Positron emission tomography for head and neck cancer

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The Medical Services Advisory Committee (MSAC) is an independent committee which has been established to provide advice to the Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

MSAC's advice does not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

The advice in this report was noted by the Minister for Health and Ageing on 8 December 2008.

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The procedure

Positron emission tomography (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). This review is restricted to an examination of PET conducted with the radiopharmaceutical ^{18}F-FDG (2-[^{18}F]fluoro-2-deoxy-D-glucose), which is a radiolabelled 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.

Dual-modality PET/CT, in which PET and 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. In the current review the term PET is used to refer to either PET or PET/CT, for simplicity.

Medical Services Advisory Committee—role and approach

The Medical Services Advisory Committee (MSAC) was established by the Australian Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the 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.

A rigorous assessment of the available evidence is thus the basis of decision making when funding is sought under Medicare. A team from the NHMRC Clinical Trials Centre was engaged to conduct a systematic review of literature on PET for head and neck cancer. An advisory panel with expertise in this area then evaluated the evidence and provided advice to MSAC.

MSAC's assessment of PET

This report updates the previous assessment of evidence for FDG–PET imaging in head and neck cancer (Medical Services Advisory Committee 2001). The previous assessment recommended interim funding for PET for the primary staging of carcinoma of the head and neck, for the further investigation of suspected residual or recurrent carcinoma of the head and neck, and for the evaluation of metastatic squamous cell carcinoma involving cervical lymph nodes from an unknown primary site. This report provides an assessment of evidence published since the 2001 review to January 2008 and evidence provided in the report of the Australian data collection study (Scott et al. 2007), initiated following the MSAC 2001 PET review.

This report focuses on an assessment of FDG–PET performed for the evaluation of three head and neck cancer indications. The specific research questions to be addressed are:

- What is the value of the addition of PET/CT in the assessment of patients with biopsy proven, clinical stage T3/4 Nx or Tx N+ newly diagnosed or recurrent carcinoma of the head and neck, considered suitable for definitive treatment on anatomical imaging?

- What is the value of PET/CT before biopsy (triage) in the assessment of suspected residual carcinoma of the head and neck (ie a suspicious lesion on prior tests) following completion of definitive treatment?

- What is the value of the addition of PET/CT to conventional staging in the assessment of patients with metastatic squamous cell carcinoma involving cervical lymph nodes from an unknown primary site?

Clinical need

Head and neck cancers (HNC) are not very common in Australia. In 2003, there were 2,476 new cases of HNC reported and 919 deaths, accounting for 2.7% of all new cases of cancer and 2.4% of cancer deaths (AIHW & AACR 2007). Approximately 40% of patients who undergo radiotherapy or surgery for HNC develop a recurrence. Cervical lymph node metastases of squamous cell carcinoma from unknown primary sites are rare, constituting only approximately 2% of all head and neck cancers.

Safety

PET and PET/CT are considered safe procedures. Patients undergoing PET/CT will have additional radiation exposure (at low doses), but the potential long-term effects of exposure to ionising radiation are unlikely to be of major concern to these patients with proven malignancies, given their reduced life expectancy.

Effectiveness

The main potential impact of PET in patients with head and neck cancer is improved pre-treatment staging. PET is expected to more accurately define the locoregional extent of disease and better detect distant metastases that would render the disease incurable.

Direct evidence

No direct evidence was found comparing the health outcomes of patients with head and neck cancer assessed with and without FDG–PET.

Linked evidence

In the absence of direct evidence for the effectiveness of PET, evidence for accuracy, change in management and the expected benefit of changes in treatment on health outcomes is presented to evaluate the effectiveness of PET using a linked evidence approach.

Newly diagnosed or recurrent carcinoma of the head and neck

Diagnostic accuracy

Two fair quality studies provided data on the accuracy of the addition of PET in staging of lymph node metastases on a per-patient basis. In one study (134 patients), sensitivity increased from 31% to 57% and specificity increased from 92% to 96%. In the other (23 patients), sensitivity remained unchanged at 90% while specificity increased from 75% to 94%. Four studies reporting lymph node level or lesion-based accuracy also found the addition of PET to increase accuracy.

One study of 48 patients reported that the addition of PET to conventional work-up was positive for additional distant disease in six patients (13%); two were true-positive for distant metastases. One large Taiwanese study of limited applicability (in patients with nasopharyngeal cancer) indicated the sensitivity for distant metastases increased from 33% with conventional staging alone to 84% when PET was added to the staging strategy. This increase in sensitivity occurred with no significant decrease in specificity, from 97% with conventional imaging to 94%, with the addition of PET.

Impact on patient management

The Australian prospective study of PET in head and neck cancer (Scott et al. 2007) provides the most applicable data to the study population under consideration in this review as the study directly reflects the clinical pathway in Australia.

The Australian study indicated that PET led to a change in management plans in 32% (95% CI: 20–46%) of 56 patients. PET detected additional lesions in 36% of patients (20/56). Of the 31 additional lesions detected, 2 were second primary tumours, 22 were lymph node metastases and 7 were distant metastases.

Of those in whom additional lesions were detected, treatment plans changed in 70% (14/20; 95% CI: 46–88%), and of those with no additional lesions detected, treatment plans changed in 11% (4/36; 95% CI: 3–26%) of patients ($p < 0.001$). Surgery was avoided in two patients (4%) and added in one patient (2%). Radiotherapy was added in two patients (4%). Descriptions of the type of surgery planned were provided, but the details were inadequate to determine whether or not the extent of surgery changed.

Changes to the radiotherapy target field or dose were seen in 21% of all patients, in 40% of those with additional lesions detected and in 11% of those with no additional lesions detected ($p = 0.02$). Overall, the radiotherapy clearly increased in five patients (9%), it clearly decreased in five patients (9%), and in two patients (4%) the target field was increased while the dose was reduced.

Impact on patient outcomes

Where PET leads to an increase in the radiotherapy administered based on more accurate staging of regional lymph nodes, this may result in an improvement in patient outcomes. The benefits will depend on the degree to which improved local disease control influences patient survival and quality of life. While this change in management is likely to lead to an improvement in overall patient health outcomes, the magnitude of this effect is not known in the absence of direct evidence.

Where PET leads to a decrease in the radiotherapy administered, this may lead to sparing of normal tissue from unnecessary irradiation, possibly decreasing the adverse consequences of regional radiotherapy. However, direct evidence for this is not available.

Suspected residual carcinoma of the head and neck

Diagnostic accuracy

Five fair quality studies indicated that PET has a low negative likelihood ratio (range 0–0.18) and a high negative predictive value (NPV, range 83–100%) in patients with suspected residual HNC after definitive treatment. Much of the data are retrospective and two of the studies are from the same centre. The two Australian studies both reported a negative likelihood ratio of 0.18 with a NPV of 94% and 95% respectively. In patients who have suspected residual disease following definitive treatment, a negative PET result is highly likely to indicate the absence of disease.

Impact on patient management

A single Australian study (Ware et al 2004) reported the impact of PET on treatment intent in 53 patients with suspected residual disease. PET findings changed management in 21 patients (40%). When the PET scan was negative, the most common change was avoidance of surgery, as reported in 88% of patients (15/17). However, in the context of this review a negative PET scan would have changed management from biopsy, rather than surgery, to observation (surveillance).

Impact on patient outcomes

The use of PET in this population has the potential to reduce of the number of unnecessary additional invasive procedures thereby improving patient outcomes through reduced morbidity and improved quality of life. The magnitude of this effect is uncertain.

Metastatic squamous cell carcinoma involving cervical nodes from an unknown primary site

Diagnostic accuracy

Evidence was limited on the additional value of PET/CT to conventional staging including panendoscopy for the assessment of patients with an unknown primary site. In three studies the yield of PET in identifying the primary tumour site ranged from 10%

(1/10) to 68% (26/38). However, histological verification of the primary tumour site was not available for all patients.

Impact on patient management

The main treatment changes that are likely to follow PET are the addition of surgery and/or the modification of the radiotherapy treatment field to include the primary site. In the prospective Australian data collection study (Scott et al. 2007) on 15 patients with an unknown primary tumour, PET detected previously unknown primary tumours in 7 of 15 patients (47%).

Management plans changed in 7 of the 15 patients (47%; 95% CI: 21–73%). When PET detected the primary tumour, management was changed in 5 of 7 cases. Treatment intent was unchanged in all 15 patients (all treated with curative intent).

Management changes included radiotherapy target field increase in three cases (combined with surgery abandoned in one case), radiotherapy added in one case and further investigation (bronchoscopy) changed to surgery in one case.

Impact on patient outcomes

As mentioned above the main treatment changes that are likely to follow PET are the addition of surgery and/or the modification of the radiotherapy treatment field to include the primary site. The benefits of identifying a primary site will depend on the degree to which improved local control of the primary tumour influences patient survival and quality of life. The impact will also depend on whether the primary tumour would have been included in the radiotherapy field regardless of the PET findings. At this stage the impact that this will have on overall patient health outcomes is uncertain.

Economic considerations

Lack of data on patient outcomes precluded cost-effectiveness analyses. The major cost implications of PET for staging of primary head and neck cancers and the assessment of residual disease were estimated. In addition, a threshold analysis was conducted to assess the potential for the addition of PET in primary staging to be cost-effective.

Newly diagnosed or recurrent carcinoma of the head and neck

The net cost for the addition of PET was estimated based on the major management changes in patients with a known primary tumour from the Australian data collection study (Scott et al 2007). The estimated cost of PET for 100 patients was $105,300 (range: $76,100–$206,700) with a slight cost offset attributable to subsequent short-term changes in patient management, giving an estimated net cost of $81,000 per 100 patients.

An exploratory threshold analysis was conducted to consider the potential impact of increasing the radiotherapy (RT) field and based on assumptions of: the positive predictive value (PPV) of PET for additional lymph node metastases; the proportion of patients in whom the RT field was increased due to additional lymph nodes being detected on PET; regional recurrence rates; and the effectiveness of radiotherapy. Based on conservative assumptions it was estimated that the cost per recurrence avoided is in the order of $151,100 (range: $109,400– $295,900). To achieve a cost-effectiveness of

$40,000 per life year gained, the average patient with recurrence avoided would need an approximate life gain of 3.8 years. Based on more favourable assumptions, the estimated cost per recurrence avoided is approximately $12,400 (range: $7,600– $23,000). To achieve a cost-effectiveness of $40,000 per life year gained, the average patient with recurrence avoided would need about a four-month life gain. While the estimates presented are indicative only, extensive modelling of the detailed cost implications of management changes due to PET would not be more informative in the absence of a known measure of effectiveness in terms of patient outcomes.

Based on an estimated utilisation of 1,007 to 1,678 scans annually the gross Medical Benefits Schedule (MBS) reimbursement cost of PET as an addition to conventional staging of patients with newly diagnosed or recurrent carcinoma of the head and neck may range from $766,300 to $3,468,400.

Suspected residual carcinoma of the head and neck

The net cost for the addition of PET in assessing suspected residual carcinoma was estimated considering cost offsets due to the avoidance of biopsy in patients with a negative PET scan. An average cost offset of approximately $466 per biopsy was estimated, assuming 75% of patients undergo fine needle aspiration biopsy, 15% core biopsy and 10% excision biopsy. For 100 patients the median cost of PET is again expected to be approximately $105,300 (range: $76,100– $206,700); the potential cost offset due to the avoidance of biopsy is $20,000–$36,800. The estimated net cost would therefore range from approximately $33,900 to $169,900 per 100 patients.

Based on an estimated utilisation of 107 to 595 scans annually the gross cost to the MBS of funding PET for the assessment of suspected residual disease is estimated to range from $81,400 to $1,229,900.

Metastatic squamous cell carcinoma involving cervical nodes from an unknown primary site

The gross cost to the MBS of funding PET in the assessment of patients with metastatic squamous cell carcinoma involving cervical lymph nodes from an unknown primary site based on the current reimbursement for 150 patients per year, is estimated to range from $114,000 to $310,100 depending on MBS reimbursement level.

Conclusions

The use of PET in addition to conventional staging of patients with newly diagnosed or recurrent carcinoma of the head and neck is considered:

- safe
- to increase accuracy for staging of regional lymph node metastases
- to increase the detection of distant metastases, although these may occur infrequently
- to detect additional lesions in approximately one-third of patients

- to lead to changes in management in approximately 70% of patients when additional lesions are identified, most commonly changes in the radiotherapy regimen. Data on modification of the extent of surgery are not available

- likely to lead to an improvement in overall patient outcomes when PET leads to an increase in the radiotherapy administered for the treatment of previously unsuspected local lymph node metastases. The magnitude of this effect has not been quantified

- likely to lead to a decrease in adverse events associated with regional radiotherapy when PET leads to a decrease in the radiotherapy administered. The magnitude of this effect has not been quantified

- to lead to an increase in costs, associated with a likely benefit of uncertain magnitude.

The use of PET as a triage to biopsy in the assessment of suspected residual carcinoma of head and neck is considered:

- to be highly predictive of the absence of disease when a PET scan is negative

- to lead in changes in management, most likely the avoidance of additional invasive procedures which may include biopsy/surgery, when a PET scan is negative

- to reduce the number of unnecessary additional invasive procedures thereby improving patient outcomes through reduced morbidity and improved quality of life. The magnitude of this effect has not been quantified

- to lead to an increase in costs, associated with a likely benefit of uncertain magnitude.

The use of PET in the assessment of patients with metastatic squamous cell carcinoma involving cervical lymph nodes from an unknown primary site is considered:

- to be able to detect a primary tumour site in some patients

- to lead to changes in management, specifically the addition of surgery and/or the modification of the radiotherapy treatment field to include the primary site

- to have an unknown impact on long term patient outcomes.

Advice

MSAC has considered the safety, effectiveness and cost-effectiveness of PET/CT for squamous cell cancer of the head and neck:

1. in addition to conventional staging of newly diagnosed or recurrent cancer;

2. in addition to conventional assessment for suspected residual cancer after definitive treatment; and

3. in addition to conventional staging of cancer metastatic to cervical lymph nodes from an unknown primary site.

MSAC finds that PET/CT is safe.

MSAC finds that PET/CT improves the accuracy of staging of newly diagnosed or recurrent cancer, and leads to a change in management in the majority of patients in whom additional disease is detected; while this is expected to improve outcomes for patients, the magnitude of this effect could not be quantified.

MSAC finds that PET/CT has a high negative predictive value in patients with suspected residual cancer, and permits the avoidance of invasive procedures, including surgery, in the majority of patients in whom these were planned; while this is expected to reduce morbidity and improve quality of life, the magnitude of this effect could not be quantified.

MSAC finds that PET/CT improves the detection of otherwise occult primary sites of metastatic head and neck cancer, leading to changes in the management of these patients; the impact of such changes on patient outcomes could not be quantified.

MSAC advises that public funding should be supported for these indications.

- The Minister for Health and Ageing noted this advice on the 8th December 2008-

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of positron emission tomography (PET), which is a diagnostic technology for staging of head and neck cancer. MSAC evaluates new and existing diagnostic technologies and procedures for which public funding is sought, in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, which includes reviews of the scientific literature and other information sources, including clinical expertise.

MSAC's terms of reference and membership are in Appendix A. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

This report updates the previous assessment of evidence for FDG–PET imaging in squamous cell carcinoma (SCC) of the head and neck (Medical Services Advisory Committee 2001). The previous assessment recommended interim funding for PET for the primary staging of SCC of the head and neck, for the further investigation of suspected residual or recurrent SCC and for the evaluation of metastatic SCC involving cervical nodes from an unknown primary site.

This report provides an assessment of evidence published since 2001 and includes the report of the Australian data collection study (Scott et al. 2007), initiated following the 2001 MSAC PET review.

Background

Positron emission tomography (PET)

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).

This review is restricted to examining the radiopharmaceutical ^{18}F-FDG (2-[^{18}F]fluoro-2-deoxy-D-glucose, FDG), which is a radiolabelled 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. The chemical modification of glucose in FDG causes it to be taken up like glucose and to become phosphorylated (and thereby become trapped intracellularly), but otherwise to remain essentially unmetabolised and thus accumulate in the target cells (Endo et al. 2006). This accumulation is seen as a 'hot spot' on PET imaging. Semiquantitative measurement may be achieved with the use of the standardised uptake value (SUV). This estimates the uptake of FDG in the volume of interest relative to the mean uptake in the rest of the body (usually normalised to body weight), with a prespecified cut-off value (typically > 2.5) being used to differentiate positive from negative areas. However, many factors can influence the measurement of the SUV (Acton et al. 2004).

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 seen as abnormal foci on PET imaging (Endo et al. 2006). FDG–PET alone does not distinguish between these benign conditions and uptake by malignancies. Where FDG–PET is being performed for a specific oncological indication, these findings are considered false-positive results. The causes of increased uptake can only be differentiated by clinical assessment, further diagnostic investigation or repeat testing.

Dual-modality PET/CT, in which PET and CT scanners are incorporated in a single device, has been developed in order to provide co-registered metabolic and anatomic information in a single examination. A recent National Coordinating Centre for Health Technology Assessment (NCCHTA) review of PET in multiple oncology indications found that PET/CT improved accuracy by 10–15% over PET alone, resolving some equivocal images (Facey et al. 2007).

In the current review the term PET will be used to refer to either PET or PET/CT. The terminology PET/CT will be used where specific reference to this modality is made. It is acknowledged that most current and future practice will relate to the use of PET/CT.

A more detailed description of PET and PET/CT is provided in the previous MSAC review of PET for recurrent colorectal cancer (Medical Services Advisory Committee 2007).

The patient's viewpoint

A health technology assessment report produced by the National Health Service (NHS) in Scotland (Bradbury et al. 2002) canvassed patient views in relation to the assessment of PET in Scotland. The considerations in this report were based on submitted evidence and information from Scottish patients and health professionals. The degree to which these issues vary between the Scottish and Australian context is not known. The only PET facility available at that time in Scotland was used for research purposes, thus few patients in Scotland had undergone a PET scan and patient experience did not relate to undergoing a PET in a standard clinical setting. Nevertheless, the main points raised in the report highlight issues related to PET use that are potentially important from the patient perspective.

> The major patient issues summarised in the Health Technology Board for Scotland PET report (Bradbury et al. 2002) were:
>
> - PET imaging is likely to be just one part of the diagnostic work-up, so it is important to co-ordinate hospital appointments for various tests to reduce the need for patient travel and to avoid delays in treatment.
> - Health professionals should inform patients about the process for PET imaging, associated risks and counselling, and check that patients understand the information received. Carers also require this information.
> - Leaflets with diagrams and clear explanations of complicated terms (such as radioisotope) should be given in addition to basic information about preparation for the scan, and what can be expected during and after the scan. The potential benefits and risks associated with PET scanning should be explained in clear and simple language.
> - The imaging environment should be comfortable and designed to alleviate patient anxieties.
> - Following consultation, there was evidence that patients value the additional information provided by PET scanning.
> - The results of a PET scan may also provide reassurance which is valued highly by some patients.

In the decentralised Australian context, equity of access to PET services is likely to be a concern for patients.

A Belgian PET health technology assessment report (Agency KCE & BHCKC 2005) included the following statement in their conclusion.

> ***Agency KCE, Belgian Health Care Knowledge Centre***
>
> From the perspective of the patient, there are three major issues related to PET: accessibility, benefits and risks. Accessibility is determined by the dispersion of PET centres across the country. The benefits of PET are its minimally invasive nature compared to some other diagnostic procedures and its value of additional information or confirmation of an earlier diagnosis. Risks of PET imaging are limited.

Intended purpose

This report focuses on an assessment of FDG–PET performed for the evaluation of head and neck cancer. The specific research questions to be addressed are:

- What is the value of the addition of PET/CT in the assessment of patients with biopsy proven, clinical stage T3/4 Nx or Tx N+ newly diagnosed or recurrent carcinoma of the head and neck, considered suitable for definitive treatment on anatomical imaging?

- What is the value of PET/CT before biopsy (triage) in the assessment of suspected residual carcinoma of the head and neck (ie a suspicious lesion on prior tests) following completion of definitive treatment?

- What is the value of the addition of PET/CT to conventional staging in the assessment of patients with metastatic squamous cell carcinoma involving cervical lymph nodes from an unknown primary site?

Head and neck cancer

The term 'head and neck cancer' refers to malignant tumours involving the skin, soft tissues or bones of the head and neck region. These cancers include mucosal squamous cell carcinoma (SCC) of the upper aerodigestive tract, metastatic cancer involving lymph nodes of the neck, salivary gland tumours, thyroid cancers, cancers of the skin of the head and neck and bone tumours, particularly of the jaw. Mucosal SCC is the most frequent malignancy of the head and neck region, accounting for approximately 85 per cent. SCCs include cancers of the oral cavity, oropharynx, larynx, hypopharynx, paranasal sinuses and nasopharynx. Patients are usually older men with a history of heavy use of tobacco and/or alcohol. There is now growing evidence that oncogenic human papillomavirus (HPV) is associated with the development of oropharyngeal cancers and cancers of the oral cavity, with a strong association with tonsillar SCC (Herrero et al. 2003).

Nasopharyngeal carcinoma (NPC) is the head and neck cancer with the greatest incidence of neck lymph node and distant metastases (Chang et al. 2005). Unlike other squamous cell carcinomas, NPC does not seem to be linked to excessive use of alcohol and tobacco. Instead, Chinese or Asian ancestry and exposure to the Epstein-Barr virus are considered risk factors for nasopharyngeal carcinoma (Chang & Adami 2006).

Thyroid cancers, skin cancers and lymphomas were not included for this assessment. Otherwise, no restrictions to histological tumour types were applied.

Carcinoma of unknown primary site

A situation where the site of origin of a histologically documented carcinoma involving the cervical lymph nodes could not be identified is referred to as 'carcinoma of unknown primary site' or 'occult primary malignancy'. Most epidermoid cancers metastatic to upper cervical lymph nodes originate from the head and neck, whereas most carcinomas metastatic to lower cervical lymph nodes arise from primary tumours of the head and neck, oesophagus, lung or gastrointestinal tract. An occult primary malignancy is defined by failure of extensive medical examinations to locate a primary tumour.

Conventional staging of head and neck cancer

Conventional diagnostic and staging procedures include laryngoscopy, oesophagoscopy or endoscopy to identify and evaluate the primary lesion. Examination under anaesthesia is generally indicated. In cases where the lesion is accessible to biopsy, fine needle aspiration of the primary and any involved lymph nodes is appropriate. X-ray computed tomography (CT) or magnetic resonance imaging (MRI) of the site may be used to help delineate the extent of the primary tumour and the presence of lymph node metastases. As head and neck cancer includes a number of different malignancies, there is no single staging system. The American Joint Committee on Cancer (AJCC) has defined staging by the size and extent of the primary tumour (T staging), the presence and extent of nodal disease (N-staging) and the presence of distant metastatic disease (M-staging) (TNM classification) (American Joint Committee on Cancer 2002). For many of the malignancies (oropharyngeal cancer, lip and oral cavity cancer, laryngeal cancer, cancer and occult primary carcinoma), the definitions used for nodal (N) and metastatic (M) involvement are the same. Definitions of the primary tumour (T) stage, however, tend to vary. Overall, AJCC stage groupings (stage I, stage II etc.) are generally similar for these diseases. Obviously, for carcinoma of unknown primary site metastatic to cervical lymph nodes, the primary tumour cannot be staged (Tx) (American Joint Committee on Cancer 2003), and there is no generally accepted Roman numeral stage for this presentation. Nasopharyngeal cancer (NPC) is staged differently to other cancers in this group and is tabulated separately.

The sixth edition of the AJCC staging system took effect from 1 January 2003. Details of the staging of head and neck cancers are tabulated in Appendix F.

Clinical need

Incidence and mortality rates of head and neck cancer

Head and neck cancers (HNC) are not very common in Australia. In 2003, there were 2,476 new cases of HNC reported and 919 deaths, accounting for 2.7% of all new cases of cancer and 2.4% of cancer deaths (AIHW & AACR 2007) In 2003, premature death from HNC was responsible for an estimated 8,418 person years of life lost before the age of 75 (AIHW & AACR 2007).

The incidence of HNC is higher in men (annual Australian age standardised incidence 19 per 100,000 based on the Australian population in 2001) than women (6 per 100,000). The incidence of HNC has decreased over the decade since 1993 by an average of 17.6% in males and 4.3% in females (AIHW & AACR 2007).

Recurrent head and neck cancer

Approximately 40% of patients who undergo radiotherapy or surgical treatment of HNC develop a recurrence (Ang et al. 2001; Lee et al. 2007), which usually leads to surgical salvage therapy. Early diagnosis and accurate identification of recurrent HNC is crucial, as patients with early-stage recurrent HNC have a 70% two-year relapse-free survival, while the two-year relapse-free survival of those with advanced-stage recurrent HNC is only 22% (Salaun et al. 2007).

Carcinoma of unknown primary site

Cervical lymph node metastases from unknown primary tumours are rare, constituting only about 2% of all head and neck cancers (Grau et al. 2000). The optimal management of these patients remains uncertain with variable use of neck dissection and radiotherapy. However, the prognosis for patients with neck node metastases from occult primary malignancies is similar to that for other head and neck cancers (Grau et al. 2000).

