vi30.
12. Centres for Medicare and Medicaid Services. Decision Memo for Positron Emission Tomography (FDG) for Solid Tumors (CAG-00181R). In: Services CfMaM, editor. USA: Centres for Medicare and Medicaid Services; 2009.
13. Australian Institute of Health and Welfare, Cancer Australia. Breast cancer in Australia: an overview. Canberra: Australian Institute of Health and Welfare, 2012.
14. Cancer Australia. What is locally advanced breast cancer? 21 September 2012 2012. <http://canceraustralia.gov.au/affected-cancer/cancer-types/breast-cancer/about-breast-cancer/types-breast-cancer/what-locally-advanced-breast-cancer> (accessed 30/10/2013 2013).
15. Cancer Australia. Breast cancer statistics. 15 October 2013 2013. <http://canceraustralia.gov.au/affected-cancer/cancer-types/breast-cancer/breast-cancer-statistics> (accessed 30/10/2013 2013).
16. Burke M, Allison R, Tripcony L. Conservative therapy of breast cancer in Queensland. *International Journal of Radiation Oncology, Biology and Physics* 1995; **31**: 295 - 303.
17. Fisher B, Anderson S, Redmond C, Wolmark N, Wickerham D, Cronin W. Reanalysis and results after 12 years of follow-up in a randomised clinical trial comparing total

- mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. *New England Journal of Medicine* 1995; **333**: 1456 - 61.
18. Group iNBCC-ABCW. Clinical practice guidelines for the management of advanced breast cancer. In: Council NHaMR, editor. Canberra: Commonwealth of Australia; 2001.
 19. Lord S, Marinovich L, Patterson J, et al. Incidence of metastatic breast cancer in an Australian population-based cohort of women with non-metastatic breast cancer at diagnosis. *Medical Journal of Australia* 2012; **196**(11): 688-92.
 20. Medical Services Advisory Committee (MSAC). Positron emission tomography for cervical cancer. Ref 35e. In: Ageing DoHa, editor. Canberra: Commonwealth of Australia; 2010.
 21. Endo K, Oriuchi N. PET and PET/CT using 18F-FDG in the diagnosis and management of cancer patients. *International Journal of Clinical Oncology* 2006; **11**(4): 286-96.
 22. Boellaard R, O'Doherty MJ, Weber WA, et al. FDG PET and PET/CT: EANM procedure guidelines for tumour PET imaging: version 1.0. *Eur J Nucl Med Mol Imaging* 2010; **37**(1): 181-200.
 23. Delbeke D, Coleman RE, Guiberteau MJ, et al. Procedure guideline for tumor imaging with 18F-FDG PET/CT 1.0. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine* 2006; **47**(5): 885-95.
 24. ICRP. Radiation dose to patients from radiopharmaceuticals. Addendum 3 to ICRP Publication 53. ICRP Publication 106. Approved by the Commission in October 2007. *Annals of the ICRP* 2008; **38**(1-2): 1-197.
 25. Donohoe K, Brown M, Collier B, et al. Society of Nuclear Medicine Procedure Guideline for Bone Scintigraphy. In: Medicine SoN, editor. Society for Nuclear Medicine Procedure Guidelines Manual. USA: Society for Nuclear Medicine; 2003. p. 205-9.
 26. Lee J, Hennessy A, Khafagi F. Bone scans. *Australian Family Physician* 2012; **41**(9): 689-92.