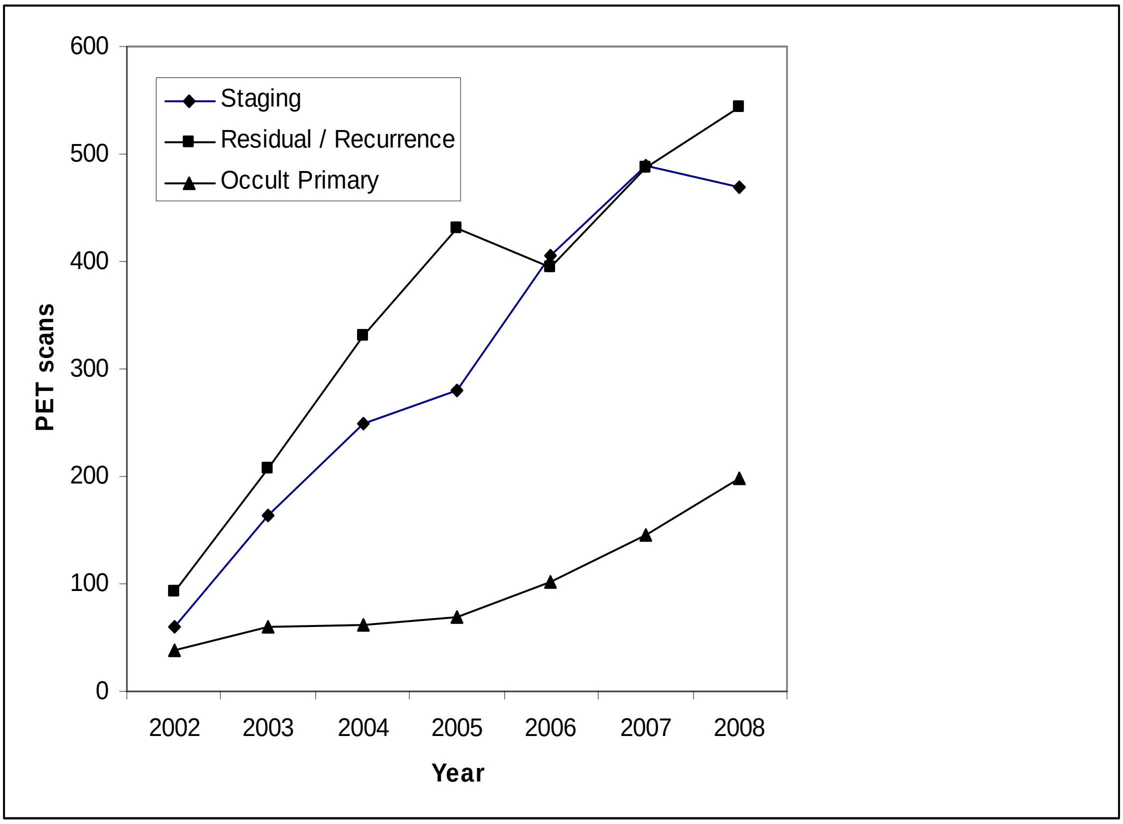
Potential utilisation of PET

Interim funding service utilisation

Over the period 2002–2007 the number of PET scans for the staging of head and neck cancer claimed annually in seven reimbursed Australian centres (listed under 'Current reimbursement arrangement', page 32) increased from 60 to 490 (Figure 1). The number of claims for PET scans increased from 93 in 2002 to 487 in 2007 for the investigation of suspected residual or recurrent carcinoma. For the staging of cervical lymph node SCC from unknown primary site, there were 39 claims in 2002, increasing to 146 in 2007. Utilisation for 2008 was extrapolated from data from the first two quarters and is presented in Figure 1.

During the interim funding period there were no reimbursed PET centres in Tasmania, the Northern Territory or the Australian Capital Territory. All reimbursed centres were located in state capitals. Therefore, access to PET services for patients from central and northern Queensland and northern Western Australia may be limited. Should the number of reimbursed services in Australia increase in the future, it is expected that utilisation would also increase.

Figure 1 Annual MBS item reimbursement for staging head and neck cancer (MBS 61595, 61598), investigation of suspected residual or recurrent carcinoma (MBS 61601, 61604) and evaluation of metastatic SCC from unknown primary site (MBS 61607, 61610, 61613)



Note: 2008 projected data based on data from the first two quarters.

Epidemiological data

If public funding is approved, it is expected that the utilisation of PET would be higher than that seen in the interim funding period, as it will likely be offered in more centres to more patients. An estimate of the potential utilisation of PET in patients with primary head and neck cancer derived from incidence and population data is presented in Table 1.

Primary and recurrent head and neck cancer staging

Patients staged T3/4 Nx or TxN+ (or stage III, VIa/b) on conventional imaging are expected to qualify for PET; patients with known distant metastases (M+) or with early stage disease (T1/2 N0) are not ordinarily considered for PET. To estimate the potential utilisation of PET in primary staging, the most recent incidence (number of reported head and neck cancer cases in Australia in 2004) (AIHW 2008) was multiplied by the current (2008) population. The proportion of patients expected to qualify for PET was estimated by subtracting estimates of those who would not qualify for PET (stage I & IIA and those with distant metastases) from the estimate of new cases in 2008. Data from the UK, US, and Romania found the proportion of patients with early stage (I & II) disease (on conventional imaging) to range from 36% to 53% (Chen et al. 2007; Lung et al. 2007; Vernham & Crowther 1994). Cancer incidence and prevalence data from NSW (Jong et al.2002) report that the proportion of patients presenting with distant metastases is 4.1% in areas with low access to health care services and 5% in areas with high access to health care services; 4.5% (the average) was used to rule these patients out of PET eligibility. Further, an Italian study by Garavello et al.(2006) reports that 9.2% of HNC patients develop distant metastases; this was used as an upper estimate of the proportion of patients ineligible for PET because of distant metastases (as it is expected that more patients will develop distant metastases than present at diagnosis). It is estimated from these data that approximately 970–1,530 patients would qualify for PET for primary head and neck cancer staging per year, if patients with early stage (T1/T2 N0) disease and those with distant metastases are considered ineligible.

If patients with early-stage disease were also considered eligible for PET services, the potential utilisation would range from between 2,330 and 2,450 per year.

Annualised recurrence rates are based on 2–5 year recurrence rates of 20% (Lee et al. 2007; Lim & Choi 2008; Studer et al. 2007), and are estimated to be between 4–10%; therefore it is estimated that annual utilisation could range from approximately 40 to 150.

Assessment of suspected residual disease and response to therapy

Interim PET funding is provided to patients for 'suspected residual or recurrent carcinoma' (MBS 61601, 61604). However, the current review considers PET for residual disease distinct from recurrent disease. The maximum number of patients undergoing PET for assessing residual disease would be all patients with apparently curable disease. This is estimated to be between 970 and 1,530. However, only a proportion of these patients are suspected to have residual disease following therapy. Vedrine et al. (2008) found 39% of stage III/IV patients with non-metastatic, non-resectable disease were suspected to have residual disease. Zhang et al. (1989) found the residual lesion rate in NPC to be 11–17%. Using these estimates it is projected that PET use for the assessment of suspected residual disease will be between approximately 110 and 600 patients annually.

Cervical lymph node metastases from an unknown primary site

The best available estimates of the proportion of patients with head and neck cancer presenting with cervical lymph node metastases from an unknown primary tumour are 2% (Grau et al. 2000) and 5% (Marur & Forastiere 2008) of cases of head and neck cancer; therefore it is estimated that approximately 50–130 patients annually would present with head and neck cancer from an unknown primary site in Australia. However, these estimates are lower than usage during the interim funding period (146 MBS reimbursements), suggesting that this group may have been over-represented in the Australian data collection study; 150 patients/year has therefore been used as an estimate of likely utilisation.

Head and neck cancer overall

Considering all three head and neck cancer indications, the overall estimate of potential PET utilisation ranges from approximately 1,260 to 2,420 (when patients with T1/T2 N0 are excluded).

Table 1 Estimated PET utilisation for assessment of head and neck cancer

	Description	Source	Low PET utilisation estimate		High PET utilisation estimate	
			Calculation/ Proportion	Patients	Calculation/ Proportion	Patients
Patients eligible for PET for staging primary and recurrent head and neck cancer						
A	Incidence of HNC 2008	2003 Australian age-standardised rate of head/neck cancer * Australia's population[a] 2008	12.1/100,000 * 21,175,347	2,562	12.1/100,000 * 21,175,347	2,562
B	Patients with clinical stage early stage HNC	36% stage I & II (Romanian population (Lung et al. 2007) 53% early stage laryngeal cancer (stage I & II) (American population) Chen et al. 2007	53%	1,358	36%	922
C	Patients with distant mets / incurable disease on conventional imaging	Patients diagnosed with distant mets in NSW 4.5% (Jong et al. 2002) Italian HNSCC patients who developed distant mets 9.2% (Garavello et al. 2006)	9.2%	236	4.5%	115
D	Patients with apparently curable HNC eligible for PET staging	A–B–C	37.8%	968	59.5%	1,525
E	Patients with recurrent disease (excludes those with distant mets)	2–5 year recurrence rates ~20%. (Lee et al. 2007; Lim & Choi 2008; Studer et al. 2007)} Annualised recurrence 4–10%	4%	39	10%	153
F	Patients eligible tor staging of primary and recurrent disease	D+E		1,007		1,678
Patients eligible for PET for assessment of residual disease						
G	Patients with apparently curable head/neck cancer	D		968		1,525
H	Patients with suspected residual disease	39% residual neck disease in stage III/IV (no mets; non-resectable) (Vedrine et al. 2008); 11–17% residual lesion rate NPC (Zhang et al. 1989)	11%	107	39%	595
Patients eligible for PET for assessment of unknown primary site						
I	Patients with metastatic HNC from unknown primary site	Proportion HNC presenting with cervical LN mets from unknown primaries (Grau et al. 2000) (Marur & Forastiere 2008)	2%	51	5%	128

Abbreviations: HNC = head and neck cancer, NSW = New South Wales, met = metastasis, HNSCC = head and neck squamous cell carcinoma, NPC = nasopharyngeal cancer, LN = lymph node
a Source: ABS 2008

Australian patients (Scott et al. 2007)

Data were collected prospectively from one PET facility in each of three states (NSW, Victoria and South Australia) over the period 2003–2006 for 71 patients with previously untreated head and neck cancer or metastatic disease involving cervical lymph nodes from an unknown primary site. The characteristics of these patients are summarised in Table 2. PET/CT scans were used in 44% and stand-alone PET scans in 56% of cases.

Mean patient age was 59 years (median 56, range 35–86 years). CT scanning was the most common test used to establish the pre-PET stage and management plan (83%). Histology or cytology had been obtained for diagnosis in 58% of patients prior to PET. Magnetic resonance imaging (MRI) was reported as the basis for diagnosis and staging of head and neck cancer in 17% of patients.

The frequency and location of the primary tumour in patients enrolled in this study is also reported in Table 2.

Table 2 Characteristics of Australian patients undergoing PET head and neck cancers (Scott et al. 2007)

Indication	N	Patient characteristics	Pre-test (post-test) management plan
Untreated head and neck cancer or metastatic disease involving cervical lymph nodes from unknown primary site	71 3 centres 2003–2006 32 referring clinicians PET/CT 44%	Age: mean 59 years (range 35–86) Males: 69% Prior tests for diagnosis: • CT 83% • Histology/cytology 58% • Clinical examination 42% • Chest x-ray 1% • MRI 17% Location of primary tumour: tongue 17.0% mouth 7.0% palate 2.8% tonsil 12.7% oropharynx 7.0% nasopharynx 9.9% hypopharynx 5.6% sinuses 4.2% larynx 12.7% Secondary and unspecified malignant neoplasm of lymph nodes 21.1%	Curative 99% (92%) Chemotherapy and radiotherapy 45% (45%) Radiotherapy alone 21% (23%) Surgery and radiotherapy 14% (15%) Surgery alone 13% (8%) Surgery and radiotherapy and chemotherapy 4% (4%)

Current treatment

Radiotherapy and surgical resection are the main treatment modalities for most head and neck cancers. For small primary cancers without regional metastases, wide surgical excision alone or curative radiotherapy alone is used. For more extensive disease including regional metastases, planned combinations of pre- or postoperative radiation and complete surgical excision are generally used.

Conventional radiotherapy exposes the salivary glands to high doses of radiation, which in many patients causes a reduction of saliva production and permanent xerostomia. However, a newer treatment is parotid sparing radiotherapy which permits more precise irradiation of the tumour volume, thus sparing adjacent healthy tissues. The main advantage of parotid sparing radiotherapy is in reducing the radiation dose to the contralateral salivary glands and partially sparing the salivary output from the parotid glands. However, if the cancer has metastasised or is widespread, conventional treatment may be more effective at slowing the progression of the disease.

Oropharyngeal and hypopharyngeal carcinoma

Oropharyngeal cancer is usually treated with surgery and/or radiotherapy (Adelstein & Adelstein 2003). For patients with disease at a later stage, concurrent multiagent chemotherapy and radiotherapy has become the standard, whereas surgery is reserved for salvage therapy in case of failure of nonoperative treatment (Forastiere et al. 2001; Adelstein & Adelstein 2003). Organ preservation and functionality are regarded as advantages of this approach.

The treatment of hypopharyngeal cancer includes both surgery and radiotherapy in most cases. In recent years, chemotherapy has been added for selected cases of advanced cancer (Hinerman et al. 2002). Local and/or regional recurrence are the most common causes of failure in the treatment of primary hypopharyngeal carcinoma. Long-term surveillance of these patients is therefore crucial.

Laryngeal carcinoma

Radiotherapy or surgery alone are the standard treatments for small laryngeal cancers. Radiotherapy can preserve the voice, and surgery is usually reserved for salvaging failures. Advanced laryngeal cancers are treated by a combination of radiation and surgery (Silver & Ferlito 1997; Wang 2008; Thawley et al. 1999; Mendenhall et al. 2005).

Oral cavity carcinoma

Early cancers (stage I and stage II) of the lip and oral cavity are generally curable by radiotherapy or by surgery, depending on the expected functional and cosmetic results of the treatment (Harrison et al. 1999).

Nasopharyngeal carcinoma

Radiotherapy combined with chemotherapy is the main treatment of nasopharyngeal cancer (Baujat et al. 2006). Surgery is usually reserved for lymph nodes that fail to regress or that reappear after radiotherapy.

Metastatic SCC from occult primary carcinoma

Patients with unknown primary tumours can either be managed with a full course of radiotherapy or adequate neck dissection. Cervical lymph node dissection can be performed in case of a persisting neck mass after completion of radiotherapy. Patients with metastatic disease above the supraclavicular region are best managed by full course radiotherapy followed by surgical resection of persisting palpable tumour (Maulard et al. 1992).

Existing procedures

Computed tomography (CT)

CT is a non-invasive imaging modality that involves measuring the x-ray attenuation coefficient of the anatomical part examined. An x-ray source with a known output rotates at high speed around the patient as the patient is moved through the machine, and the transmitted (attenuated) x-rays are detected in multiple rows of detectors in the gantry. Computer reconstruction of image data is performed from the attenuation coefficient information in axial cross-section and may be reformatted in other planes, or displayed as a 3D-rendered image of the area examined. Intravenous and oral contrast material is usually given during the examination.

Magnetic resonance imaging (MRI)

MRI uses the physical properties of unpaired hydrogen protons in different chemical, structural and magnetic environments to produce images of tissues. Unlike PET and CT, it does not employ ionising radiation. Normally, the magnetic axes of unpaired protons spinning within tissues are randomly distributed. MRI subjects the patient to a strong external magnetic field, causing the magnetic axes of hydrogen protons to align along the axis of the applied field. A radiofrequency pulse is then applied which causes the axes of all the protons to align momentarily against the applied magnetic field axis in a higher energy state. When the pulse is removed, the protons 'relax' back to their baseline state within the magnetic field with a magnitude and rate of energy release, and a degree of 'wobble' (precession) which is dependent on the protons' immediate physicochemical environment. 'T1 relaxation' reflects the rate of realignment, and 'T2 relaxation' reflects the degree of precession, both recorded as spatially localised signal intensities in a radiofrequency antenna (receiving coil). The timing and strength of the radiofrequency pulse can be varied to emphasise either T1-relaxation (T1-weighted) or T2-relaxation (T2-weighted) in order to optimise imaging. 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. Contrast-enhanced MRI typically uses intravenous administration of gadolinium attached to a chelating agent such as DTPA (diethylene triamine pentaacetic acid).

Fiberoptic endoscopy (nasal endoscopy, nasopharyngoscopy, laryngoscopy)

Fiberoptic endoscopy is performed in order to directly visualise the upper aerodigestive tract, and to obtain visually-guided biopsy material. Fiberoptic endoscopy can be performed with or without conscious sedation.

Potential impact of PET on patient outcomes

The main potential impact of PET in patients with head and neck cancer is improved pre-treatment staging. PET should more accurately define the locoregional extent of disease and better detect distant metastases that would render the disease incurable.

In newly diagnosed or recurrent head and neck cancer, the addition of PET is expected to lead to changes in management by more accurately defining active locoregional disease, thus reducing radiotherapy volume where PET defines a smaller gross tumour volume than that assumed from anatomical imaging, or extending radiotherapy volume where PET detects additional locoregional disease. Furthermore, PET is expected to identify patients in whom, due to metastatic disease, definitive local treatment would not be beneficial. PET is thus expected to improve patient outcomes through reduced treatment morbidity and improved quality of life by avoiding non-beneficial interventions and guiding the selection of optimal management.

In patients with suspected residual carcinoma, PET is expected to: a) avoid unnecessary biopsy by ruling out residual active disease; and b) identify patients in whom salvage surgery would not be beneficial due to the presence of metastatic disease.

In patients with occult primary carcinoma, PET is expected to modify the treatment field to permit definitive treatment of the primary site when a primary site is identified. Treating the primary tumour will often lead to a reduced radiotherapy volume, but it may also increase the radiotherapy volume. On the other hand, changing treatment intent from curative to palliative could be expected when distant metastases are identified with PET.

Reference standard

Pathologic confirmation (histopathology or cytopathology), or clinical follow-up of at least six months, were considered the most valid reference standards to determine the true disease status of patients for assessment of PET accuracy in this review.

Comparator

This report compares the addition of PET to prior tests against prior tests alone. Prior tests include physical examination, CT, MRI, panendoscopy and biopsy.

For patients with newly diagnosed or recurrent cancer, prior tests include panendoscopy with or without biopsy, CT and optional MRI.

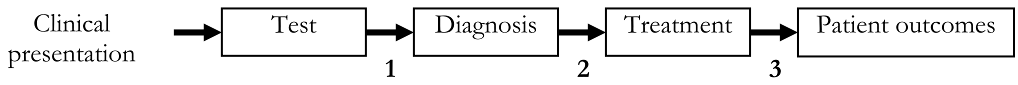
In patients with a suspected residual carcinoma, prior tests are clinical examination, CT and optional MRI. Biopsy would only be performed after PET when PET is available.

In cases of an unknown primary tumour, prior tests include physical examination, CT and optional MRI, panendoscopy and biopsy.

Methodological issues

The clinical value of a test depends on whether its use improves patient outcomes (Medical Services Advisory Committee 2005; Schunemann et al. 2008). This is determined by its ability to accurately detect or exclude disease; whether this information influences treatment decisions; and the effectiveness of the treatment selected (Figure 2).

Figure 2 Causal pathway and determinants of the clinical value of a test



1. Diagnostic accuracy
2. Therapeutic impact
3. Treatment effectiveness

If randomised controlled trials are not available to assess whether adopting a new test improves patient outcomes compared to standard testing practice, evidence from studies assessing test accuracy and therapeutic impact can be linked to evidence about treatment efficacy or improved prognosis to infer effectiveness in some situations.

There are guidelines for designing, conducting, reporting and appraising studies of test accuracy, treatment efficacy and patient prognosis (NHMRC 1999), however the methods for designing and interpreting therapeutic impact studies are less well established. The role of these studies is to provide evidence that the test information has an impact on clinical decision-making, for example by demonstrating changes in clinician diagnostic certainty, test ordering and/or treatment plans. This evidence is interpreted with evidence about the benefits or harms of these decisions, either through a simple descriptive assessment or quantitatively using decision analytic methods, for a judgment about the potential clinical value of the test or the need for further research to demonstrate effectiveness.

Demonstrating a change in diagnosis and/or treatment does not by itself provide evidence of effectiveness. Therefore therapeutic impact studies need to be carefully designed to address a clearly defined question about the potential benefits of the test on clinical decision-making, with an explicit statement about existing evidence for the effectiveness or cost-effectiveness of these decisions, for example, improved patient outcomes through reduction of invasive testing, increase in effective treatment and reduction in patient anxiety). Therapeutic impact studies can be designed as randomised trials to assess clinician diagnostic certainty, diagnosis and treatment selection with and without the new test, or as observational studies including pre-and post-test studies where clinicians are asked to record their provisional diagnosis, diagnostic certainty and proposed management plan before and after testing. Data are analysed to report on change in diagnostic thinking and therapeutic plans and interpreted with information about the accuracy of the test and the true disease state of the subject to assess the benefits or harms of the test information.

MSAC 2001 review

An assessment of PET by the Medical Services Advisory Committee in 2001 reviewed the clinical effectiveness of PET for three indications including squamous cell carcinoma of the head and neck (Medical Services Advisory Committee 2005). This review found that there was insufficient evidence at the time from which to draw definitive conclusions about the clinical effectiveness and cost-effectiveness of FDG–PET. A summary of the characteristics, quality assessment and relevant conclusions of this review is provided in Appendix D (page 112).

The MSAC 2001 review was based on 48 studies. These included 22 studies for primary staging, 22 studies for detecting residual disease or unknown primary site and 4 studies on the evaluation of therapy:

The conclusions of the 2001 review were as follows.

- FDG–PET has high diagnostic accuracy in the detection of primary site and nodal disease in patients with newly diagnosed SCC of the head and neck.
- It is comparable to, or better than, CT, MRI or the combination of CT/MRI in the detection of nodal involvement in staging patients with newly diagnosed head and neck cancer.
- PET appears to offer additional information in the assessment of nodal involvement in newly diagnosed patients, and this information has the potential to affect patient management. As yet it is unclear whether changes in management improve ultimate patient outcomes.
- In the detection of residual or recurrent disease, PET had high sensitivity and overall accuracy, which appeared to be better than CT, MRI or a combination of CT/MRI (based on small patient numbers). The high negative predictive value of PET suggests that a negative PET scan is likely to represent a true absence of disease.
- PET appears to offer additional useful information in the assessment of suspected recurrent or residual disease, and this information has the potential to affect patient management. The high negative predictive value of PET suggests that unnecessary therapy for recurrent disease could be avoided in patients with a negative PET scan.
- PET has the potential to allow the earlier introduction of treatment for recurrent disease (surgery, radiotherapy, chemotherapy). As yet it is unclear whether earlier treatment improves ultimate patient outcomes.
- PET appears to be of value in the detection of occult squamous cell primary tumours in patients diagnosed with SCC cervical node metastases, particularly where other methods have failed to identify the tumour. PET detected approximately 30 per cent of primary tumours where conventional work-up failed to identify the primary site.

- Detection of the primary site has the potential to lead to changes in patient management where disease is detected. At this stage, it is unclear whether detection of the primary site of disease leads to improvements in patient prognosis of long-term outcomes.

- The role of PET in assessing or predicting treatment response requires further evaluation.

Current reimbursement arrangement

Medicare rebates are currently available for specific PET indications performed at seven designated PET facilities nationally. The designated centres are: the Royal Prince Alfred and Liverpool hospitals in 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.

In addition, the Australian Government funds PET scans at the Austin Hospital, Melbourne and Westmead Hospital, Sydney, through a grant arrangement. The Austin Hospital was required to participate in the data collection program, whereas the Westmead hospital was not.

The recommendation of MSAC's original review of PET (Medical Services Advisory Committee 2005) was for funding to be made available on an interim basis contingent on the collection of data relating to PET's clinical and/or cost-effectiveness. The resulting data collection is described in this report.

Reimbursement under the MBS interim funding arrangement has been for the following items:

- MBS Item No. 61595/61598: (Whole body) FDG PET study, performed for the primary staging of carcinoma of the head and neck
  $918.00/953.00

- MBS Item No. 61601/61604: (Whole body) FDG PET study for the further investigation of suspected residual or recurrent carcinoma of the head and neck
  $918.00/953.00

- MBS Item No. 61607/61610/61613: (Whole body) FDG PET study for the evaluation of metastatic squamous cell carcinoma involving cervical nodes from an unknown primary site, with or without catheterisation of the bladder
  $918.00/953.00/975.00

Approach to assessment

Research question

Specific research questions addressing the value of PET as a diagnostic test for the assessment of head and neck cancer were developed by the evaluators working in consultation with members of the Advisory Panel (Appendix B). These questions were formulated *a priori* based on information about the characteristics of head and neck cancer, current practice and the intended purpose of the technology using the 'PPICO' (Population, Prior tests, Intervention, Comparator, Outcomes) criteria (Richardson et al. 1995). All PPICO tables can be found in Appendix E.

Flow charts (Figure 3 to Figure 5) depicting the clinical pathways for the diagnosis and staging of head and neck cancer were developed with the Advisory Panel. These flow charts were used to define the potential role of PET in patient management.

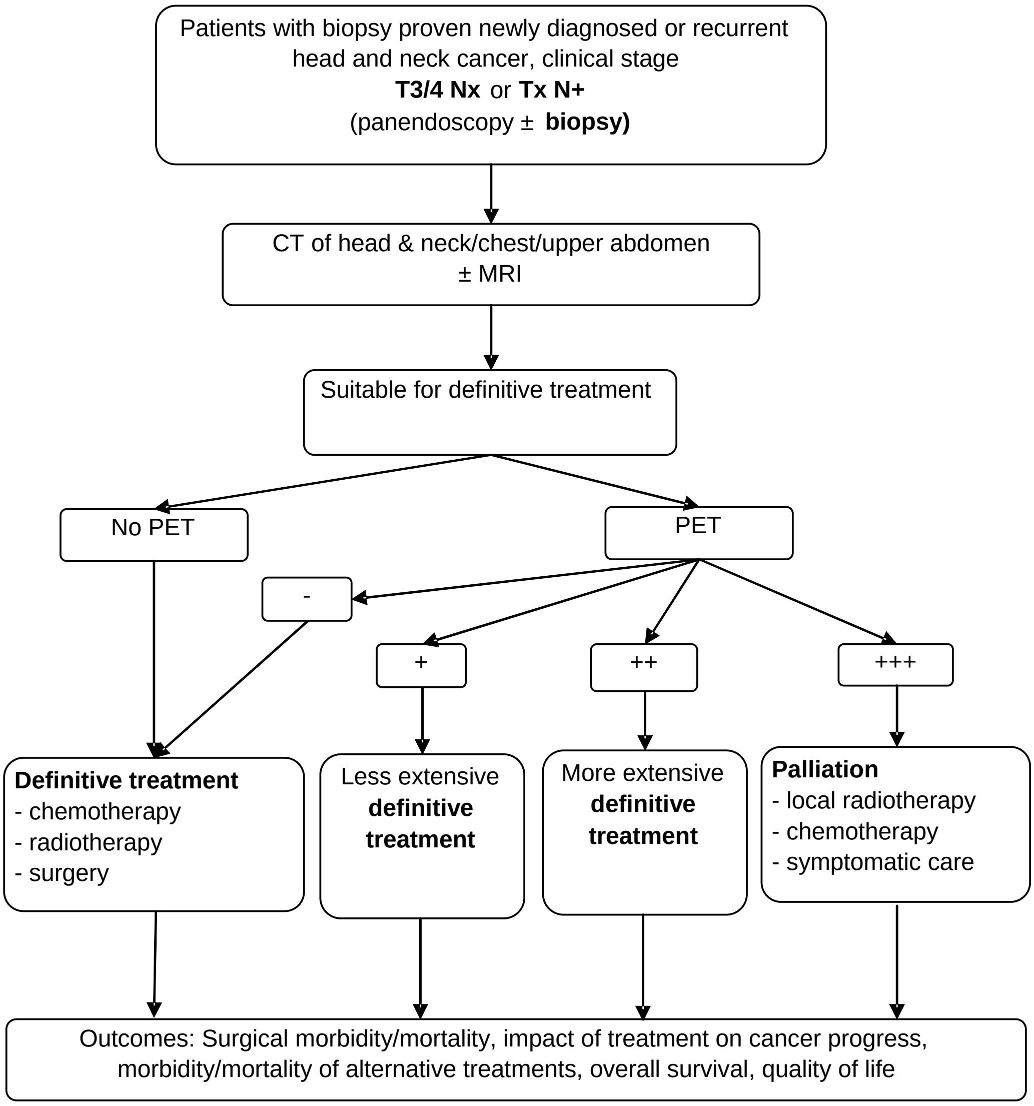
The research questions were:

- What is the value of the addition of PET/CT in the assessment of patients with biopsy proven, clinical stage T3/4 Nx or Tx N+ newly diagnosed or recurrent carcinoma of the head and neck, considered suitable for definitive treatment on anatomical imaging?

- What is the value of PET/CT before biopsy (triage) in the assessment of suspected residual carcinoma of the head and neck (ie a suspicious lesion on prior tests) following completion of definitive treatment?

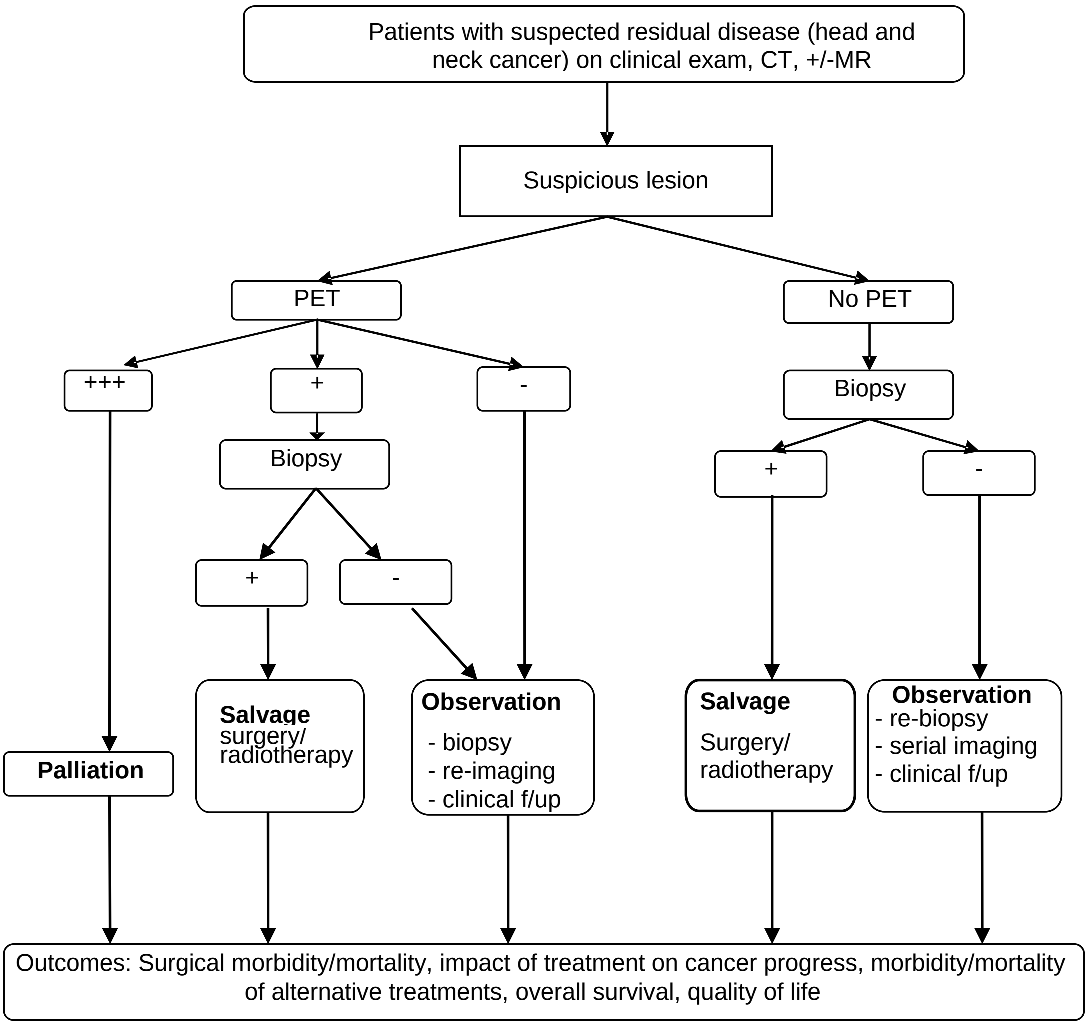
- What is the value of the addition of PET/CT to conventional staging in the assessment of patients with metastatic squamous cell carcinoma involving cervical lymph nodes from an unknown primary site?

Figure 3	Clinical flow chart for the role of PET in staging newly diagnosed or recurrent carcinoma of the head and neck



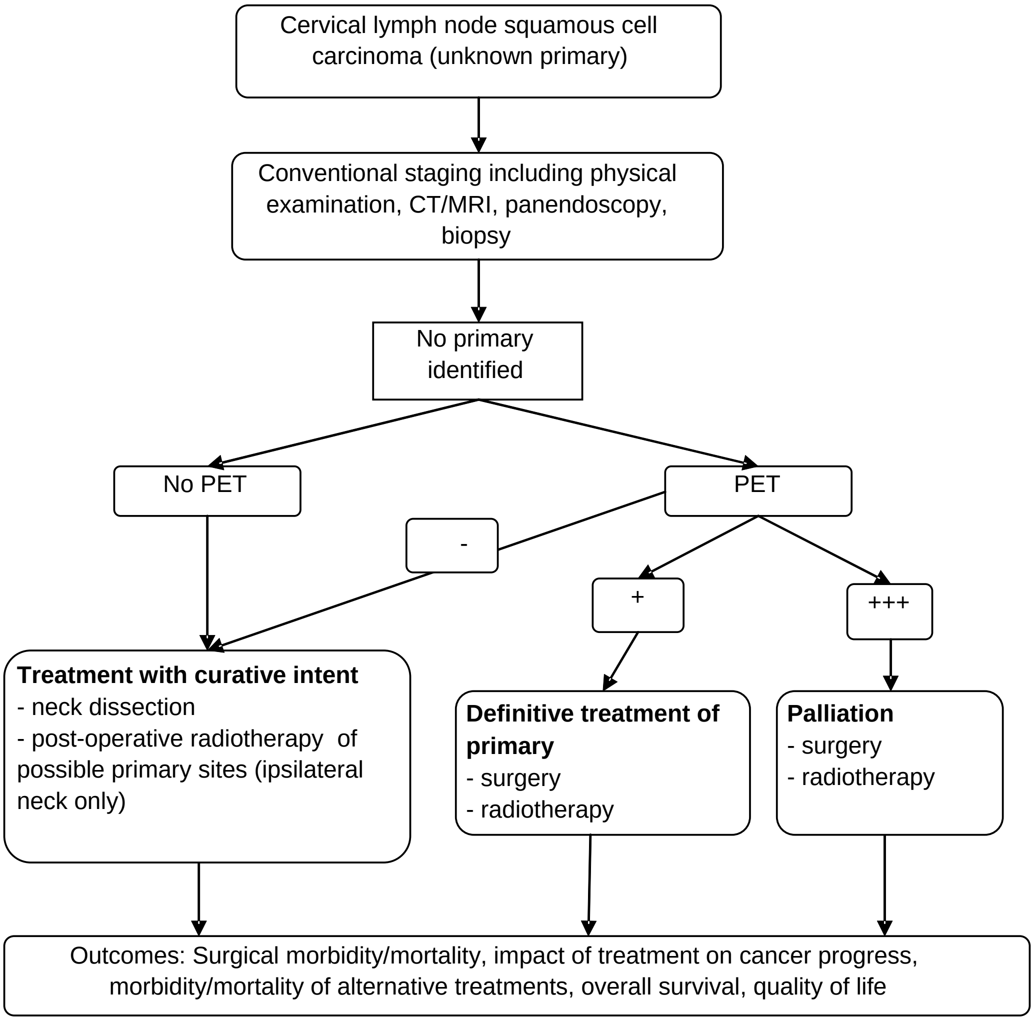
PET –	primary tumour not detected
PET +	smaller gross tumour volume
PET ++	additional locoregional disease
PET +++	distant metastases

Figure 4 Clinical flow chart for the role of PET in assessment of suspected residual carcinoma of the head and neck (including evaluation of response to therapy)



PET – no residual disease detected
PET + residual mass
PET +++ distant metastases

Figure 5 Clinical flow chart for the role of PET in staging cervical lymph node metastases of SCC from unknown primary site



PET – no primary detected
PET + primary detected
PET +++ distant metastases

Assessment framework

Types of evidence

In the absence of any direct evidence for the effectiveness of PET, effectiveness evidence is presented with a linked approach, considering the evidence for accuracy, change in management and the expected benefit of changes in treatment on health outcomes.

Review of the literature

A systematic review of the medical literature was conducted to identify relevant studies. Websites of international health technology assessment (HTA) agencies were searched for existing HTA reports (Appendix C, page 110) and electronic databases of published research (Table 3) were searched for original research papers, including systematic reviews.

Table 3 Electronic databases searched

Database	Period covered
EMBASE.com (includes EMBASE and MEDLINE)	January 2005–23 January 2008
PreMedline	January 2005–23 January 2008
Current Contents	January 2005–23 January 2008
The Cochrane Library Controlled Clinical Trials Registry	Issue 3, 2006

A search of clinical trial databases (Table 4), the American College of Radiology Imaging Network database and the UK National Institute for Health Research's Health Technology Assessment Programme database was undertaken, supplemented by information provided by the applicant, to identify ongoing studies.

Table 4 Clinical trials databases searched to identify ongoing studies

- www.controlled-trials.com
- clinicaltrials.gov
- www.actr.org.au
- www.acrin.org
- www.cancer.gov/search/clinical_trials/
- http://www.ncchta.org/projectdata/projectsearch.asp

Search strategy

The search strategy was developed using the key elements of the clinical question. The search strategy shown in

Table 5 was used to identify papers in EMBASE.com (EMBASE and MEDLINE). This search was adapted for the other databases described in Table 3.

Table 5 Search strategy for EMBASE.com (containing MEDLINE and EMBASE)

Element of clinical question	Suggested search terms
Population	1 'head and neck cancer'/syn
	2 'head and neck carcinoma'/syn
	3 'head and neck' OR nasopharyn* OR laryn* OR oropharyn* OR hypopharyn* : ti,ab [in Field search]
	4 tumo*r* OR cancer* OR carcinoma* OR neoplasm* : ti,ab
	5 3 AND 4
	6 1 OR 2 OR 5
	7 Limit 6 to [2005–present]/py
Intervention/test	1 'emission tomography'/syn
	2 pet OR pet*ct OR spect : ti,ab [Field search]
	3 'coincidence imaging' : ti,ab [Field search]
	4 'gamma camera' : ti,ab [Field search]
	5 'fluorodeoxyglucose f 18'/syn
	6 'fluorodeoxyglucose'/syn
	7 *fdg* OR *deoxy*glucose : ti,ab [Field search]
	8 or/1–7
	9 8 AND [Population search string]

Reference lists of included publications were also checked and experts in the area were contacted to identify additional published or unpublished citations.

Search results

Existing health technology assessment (HTA) reports

Six HTA reports on the value of PET for the investigation of head and neck cancer published between 2001 and 2007 were identified by the search (see Appendix G). The most recent HTA report was from the Agency for Health Technology Assessment Poland (AHTAPol), which reviewed publications to March 2006 and included an economic analysis of PET–CT versus CT alone. However, the quality of the AHTAPol report was considered to be low and the economic evaluation did not address the incremental value of PET (see Appendix H). The UK NCCHTA report superseded the other reports for the assessment of head and neck cancer, reviewing evidence to August 2005. The UK NCCHTA report was considered a high quality systematic review. Data from studies in this HTA report were used as the basis of this assessment. No additional data extraction or re-appraisal of individual study quality or applicability was undertaken with the exception of the Ware et al. (2004) study. A systematic review was also undertaken to include more recent studies. The current assessment takes the approach of summarising and updating this report.

Eligibility criteria for studies

The search strategy retrieved a total of 874 non-duplicate citations. The citations were evaluated by two independent reviewers who determined whether the studies met the eligibility criteria outlined in Table 6. Discrepancies in the results of the screening process were resolved by discussion.

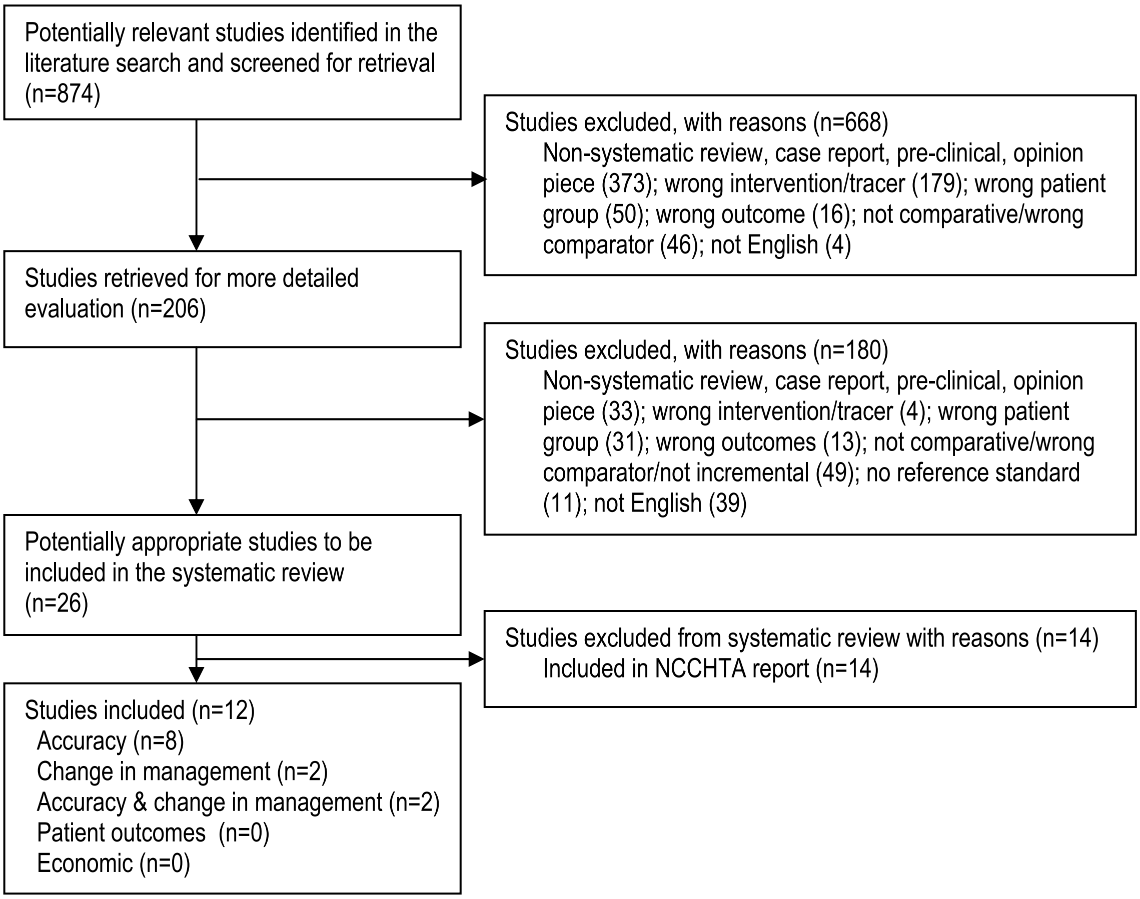
Table 6 Inclusion criteria for identification of relevant studies

Characteristic	Inclusion criteria
Publication type	Clinical studies included. Non-systematic reviews, letters, editorials, animal, in-vitro, laboratory studies, conference abstracts and technical reports excluded Systematic reviews Systematic reviews that have been superseded will be excluded Primary studies Primary studies published during the search period of included systematic reviews will be excluded Accuracy studies excluded if: • patients were selected for inclusion in the study based on their known disease (case-referent, case-control studies) Change in patient management studies will be excluded if: • change in therapeutic impact is not determined by comparison to a clearly defined no-PET or pre-PET management plan • reported outcomes are a subjective rating of physician's perceived usefulness of the test without actual changes in management plan Prognostic studies of survival outcomes included if: • all patients receive the same treatment following PET, regardless of PET test result • all patients receive a specific therapy selected with versus without PET
Patients	≥ 70% of patients with one of the following indications: • patients with biopsy proven newly diagnosed or recurrent carcinoma of the head and neck, clinical stage T3/4 Nx or Tx N+, and considered suitable for definitive treatment on anatomical imaging • patients with residual carcinoma of the head and neck (suspicious lesion on prior tests) • patients with metastatic squamous cell carcinoma involving cervical nodes from an unknown primary site (no primary identified on conventional staging) Studies with <20 patients undergoing PET for the indication of interest excluded Studies in patients with thyroid or skin cancer or lymphoma were excluded
Intervention/test	FDG–PET FDG–PET/CT Plus prior tests
Comparator	Standard prior tests including CT, MRI, physical examination, panendoscopy, biopsy
Outcome	Studies must report on at least one of the following outcomes: • diagnostic accuracy: sensitivity and specificity (or data enabling calculation); diagnostic odds ratios or ROC curves; Q*; additional TP and FP • impact of PET results on clinical management (definitive treatment avoided, investigations avoided, definitive treatment instigated, overall change, type of change occurring in ≥10% patients) • patient outcomes (morbidity, mortality, survival, progression, adverse events, quality of life) • prognostic value of PET results (patient outcomes following specific therapy selected with PET vs without PET; patient outcomes in PET+ or PET- undergoing same treatment)
Language	Non-English language articles excluded

Based on these criteria, 863 citations were excluded from the review. The QUOROM (QUality Of Reporting Of Meta-analyses) flow chart (Figure 6) summarises the results of the literature search and the application of the study exclusion criteria.

QUOROM flow chart

Figure 6 Summary of the process used to identify and select primary studies published since August 2005



Adapted from Moher et al. 1999

The 12 publications meeting criteria for inclusion in the review conducted to identify primary studies published since August 2005 were 9 studies of diagnostic test accuracy and 2 therapeutic impact studies. Including the Australian data collection study and the UK NCCHTA report, 13 studies in total were included in the current review.

Evidence appraisal

Assessment of eligible studies

The evidence presented in the selected studies was appraised and classified using the NHMRC Dimensions of Evidence (NHMRC 1999, 2005) and the MSAC Diagnostic Test Guidelines (Medical Services Advisory Committee 2005). These dimensions

(Table 7) consider important aspects of the evidence supporting a particular diagnostic test and include three main domains: strength of the evidence, size of the effect and relevance of the evidence. The first domain is derived directly from the literature identified for a particular diagnostic test. The last two require expert clinical input as part of their determination.

Table 7 Dimensions of evidence[1]

Type of evidence	Definition
Strength of the evidence	
Level	The study design used, as an indicator of the degree to which bias has been eliminated by design (Table 8)
Quality	The methods used by investigators to minimise bias within a study design
Statistical precision	The *p*-value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect
Size of effect	The distance of the study estimate from the 'null' value and the inclusion of only clinically important effects in the confidence interval
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used

1 Adapted from NHMRC 1999 and MSAC 2005

Individual studies assessing diagnostic effectiveness were graded according to pre-specified quality and applicability criteria (Medical Services Advisory Committee 2005), as shown in Table 8.

Table 8 Grading system for the appraisal of studies evaluating diagnostic tests

Validity criteria	Description	Grading system
Appropriate comparison	Did the study evaluate a direct comparison (provide incremental information) of the index test strategy versus the comparator test strategy?	C1 direct comparison CX other comparison
Applicable population	Did the study evaluate the index test in a population that is representative of the subject characteristics (age and sex) and clinical setting (disease prevalence, disease severity, referral filter and sequence of tests) for the clinical indication of interest? Applicable = directly applicable to Australian health context based on above criteria Limited = probably applicable to Australian context with some caveats as per above criteria Different population = not applicable	P1 applicable P2 limited P3 different population
Quality of study	Was the study designed to avoid bias? High quality = no potential for bias based on pre-defined key quality criteria Fair quality = some potential for bias in areas other than those pre-specified as key criteria Poor quality = poor reference standard and/or potential for bias based on key pre-specified criteria	Q1 high quality Q2 fair Q3 poor reference standard poor quality or insufficient information

The three sub-domains (level, quality and statistical precision) are collectively a measure of the strength of the evidence. The designations of the levels of evidence are shown in Table 9.

Table 9 Designations of levels of evidence (pilot) (NHMRC 2005)

Level	Intervention	Diagnosis
I	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive patients with a defined clinical presentation
III-1	A pseudorandomised controlled trial (ie alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive patients with a defined clinical presentation
III-2	A comparative study with concurrent controls: Non-randomised, experimental trial Cohort study Case-control study Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence
III-3	A comparative study without concurrent controls: Historical control study Two or more single arm study Interrupted time series without a parallel control group	Diagnostic case-control study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)

Quality appraisal

The quality of a study refers to the extent to which it has been designed and conducted to reduce bias in the estimation of the outcome. The potential sources of bias vary according to whether the study is designed to estimate the impact of the test on health outcomes (where the ideal is a randomised trial of alternative tests) or to estimate the diagnostic accuracy of the test (for which the ideal is cross-sectional analytic studies of consecutive patients tested using both the test of interest and a valid reference standard).

A structured appraisal was performed to assess the quality of all additional included studies (published since August 2005). The quality of studies of diagnostic test accuracy was assessed using a checklist of 12 items adapted from the QUADAS (QUality Assessment of studies of Diagnostic Accuracy included in meta-analyseS) tool developed by (Whiting et al. 2003) (Table 10). This tool was developed by experts in the field following a systematic review of the evidence relating to sources of bias and variation relevant to studies of diagnostic test accuracy. Studies were required to meet all 12 criteria to be assessed as high quality (see details in footnote to Table 10). In addition, only prospective diagnostic test accuracy studies were assessed as high quality. Studies that did not use a valid reference standard in all patients were classified as low quality.

Table 10 Criteria used to assess the quality of diagnostic accuracy studies—the QUADAS tool (adapted from Whiting et al. 2003)

Item	
1	Were patients prospectively recruited?
2	Were patients consecutively recruited (ie a consecutive group of patients presenting with a defined clinical presentation)?
3	Were selection criteria explicitly described (ie in enough detail to clearly define eligibility of patients and to be reproducible)?
4	Is the reference standard likely to correctly classify the target condition (valid/invalid/optimal)?
5	Did all patients receive verification using a reference standard?
6	Is the time period between reference standard, comparator and index test short enough to be reasonably sure that the target condition did not change between the tests?
7	Was the execution of the index test described in sufficient detail to define applicability of the test?
8	Were PET/comparator results interpreted blind to reference standard?
9	Were reference standard results interpreted blind to PET/comparator results?
10	Were the same clinical data, including conventional imaging, available when test results were interpreted as would be available when the test is used in practice?
11	Were uninterpretable/intermediate test results reported?
12	Were withdrawals from the study explained?

High quality: Yes to 1, 3, 4, 5, 10, 11; other items required to be either Yes or Unclear
Poor quality: No/Unclear for either 4, 5
Other studies are assessed as fair quality

Seven criteria were applied to assess the quality of systematic reviews, as outlined below (Table 11). For the criterion addressing heterogeneity, systematic reviews that did not undertake a meta-analysis were rated 'Not Applicable' (N/A), unless heterogeneity was specifically mentioned. Studies were required to meet all seven criteria to be assessed as high quality. A study with four or fewer 'yes' or 'N/A' ratings was considered to be of low quality.

Table 11 Criteria used to assess the quality of effectiveness studies (adapted from NHMRC 2000 and CRD 2001)

Study design	Quality checklist
Systematic review*	Was the research question specified?
	Was the search strategy explicit and comprehensive?
	Were the eligibility criteria explicit and appropriate?
	Was a quality assessment of included studies undertaken?
	Were the methods of the study appraisal reproducible?
	Were sources of heterogeneity explored?
	Was a summary of the main results clear and appropriate?
Studies evaluating effectiveness of an intervention on health outcomes	
Randomised controlled trial	Were the inclusion and exclusion criteria specified?
	Was the assignment to the treatment groups really random?
	Was the treatment allocation concealed from those responsible for recruiting subjects?
	Was there sufficient description about the distribution of prognostic factors for the treatment and control groups?
	Were the groups comparable at baseline for these factors?
	Were outcome assessors blinded to the treatment allocation?
	Were the care providers blinded?
	Were the subjects blinded?
	Were all randomised participants included in the analysis?
	Was a point estimate and measure of variability reported for the primary outcome?

* High quality: yes or N/A to all seven criteria
Low quality: four or less yes or N/A
Other studies will be assessed as fair quality

Criteria for appraising the quality of therapeutic impact studies were not available. Therefore a checklist was developed based on criteria discussed by Guyatt et al. (1986).

Potential sources of bias in therapeutic impact studies are described in Guyatt et al. (1986). To minimise bias and maximise applicability of the results, studies should be conducted prospectively in a routine clinical setting using patient eligibility criteria that reflect the intended use of the test in practice and target test population; document what proportion of consecutive eligible patients were included in the study and reasons for exclusion of eligible patients; include all patients enrolled in data analysis; include independent assessment of the influence of test results on reported treatment decisions; document actual treatment received for comparison with clinician recorded planned treatment; include an assessment of test accuracy per patient and adequate follow-up of included subjects to capture potential false-negatives.

Data provided by PET sites about the impact of PET results on patient management were appraised using this checklist (Table 12).

Table 12 Criteria used to assess the quality of therapeutic impact studies (adapted from Guyatt et al. 1986)

Item	Criteria
1	Was the study designed and conducted prospectively?
2	Explicit eligibility criteria reflecting specific presentation or clinical problem?
3	Consecutive recruitment of all patients eligible for testing?
4	Referring clinician determining management plan?
5	Test accuracy documented concomitantly?
6	Pre-test plan independently assessed?
7	Blinding to study test results at pre-test measurement?
8	Association between management change and study test result independently assessed?
9	Management changes reported for specific test use and patient presentation?
10	Management changes reported in adequate detail (eg surgery avoided, additional investigations etc.)?
11	Descriptive information about patient outcomes reported?
12	Physician experience reported?

Data analysis

The characteristics of the study population, type of diagnostic test, reference standard, comparator, study quality and relevant end points were extracted for included studies.

Ninety-five per cent confidence intervals were calculated for studies where these were not presented. Comparisons of proportions were conducted using Pearson's χ^2 test.

Measurement of test accuracy

The accuracy of a test is determined by its ability to identify the target condition compared to a reference standard test that is used as a proxy for true disease status. Subjects who test positive using the reference standard are classified as having the disease and those who test negative are classified as disease-free.

Results of the index test and reference standard for a group of tested subjects were summarised in a two-by-two table where appropriate as shown in Figure 7.

Figure 7 Two-by-two table of data used to determine test accuracy

	Reference standard: disease +	Reference standard: disease –
Index test	true-positive (TP)	false-positive (FP)
	false-negative (FN)	true-negative (TN)
	TP + FN	TN + FP

Total number of subjects tested = TP + TN + FP + FN
Number of subjects with disease = TP + FN
Number of subjects without disease = TN + FP

As shown, subjects who test positive for the disease of interest by both the index test and the reference standard were recorded as true-positive (TP). Subjects without the target condition who test negative by both tests were recorded as true-negative (TN). The index test result was recorded as a false-positive (FP) if it detected the target condition and the reference standard did not. A false-negative (FN) was recorded if the reference standard confirmed the target condition and the index test did not.

Sensitivity and specificity

The sensitivity of a test is the probability of a positive test in subjects with the disease of interest. The specificity of a test is the probability of a negative result in subjects without the disease. The sensitivity and specificity of a test are always considered together and vary according to the threshold used to define a positive test. Sensitivity and specificity are known to vary according to the spectrum of disease (for example, variation in disease severity) in the patient group tested. High sensitivity is particularly important if the penalty for missing a disease is high. However, high specificity is particularly important if a false-positive result can harm the patient.

Calculation

Sensitivity = TP/(TP + FN)

Specificity = TN/(TN + FP)

Positive and negative predictive value

In studies reporting the additional value of a test, only patients testing positive may receive follow-up with the reference standard. In this case the proportion of positive test results that were correct (positive predictive value, PPV) was calculated. Where patients with discordant negative results also receive the reference standard, the proportion of negative test results that were correct (negative predictive value, NPV) was calculated. PPV and NPV vary according to the prevalence of disease in the population.

Calculation

Positive predictive value = TP/(TP + FP)

Negative predictive value = TN/(TN + FN)

Likelihood ratio

The likelihood ratio measures the probability of the test result in patients with the disease compared to those without the disease.

Calculation

Likelihood ratio positive (LR+): The odds that a positive test result would be found in a patient with, versus without, a disease.

LR(+) = [TP / (TP + FN)] / [FP / (FP + TN)]

Likelihood ratio negative (LR–): The odds that a negative test result would be found in a patient without, versus with, a disease.

LR(–) = [FN / (TP + FN)] / [TN / (FP + TN)]

Interpretation

A likelihood ratio of 1 indicates that the test does not provide any useful diagnostic information.

- Positive likelihood ratios > 10 and negative likelihood ratios < 0.1 can provide convincing diagnostic evidence.
- Positive likelihood ratios > 5 and negative likelihood ratios < 0.2 can provide strong diagnostic evidence.
- However, the interpretation depends on the context in which the test is used and the pretest probability.

Data extraction

Data were extracted using a standardised instrument designed for this review. Data extraction was performed by one reviewer and checked by a second reviewer. Any discrepancies were resolved by discussion and involvement of a third reviewer if necessary. The data extraction tables are provided in Appendix I (page 124). Where possible, two-by-two tables were reconstructed from study data to estimate sensitivity, specificity and associated 95% confidence intervals for each test.

Expert advice

An advisory panel with expertise in nuclear medicine, medical oncology, radiation oncology, head and neck surgery and consumer affairs was established to evaluate the evidence and provide advice to MSAC from a clinical perspective. In selecting members for advisory panels, MSAC's practice is to approach the appropriate medical colleges, specialist societies, associations and consumer bodies for nominees. Membership of the Advisory Panel is listed in Appendix B (page 108).

Results of assessment

Is it safe?

FDG–PET and PET/CT are considered safe procedures. A discussion of relevant safety issues is provided in the recent MSAC assessment report on PET for recurrent colorectal cancer (Medical Services Advisory Committee 2007).

Patients undergoing PET/CT will have additional radiation exposure to that of PET alone from the CT component, but doses used are typically lower than with diagnostic CT. The potential long-term effects of exposure to ionising radiation are unlikely to be of major concern to these patients with proven malignancies, given their reduced life expectancy.

Is it effective?

Existing health technology assessment reports

A search for existing HTA reports and published systematic reviews on PET in the assessment of head and neck cancers yielded six reports published between 2001 and 2007 (see Appendix G, page 122), including the NCCHTA report from the UK (Facey et al. 2007). This report was classified as a high quality systematic review. The characteristics and quality assessment of this report are presented in Table 13.

The data from eligible studies provided in this HTA report were used as the basis of this assessment. A systematic review was also undertaken to include more recent studies.

Table 13 Characteristics and appraisal of NCCHTA report

Author (year) Country	Objective and methods	Included studies	Quality assessment of review
UK NCCHTA Facey et al. (2007) United Kingdom	Objective: To assess the clinical effectiveness of PET to aid management decisions relating to diagnosis, staging/restaging, recurrence, treatment response, and radiotherapy planning for 8 indications including head and neck cancer Literature review: *Databases:* *Time period:* To August 2005. Systematic reviews since 1966, primary studies from 2000 *Inclusion/Exclusion criteria:* Suspected or biopsy-proven head and neck cancer including carcinoma of the mouth, lip, tongue, pharynx and larynx. Brain tumours and nasopharyngeal carcinoma were excluded *Intervention:* PET or PET/CT *Outcomes:* Accuracy, change in management or clinical outcomes *Language:* English and Western European foreign language articles	Head and neck cancer: 4 systematic reviews (2000–2003) 41 primary studies (2001–2005)	Quality: high Explicit review questions: yes Explicit & appropriate eligibility criteria: yes Explicit & comprehensive search strategy: yes Quality of included studies appraised: yes Methods of study appraisal reproducible: yes Heterogeneity between studies assessed: N/A Summary of main results clear and appropriate: yes

Abbreviations: CT = computed tomography, N/A = not applicable, PET = positron emission tomography

Direct evidence

This review did not identify any studies reporting the health outcomes of patients with head and neck cancer, assessed with and without FDG–PET.

Studies of patient prognosis following the use of PET are not designed to compare patient survival or disease progression for patients staged with PET versus conventional testing alone and therefore conclusions about the impact of adopting PET on patient outcomes cannot be made based on this type of evidence. However, these studies may provide some supportive evidence for the role of PET. Information from studies reporting patient prognosis following PET is discussed under 'Prognosis following PET' (see page 91).

The UK NCCHTA report found no studies which demonstrated that PET leads to an improvement in patient outcomes in any indication (Facey et al. 2007). This report also explains that while some studies make survival predictions and assess disease progression in follow-up, they are difficult to judge outside a randomised setting due to potential confounding by other factors.

In the absence of direct evidence for the effectiveness of PET, evidence of accuracy, change in management and the expected benefit of changes in treatment on health outcomes is presented in conclusions about the effectiveness of PET using a linked evidence approach.

Indirect evidence

Included studies

Studies identified in the UK NCCHTA report

Data from the UK NCCHTA report (Facey et al. 2007) relevant to the current review were included in this assessment report. The UK NCCHTA report was considered a high quality systematic review.

Studies providing relevant data in the UK NCCHTA report included in this assessment were:

- four primary studies reporting the additional value of PET to CT or MRI for the initial staging of head and neck cancer
- two primary studies assessing the additional value of PET in patients with suspected residual disease
- three primary studies evaluating PET in the assessment of patients with occult primary tumours
- three primary studies providing information on the therapeutic impact of PET results.

Four accuracy studies on primary staging and one on suspected residual disease were not included, as sample sizes were less than 20 patients in each study. Five studies on primary staging were excluded because they reported the *comparative,* rather than the *incremental*, performance of PET relative to other imaging modalities, and four studies were excluded because they did not compare PET with other tests. With respect to unknown primary tumours, due to the paucity of evidence for this indication, studies were included that had fewer than 20 eligible patients or where panendoscopy was performed post-PET.

Studies identified in systematic literature search for primary studies published since August 2005

The systematic review conducted to identify primary studies published since the UK NCCHTA report identified three primary studies that investigated the additional value of PET in *staging of primary head and neck tumours* (Liu et al. 2007; Murakami et al. 2007; Ng et al. 2006). One of the three studies was concerned with the role of PET in M-staging of non-keratinising nasopharyngeal carcinoma (Liu et al. 2007).

Three primary studies were identified which reported the utility of PET for the *assessment of suspected residual carcinoma and response to therapy*. A number of studies reported on the value of PET in assessing treatment response following completion of definitive treatment but were excluded as they were not directed specifically at patients with suspected recurrence (ie a suspicious lesion on prior tests). This included an Australian paper (Connell et al. 2007). PET in this context was used as a replacement test for CT or MRI to identify residual disease.

Five primary accuracy studies that investigated the additional value of PET in *identifying unknown primary tumours* were included for review. One of these studies was excluded as no reference standard was reported for confirmation of the accuracy of PET for detection of the primary tumour (Nassenstein et al. 2007). Three studies are included but two have limitations with respect to histological verification of positive PET results; the remaining study reported PET results prior to panendoscopy (Kumar et al. 2005). One additional systematic review on the value of PET in identifying unknown primary tumours was excluded as the search dates were superseded by the UK NCCHTA report (Delgado-Bolton et al. 2006).

Three studies reporting the *therapeutic impact of PET* on treatment planning were identified (Connell et al. 2007; Ha et al. 2006; Wartski et al.2007). In addition to the published literature, this review includes data from the Australian data collection study (Scott et al. 2007), initiated following the MSAC 2001 PET review. Original data and unpublished analyses from this study were made available for this report. Results from this study have recently been published (Scott et al. 2008).

The study by Ware et al. (2004), which was included in the UK NCCHTA report, has also been included in this section as a primary study. This is because the Australia data collection study does not report on patients with suspected residual disease. The study by Ware et al. (2004) is on an Australian population and reports on change in management.

Full details of the characteristics and appraisal of the 12 additional primary studies reviewed to update the UK NCCHTA report are provided in Appendix I (page 124). The key characteristics and quality appraisal of included studies are discussed below.

Study characteristics and appraisal

Newly diagnosed or recurrent carcinoma of the head and neck

The characteristics of studies included in the UK NCCHTA report (Facey et al. 2007) providing data on the accuracy of PET as an additional test for the initial staging of head and neck cancer that are included in the current review, are summarised in Table 14.

Table 14 Characteristics of studies of PET for initial staging patients with HNC included from UK NCCHTA report

Author (year) Country	Design	N	Population	Test comparison	Outcomes
Schwartz et al. (2005) USA	Diagnostic accuracy study	20 (96 nodal levels)	HNC patients referred for radiotherapy	PET + CT vs CT	Accuracy Incremental staging accuracy (node level based)
Yen et al. (2005) Taiwan	Diagnostic accuracy study	51 (357 lesions, 306 LN)	Patients with buccal mucosa SCC	PET + CT/MRI vs CT/MRI	Accuracy Incremental staging accuracy (lesion based/nodal based)
Ng et al. (2005) Taiwan	Diagnostic accuracy study	124 (493 LN)	Newly diagnosed SCC of oral cavity scheduled for ND	PET + CT/MRI vs CT or MRI	Accuracy Incremental staging accuracy (nodal based)
Schmid et al. (2003) Switzerland	Diagnostic accuracy study	48	Newly diagnosed locally advanced HNC (N2+ or T3)	PET vs CWU (biopsy, endoscopy, CXR, CT)	Accuracy Discordant PET results

Abbreviations: HNC = head and neck cancer, LN = lymph node, SCC = squamous cell carcinoma, ND = neck dissection, PET = positron emission tomography, CT = computed tomography, MRI = magnetic resonance imaging, CXR = chest x-ray

Three additional primary accuracy studies published since August 2005 provided data on the staging accuracy of PET as an additional test to conventional imaging in patients with primary head and neck cancer (Liu et al. 2007; Murakami et al. 2007; Ng et al. 2006). None of these studies presented data on therapeutic impact. The characteristics and appraisal of the three studies are summarised in Table 15.

The study conducted by Liu et al. assessed M-staging in patients with non-keratinising nasopharyngeal cancer (Liu et al. 2007), an entity distinct from other head and neck cancers as it is endemic in South-East Asia and characterised by early locoregional spread and a higher incidence of distant metastasis. Hence, accuracy data from this study cannot be easily generalised to all head and neck cancers. Data were collected prospectively, and the reference standard consisted of histologic proof or clinical or radiological evidence of distant metastasis within one year. PET results were interpreted blind to clinical information, limiting the applicability of the study results to clinical practice.

Ng et al. studied nodal staging in patients with oral cavity squamous cell carcinoma scheduled for surgery (Ng et al. 2006). Only patients with no palpable abnormality in the neck were included which possibly selected patients with less advanced cancer than specified in the clinical question for this review. In addition, as no uninterpretable or intermediate test results were reported, this study was considered of fair quality. However, patients were prospectively recruited, and histopathology results of neck dissections were used as the reference standard.

Murakami et al. (2007) conducted a retrospective study on patients with head and neck SCC planned for resection of the primary tumour. This study was considered of fair quality, as no explicit inclusion criteria were described and the time period between reference standard, comparator tests and PET was not stated. Furthermore, no information on blinding was given.

Table 15 Characteristics and appraisal of primary accuracy studies in patients with primary head and neck cancer

Author (year) Country Setting	N	Test comparison	Population	Study design	Accuracy quality and applicability
Liu (2005) Taiwan Single centre Apr 2002–Aug 2005	300	PET, vertex to upper thigh *in addition to* conventional imaging • Chest x-ray, abdominal US, whole-body skeletal scintigraphy (M-staging) • MRI of head and neck (locoregional staging) • CT if any conventional imaging test or FDT–PET suggestive for distant metastases	• Histologically proven non-keratinising nasopharyngeal carcinoma, no prior treatment • Mean 50 years • 70% males • 20% had distant metastases	Study design: Diagnostic accuracy study Reference standard: Histologic proof OR unequivocal evidence in imaging/clinical course OR equivocal evidence in imaging with subsequent histologic proof (within one year) Outcomes: Accuracy for detection of distant metastases	NHMRC level of evidence: III-2 Comparison: C1 Applicability: P2 Quality: Q2 Prospective
Ng (2005) Taiwan Single centre Jan 2003–Dec 2005	134	PET, vertex to upper thigh *in addition to* CT/MRI	• Clinical diagnosis of SCC in oral cavity, scheduled for surgery • No palpable lymph node • 52.1 (26–82) yrs • 96% males	Study design: Diagnostic accuracy study Reference standard: Histologic proof from neck dissections Outcomes: Accuracy of nodal staging	NHMRC level of evidence: III-2 Comparison: C1 Applicability: P1 Quality: Q2 Prospective
Murakami (2005) Japan Single centre Dec 2004–Jan 2006	23	PET/CT, skull base to pelvis *in addition to* conventional imaging (endoscopy, CT, MRI)	• SCC prior to resection of primary tumour and neck dissection • 66.9 (26–82) yrs • 87% males	Study design: Diagnostic accuracy study Reference standard: Pathological findings Outcomes: Accuracy of nodal staging	NHMRC level of evidence: III-2 Comparison: C1 Applicability: P1 Quality: Q2 Retrospective

Abbreviations: SCC = squamous cell carcinoma, PET = positron emission tomography, CT = computed tomography, MRI = magnetic resonance imaging, CXR = chest x-ray, US = ultrasonography

Suspected residual carcinoma of the head and neck (including response to therapy)

The characteristics of studies included in the UK NCCHTA report (Facey et al. 2007) that provided data on the accuracy of PET in assessing suspected residual carcinoma of head and neck cancer are summarised in Table 16.

Porceddu et al. (2005) reported on 39 patients who had undergone chemoradiotherapy and had complete regression of the primary tumour but a residual mass on palpation or CT scan. All patients had follow-up greater than 12 months (range 16–86 months) and 12 patients had histological verification of their disease status (neck dissection).

Ware et al. (2004) assessed 53 patients with residual abnormalities on conventional evaluation (CE) following radiotherapy. Conventional evaluation included structural imaging, clinical evaluation and biopsy, if performed. Forty-six patients were considered evaluable for the study, with seven patients ineligible as the true extent of disease could not be determined. Patients were classified as disease-free on CE only if the biopsy was negative, but these patients remained eligible for study entry if a PET scan was requested when significant clinical suspicion of active disease remained. Patients had a median follow-up of 55 months (41–75 months).

Table 16 Characteristics of studies of PET in patients with suspected residual head and neck cancer included from UK NCCHTA report

Author (year) Country	Design	N	Population	Test comparison	Outcomes
Porceddu et al. (2005) Australia	Diagnostic accuracy study	} 39	Suspected residual disease following definitive treatment	PET (CT prior)	Accuracy Sens and spec for residual tumour Change in management Surgery avoided
Ware et al. (2004) Australia	Diagnostic accuracy study and change in planned management	} 53 (46 evaluable)	Suspected residual disease following definitive treatment	PET (CT prior)	Accuracy TP, FP, TN, FN (detection of residual disease) Change in management Surgery avoided

Abbreviations: CT = computed tomography, PET = positron emission tomography, TP = true positive; FP = false positive; TN = true negative; FN = false negative

Three additional primary accuracy studies published since August 2005 provided data on the value of PET as a triage test in patients with suspected residual carcinoma of the head and neck. Table 17 presents an overview of the characteristics and appraisal of these studies.

The study conducted by Andrade et al. (2006) assessed the value of PET/CT in the assessment of treatment response and the detection of residual disease after chemoradiotherapy. Twenty-eight patients were enrolled in the study, of whom 23 (82%) are considered applicable to the current review. All 23 patients had a suspicious lesion on either CT or clinical examination, with 20 patients having a suspicious lesion on CT imaging only, 14 on clinical examination only and 11 patients on both CT and clinical examination. Five patients had no prior tests and are not reported on here. All patients underwent a post-treatment PET/CT scan an average of 8 weeks (range 4–15.7 weeks) after completing chemoradiotherapy. Pathological findings and clinical follow-up (range 4.5–33.6 months, median 17.6 months) served as the reference standard. Pathological (surgery/biopsy) results were available in 43% of patients (10/23) with either suspicious CT or clinical examination findings. This study was considered of fair quality given histological or long-term follow-up was not available in all patients, data were collected retrospectively and a significant proportion of patients (n=17) had a PET/CT scan within eight weeks of completing treatment. At this time there is still debate as to the optimal time to use PET to assess treatment response, with earlier use possibly resulting in decreased accuracy (Canning et al. 2005).

Two studies were identified by Yao et al. (2005, 2007) that provided information on PET in patients with residual disease following definitive treatment. Both are considered to report on an applicable population. In the first paper Yao (2005) reports on 53 patients (70 hemi-necks) who at 1 month had a complete response of the primary tumour after definitive radiation. At a follow-up of 2–6 months, 28 of these patients were suspected to have residual disease on CT or MRI. Pathological findings and clinical follow-up served as the reference standard. Neck dissections were performed in 10 patients, and fine needle biopsy in 5 patients. Thirteen patients were followed clinically, with a median follow-up of 27 months (13–41 months). The median time to obtain PET after definitive treatment was 15 weeks (range 5–29 weeks). The study was considered fair quality given data were collected retrospectively and there appeared to be some inconsistencies as to how residual disease was determined and whether PET was part of this process. It was also unclear if the analysis was undertaken based on hemi-necks or individual patients.

Similarly in the second study by Yao (2007), it is unclear as to the placement and role of PET in the diagnostic pathway. It is again a retrospective study and of fair quality. The study reports on 23 patients (24 hemi-neck sites) with SCC who completed definitive radiotherapy with or without chemotherapy and had a residual mass or lymphadenopathy. The authors state that CT images were obtained on the same day as PET scans and patients with residual lymph nodes larger than 1.0 cm were considered to have residual disease and underwent further evaluation. Pathological results from neck dissections or fine needle biopsy were used as a reference standard.

Table 17 Characteristics and appraisal of primary studies of PET in patients with suspected residual carcinoma of the head and neck

Author (year) Country Setting	N (n with suspected disease)	Test comparison	Population	Study design	Accuracy quality and applicability
Andrade et al. (2006) US Single centre Study period NR	28 (23)	PET/CT PET in those with a suspicious lesion found on CT PET in those with a suspicious lesion found on CT and/or CE	• Treatment of response following definitive treatment, chemoradiotherapy for head and neck cancer • Mean age 58 years • 75% males • 11 patients had suspicious lesion on CT • 23 patients had suspicious lesion on CT and CE	**Study design**: Diagnostic accuracy study **Reference standard:** Pathological findings and clinical follow-up. Pathological (surgery/biopsy) results were available in 43% of patients (10/23) Follow-up for all patients ranged from 4.5 to 33.6 months, median 17.6 months **Outcomes:** Accuracy for detection of residual disease	NHMRC level of evidence: III-2 Comparison: C1 Applicability: P1 Quality: Q2 Retrospective, – subset had suspicion based on CT or CE
Yao et al. (2005) US Single centre 1999–2004	53 (28 hemi-necks)	PET/CT PET in those with a suspicious lesion found on CE or CT/MRI	• Treatment of response following definitive treatment for head and neck cancer • Mean age 55.5 years • 81% males • 28 patients had suspicious lesion on CT and CE	**Study design**: Diagnostic accuracy study **Reference standard:** Pathological findings and clinical follow-up. Fifteen patients had either neck dissections or biopsies. Thirteen patients were followed up with a median follow-up of 27 months (13–41 months) **Outcomes:** Accuracy for detection of residual disease	NHMRC level of evidence: III-2 Comparison: C1 Applicability: P1 Quality: Q2 Retrospective, – subset had suspicion based on CT/MRI
Yao et al. (2007) US Single centre Study period NR	23 (24 hemi-necks)	PET/CT PET in those with a suspicious lesion found on CT	• Treatment of response following definitive treatment for head and neck cancer • Mean age 52.5 years • 96% males	**Study design**: Diagnostic accuracy study **Reference standard:** Pathological results from neck dissections or fine needle biopsy were used as a reference standard **Outcomes:** Accuracy for detection of residual disease	NHMRC level of evidence: III-2 Comparison: C1 Applicability: P1 Quality: Q2 Retrospective

Abbreviations: CE = clinical examination, CT = computed tomography, PET = positron emission tomography, MRI = magnetic resonance imaging

Metastatic squamous cell carcinoma involving cervical nodes from an unknown primary site

The characteristics of studies included in the UK NCCHTA report (Facey et al. 2007) that provided some data relevant to detecting unknown primary tumours are summarised in Table 18. None of these studies fulfilled all of the inclusion criteria detailed in Table 6 but are included in the current review and summarised below for completeness.

Table 18 Characteristics of studies of PET in patients with unknown primary head and neck cancer included from UK NCCHTA report

Author (year) Country	Design	N	Population	Test comparison	Outcomes
Miller et al. (2005) USA	Diagnostic accuracy study	26	Positive biopsy results from cervical lymph nodes and no visible primary site in CT or MRI	PET + CT or MRI	Accuracy TP, FP, FN (detection of primary tumour)
Freudenberg et al. (2005) Germany	Diagnostic accuracy study	21	Detection of occult primary tumour in patients with cervical lymph node metastases	PET/CT + CT	Accuracy TP, FP (detection of occult primary tumour)
Stoeckli et al (2003)	Diagnostic accuracy study	18 (10)	Detection of occult primary SCC in head and neck in patients with cervical LN metastases from unknown primary tumour	PET + CT	Accuracy TP, FP (detection of occult primary tumour)

Abbreviations: SCC = squamous cell carcinoma, LN = lymph node, CT = computed tomography, PET = positron emission tomography, MRI = magnetic resonance imaging; TP = true positive; FP = false positive; FN = false negative

Three additional primary accuracy studies published since August 2005 provided data on the accuracy of PET in detecting primary tumours as an additional test to conventional imaging in patients with metastases to cervical lymph nodes. Two have limitations in respect to histological verification of PET positive results and in the remaining study PET was performed prior to panendoscopy. The characteristics and appraisal of these studies are presented in Table 19.

Silva et al. (2006) conducted a study in which 25 patients were enrolled with histologically-proven SCC head and neck metastases, with no identifiable primary tumour on clinical examination, CT or MRI, and panendoscopy. The study is considered applicable but of fair quality due to the issues around the reference standard. Histological findings and clinical follow-up served as the reference standard. Of the nine patients with positive PET results, four had histological confirmation. The remaining patients were followed up (median 3 years, range 10–64 months), but since it is likely that treatment was delivered based on the PET result, the failure of a primary site to emerge at follow-up may not be indicative of a false-positive PET result.

The study by Wartski et al. (2007) included 38 patients, 84% (32/38) of whom had histologically-proven squamous cell carcinoma. Patients had no identifiable primary tumour on clinical examination, fibre-optic laryngoscopy and nasopharyngoscopy, CT and/or MRI scan, panendoscopy and biopsy (applicable population). PET was performed at least four weeks after panendoscopy and biopsy and scans were reviewed independently by two clinicians. Patients underwent a second panendoscopy if PET was positive, with the results of the panendoscopy acting as a reference standard. Nine PET-positive patients did not have a second panendoscopy due to co-morbidities. It appears from the text that the remaining patients were followed up until the time of writing, but specific follow-up duration was not reported. As such the study is considered fair quality.

Miller et al. (2008) studied 31 patients with histologically-proven SCC head and neck metastases, with no identifiable primary tumour on endoscopy, CT or MRI. After the PET scan was completed, each patient underwent a panendoscopy with directed biopsies. Histological findings served as the reference standard. However, since panendoscopy was not performed as part of routine pre-PET work-up, the patient group in this study does not reflect the patient group with 'unknown primaries' as defined by the clinical flow chart in this evaluation and is considered of fair quality and limited applicability.

Table 19 Characteristics and appraisal of primary studies of PET in patients with cervical lymph node metastases from unknown primary head and neck cancer

Author (year) Country Setting	N	Test comparison	Population	Outcomes	Accuracy quality and applicability
Silva et al (2006) UK Single centre 1999–2003	25	PET *in addition to* conventional imaging	True unknown primary, no evidence of any primary malignancy • Mean age 52.5 years • 96% males	Study design: Diagnostic accuracy study Reference standard: Pathological findings and clinical follow-up Outcomes: Accuracy (yield) for detection of unknown primary	NHMRC level of evidence: III-2 Comparison: C1 Applicability: P1 Quality: Q2
Wartski et al. (2007) France 2002–2005	38	PET *in addition to* conventional imaging	Patients with cervical lymph node metastases, no evidence of any primary malignancy • Mean age 52.5 years • 96% males	Study design: Diagnostic accuracy study Reference standard: Pathological findings in a subset (n=17) Outcomes: Accuracy (yield) for detection of unknown primary	NHMRC level of evidence: III-2 Comparison: C1 Applicability: P1 Quality: Q3 (reference standard)
Miller et al. (2008) US NR	38	PET *in addition to* conventional imaging (excluding panendoscopy)	Patients with cervical lymph node metastases, no evidence of any primary malignancy • Mean age 60.5 years • 87% males	Study design: Diagnostic accuracy study Reference standard: Pathological findings Outcomes: Accuracy (yield) for detection of unknown primary	NHMRC level of evidence: III-2 Comparison: C1 Applicability: P2 Quality: Q2

Abbreviations: PET = positron emission tomography

Therapeutic impact: Australian data collection

In addition to the published literature, this review includes data from the prospective Australian study of Scott et al. (2007), initiated following the MSAC 2001 PET review (Medical Services Advisory Committee 2001). The data collected over this period included patient demographics, the pre-PET and post-PET therapeutic plans and disease progression during follow-up (Table 20). These data and unpublished analyses were made available for this report. They provided details of surgery, radiotherapy and chemotherapy management plans as collected and described in Table 20. Results from this study have recently been published (Scott et al. 2008).

Table 20 Data collected from three Australian PET facilities 2003–2006

Patient characteristics and PET findings	Impact on clinician management plan	Patient outcomes
Number of scans performed Indication for PET Patient age and gender Prior tests and results Disease stage PET findings Validation of PET findings by histology or follow-up to 12 months to report on sensitivity and specificity per lesion PET adverse events	Clinician management plan pre and post-PET Actual versus planned treatment received • Surgery - type • Radiotherapy - dose per fraction - number of fractions - total dose - planned and actual total dose and field - PET-prompted treatment change, increase or decrease • Chemotherapy - type of chemotherapy - prospective PET-prompted change of drug combination, duration, intensity of planned therapy	Patient follow-up at 12 weeks, then at 3-monthly intervals to 12 months post-treatment Progression-free survival

Abbreviations: PET = positron emission tomography

The study is included in this review as a report of the impact of PET on patient management. A discussion of the interpretation and potential biases in therapeutic impact studies is included on page 44. The study characteristics and appraisal are summarised in Table 21.

Table 21 Characteristics and appraisal of Australian change in patient management study

Author (year) Country Setting	N	Test comparison	Population	Outcomes	Management quality and applicability
Scott et al. (2007) Australia 3 centres Dec 2003–Dec 2006 (data collection exercise)	71 (56 with known primary, 15 with unknown primary tumour)	PET/CT 44% PET 56% *in addition to* CT (83%), MRI (17%)	Previously untreated carcinoma of the head and neck or metastatic disease involving cervical lymph nodes from unknown primary site Median 56 years (range 35–86) 69% male	PET detection of additional sites of disease (poor accuracy analysis) Change in management, proportion up and down staged, curative vs palliative intent Progression-free survival	Prospective: Yes Explicit criteria: Yes Consecutive patients: NR (exclusions) Referring clinician: Yes Accuracy: no Plans independently assessed: NR Blinding to study results: no Explicit outcomes: Yes Patient outcomes: Yes Physician experience: NR

Abbreviations: CT = computed tomography, PET = positron emission tomography, vs = versus

This prospective Australian multicentre study provides data on the impact of PET on management plans in patients with carcinoma of the head and neck or with metastatic disease involving cervical lymph nodes from an unknown primary site. This study enrolled patients highly applicable to the patient populations under consideration for this review as it directly reflects the population and clinical pathway in Australia. In addition, this is the largest study identified reporting change in management in this patient population.

The study prospectively enrolled 72 patients. Clear inclusion criteria specifying prior diagnosis of head and neck cancer were described. Patients must either have had a previously untreated carcinoma of the nasal cavity, nasopharynx, oral cavity, oropharynx, hypopharynx or larynx, or metastatic disease involving cervical lymph nodes from an unknown primary site.

Pre- and post-PET management plans were documented for all patients. Confirmation that assessment of eligibility for surgery was completed prior to determining the pre-PET management, and that the pre-PET plan was completed prior to obtaining the PET results, was not reported. The study did not specifically request information on further diagnostic investigations. The study also reported agreement of actual patient therapy with the post-PET management plan three months after treatment. Only those patients with complete pre- and post-PET treatment plans, and confirmation that treatment plans were initiated, were eligible for data analysis. One patient was lost to follow-up before it could be confirmed that his treatment plan had been initiated, leaving 71 patients in the data analysis.

Upon agreement with both the authors of the study report and the Australian and New Zealand Association of Physicians in Nuclear Medicine (ANZAPNM), individual patient data were made available to the Advisory Panel, allowing for detailed analyses of the impact of PET on patient management. In particular, separate analyses for patients with a known primary tumour (n=56) and patients with an unknown primary site (n=15) could be performed.

The report also provides detailed information about the spectrum of patients tested, type of management received, and patient outcomes at 12 months. These findings are summarised on pages 26 ('Australian data') and 91 ('Prognosis following PET').

Therapeutic impact data included in the UK NCCHTA report

Two primary studies included in the UK NCCHTA report provided data on change in management or diagnostic thinking in patients with newly detected head and neck cancer (see Table 22). These were considered as supportive data in this review. Some of these data were extracted from the appendices of the report, but were not reported in the main text of the UK NCCHTA report (the exception to this is the Ware et al. (2004) study which is included in Table 23). The quality and design of the studies for reporting change in management data are unclear. It is possible that the data are from studies that may not have recorded a pre-test management plan. Therefore, there may be significant potential for bias in these findings and they may not reflect *changes* in pre-specified management plans.

Table 22 Characteristics of studies of PET in patients with data on change in management included from UK NCCHTA report

Author (year) Country	Design	N	Population	Test comparison	Outcomes
Koshy et al. (2005) USA	Retrospective study of radiotherapy planning	36	Patients with SCC head and neck cancer (incl. 3 with OPT)	PET vs conventional work-up (CT, MRI, CXR)	Change in management Radiation volume and dose
Nishioka et al. (2002)	Radiotherapy planning	21	HNC patients referred for radiotherapy	PET + CT (visually fused) vs CT or MRI	Change in management Number of nodes to irradiate (tumour volume estimation)

Abbreviations: CT = computed tomography, CXR = chest x-ray, HNC = head and neck cancer, MRI = magnetic resonance imaging, OPT = occult primary tumour PET = positron emission tomography, SCC = squamous cell carcinoma, vs = versus

Primary therapeutic impact studies

Three published studies reporting the therapeutic impact of PET/CT in 36 patients (Ha et al. 2006), 35 patients (Connell et al. 2007), 38 patients (Wartski et al. 2007) respectively, with newly diagnosed head and neck cancer or unknown primary site were included in the review. The quality of all three studies was limited by the fact that pre-PET plans were not reported, although it is stated in the methods section that they had been generated. The characteristics and appraisal of the two studies are presented in Appendix I.

One additional paper (Ware et al. 2004) that reported on management in patients with suspected residual disease was included in this review. The study included 53 patients with residual disease on clinical examination. A pre-PET plan was available for all patients, but in 25% of patients (13/53) the responsible clinician had not prospectively recorded this plan and it was instead formulated by the study authors based on institutional protocols and available clinical information. The characteristics and appraisal of this study are presented in Appendix I (page 124).

Table 23 Characteristics of primary therapeutic impact studies

Author (year) Country	Design	N	Population	Test comparison	Outcomes
Ware et al. (2004) Australia	Diagnostic accuracy study and change in planned management	53	HNC patients after 'definitive' therapy but residual abnormality on clinical evaluation	PET Prior tests: clinical evaluation (incl. CT, MRI)	Change in management Surgery to observation, palliative to radical radiotherapy
Ha et al. (2006) USA	Change in management study	36	Patients with suspected head and neck squamous cell cancer	PET–CT In addition to clinical examination, CT or MRI	Change in management Unimodality to multimodality approach
Connell et al. (2006) Australia	Change in management study	76 (n=35 with primary HNC)	Patients with primary head and neck squamous cell carcinoma	PET/CT In addition to CT or MRI	Change in management Radiotherapy field and dose changes
Wartski et al. (2007) France	Diagnostic accuracy study and change in planned management	38	Patients with cervical lymph node metastases, no evidence of any primary malignancy	FDG–PET in addition to conventional imaging	Change in management Comprehensive radiotherapy to targeted radiotherapy, palliative radiotherapy added or surgery of the primary combined with radiotherapy

Abbreviations: HNC = head and neck cancer, CT = computed tomography, PET = positron emission tomography, MRI = magnetic resonance imaging

Newly diagnosed or recurrent carcinoma of the head and neck

Summary

Accuracy

- Two fair quality studies reported the accuracy of the addition of PET to staging of lymph node metastases on a per-patient basis.
- In one study (134 patients), sensitivity increased from 31% to 57% with no significant change in specificity (92% to 96%); in the other (23 patients), sensitivity remained unchanged at 90% while specificity increased from 75% to 94%.
- Per-lymph node level or per-lesion results from four studies were consistent with patient-based analyses.
- The addition of PET increased the sensitivity for distant metastases from 33% to 84%, with no significant change in specificity (from 97% to 94%) in one large study of patients with nasopharyngeal cancer. In a smaller, more applicable study, the yield was 13% (6/48); two were true-positive for distant metastases.

Change in management

Australian data collection

- A total of 56 patients with known primary tumour sites were included in this study. Pre-PET treatment intent was curative in 98% (55/56).
- PET detected additional lesions in 36% of patients (20/56). Of the 31 additional lesions detected, 2 were second primary tumours, 22 were lymph node metastases and 7 were distant metastases.
- Overall, management plans changed in 32% (18/56) of all patients (95% CI: 20–46%).
- In patients with additional lesions detected by PET, plans changed in 70% (14/20; 95% CI: 46–88%), compared to 11% (4/36: 95% CI: 3–26%) of patients with no additional lesions detected ($p < 0.001$).
- Surgery was avoided in two patients (4%) and added in one patient (2%). Radiotherapy was added in two patients (4%). Data on modification of surgical extent were not available.
- Changes to the radiotherapy target field or dose were seen in 21% of all patients: 40% of those with additional lesions detected and in 11% of those with no additional lesions detected ($p = 0.02$). Overall, the radiotherapy clearly increased in five patients (9%), it clearly decreased in five patients (9%), and in two patients (4%) the target field was increased while the dose was reduced.

Evidence from published literature

- Four published therapeutic impact studies report changes in patient management ranging from 25% to 40%. Most changes include increasing RT dose/volume or adding treatment modalities due to upstaging of the disease.

Patient outcomes

The main change in management affects radiotherapy. Where this is based on more accurate staging of regional lymph nodes, this should result in an improvement in patient outcomes.

Where PET leads to an increase in the radiotherapy administered, the benefits will depend on the degree to which improved local control of lymph node metastases influences patient survival and quality of life. While this change in management is likely to lead to an improvement in overall patient health outcomes, the magnitude of this effect is not known in the absence of direct evidence.

Where PET leads to a decrease in the radiotherapy administered, this may lead to the avoidance of normal tissue being unnecessarily irradiated, possibly decreasing adverse events associated with regional radiotherapy. However, direct evidence for this is not available.

Is it accurate?

Many studies exist which report the comparative accuracy of PET and conventional imaging tests. These studies provide data on the value of PET as a replacement for conventional imaging. However, the current assessment addresses the incremental value of PET. The accuracy of PET in providing incremental information over that of anatomical imaging (CT or MRI) is the most relevant measure to answer these clinical questions (Kalff et al. 2002). This information can only be obtained from studies reporting:

- the accuracy of PET plus conventional imaging versus conventional imaging alone (ie PET+CT/MRI vs CT/MRI), or

- the accuracy of PET in a group of patients recruited on the basis of the relevant prior test result (eg PET accuracy for metastases in patients negative for metastatic disease on CT/MRI)

- discordant test results (or individual patient data) where both tests are performed in all patients – ie the discordant positive PET results for distant metastases are those where PET was positive and CT/MRI negative.

PET is proposed for use in patients with biopsy-proven newly diagnosed or recurrent carcinoma of the head and neck which has been judged to be suitable for definitive treatment as assessed by anatomical staging. PET is then used to more accurately define active locoregional disease, thus reducing radiotherapy volume where PET defines a smaller tumour volume (including regional lymph nodes) than that assumed from anatomical imaging, or expanding radiotherapy volume where PET detects additional locoregional disease. Scott et al. (2007) have suggested that PET is particularly useful in the detection of occult nodal metastases. Highly relevant PET results are therefore PET scans positive for additional nodal metastatic disease, where CT or MRI was negative (PET-detected, CT/MRI-occult disease). However, any discordance (true or false) between PET and CT/MRI assessment of nodal metastases may influence the calculation of the locoregional radiotherapy volume and thus potentially influence patient management.

In some cases (in particular in nasopharyngeal carcinoma), PET is also used for better detection of distant metastases that would identify patients in whom radical treatment would not be beneficial. Here, the most relevant PET results are a positive PET scan for additional distant metastatic disease, where CT was negative (PET-detected, CT-occult disease).

Additional value

The value of PET as an additional test to conventional imaging in staging primary carcinoma of the head and neck is shown in Table 24, Table 25, and Table 26. Data are from three studies identified in the current systematic review and four studies from Facey et al. (2007).

Table 24 presents data on the accuracy of PET in addition to conventional imaging in detecting *lymph node metastases*, analysed on a per-patient, per-lymph node level and per-lymph node basis.

In two studies reporting patient-based data, the addition of PET to the conventional work-up increased accuracy for nodal staging. In one study of 134 patients, sensitivity increased from 31% to 57% and specificity increased from 92% to 96% (Ng et al. 2006). In the other study of 23 patients, sensitivity was unchanged while specificity increased from 75% to 94% (Murakami et al. 2007).

Murakami et al. (2007) also reported accuracy according to lymph node level with a total of 112 lymph node levels in 23 patients. The addition of PET did not change sensitivity (74%), but specificity increased from 95% to 99%. One study from Facey et al. (2007) reporting accuracy at lymph node level (96 levels in 20 patients) showed an increase in sensitivity from 78% to 96% while specificity remained unchanged at 99%. Also, the accuracy of PET in studies analysed on a per-lesion basis was consistent with patient-based and level-based analyses (Table 24).

Table 25 presents the accuracy of PET lymph node findings that are discordant with prior imaging. Data are from one study of 48 patients which was included in Facey et al. (2007). PET identified additional lymph node metastases in three patients, all of which were true-positive findings upon pathological confirmation. In addition to the main intended use of PET to detect additional disease, PET may give a negative result for metastatic lymph nodes identified as enlarged on prior imaging. This occurred in four patients; two of these discordant negative findings were true-negative, whereas the other two were false-negative as determined by pathology. The false-negative findings occurred when the lymph node was too close to the primary tumour to be resolved by PET.

The addition of PET did not increase the number of false-positive findings for lymph node metastases in the included studies. In four of five studies PET increased the true-positive detection of true lymph node metastases. In Ng et al. (2006) the incremental yield of PET staging of lymph node metastases was true-positive in nine patients, but false-positive in none, suggesting an incremental PPV of 100% (95% CI: 66–100%).

Table 26 summarises data from a single study on the accuracy of PET in detecting *distant metastases*, reported on a per patient basis. The study was conducted in Taiwan in patients with nasopharyngeal cancer (Liu et al. 2007). The prevalence of distant metastases is expected to be higher in patients with this type of tumour than other types of HNC, thus this study is considered of limited applicability since in the Australian data collection study, nasopharyngeal cancer accounted for only 10% of all patients (13% of those with a known primary site of malignancy); none of the seven occult distant metastases detected by PET originated from a nasopharyngeal carcinoma. In the Liu study, the addition of PET to conventional work-up (CWU) increased sensitivity from 33% (95% CI: 21–46%) to 84% (95% CI: 72–92%) with no significant decrease in specificity (from 97% [95% CI: 94–99%] to 94% [95% CI: 90–96%]). PET identified additional abnormal foci in 13% (38/300) of patients (both true- and false-positive findings for metastatic disease). The inclusion of PET in the staging strategy increased the ratio of true-positive to false-positive findings to 3.4:1 compared to 2.5:1 for CWU alone. The predictive value for additional positive findings on PET (PPV) was 82% (31/38).

One study from Facey et al. (2007) reported that PET was positive for distant disease in 6 of 48 patients (13%) with head and neck SCC (Schmid et al. 2003). Of these, 2 were true-positive for metastatic disease and 2 were false-positive according to biopsy. In addition, there were findings consistent with synchronous primary tumours in 2 patients, 1 of which was malignant and 1 of which was benign (bronchoscopy confirmed one non-small cell lung cancer, rectosigmoidoscopy revealed benign polyposis without evidence of cancer). Thus, the PPV for metastases from head and neck cancer was 33%, and the PPV for malignancy was 50%. The true-positive to false-positive ratio of PET for detecting distant metastases from HNC was 1:2.

The Australian data collection study (Scott et al. 2007) indicated that M-staging was changed from Mx or M0 to M1 in 2 patients (4%, 2/56). No accuracy data were provided in this study. The apparently low prevalence of distant metastases in this population may partly explain the paucity of data on the accuracy of PET for these lesions.

Table 24 Accuracy studies of the additional value of PET in nodal staging of newly diagnosed or recurrent head and neck cancer

Author (year)	N prev (n, %)	Population	Prior tests Index test	CWU						CWU + PET						Quality and applicability
				TP	FP	TN	FN	Sn % [95% CI]	Sp % [95% CI]	TP	FP	TN	FN	Sn % [95% CI]	Sp % [95% CI]	
Lymph nodes (patient based)																
Ng et al. (2006)	134 (35, 26%)	SCC in oral cavity, no palpable LN	CT, MRI PET	11	8	91	24	31 [17–49]	92 [85–96]	20	4	95	15	57 [39–74]	96 [90–99]	Fair quality, limited applicability
Murakami et al. (2007)	23 (15, 65%)	HNC patients prior to tumour resection	CT, MRI, US PET/CT	13.5 *	2*	6*	1.5*	90*	75*	13.5*	0.5*	7.5*	1.5*	90*	94*	Fair quality, limited applicability
Lymph nodes (node level based)																
Murakami et al. (2007)	112 (23 pts)	HNC patients prior to tumour resection	CT, MRI, US PET/CT	14*	5*	88*	5*	74*	95*	14*	1*	92*	5*	74*	99*	
UK NCCHTA Schwartz et al. (2005)	96 levels (20 pts)	HNC patients referred for radiotherapy staging	CT PET	21	1	68	6	78	99	26	1	68	1	96	99	High quality systematic review

Lymph nodes (lesion based)																
UK NCCHTA Yen et al. (2005)	306 LN (51 pts)	Patients with buccal mucosa SCC	CT/MRI PET	25	12	254	15	63	96	34	7	259	6	85	97	High quality systematic review
UK NCCHTA Ng et al. (2005)	493 LN (124 pts)	Newly diagnosed SCC of oral cavity planned for ND	CT/MRI PET	50	22	376	45	53	95	74	22	376	21	78	95	

Abbreviations: prev = prevalence, CWU = conventional work-up, Se = sensitivity, Sp = specificity, SCC = squamous cell carcinoma, HNC = head and neck cancer, ND = neck dissection, CT = computed tomography, MRI = magnetic resonance imaging, US = ultrasonography, PET = positron emission tomography, TP = true positive, TN = true negative, FP = false positive, FN = false negative

*average of two observers

Table 25 Value of addition of PET in the nodal staging of newly diagnosed or recurrent head and neck cancer

Author (year)	N prev (%) Test	Population	Prior tests		Discordant positive findings					Discordant negative findings					Quality and applicability
			Index test	Outcome	Pos N (%)	TP N (%)	FP N (%)	PPV %	TP/FP	Neg N (%)	TN N (%)	FN N (%)	NPV %	TN/FN	
Analyses by patient															
UK NCCHTA Schmid, 2003	48 (nr)	Newly diagnosed locally advanced HNC (N2+ or T3)	CWU (incl. CT) PET	Extra LN mets	3	3	0	100	∞	4	2	2	50	1	High quality systematic review

Abbreviations: CWU = conventional work-up, FP= false positive, FN=false negative HNC = head and neck cancer, LN = lymph node, mets = metastases, , PET = positron emission tomography, PPV = positive predictive value, NPV = negative predictive value, TP = true positive, TN = true negative

Table 26 Accuracy studies of the additional value of PET in M-staging of newly diagnosed or recurrent head and neck cancer

Author (year)	N prev (%)	Population	Prior tests	CWU						CWU + PET						Quality and applicability
			Index	TP	FP	PPV %	TP/FP	Sn %	Sp %	TP	FP	PPV %	TP/FP	Sn %	Sp %	
Distant metastases (patient based)																
Liu et al. (2007)	300 (20)	Nasopharyn-geal carcinoma	CWU (MRI) PET	20	8	71	2.5	33	97	51	15	77	3.4	84	94	Fair quality, limited applicability
UK	48 (nr)									PET (incremental positives)						High quality
NCCHTA		Newly diagnosed locally advanced HNC (N2+ or T3)	CWU (incl. CT) PET							*metastases*						systematic review
Schmid, 2003										2	4	33	0.5	–	–	
										any malignancy						
										3	3	50	1	–	–	

Abbreviations: CWU = conventional work-up, FP= false positive, FN=false negative HNC = head and neck cancer, LN = lymph node, mets = metastases, , PET = positron emission tomography, PPV = positive predictive value, NPV = negative predictive value, TP = true positive, TN = true negative

Does it change patient management?

Australian data

Additional positive results detected by PET can lead to changes in management by identifying patients in whom radical radiotherapy and/or surgery may not be beneficial, thus avoiding futile attempts at treatment with curative intent (and the associated risks of morbidity and mortality) and guiding selection of optimal treatment for metastatic disease. Other changes in management include the avoidance of further investigations and a change of the extent of radiotherapy field or dose. However, the proportion of patients in whom treatment changes will occur cannot be predicted from accuracy data alone as decisions regarding management will be influenced by factors other than the PET result, for example the location of an identified lesion, symptom level and the health status of the patient. Also, a proportion of patients may undergo treatment with palliative intent.

Evidence that PET leads to a change in patient management is a necessary but not sufficient condition for concluding that it leads to an improvement in health outcomes. Where studies indicate that the test does not change patient management, effectiveness is disproven.

The Australian prospective study of PET in head and neck cancer (Scott et al. 2007) provides the most applicable data to the study population under consideration in this review as the study directly reflects the clinical pathway in Australia. In addition, this is the largest study identified reporting change in management in patients with head and neck cancer.

The results of the Australian study are detailed in Appendix J (page 139). Seventy-one patients with previously untreated carcinoma of the head and neck region, including 15 patients with metastatic SCC of unknown primary site, were included in the analysis. Individual patient data were provided by the authors on request. In this section, the management changes of the 56 patients with a known primary tumour are presented. Table 27 presents the key therapeutic impact outcomes extracted from the report and individual patient data.

Pre-PET treatment plans included radiotherapy in 51 patients (91%), chemotherapy in 31 patients (55%) and surgery in 12 patients (21%).

The most common clinical stages were T2 N0, affecting 12 patients (21%), followed by T4 N1 in six patients (11%). According to the clinical question for this review (page 33), PET is particularly indicated for patients with stages T3/4 Nx or Tx N+. Before PET was performed, 42/56 patients (75%) had higher staging than T1/T2 N0. Thus, 75% of patients in this study were considered directly applicable to the clinical question. Pre-PET, one patient had a known distant metastasis and five patients had an unclear M-stage. For more details on TNM stages, see Appendix J (page 139).

PET detected additional lesions in 36% of patients (20/56). Of the 31 additional lesions detected in 20 patients, 2 were second primary tumours, 22 were lymph node metastases and 7 were distant metastases.

Changes in treatment intent

Pre-PET, the intent of treatment was curative in all but one of the 56 patients. After PET, treatment intent changed in 13% of patients (7/56). In the 20 patients where PET detected *additional lesions*, treatment intent changed from curative to palliative in four patients (20%; 95% CI: 6–44%). Treatment intent changed from palliative to curative in one case (5%; 95% CI: 0–25%). In the 36 patients with *no additional lesions*, treatment intent changed from curative to palliative in two cases (6%; 95% CI: 1–19%).

Changes in TNM staging

After PET, T-staging was changed in 7% (4/56), N-staging in 21% (12/56) and M-staging in 14% (8/56) of patients. In the 20 patients with *additional lesions* on PET, T-staging was changed in one case from Tx to T3. N-staging was downstaged in one case from N2 to N1, and eight cases were upstaged. M-staging was changed to M0 from Mx or M1 in four patients and upstaged to M1 in two cases, one from Mx and one from M0.

In the 36 patients with *no additional lesions*, T-staging was changed from T4 to Tx in one case, one patient was upstaged from T3 to T4, one was downstaged from T2 to T1. N-staging was changed to N1 in two cases, one from Nx and one from N2. One patient was upstaged from N2 to N3. M-staging was changed from Mx to M0 in two cases. All 36 patients were negative for distant metastases after PET.

Changes in management plans

Overall, management plans changed in 32% (18/56) of all patients (95% CI: 20–46%). Of those in whom additional lesions were detected plans changed in 70% (14/20) (95% CI: 46–88%), and of those with no additional lesions detected plans changed in 11% (4/36) of patients (95% CI: 3–26%) ($p < 0.001$). Surgery was avoided in two patients (4%) and added in one patient (2%). Radiotherapy was added in two patients (4%).

Description of the type of surgery planned was provided, but the details were inadequate to determine whether or not the extent of surgery changed.

Changes to the radiotherapy target field or dose were seen in 21% of all patients (12/56): in 40% (8/20) of those with additional lesions detected and in 11% (4/36) of those with no additional lesions detected ($p = 0.02$). Overall, the radiotherapy clearly increased (ie increased field with same or increased dose) in five patients (9%), it clearly decreased (ie decreased field with same or decreased dose) in five patients (9%), and in two patients (4%) the target field was increased while the dose was reduced. PET had detected additional lesions in four of the five patients with a clear increase in total radiotherapy, and in six of the seven patients (86%) with an increase in radiotherapy field. Radiotherapy was added to the treatment plan in 10% (2/20) patients with additional lesions on PET, but in no patients without additional lesions.

In patients with *additional lesions,* the target field was increased in six patients (combined with an increase of radiotherapy dose in one and a decrease of the dose in two cases). In two patients, the target field was decreased, with a reduction in dose in one patient. Chemotherapy was abandoned in two cases, but added in three. Surgery was abandoned in two cases, added in one case and extended in one case (local resection of tongue base extended to neck dissection).

In the five patients with *additional distant metastases* identified on PET, treatment intent was changed from curative to palliative in two cases (surgery abandoned and radiotherapy administered in one case; radiotherapy field and dose decreased and chemotherapy added in one case). In one instance, chemotherapy was added, one case was further investigated (lung surgery) and in one case treatment was not changed (chemoradiotherapy).

In patients with *no additional lesions,* treatment changes included chemotherapy abandoned and radiotherapy dose decreased in two cases, radiotherapy field increased in one case, and radiotherapy field decreased in one case.

Low-dose radiotherapy of contralateral neck nodes

The Advisory Panel indicated that PET may be used to more accurately exclude contralateral disease and guide radiotherapy planning towards a low-dose treatment of contralateral tissues, thus sparing the contralateral parotid gland. Lower-dose radiotherapy of salivary glands reduces side effects such as xerostomia, 'radiation caries', dysphagia, hoarseness and soft tissue fibrosis (Eisbruch et al. 2001; Jellema et al. 2007).

The Advisory Panel indicated that if radiotherapy planning is based on CT alone, uninvolved sites are usually irradiated to 50 Gy, typically on both sides of the neck. This dose is not expected to cause parotid damage. However, bilateral irradiation to 70 Gy is performed where there is evidence of contralateral disease (Advisory Panel expert opinion).

The Advisory Panel suggested that the impact of PET on parotid damage could be estimated from the individual patient data by determining the laterality of planned radiotherapy. The localisation of the primary tumour and positive neck node metastases was thus examined to estimate whether unilateral or bilateral radiotherapy would have been indicated. It must be noted that only rough estimates were possible as for many cases there was insufficient information available to assess the potential laterality of radiotherapy. In particular, the individual patient data did not indicate whether primary tumours crossed the midline. These theoretically derived radiation plans were defined by the reviewers for each patient before and after PET results were available. The laterality of radiotherapy in pre-PET and post-PET treatment plans was then compared.

This approach of estimating the laterality of radiotherapy suggested that the number of patients potentially receiving bilateral high dose radiotherapy would increase from 26 patients (46%) to 28 patients (50%) when PET results were added. Accordingly, unilateral radiotherapy might have decreased from 27 patients (48%) pre-PET to 22 patients (39%) post-PET.

Table 27 Impact of PET for head and neck cancer on patient management—Australian data collection

Author (year)	N	Population	Total % change (95% CI)	Surgery/RT avoided n (%)	Surgery/RT added n (%)	RT dose/field changes n (%)	Other changes n (%)	Treatment intent changes % (95% CI)
Scott et al. (2007) (and additional analyses)	56	Patients with newly diagnosed head and neck cancer	32 (20–46)	Surgery: 2 (4) RT: nil	Surgery: 1 (2) RT: 2 (4)	Any: 12 (21) Field & dose increase: 1 (2) Only field increase: 4 (7) Field increase, dose decrease: 2 (4) Field & dose decrease: 1 (2) Only field decrease: 2 (4) Only dose decrease: 2 (4)	ChT abandoned: 4 (7) ChT added: 3 (5)	Curative to palliative: 11 (4–22) Palliative to curative: 2 (0–10)
	20	Additional lesions detected on PET Curative intent in 19/20 (95%)	70 (46–88)	Surgery: 2 (10) RT: nil	Surgery: 1 (5) RT: 2 (10)	Any: 8 (40) Field & dose increase: 1 (5) Only field increase: 3 (15) Field increase, dose decrease: 2 (10) Field & dose decrease: 1 (5) Only field decrease: 1 (5)	ChT abandoned: 2 (10) ChT added: 3 (15)	Curative to palliative: 20 (6–44) Palliative to curative: 5 (0–25)
	36	No additional lesion detected on PET Curative intent in all patients	11 (3–26)	Surgery: nil RT: nil	Surgery: nil RT: nil	Any: 4 (11) Only field increase: 1 (3) Only field decrease: 1 (3) Only dose decrease: 2 (6)	ChT abandoned: 2 (6)	Curative to palliative: 6 (1–19)

Abbreviations: PET = positron emission tomography, ChT = chemotherapy, RT = radiotherapy

Evidence from published literature

Ha et al. (2006) reported on the therapeutic impact of PET/CT in 36 patients with newly diagnosed head and neck cancer, five of whom had an unknown primary tumour site. An overall change in management due to PET/CT was seen in 11 patients (31%), including the identification of one unknown primary site. Most alterations of treatment plans were a result of upstaging of tumours (6/11 cases). In five patients neck disease was only detected with PET/CT; in three patients PET/CT identified suspicious lesions in the lungs. A total of 18 patients (50%) underwent surgical interventions. Most changes of treatment plans included the addition of chemotherapy or radiotherapy, thus favouring a multimodality approach. However, this study failed to report management changes in adequate detail, in particular no pre-PET treatment plans were listed. The authors conclude that patients with early-stage disease can benefit from the detection of nodal metastases, while in advanced-stage disease the detection of distant metastases and contralateral neck disease is the major benefit.

Connell et al. (2007) assessed the clinical impact of PET/CT in 35 patients who were examined for staging of primary head and neck cancer. Two patients had disease downstaged (N-staging), 10 patients had disease upstaged (one T-stage, eight N-stage, one M-stage). In 4/35 patients (11%), PET had a 'high impact' by changing the treatment modality. In 10/35 patients (29%) the impact was considered 'medium' as radiotherapy planning technique or dose was altered. Seven patients experienced an increase of the planned dose volume due to nodal or primary upstaging. However, no pre-PET plans were reported in this study.

Evidence from the two therapeutic impact studies identified in the Facey et al. (2007) report provides supportive information on the impact of PET on radiotherapy planning in patients with newly diagnosed head and neck cancer. In a retrospective study on radiotherapy planning in 36 patients, Koshy et al. (2005) reported that PET/CT altered TNM staging in 13 patients (36%), which had an important impact on radiation volume and dose. Overall PET/CT changed patient management in nine patients (25%), radiotherapy volume was changed in five, radiotherapy dose was changed in four patients (generally increased). Nishioka et al. (2002) reported that in 21 patients the estimated gross tumour volume (GTV) was similar for CT/MRI and when PET was added, with the exception of two patients with a 49% increase in one and a 45% decrease in the other case. But PET increased the number of lymph nodes to be irradiated to 39, compared with 28 on CT/MRI.

Does change in management improve patient outcomes?

Where the use of PET improves diagnostic accuracy (see page 66), it should also improve outcomes for patients if it results in more appropriate management.

The main change in management following PET for the staging of primary or recurrent head and neck cancer is a change in radiotherapy regimen. This occurred in 21% of patients in the Australian data collection (Scott et al. 2007). Where this is based upon more accurate staging of regional lymph nodes, this is likely to result in an improvement in patient outcomes.

Where PET leads to an increase in the radiotherapy administered, it is likely that this follows PET identification of metastatic lymph nodes that would not otherwise have been treated. In the Australian study, an increase of the radiotherapy field occurred due to the identification of additional lesions by PET in six of seven patients. The benefits will depend on the degree to which improved local control of lymph node metastases influences patient survival and quality of life. If additional lymph node metastases which are negative on anatomical imaging (PET+, CT–) have a different risk of disease progression than lymph node metastases positive on conventional imaging (CT+, PET+), then the trade-off between the benefits and harms of radiotherapy may also differ for these patients. Irradiating local metastatic lymph nodes may reduce the risk of regional recurrence. This in turn may lead to improved progression-free or overall survival in some patients. However, in patients in whom disease dissemination and recurrence occurs via other sites or mechanisms, this treatment change may not translate into an overall improvement in outcomes. Therefore, while this change in management is likely to lead to an improvement in overall patient health outcomes, the magnitude of this effect cannot be quantified in the absence of direct evidence.

Where PET leads to a decrease in the radiotherapy administered (as occurred in 9% of patients), this treatment change may lead to sparing of the normal tissue from unnecessary irradiation, and thus decrease the adverse consequences of regional radiotherapy. Adverse events resulting from radiotherapy include the consequences of a reduction of salivary flow (eg xerostomia and dental caries) and irradiation of the thyroid (see Appendix K).

Suspected residual carcinoma of the head and neck

Summary

Accuracy

- Five fair quality studies indicated that PET has a low negative likelihood ratio (range 0–0.18) and a high negative predictive value (range 83–100%).
- Much of the data are retrospective and two of the studies are from the same centre.
- The two Australian studies both reported a negative likelihood ratio of 0.18 with a NPV of 94% and 95% respectively.
- In patients who have suspected residual disease following definitive treatment a negative PET result is highly likely to indicate the absence of disease.

Change in management

- One prospective Australian study of 53 patients provided information on the impact of PET on patients with suspected residual carcinoma. A pre-PET management plan was recorded in 75% of patients.
- PET findings changed management in 21 patients (40%), of which 20 could be validated by further tests and 19/20 found to be appropriate.
- When PET scan was negative, the most common change was avoidance of surgery (in 88% [15/17] of patients).

Patient outcomes

- The use of PET in this population has the potential to reduce of the number of unnecessary additional invasive procedures thereby improving patient outcomes through reduced treatment morbidity and improved quality of life.

Is it accurate?

PET is proposed for use in patients in whom post-therapy evaluation (clinical examination and/or CT) has identified a structural abnormality suspicious for residual head and neck carcinoma. This includes the evaluation of response to therapy. PET in this context is used as a triage test to reduce the number of additional invasive diagnostic procedures. PET may improve patient outcomes by avoidance of biopsy in patients in whom residual disease is ruled out (PET scan negative). The most relevant PET result is therefore a negative PET scan for residual disease, where CT or clinical examination was positive. As patients with a negative PET result will avoid biopsy, the ability of PET to 'rule out' disease is the most important outcome.

PET may also be used to identify patients in whom salvage surgery will not be beneficial due to the presence of distant metastases. PET can then guide the selection of optimal treatment: for example in situations where CT failed to detect distant metastases, a positive PET scan may change treatment intent from curative to palliative. PET may thus lead to the avoidance of non-beneficial interventions, improving patient outcomes by avoiding treatment morbidity and improving quality of life.

In contrast, a PET result positive for residual disease will not alter patient management in comparison to a non-PET staging strategy as PET-positive patients will be managed according to the confirmatory biopsy result (see current management in Australia as specified in the clinical flow chart, Figure 4).

Triage to biopsy (PET scan negative/CT positive)

The value of PET before biopsy (triage) in the assessment of residual carcinoma is shown in Table 28. The data presented are the negative PET findings from studies in patients who have suspicious (positive) findings for residual disease on CT or clinical examination. Data are from three studies identified in the current systematic review and two studies presented in the UK NCCHTA report.

In all studies, the true-negative rate for PET was higher (43–79%) than the false-negative rate (3–9%). Across the five studies the negative likelihood ratio and negative predictive value ranged from 0–0.18 and 83–100% respectively. In two studies, both from the same centre, the negative likelihood ratio was zero with a negative predictive value of 100%. The analyses in both these studies were based on number of hemi-necks although some individual patient details were provided.

Two studies had a 9% false-negative rate. In the first study of 46 patients, 4 false-negatives were reported, with 3 patients found to have pathological evidence of microscopic residual disease (no details were provided for the fourth patient) (Ware et al. 2004). In a second study of 23 patients there were two false-negative PET findings as determined by pathological evidence, with both scans performed 4–8 weeks after completing chemoradiotherapy.

These negative PET results have the potential to lead to changes in management by avoiding biopsy of lesions considered suspicious on anatomical imaging.

Detection of distant metastases

PET may also identify distant metastases, changing treatment intent from curative to palliative. Two studies noted that distant metastases were identified as a result of using PET in 2% (1/46)–10% (4/39) of patients, but no data were provided on the accuracy of these findings (Ware et al. 2004) (Porceddu et al. 2005).

Table 28 Accuracy studies of the value of PET in patients with suspected residual carcinoma of head and neck (determined by prior tests)

Author (year)	N Test	Population	Prior tests Index test	Negative findings Neg N (%)	TN N (%)	FN N (%)	NPV % [95% CI]	Sn % % [95% CI]	Sp % % [95% CI]	LR +	LR–	Quality and applicability
Andrade et al. (2006)	11	Treatment response Suspicious lesion on CT *and* CE	CT and CE	6 (55)	5 (45)	1 (9)	83 [36–99]	83 [36–99]	100 [46–100]	∞	0.17	NHMRC level of evidence: III-2 Comparison: CX Applicability: P1 Quality: Q2
	23	Treatment response Suspicious lesion on CT *or* clinical examination	CT or CE	13 (57)	11 (48)	2 (9)	85% [54–97]	83 [51–97]	100 [68–100]	∞	0.17	NHMRC level of evidence: III-2 Comparison: CX Applicability: P1 Quality: Q2
Yao et al. (2005)	28	Suspicious lesion on CT	CE/CT/MRI	21 (75)	21 (75)	(0)	100 [80–100]	100 [31–100]	84 [63–95]	6.3	0	NHMRC level of evidence: III-2 Comparison: CX Applicability: P1 Quality: Q2
Yao et al. (2007)	24 hemi-necks (23 patients)	Suspicious lesion on CT	CT	13 (57)	13 (57)	0	100 [76–100]	100 [46–100]	68 [43–86]	3	0	NHMRC level of evidence: III-2 Comparison: CX Applicability: P12 Quality: Q2
	24 hemi-necks (23 patients)	Suspicious lesion on CT 'Negative' PET result is SUV < 3.0	CT	16 (70)	16 (70)	0	100 [76–100]	100 [46–100]	84 [60–96]	6.3	0	NHMRC level of evidence: III-2 Comparison: CX Applicability: P1 Quality: Q2

UK NCCHTA Porceddu et al. (2005)	39	Residual mass following definitive treatment	CT	32 (82)	31 (79)	1 (3)	97	83	94	13.8	0.18	High quality systematic review
UK NCCHTA Ware et al. (2004)	46	Residual mass following definitive treatment	CT/CE	24 (52)	20 (43)	4 (9)	83 [63–94]	83 [60–94]	95 [74–100]	17.3	0.18	High quality systematic review

Abbreviations: CE = clinical examination, CT= computed tomography, MRI = magnetic resonance imaging, PET = positron emission tomography, SUV = standard uptake value, PET = positron emission tomography, PPV = positive predictive value, NPV = negative predictive value, TP = true positive, TN = true negative

Does it change patient management?

Evidence from published literature

One study provided information on the impact of PET on patients with suspected residual carcinoma. This study was included in the UK NCCHTA report (Facey et al. 2007). Ware et al. (2004) reported on 53 HNC patients who had a residual abnormality on conventional imaging or clinical evaluation after definitive therapy.

A pre-PET plan was available for all patients, but in 25% of patients (13/53) the responsible clinician had not prospectively recorded this plan and this was instead formulated by the study authors based on institutional protocols and available clinical information. The post-PET plans were determined by review of records or contact with the responsible clinician subsequent to the PET results being known. Management impact was rated 'high' when treatment intent or modality was changed, 'low' when the PET scans results were consistent with the pre-PET plan and 'none' when PET results were inconsistent with the pre-PET plan. In both the 'low' and 'none' groups PET did not change management.

PET findings changed management in 21 patients (40%): 20 of these changes could be validated and 19/20 were found to be appropriate. The most common change was avoidance of an interventional procedure when the PET scan was negative.

Seventeen patients' management plans changed from surgery alone to observation (14), palliative chemotherapy (1), supportive care (1) or an additional invasive diagnostic procedure (1). In this group all 14 patients who avoided surgery had a negative PET scan.

A further three patients who were PET negative were observed instead of having an invasive diagnostic procedure, surgery/radiotherapy or radical radiotherapy. One other patient had curative rather than palliative radiotherapy as a result of the PET findings.

Management was not changed in 32 patients (60%)—these patients representing the 'low' and 'none' groups. In these patients the pre-PET plans were surgery (22), invasive diagnosis (4), radical radiotherapy (2), supportive care (2), palliative chemotherapy (2).

While this study provides evidence that PET can lead to the avoidance of surgery in patients with residual disease, the study pathway differs from that described in the flow chart for this review (Figure 4) where a negative PET scan would have changed management from biopsy to observation (surveillance). Thus, according to the clinical question and flow chart for this review, a negative PET would avoid biopsy, rather than surgery.

Does change in management improve patient outcomes?

The main role of PET in patients with suspected residual head and neck cancer is to identify those patients who are unlikely to require further invasive evaluation. Therefore, the main treatment change likely to follow a negative PET scan is the avoidance of unnecessary additional procedures, thereby improving patient outcomes through reduced treatment morbidity and improved quality of life.

Expert opinion

Emerging role of PET

It is the expert opinion of the Advisory Panel that PET/CT is increasingly being used earlier in the clinical pathway for patients with head and neck cancer to assess treatment response following completion of initial definitive treatment, not limited to those patients with suspected residual disease on prior tests.

PET/CT in this context may be used as a replacement for CT or MRI to exclude residual active disease and as a triage to more invasive interventions such as neck dissection when this would otherwise have been planned. Currently, neck dissection may be recommended in patients with N2 or N3 disease at initial staging who achieve a complete clinical response to radiotherapy. If its high negative predictive value is maintained in this setting, PET/CT has the potential to change management, with those patients who have a negative PET/CT scan post-radiotherapy being observed rather than proceeding to neck dissection. Outcome data to support this approach are awaited from clinical trials.

Metastatic squamous cell carcinoma involving cervical nodes from an unknown primary site

Summary

Accuracy

- Three studies were included that provided data on the accuracy of PET in detecting primary tumours in patients who have a panendoscopy prior to PET. All three studies have limitations either in respect to sample size or histological verification of PET positive results.

- Across the three studies the yield of PET in identifying a primary tumour site ranged from 10% (1/10) to 68% (26/38).

Change in management

Australian data collection

- Data are available on 15 patients with an unknown primary tumour. PET detected previously unknown primary tumours in 7 of 15 patients (47%).

- Management plans changed in 7 of 15 patients (47%; 95% CI: 21–73%). When *PET detected the primary tumour*, management was changed in 5 of 7 cases. Treatment intent was unchanged in all 15 patients (all curative).

- Management changes included radiotherapy target field increase in three cases (combined with surgery abandoned in one case), radiotherapy added in one case and further investigation (bronchoscopy) changed to surgery in one case.

Evidence from published literature

- One published study provided information on the impact of PET in 38 patients with an unknown primary tumour. PET identified a primary site in 26 patients, of whom 13 were pathologically confirmed. This study did not clearly define a pre- and post-PET plan as specified in the inclusion criteria but was included in the review due to the limited evidence available for this indication.

Patient outcomes

- The main treatment changes that follow PET are the addition of surgery and/or the modification of the radiotherapy treatment field to include the primary site. The impact that these changes will have on health outcomes is uncertain.

Is it accurate?

PET is proposed for use in the assessment of patients with metastatic squamous cell carcinoma involving cervical lymph nodes from an unknown primary site. The accurate localisation of otherwise occult primary disease is expected to change management by modifying a speculative treatment field to definitive treatment of the primary site, or to change treatment intent from curative to palliative when distant metastases are identified.

Three studies included from the UK NCCHTA report and three studies from the current review provide data on the accuracy of PET in identifying an unknown primary following prior tests, including CT and MRI.

Three studies report on patients in whom the primary tumour was not detected by earlier diagnostic work-up including panendoscopy, whereas in the remaining three studies panendoscopy was not performed as part of the routine pre-PET work-up. The latter three studies do not fulfil the inclusion criteria as detailed in Table 6 but are described below for completeness.

Table 29 depicts the value of PET in identifying primary tumours in patients with SCC metastatic to cervical lymph nodes.

No primary tumour detected on prior tests (including CT, MRI and panendoscopy)

A recent study conducted in the UK enrolled 25 patients with histologically proven SCC head and neck metastases, with no identifiable primary tumour on clinical examination, CT or MRI, and panendoscopy (Silva et al.2006). The yield of PET in identifying a likely primary tumour site was 9/25 (36%), three of which were confirmed to be true-positive by histology or follow-up (PPV=33%). Of the six false-positive PET findings, two declared a primary at a different site, two had contradictory histology, and two did not have a demonstrable primary at follow-up. Since it is likely that treatment was delivered based on the PET result, the failure of a primary site to emerge at follow-up may not indicate a false-positive PET result, but rather that the radiotherapy field may have included and cured the primary site in these two patients. The PPV may therefore be underestimated by this study.

In another study, 38 patients with cervical lymph node metastases, in whom the primary was not detected by earlier diagnostic work-up including clinical evaluation, CT, MRI, nasopharyngoscopy, laryngoscopy and panendoscopy, underwent a PET scan (Wartski et al. 2007). The yield of PET in identifying a primary tumour site was 26/38 (68%), but only 17 patients went on to have histological verification (biopsies performed during a second panendoscopy), 13 of whom were considered true-positive (76%). The remaining nine PET-positive patients were considered unable to undergo a second panendoscopy, but they had their radiation treatment plan modified as result of PET. One false-negative was reported.

In the study by Stoeckli et al. (2003), panendoscopy was conducted after PET, but since panendoscopy was performed blinded to the PET results the incremental value of PET may be derived. Eighteen consecutive patients with SCC lymph node metastases and no evidence of a primary tumour on clinical examination and CT were included. Subsequent panendoscopy identified the primary site in 8 cases, leaving 10 patients with an unknown primary as defined by the current evaluation. PET identified a primary site in 1/10 patients (10%); biopsy determined that this was a false-positive result (PPV=0%).

Unknown primary following limited prior testing (excluding panendoscopy)

Freudenberg et al. (2005) enrolled 21 patients with cervical lymph node metastases (cytology revealed SCC in only 14 patients [67%]). Eligible patients had no evidence of a primary site on clinical, endoscopic, sonographic or planar radiological staging. CT was not conducted as part of routine patient work-up, but was compared with PET, PET/CT, and PET and CT images interpreted together to identify a primary site. CT identified a primary site which was confirmed by histopathology in five patients; these patients may be excluded to determine the incremental value of PET over CT and clinical examination (n=16). The incremental yield of PET was 8/16 (50%); there were 6 true positives (PPV=75%). When PET was read in conjunction with CT, the yield decreased to 7/16 (44%); all were true positives (PPV=100%). Note that the proportion of patients with SCC in this study (67%) is not sufficient to meet the inclusion criterion of 70% used in the present assessment. Panendoscopy was not performed as a prior test, and therefore the yield and PPV reported in this study are likely to be overestimates of the incremental value of PET over panendoscopy.

Miller et al. (2005) identified 27 consecutive patients with biopsy-proven SCC metastases to the cervical lymph nodes, with no primary site identified by clinical examination, CT and/or MRI, and chest x-ray. PET was performed in these patients to identify the primary, followed by panendoscopy guided by the PET results. Since panendoscopy was not performed as part of routine pre-PET work-up, the patient group in this study does not reflect the patient group with 'unknown primaries' as defined by the standard clinical flow chart in this evaluation. One patient was excluded due to an incomplete PET scan, leaving 26 patients included in the analysis. PET detected 9/26 primary tumours (35%), with 8 verified as true positive by panendoscopy. Since the PET results guided panendoscopy, it is not possible to derive the incremental value of PET over panendoscopy from this study. The authors note that of 8 primaries identified by both PET and panendoscopy, only 2 would have been identified by panendoscopy alone; the remaining 6 primaries were only detected because PET was positive and deep biopsies were taken as a result. This qualitative conclusion about the potential incremental yield of PET over panendoscopy must be regarded as speculative.

In another paper by Miller et al. (2008), 31 consecutive patients were enrolled with biopsy-proven SCC metastases with no primary site identified by clinical examination, CT and/or MRI, and chest x-ray. PET was performed in these patients to identify the primary, followed by panendoscopy guided by the PET results. PET detected 10/31 primary tumours (32%), with 9 verified as true positive by biopsy. There was one false-positive PET study. Five additional patients with a negative PET scan had the primary detected on panendoscopy with all 5 sites confirmed. As above, it is not possible to derive the incremental value of PET over panendoscopy from this study given that PET results guided panendoscopy.

Table 29 Incremental value of PET in the detection of occult primary tumours

Author (year)	N	Population	Prior tests	Incremental positive findings (Primary tumour detected) Yield N	TP N	FP N	PPV	TP/FP	Sn %	Sp %	Quality and applicability
Studies with extensive prior tests											
Silva et al. (2006)	25	True unknown primary site	Clinical evaluation, CT, MRI	9	3	6	33	0.5	60	80	NHMRC level of evidence: III-2 Comparison: CX Applicability: P1 Quality: Q2
Wartski et al. (2007)	38	Positive cervical lymph nodes, no visible primary site	Clinical evaluation, CT, MRI, Nasopharyngoscopy, laryngoscopy panendoscopy	26	13/17	4/17	_	_	_	_	NHMRC level of evidence: III-2 Comparison: CX Applicability: P1 Quality: Q3
UK NCCHTA Stoeckli et al. (2003)	18 (10)	Positive cervical lymph nodes, no visible primary site	Clinical evaluation, CT, panendoscopy (blinded)	1	0	1	0	0	_	_	High quality systematic review
Studies with limited prior tests											High quality systematic review
UK NCCHTA Freudenberg et al. (2005)	21	Positive cervical lymph nodes, no visible primary site	Clinical, endoscopic, sonographic or planar radiological staging	8	6	2	75	3	_	_	
Freudenberg et al. (2005)	21 (read in conjunction with CT)			7	7	0	100	_	–	–	High quality systematic review
UK NCCHTA Miller et al. (2005)	26	Positive cervical lymph nodes, no visible primary site	Nasopharyngoscopy, laryngoscopy, CT or MRI	8	7	1	88	7	–	–	High quality systematic review
Miller et al. (2008)	31	Positive cervical lymph nodes, no visible primary site	Endoscopy, CT and MRI	10	9	1	90	9	_	_	NHMRC level of evidence: III-2 Comparison: CX Applicability: P3 Quality: Q2

Abbreviations: CT = computed tomography, MRI = magnetic resonance imaging, PET = positron emission tomography, PPV = positive predictive value

Does it change patient management?

Australian data

In this section the management changes for the 15 patients in the Australian data collection study with an unknown primary tumour are presented. Pre-PET treatment plans included radiotherapy in 9 patients (60%), surgery in 10 patients (67%) and chemotherapy in 4 patients (27%). All patients were considered for curative treatment.

Pre-PET, three patients were staged N1, three had stage Nx, seven patients had higher N-stages. Two patients were staged M1, two were Mx, 11 were staged M0.

PET detected 12 additional lesions in 8 patients (53% of patients). Five of the 12 additional lesions were lymph node metastases. PET detected previously unknown primary tumours in 7 of 15 patients (47%).

Management plans changed in 7 of the 15 patients (47%; 95% CI: 21–73%). Treatment intent was unchanged in all 15 patients (all curative). When *PET detected the primary tumour*, management was changed in 5 of 7 cases. These changes included radiotherapy target field increase in three cases (combined with surgery abandoned in one case), radiotherapy added in one case, further investigation (bronchoscopy) changed to surgery in one case. When *PET did not detect the primary tumour,* management plans were changed in 2 of 8 cases, including radiotherapy target field decrease in one case and change in surgery (parotidectomy planned after initial surgery) in one case.

Evidence from published literature

One study provided information on the impact of PET on patients with an unknown primary. This study did not clearly define a pre- and post-PET plan as specified in the inclusion criteria (Table 6). However, it has been included here to give an indication of expected management changes in this population.

The study by Wartski et al. (2007) included 38 patients with cervical lymph node metastases from an unknown primary tumour. PET identified a primary site in 26 patients; pathological evidence was available in 17 patients, with 13 primary tumours confirmed. Pre- and post-PET plans were determined by consensus between oncologists and surgeons.

In the 13 patients with a positive PET result and histological confirmation of the primary tumour, 8 patients underwent surgery of the primary combined with post-operative radiotherapy, three received targeted radiation instead of comprehensive radiation and two patients had palliative chemotherapy added to radiotherapy.

Changes in management were also made in patients with no histological confirmation of disease. In the remaining 13 patients, in whom PET detected a likely primary tumour for which there was no histological confirmation, it was reported that 10 had management changes as a result of PET. Nine of these changes related to alteration of the radiotherapy plan with one patient undergoing palliative chemotherapy in addition to radiotherapy for distant metastases.

Does change in management improve patient outcomes?

The main role of PET in patients with an unknown primary tumour is to identify the primary tumour site. Therefore the main treatment changes that follow PET are the addition of surgery and/or the modification of the radiotherapy treatment field to definitively target the primary site.

For patients with unknown primary disease the prognosis is generally quite poor, as their initial presentation is with metastatic disease (Pimiento et al. 2007). Therefore, the benefits of identifying a primary site will depend on the degree to which improved local control of the primary tumour influences patient survival and quality of life. Also the impact will depend on whether the primary tumour would have been included in the radiotherapy field regardless of the PET findings. Therefore, at this stage it is not clear that detecting the primary tumour leads to an improvement in health outcomes. The potential impact of modifying the radiotherapy field has already been discussed (see 'Newly diagnosed or recurrent carcinoma of the head and neck').

PET may also have a role in detecting distant metastases. Treatment intent may then be changed from curative to palliative, and patients would be spared the morbidity of aggressive radical treatment. However, it is unclear whether this would outweigh any patient benefit of local/distant control given that PET–detected, CT-occult metastases may be at an earlier stage of development than metastases detectable on conventional imaging. Thus, the impact that this will have on overall patient health outcomes is uncertain.

Prognosis following PET

Patients with PET-detected metastases may not have an equivalent prognosis (or response to treatment) to those with metastases detected upon anatomical imaging (Lord et al. 2006).

PET is used as an additional test following conventional imaging in the diagnostic pathway. PET may detect patients with a different spectrum of disease to those detected with conventional imaging. It is reasonable to assume that patients with PET-detected, CT-occult metastatic disease will have a worse prognosis than patients with no additional sites of disease detectable by either PET or CT, but it is possible their prognosis may still be better than that of patients with metastatic disease detectable by CT ± MRI. Similarly, the response to therapy of these patient groups may differ.

Studies of patient prognosis following the use of PET are not designed to compare patient survival or disease progression for patients staged with PET versus conventional testing alone and, therefore, conclusions about the impact of adopting PET on patient outcomes cannot be made based on this type of evidence. However, well designed studies could provide some supportive evidence for a role of PET. Such studies would require a comparison of outcomes in either a) patient groups selected for the *same* treatment after staging by conventional imaging or by PET, or b) patients treated according to conventional staging, blinded to PET findings. Studies with these designs would provide information on the prognostic value of PET without contamination by different treatment effects between groups. However, in some circumstances these studies may not be feasible.

Australian data

The Australian data collected from the three PET facilities between 2003 and 2006 provide some information on patient response to treatment, time to progression and disease-free survival following PET (Table 30 and Table 31) (Scott et al. 2007). These data are for patients undergoing PET for staging of primary head and neck cancer or malignant cervical lymph nodes from an unknown primary site. Data were not reported separately for these two indications.

This study was not designed to compare these outcomes for patients staged with PET versus conventional testing alone and therefore valid conclusions about the direct impact of PET on patient outcomes cannot be made. Data provided on outcomes based on pre-PET staging are not considered informative as treatment was modified by the PET results.

The study compared residual disease after treatment on follow-up imaging in patients who had additional lesions identified on PET before treatment compared to those who had no additional lesions identified (Table 30). While patients with additional lesions identified by PET were more likely to have residual disease following treatment than patients with no additional lesions detected, as determined by either follow-up imaging (relative risk [RR] = 1.88, 95% confidence interval [CI] 0.87–4.02%) or according to clinical response (RR = 1.71, 95% CI: 0.84–3.47%), the difference was not statistically significant.

Table 30 Response to treatment following PET selected therapy for head and neck cancer in Australian patients

Outcome	PET classification n/N (%)		Relative risk (95% CI)	P
	Additional lesions	No additional lesions		
Incomplete response on follow-up imaging	6/10 (60)	8/25 (32)	1.88 (0.87–4.03)	0.10[a]
Incomplete clinical response	11/27 (41)	10/42 (24)	1.71 (0.84–3.47)	0.14[b]

Abbreviations: CI = confidence interval; PET = positron emission tomography
[a] Fisher's exact test; [b] X^2 test

The study also compared disease progression and disease-free survival in patients classified by PET (Table 31). These data demonstrated that patients classified by PET as incurable have a higher risk of disease progression at 12 months than those classified by PET as potentially curable (RR = 3.00, 95% CI: 2.10–4.29%). However, these patient groups received treatment modified by their PET findings.

Table 31 Prognosis following PET selected therapy for head and neck cancer in Australian patients

Patient group / outcome	PET classification n/N (%)		Relative risk (95% CI)	Fisher's exact test *P*
	Curable	Incurable		
Disease progression by 12 months	20/60 (33)	4/4 (100)	3.00 (2.10–4.29)	0.02

Abbreviations: CI = confidence interval; PET = positron emission tomography

What are the economic considerations?

The standard process for an economic evaluation is first to consider the additional benefits accrued with the new device/procedure relative to the comparator (ie the incremental effectiveness), and then determine cost differences between the new procedure and the comparator (ie incremental costs). Effectiveness is measured in clinically appropriate natural units or a multidimensional measure such as quality adjusted life years (QALYs). When both costs and effects are known an incremental cost-effectiveness ratio (ICER) can be determined. If data on patient health outcomes is inadequate, it is not appropriate to conduct a cost-effectiveness analysis or calculate an ICER.

Given the lack of data on patient outcomes resulting from PET in staging primary head and neck cancers and assessment of residual disease (see 'Does change in management improve patient outcomes?', page 76) cost-effectiveness analyses are not feasible. The lack of quantifiable evidence of effectiveness (either direct or linked) precludes a quantitative assessment of the benefit of PET in head and neck cancer. PET for the assessment of residual disease may lead to the avoidance of biopsy, but unlike the use of PET for some other solid tumours, the use of PET in head and neck cancer does not lead to the avoidance of radical surgery or radiotherapy with sufficient frequency to realise a significant cost offset.

In the absence of a cost-effectiveness or modelled cost-consequence analysis, an estimate of the major cost implications (major management changes only) of PET for staging of head and neck cancers is provided based on primary data from the Australian data collection study (Scott et al. 2007). Further, a threshold analysis has been conducted to assess the potential for the addition of PET in primary staging to be cost-effective. The potential cost offset of avoiding biopsy in the assessment of residual disease has also been estimated.

An economic evaluation of PET for identification of an unknown primary is not provided given that evidence of efficacy is unavailable.

Existing literature

The UK NCCHTA report (Facey et al. 2007) identified only one cost-effectiveness analysis of PET in head and neck cancer (Hollenbeak et al. 2001). Specifically, the cost-effectiveness analysis pertained to N0 neck SCC. A review of literature post-2005 did not identify any further economic evaluations on the use of PET after conventional work-up in head and neck cancers.

Hollenbeak et al. (2001) assessed the cost-effectiveness of PET as part of a treatment strategy for CT-staged N0 neck SCC. The analysis compared the choice of additional diagnostic imaging with PET to no additional imaging. The study derived sensitivity and specificity values from the literature (sensitivity 86.9%; specificity 94.8%); however, values were not varied in the analysis (ie no sensitivity analysis on these probabilities was conducted in the decision analysis). The PET arm was associated with a higher cost ($4,679 versus $3,572), but marginally higher life expectancy (+0.2 years) and improved quality of life (+0.4 QALYs; QoL values were elicited from eight head and neck surgery residents). The improvement in survival was driven by an assumption that if nodal metastases were detected early patients would get a modified radical neck dissection, and consequently have a life expectancy equivalent to patients with no nodal involvement (personal correspondence with Hollenbeak, September 2008). The overall cost-effectiveness ratio was found to be $8,718 per life year saved and $2,505 per QALY. The study concluded that the addition of PET is a cost-effective strategy for the staging of N0 head and neck SCC. This study has limited applicability in the Australian context because most patients with N0 disease are not expected to require PET in Australia, and the assumed life expectancy gain is not supported by empirical data.

The cost of PET in Australia

As part of the Australian PET data collection study, a costing study was conducted at eight of the nine funded PET sites to assess resource use associated with undertaking a PET scan in Australia. An unpublished report summarising the Australian cost data was made available for this assessment (ANZAPNM 2007). A detailed description of this report is provided in the previous MSAC review of PET for recurrent colorectal cancer (Medical Services Advisory Committee 2007).

Cost data (total costs by labour/non-labour costs) were available from all eight sites for costs of standard whole body scan and long whole body scan for 2005/06 (Appendix L, page 144). Total costs for a standard whole-body PET scan (appropriate for primary head and neck cancer) ranged between $761 and $2,067 (mean [SD]: $1,265 [$482]; median: $1,053).

Net costs in staging primary head and neck cancer

The main consequences of adding PET to the conventional staging pathway is an increased diagnostic accuracy in lymph node staging. This can lead to changes in patient management, and may result in improved patient outcomes.

The results of the Australian data collection study are presented and summarised under 'Does it change patient management?' (page 72). This study demonstrated that that management changed in 32% (18/56) of all patients.

The main changes in management from the study and subsequent cost implications are shown in Table 32. Although there were frequent management changes, the net change in management was marginal. Nonetheless, PET was apt to modify radiotherapy treatment, notably a net increase in RT fields of 9%. This increase in RT fields could improve patient outcomes, but direct evidence for this is not available (see 'Does change in management improve patient outcomes?', page 76).

Table 32 Net cost of PET: Australian data collection

	Net change n/56 (%)	Estimated cost per patient (range)	Total cost (per 56 patients)	Expected cost per 100 patients
PET	+56 (100)	$1,053 [a]	$58,968	$105,300
		($761–$2,067)	($42,616–$115,752)	($76,100–$206,700)
Surgery	–1 (–2)	–$12,500	–$12,500	–$25,000
		($5,561[b] –$19,996[c])	($5,561–$19,996)	($11,122–$39,992)
Chemotherapy	–1 (–2)	–$570	–$570	–$1,140
		($58.75 [d] –$1,087 [e])	($58.75 –$1,087)	($118–$2,174)
Radiotherapy	+2 (4)	$400	$800	$1,600
		($49.40[f] –$740 [g])	($99–$1,480)	($198–$2,960)
Radiotherapy field	+5 (9)	$34.25[h]	$171	$308
Radiotherapy dose	–4 (–7)	n/a	–	–
Total			$46,869	$81,068
			($21,803–$111,783)	($34,440–$198,728)

a Median PET cost from ANZAPNM (range: $761–$2,067); b AR-DRG : D04B Maxillofacial surgery without complications; c AR-DRG: D02A Head and Neck procedure with major complication (cscc); d MBS: 13915 Cytotoxic Chemotherapy e AR-DRG: R63Z Chemotherapy; f MBS: 15211 Radiation Oncology Treatment; g AR-DRG: R64Z Radiotherapy; h MBS: 15214,15215,15218,15221,15224,15227,15245,15248,15251,15254,15257.Two or more fields (maximum of 5 fields).

Overall, in the 56 patients with newly diagnosed head and neck cancer, the estimated PET cost was $59,000 (range: $43,000–$116,000) with a slight cost offset attributable to subsequent changes in patient management. The net cost was estimated at $47,000 in the 56 patients; or $81,000 per 100 patients when the cost of PET and the major management changes were considered.

The addition of PET for primary staging of head and neck cancers leads to an additional cost and a potential benefit of uncertain magnitude.

Net costs in assessment of residual disease

The main management change resulting from using PET in the assessment of suspected residual disease is expected to be the avoidance of biopsy after a negative PET scan. The average cost per biopsy avoided is presented in Table 33.

Table 33 Estimated cost of biopsy for suspected residual disease

	Cost item	MBS	Unit cost $	Proportion of patients*	Cost weight $
Fine Needle Biopsy	Aspiration Biopsy	52021	26.60	75%	20.00
Core Biopsy	Lymph node of Neck	52025/ 31420	166.05	15%	25.00
Excision Biopsy	Lymph Nodes of Neck	31423	362.75	10%	36.00
Anaesthesia	Treatment under general anaesthesia	85949	127.70	100%	128.00
Computed Tomography Guidance	Computed Tomography (conjunction with surgical)	57341	470.00	45%	212.00
Ultrasound Guidance	Head/Neck Ultrasound	55028/ 55032	109.10	45%	49.00
Examination of Biopsy	Tissue Pathology (complexity level 2)	72813	72.15	100%	72.00
Initiation of Patient Episode	Patient episode associated with MBS 72813	73924	14.75	100%	15.00
Average patient cost					$466.00

*Estimated by expert opinion

PET has a high negative predictive value, and disease is truly absent in 43–79% of patients with a negative PET result (see 'Triage to biopsy (PET scan negative/CT positive)'); if these patients avoid biopsy an average cost offset of approximately $466 per biopsy could ensue. A cost offset is only applied to true-negative PET findings. Is it assumed that false-negative PET results will be corrected and followed by biopsy or surgical resection as disease progresses. For 100 patients the cost of PET is expected to be approximately $105,300 (range: $76,100–$206,700); the potential cost offset due to the avoidance of biopsy is $20,000–$36,800. The estimated net cost would therefore range from approximately $33,900 to $169,900.

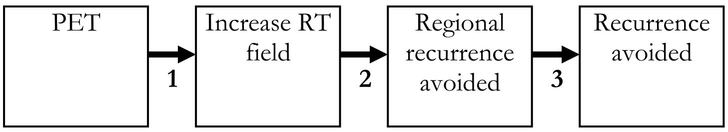
The addition of PET in the assessment of residual disease in head and neck cancers leads to an additional cost and a potential benefit of uncertain magnitude.

Threshold analysis for staging primary head and neck cancer

A threshold analysis was conducted as a means of assessing the potential cost-effectiveness of adding PET to the conventional pathway in staging of primary head and neck cancer. Analyses for other indications were not conducted due to small patient numbers.

The evidence from the systematic review showed that the addition of PET increases diagnostic accuracy for lymph node staging. PET identifies true additional local disease; thus treatment of this additional disease (mainly by increasing the radiotherapy field) is likely to result in improved patient outcomes. However, evidence to quantify any increase in effectiveness is currently not available. The threshold analyses are estimates of the *potential* cost-effectiveness of PET for this specific purpose. In the absence of data on patient outcomes, the analyses are based on assumptions and supported by: the data collected from the PET data collection study, published literature and expert opinion. Two approaches have been taken: the first is an estimate based on conservative assumptions of the benefit of PET; the second is based on more favourable assumptions and expert opinion. Results must be considered within the limitations of these assumptions. Figure 8 presents the basic pathway, assumptions, and costs for the analysis.

Figure 8 Pathway and costs for recurrence avoided attributable to PET



1. Additional lymph node metastases detected by PET leads to an increase in RT field
2. PET PPV; RT prevents regional recurrence
3. Regional recurrence rate

The assumptions underlying the conservative threshold estimate are:

- PET has a PPV for additional lymph node metastases of 66% (lower bound 95% CI from Ng et al. [2006], see 'Is it accurate?').
- RT field is increased in 13% of patients due to additional disease detected on PET in 86% of patients (see 'Changes in management plans', page 73).
- Regional recurrence would have occurred in 12% of patients with PET-detected, CT occult lymph node metastases (equivalent to the overall 2–5 year regional recurrence rate; 11% in Swiss study (Studer et al. 2007); and 13% in Korean study (Lim et al. 2008)). It is assumed regional recurrence would not have presented in all patients due either to slow regional disease progression or regression given that lymph node disease may have been detected at an early stage.
- RT is effective in preventing recurrence in 73% of patients in whom additional lymph node metastases are identified (mean baseline rate of local recurrence following definitive RT from a meta-analysis by Chen et al. (2007) = 24.7%, range: 9–27%).

Based on these conservative assumptions it is estimated that the cost per recurrence avoided is in the order of $151,100 (range: $109,400–$295,900). To achieve a cost-effectiveness of $40,000 per life year gained, the average patient with recurrence avoided would need an approximate life gain of 3.8 years.

The assumptions underlying the more favourable threshold estimate are:

- PET has a PPV for additional lymph node metastases of 100% (ie no false-positives, point estimate from Ng et al. (2006), see 'Is it accurate?').
- RT field is increased in 13% of patients due to additional disease detected on PET in 86% of patients (see 'Changes in management plans', page 73).
- Recurrence would have occurred in 100% of patients if PET had not detected additional disease.
- Radiotherapy is effective at preventing recurrence in 85% (range: 80–90%).

Based on these more favourable assumptions it is estimated that the cost per recurrence avoided is approximately $12,400 (range: $7,600–$23,000). To achieve a cost-effectiveness of $40,000 per life year gained, the average patient with recurrence avoided would need about a four-month life gain. If PPV for additional lymph node metastases is only 66%, the cost per recurrence avoided could be up to $35,000; or a life gain of 10–11 months to achieve a cost-effectiveness level of $40,000 per life year gain.

The potential cost-effectiveness of PET in this setting will then depend on average life years gained and quality of life implications due to regional recurrence being avoided. While the estimates presented are indicative only, extensive modelling of detailed costs implications of management changes due to PET would not be more informative in the absence of a known measure of effectiveness in terms of patient outcomes.

Financial implications

The potential cost of PET to the federal government (not discounted for the 75–85% rate of MBS reimbursement to patients) was estimated based on the potential utilisation of PET (see 'Potential utilisation of PET'). Patient uptake of PET in head and neck cancer has increased over the interim funding period (Figure 1). It is expected that implementation of public funding for PET would lead to a further increase, particularly if PET service provision is extended beyond the currently funded PET sites.

The calculation of financial implications considers a range for the expected utilisation of PET in Australia to be between 1,010 and 1,680 scans for primary and recurrent head and neck cancer staging, 110–600 for assessment of suspected residual disease, and 150 for the assessment of cancers presenting with cervical lymph node metastases from unknown primary sites.

The gross annual reimbursement cost of PET to the MBS is estimated in Table 33. Potential utilisation estimates for Australia are multiplied by the expected cost of PET from the ANZAPNM cost data report (ANZAPNM 2007); a range of minimal and maximal cost estimates is provided (ie lower bound: minimum cost observed in the PET cost data report [$761] and the low utilisation estimate; upper bound: maximum cost observed in the PET cost data report [$2,067] and the high utilisation estimate).

Table 34 Estimated financial implications of funding PET for head and neck cancers

Indication	Utilisation estimate	MBS cost estimate[a]
Primary and recurrent head and neck cancer staging	1,007–1,678	$766,300–$3,468,400
Assessment of suspected residual disease	107–595	$81,400–$1,229,900
Assessment of unknown primary site	150	$114,200–$310,100
Total	$962,000–$5,008,000	

a With PET cost estimated at $761–$2,067.

It is important to note that these estimates are gross PET costs and are highly dependent both on utilisation and on the median cost of PET if funded. The net short-run financial impact associated with PET is not considered in these figures; but is likely to be slightly lower (see 'Net costs in staging primary head and neck cancer'; 'Net costs in assessment of residual disease'). The long-run implications are unclear.

These estimates are based on limiting staging of primary cancers to patients with stage T3/T4Nx or TxN+ disease. If reimbursement of PET for staging of primary head and neck cancer was not limited to these patients, the estimated total usage for this indication could range from 2,330 to 2,450; and the cost to the MBS for initial staging could range from between $1,773,100 and $5,064,200. Thus, the total cost for all indications could range from $2,751,900 to $8,737,200.

As discussed previously (Medical Services Advisory Committee 2007), the number of reimbursed PET sites may have implications for total health care expenditure due to the impact of patient throughput on the actual cost of a PET scan per patient. However, from the Federal government perspective (not considering Medicare safety net provision), Medicare reimbursement of individual PET services would not be affected, as the cost of a PET scan would be fixed by the fee for Medicare benefit. From this perspective, the total cost of PET would primarily be determined by total patient throughput at all sites (utilisation).

A detailed assessment of how the number of reimbursed centres may impact on the financial implications of PET service provision, including an analysis of required capacity for PET scanners in Australia, would be useful (Cleemput et al. 2005; Facey et al. 2007), but is beyond the scope of this report. As well as financial implications and potential cost-effectiveness, the question of equity in access needs to be considered when making decisions about public funding of PET.

Summary

The main potential impact of PET in patients with head and neck cancer is improved pre-treatment staging. PET is expected to more accurately define the extent of locoregional disease and better detect distant metastases that would render the disease incurable.

Safety

PET is considered a safe procedure. PET/CT is not associated with any additional safety concerns as the level of exposure to ionising radiation is acceptable for this patient population.

Effectiveness

The specific research questions for this review were:

- What is the value of the addition of PET/CT in the assessment of patients with biopsy proven, clinical stage T3/4 Nx or Tx N+ newly diagnosed or recurrent carcinoma of the head and neck, considered suitable for definitive treatment on anatomical imaging?

- What is the value of PET/CT before biopsy (triage) in the assessment of residual carcinoma of the head and neck (ie a suspicious lesion on prior tests) following completion of definitive treatment?

- What is the value of the addition of PET/CT to conventional staging in the assessment of patients with metastatic squamous cell carcinoma involving cervical lymph nodes from an unknown primary site?

Newly diagnosed or recurrent carcinoma of the head and neck

Diagnostic accuracy

Two fair quality studies provided data on the accuracy of the addition of PET in staging of lymph node metastases on a per-patient basis. In one study (134 patients), sensitivity increased from 31% to 57% and specificity increased from 92% to 96%. In the other (23 patients), sensitivity remained unchanged at 90% while specificity increased from 75% to 94%. Four studies reporting lymph node level or lesion based accuracy data similarly found the addition of PET to increase accuracy.

One study of 48 patients reported that the addition of PET to conventional work-up was positive for additional distant disease in six patients (13%), two were true-positive for distant metastases. One large Taiwanese study of limited applicability (in patients with nasopharyngeal cancer) indicated the sensitivity for distant metastases increased from 33% with conventional staging alone to 84% when PET was added to the staging strategy. This increase in sensitivity occurred with no significant decrease in specificity from 97% with conventional imaging to 94% with the addition of PET.

Impact on patient management

The Australian prospective study of PET in head and neck cancer (Scott et al. 2007) provides the most applicable data to the study population under consideration in this review as the study directly reflects the clinical pathway in Australia.

The Australian study indicated that PET led to a change in management plans in 32% (95% CI: 20–46%) of 56 patients. PET detected additional lesions in 36% of patients (20/56). Of those in whom additional lesions were detected, treatment plans changed in 70% (14/20; 95% CI: 46–88%), and of those with no additional lesions detected treatment plans changed in 11% (4/36; 95% CI: 3–26%) of patients ($p < 0.001$). Surgery was avoided in two patients (4%) and added in one patient (2%). Radiotherapy was added in two patients (4%). Descriptions of the type of surgery planned were provided, but the details were inadequate to determine whether or not the extent of surgery changed.

Changes to the radiotherapy target field or dose were seen in 21% of all patients, in 40% of those with additional lesions detected and in 11% of those with no additional lesions detected ($p = 0.02$). Overall, the radiotherapy clearly increased in five patients (9%), it clearly decreased in five patients (9%), and in two patients (4%) the target field was increased while the dose was reduced.

Impact on patient outcomes

Where PET leads to an increase in the radiotherapy administered based on more accurate staging of regional lymph nodes, this may result in an improvement in patient outcomes. The benefits will depend on the degree to which improved local disease control influences patient survival and quality of life. While this change in management is likely to lead to an improvement in overall patient health outcomes, the magnitude of this effect is not known in the absence of direct evidence.

Where PET leads to a decrease in the radiotherapy administered, this may lead to sparing of normal tissue from unnecessary irradiation, possibly decreasing the adverse consequences associated with regional radiotherapy. However, direct evidence for this is not available.

Suspected residual carcinoma of the head and neck

Diagnostic accuracy

The available evidence indicates that in patients with suspected residual disease on prior tests PET has a low negative likelihood ratio (range 0–0.18) and a high negative predictive value (range 83–100%). This means a negative PET scan is highly predictive of the absence of disease.

Impact on patient management

A single Australian study reported the impact of PET on treatment intent in 53 patients with suspected residual disease. PET findings changed management in 21 patients (40%). When the PET scan was negative, the most common change was avoidance of surgery, as reported in 83% of patients (15/18). However, in the context of this review a negative

PET scan would have changed management from biopsy, rather than surgery, to observation (surveillance).

Impact on patient outcomes

The use of PET in this population has the potential to reduce of the number of unnecessary additional invasive procedures thereby improving patient outcomes through reduced morbidity and improved quality of life. The magnitude of this effect is uncertain.

Metastatic squamous cell carcinoma involving cervical nodes from an unknown primary site

Diagnostic accuracy

Evidence was limited on the additional value of PET/CT to conventional staging including panendoscopy for the assessment of patients with an unknown primary. In three studies the yield of PET in identifying the primary tumour site ranged from 10% (1/10 to 68% (26/38). However, histological verification of the primary tumour site was not available for all patients.

Impact on patient management

The main treatment changes that are likely to follow PET are the addition of surgery and/or the modification of the radiotherapy treatment field to include the primary site. In the prospective Australian data collection study (Scott et al. 2007) on 15 patients with an unknown primary tumour, PET detected previously unknown primary tumours in 7 of 15 patients (47%).

Management plans changed in 7 of the 15 patients (47%; 95% CI: 21–73%). When PET detected the primary tumour, management was changed in 5 of 7 cases. Treatment intent was unchanged in all 15 patients (all treated with curative intent).

Management changes included radiotherapy target field increase in three cases (combined with surgery abandoned in one case), radiotherapy added in one case and further investigation (bronchoscopy) changed to surgery in one case.

Impact on patient outcomes

As mentioned above, the main treatment changes that are likely to follow PET are the addition of surgery and/or the modification of the radiotherapy treatment field to include the primary site. The benefits of identifying a primary site will depend on the degree to which improved local control of the primary tumour influences patient survival and quality of life. The impact will also depend on whether the primary tumour would have been included in the radiotherapy field regardless of the PET findings. At this stage the impact that this will have on overall patient health outcomes is uncertain.

Economic considerations

Lack of data on patient outcomes precluded cost-effectiveness analyses. An estimate of the major cost implications of PET for staging of primary head and neck cancers and the assessment of residual disease was estimated. In addition, a threshold analysis was conducted to assess the potential for the addition of PET in primary staging to be cost-effective.

Newly diagnosed or recurrent carcinoma of the head and neck

The net cost for the addition of PET was estimated based on the major management changes in patients with a known primary tumour from the Australian data collection exercise. The estimated cost of PET for 100 patients was $105,300 (range: $76,100–$206,700) with a slight cost offset attributable to subsequent short-term changes in patient management, giving an estimated net cost of $81,000.

An exploratory threshold analysis was conducted considering the potential impact of increasing the radiotherapy field. Based on conservative assumptions it was estimated that the cost per recurrence avoided is in the order of $151,100 (range: $109,400–$295,900). To achieve a cost-effectiveness of $40,000 per life year gained, the average patient with recurrence avoided would need an approximate gain in life of 3.8 years. Based on more favourable assumptions the estimated cost per recurrence avoided is approximately $12,400 (range: $7,600–$23,000). To achieve a cost-effectiveness of $40,000 per life year gained, the average patient with recurrence avoided would need about a four-month life gain.

Based on an estimated utilisation of 1,007 to 1,678 scans annually, the gross MBS reimbursement cost of PET as an addition to conventional staging of patients with newly diagnosed or recurrent carcinoma of the head and neck may range from $766,300 to $3,468,400.

Suspected residual carcinoma of the head and neck

The net cost for the addition of PET in assessing suspected residual carcinoma was estimated considering cost offsets due to the avoidance of biopsy in patients with a negative PET scan. For 100 patients the cost of PET is expected to be approximately $105,300 (range: $76,100–$206,700); the potential cost offset due to the avoidance of biopsy is $20,000–$36,800. The estimated net cost would therefore range from approximately $33,900 to $169,900 per 100 patients.

Based on an estimated utilisation of 107 to 595 scans annually; the gross cost to the MBS of funding PET for the assessment of suspected residual disease is estimated to range from $81,400 to $1,229,900.

Metastatic squamous cell carcinoma involving cervical nodes from an unknown primary site

The gross cost to the MBS of funding PET in the assessment of patients with metastatic squamous cell carcinoma involving cervical lymph nodes from an unknown primary site based on the current reimbursement for 150 patients per year, is estimated to range from between $114,000 and $310,100 depending on MBS reimbursement level.

Conclusions

Newly diagnosed or recurrent carcinoma of the head and neck

The use of PET in addition to conventional staging in the staging of patients with newly diagnosed or recurrent carcinoma of the head and neck is considered:

- safe
- to increase accuracy for staging of regional lymph node metastases
- to increase the detection of distant metastases, although these may occur infrequently
- to detect additional lesions in approximately one-third of patients
- to lead to changes in management in approximately 70% of patients when additional lesions are identified, most commonly changes in the radiotherapy regimen. Data on modification of the extent of surgery are not available
- likely to lead to an improvement in overall patient outcomes when PET leads to an increase in the radiotherapy administered for the treatment of previously unsuspected local lymph node metastases. The magnitude of this effect has not been quantified
- likely to lead to a decrease in adverse events associated with regional radiotherapy when PET leads to a decrease in the radiotherapy administered. The magnitude of this effect has not been quantified
- to lead to an increase in costs, associated with a likely benefit of uncertain magnitude.

Suspected residual carcinoma of the head and neck

The use of PET as a triage to biopsy in the assessment of suspected residual carcinoma of head and neck is considered:

- to be highly predictive of the absence of disease when a PET scan is negative
- to lead in changes in management, most likely the avoidance of additional invasive procedures which may include biopsy/surgery, when PET is negative
- to reduce the number of unnecessary additional invasive procedures thereby improving patient outcomes through reduced morbidity and improved quality of life. The magnitude of this effect has not been quantified
- to lead to an increase in costs, associated with a likely benefit of uncertain magnitude.

Metastatic squamous cell carcinoma involving cervical nodes from an unknown primary site

The use of PET in the assessment of patients with metastatic squamous cell carcinoma involving cervical lymph nodes from an unknown primary site is considered:

- to be able to detect a primary tumour site in some patients
- to lead to changes in management, specifically the addition of surgery and/or the modification of the radiotherapy treatment field to include the primary site
- to have an unknown impact on long-term patient outcomes.

Advice

MSAC has considered the safety, effectiveness and cost-effectiveness of PET/CT for squamous cell cancer of the head and neck:

1. in addition to conventional staging of newly diagnosed or recurrent cancer;
2. in addition to conventional assessment for suspected residual cancer after definitive treatment; and
3. in addition to conventional staging of cancer metastatic to cervical lymph nodes from an unknown primary site.

MSAC finds that PET/CT is safe.

MSAC finds that PET/CT improves the accuracy of staging of newly diagnosed or recurrent cancer, and leads to a change in management in the majority of patients in whom additional disease is detected; while this is expected to improve outcomes for patients, the magnitude of this effect could not be quantified.

MSAC finds that PET/CT has a high negative predictive value in patients with suspected residual cancer, and permits the avoidance of invasive procedures, including surgery, in the majority of patients in whom these were planned; while this is expected to reduce morbidity and improve quality of life, the magnitude of this effect could not be quantified.

MSAC finds that PET/CT improves the detection of otherwise occult primary sites of metastatic head and neck cancer, leading to changes in the management of these patients; the impact of such changes on patient outcomes could not be quantified.

MSAC advises that public funding should be supported for these indications.

- The Minister for Health and Ageing noted this advice on the 8th December 2008-

Appendix A MSAC's terms of reference and membership

MSAC's terms of reference are to:

- 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, accuracy, 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 AHMAC.

The membership of MSAC comprises a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning:

Member	**Expertise or affiliation**
Dr Stephen Blamey (Chair)	General surgery
Professor Brendon Kearney (Deputy Chair)	Health administration and planning
Dr William Glasson (Deputy Chair)	Ophthalmology
Associate Professor John Atherton	Cardiology
Associate Professor Michael Cleary	Emergency medicine
Associate Professor Paul Craft	Clinical epidemiology and oncology
Professor Geoff Farrell	Gastroenterology
Dr Kwun Fong	Thoracic medicine
Professor Richard Fox	Oncology
Professor Jane Hall	Health economics
Professor John Horvath	Department of Health and Ageing Chief Medical Officer
Associate Professor Terri Jackson	Health economics
Associate Professor Frederick Khafagi	Nuclear medicine
Associate Professor Ray Kirk	Health research
Dr Ewa Piejko	General practice
Dr Ian Prosser	Haematology

Mrs Sheila Rimmer	Consumer health issues
Dr Judy Soper	Radiology
Professor Ken Thomson	Radiology
Dr David Wood	Orthopaedics

Appendix B Advisory Panel and Health Technology Assessors

Advisory Panel – Reference 35b(ii)

Member	Nomination / Expertise or affiliation
Associate Professor Frederick Khafagi (Chair)	MSAC Member Nuclear medicine
Associate Professor Bryan Burmeister	Royal Australian and New Zealand College of Radiologists nominee Radiation oncology
Professor Glyn Jamieson	Co-opted member Upper gastrointestinal surgery
Professor Brendon Kearney	Deputy Chair of MSAC Health administration and planning
Dr George Larcos	Australian and New Zealand Association of Physicians in Nuclear Medicine (ANZAPNM) nominee Nuclear medicine
Mr Bernard M Lyons	Royal Australasian College of Surgeons (RACS) nominee Otolaryngology Head and Neck Surgery
Professor Bruce Mann	Co-opted member Surgical oncology
Mr Brian Stafford	Consumers' Health Forum of Australia nominee Consumer health issues
Dr Brian Stein	Medical Oncology Group of Australia nominee Oncology

Health Technology Assessors

Name	Organisation
Dr Lukas Staub	NHMRC Clinical Trials Centre
Ms Michelle McIsaac	
Ms Sally Wortley	
Dr Suzanne Dyer	
Mr Luke Marinovich	

Appendix C Electronic databases and HTA websites

1. International electronic databases

NHS Centre for reviews and Dissemination (CRD) databases/ International Network of Agencies for Health Technology Assessment (INAHTA) http://www.york.ac.uk/inst/crd/

- Economic evaluation database (EED)
- Database of abstracts of reviews of effectiveness (DARE)
- Heath Technology Assessment (HTA)

Cochrane Database of Systematic Reviews and Cochrane Controlled Trials Register
http://www.cochrane.org

2. Individual HTA agencies

AUSTRALIA

- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S) http://www.surgeons.org/Content/NavigationMenu/Research/ASERNIPS/default.htm
- Centre for Clinical Effectiveness, Monash University http://www.med.monash.edu.au/healthservices/cce/evidence/
- Health Economics Unit, Monash University http://chpe.buseco.monash.edu.au

AUSTRIA

Institute of Technology Assessment / HTA unit http://www.oeaw.ac.at/ita/e1-3.htm

CANADA

- Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS) http://www.aetmis.gouv.qc.ca/en/
- Alberta Heritage Foundation for Medical Research (AHFMR) http://www.ahfmr.ab.ca/publications.html
- Canadian Agency for Drugs and Technologies in Health (CADTH) http://www.cadth.ca
- Canadian Health Services Research Foundation (CHSRF)) – Cabot database http://www.chsrf.ca
- Centre for Health Economics and Policy Analysis (CHEPA), McMaster University http://www.chepa.org
- Centre for Health Services and Policy Research (CHSPR), University of British Columbia http://www.chspr.ubc.ca
- Health Utilities Index (HUI) http://www.fhs.mcmaster.ca/hug/index.htm
- Institute for Clinical Evaluative Sciences (ICES) http://www.ices.on.ca

DENMARK

- Danish Centre for Health Technology Assessment (DACEHTA) http://www.sst.dk/Planlaegning_og_behandling/Medicinsk_teknologivurdering.aspx?lang=en
- Danish Institute for Health Services Research (DSI) http://www.dsi.dk/engelsk.html

FINLAND

Finnish Office for Health Technology Assessment (FINOHTA) http://www.stakes.fi/finohta/e/

FRANCE

Haute Autorité Santé (HAS) http://www.has-sante.fr/

GERMANY

German Institute of Medical Documentation and Information (DIMDI) / HTA
http://www.dimdi.de/static/en/index.html

THE NETHERLANDS

Health Council of the Netherlands (Gezondheidsraad) http://www.gr.nl/adviezen.php

NEW ZEALAND

New Zealand Health Technology Assessment (NZHTA) http://nzhta.chmeds.ac.nz/

NORWAY

Norwegian Knowledge Centre for the Health Services http://www.kunnskapssenteret.no/

SPAIN

- Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud 'Carlos III' Healthcare Technology Evaluation Agency (AETS) http://www.iscii.es/htdocs/en/investigacion/Agencia_quees.jsp
- Catalan Agency for Health Technology Assessment (CAHTA) http://www.aatm.es/cgi-bin/frame.pl/ang/pu.html

SWEDEN

- Swedish Council on Technology Assessment in Health Care (SBU) http://www.sbu.se/en
- Center for Medical Health Technology Assessment http://www.cmt.liu.se/english?l=en

SWITZERLAND

Swiss Network for Health Technology Assessment (SNHTA) http://www.snhta.ch/

UNITED KINGDOM

- Health Technology Board for Scotland http://www.nhshealthquality.org/nhsqis/4567.140.1126.html
- National Health Service Health Technology Assessment (UK) / National Coordinating Centre for Health Technology Assessment (NCCHTA) http://www.hta.nhsweb.nhs.uk/
- University of York NHS Centre for Reviews and Dissemination (NHS CRD) http://www.york.ac.uk/inst/crd/
- National Institute for Clinical Excellence (NICE) http://www.nice.org.uk/

UNITED STATES

- Agency for Healthcare Research and Quality (AHRQ) http://www.ahrq.gov/clinic/techix.htm
- Harvard School of Public Health – Cost-Utility Analysis Registry http://www.tufts-nemc.org/cearegistry/index.html
- U.S. Blue Cross/ Blue Shield Association Technology Evaluation Center
- (TEC) http://www.bcbs.com/consumertec/index.html

Appendix D MSAC (2001)

Author (year)	Objective of report	Number and publication dates of included studies	Population considered in included studies Test comparison	Conclusion/ recommendation	Quality assessment[a]
Medical Services Advisory Committee (2001) *Positron emission tomography Part 2(i)*	To assess the clinical effectiveness of PET for 3 indications including assessment of patients with squamous cell carcinoma of the head and neck for staging prior to initial definitive treatment	Included articles published in English up to March 2001: 12 studies: PET for staging of newly diagnosed HNC (1992–2001) 10 studies: PET for staging and detection of primary and residual/recurrent HNC (mixed primary and suspected recurrent patients) (1994–1999) 13 studies: PET for detection of recurrent/residual HNC (1995–2001) 9 studies: PET for detection of unknown primary disease (1998–2000) 4 studies: PET for evaluation of response to therapy in HNC (1993–1998)	Population Patients with squamous cell carcinoma of the head and neck (including patients with unknown primary cancer) Test comparison PET + conventional imaging versus conventional imaging alone	Overall conclusion FDG–PET is safe, has good diagnostic accuracy and is potentially clinically and cost-effective for the assessment of patients with head and neck cancer Recommendation A whole body PET study should be funded on an interim basis for the following clinical scenarios: • Primary staging of squamous cell carcinoma of the head and neck • Further investigation of suspected residual or recurrent squamous cell carcinoma of the head and neck • Evaluation of metastatic squamous cell carcinoma involving cervical nodes from an unknown primary site	Quality: high Explicit review questions: yes Explicit and appropriate eligibility criteria: yes Explicit and comprehensive search strategy: yes Quality of included studies appraised: yes Methods of study appraisal reproducible: yes Heterogeneity between studies assessed: N/A Summary of main results clear and appropriate: yes (Note: assessment of heterogeneity and summary of main results was limited by the lack of evidence identified)

Results

Newly diagnosed head and neck cancer:

Included studies

22 studies for staging newly diagnosed HNC were identified, 14 out of these provided some information on the accuracy of PET for staging newly diagnosed HNC.

Accuracy

Studies primarily reported on the detection of nodal involvement by PET (ie N-staging), no paper reported on M-staging. Sample sizes were generally small (range: n=11 to n=70). PET appeared to have quite high diagnostic accuracy in the detection of nodal disease (range: 75–94%) with comparable or better results than CT and/or MRI (range: 56–91%). Calculations where nodes or node groups were used instead of patients showed higher absolute estimates of diagnostic accuracy for both PET (range: 82–100%) and its comparators (range: 53–95%).

Change in management

One study (Porceddu et al. (1998)) reported that PET changed management in 19/50 of patients (6 additional investigations, 2 intent of management changed, 11 mode or technique changed). In another study PET correctly indicated the need for surgery in all cases with metastatic involvement, but incorrectly indicated the need for surgery in 5/12 cases.

PET appears to offer additional information in assessing the nodal involvement, which has the potential to affect patient management. It is possible that PET would avoid the need for neck dissection for patients where CT or MRI had incorrectly indicated cervical lymph node involvement. PET may be able to identify smaller volume disease, and thus appropriately indicate surgery or radiotherapy in patients with smaller volume nodal involvement missed by CT or MRI.

Health outcomes

No studies reported on the impact of PET on ultimate patient outcomes.

Detection of residual/recurrent head and neck cancer:

Included studies

18 studies for residual/recurrent HNC were identified, 15 out of these provided some information on the accuracy of PET in the evaluation of suspected residual or recurrent disease.

Accuracy

PET appeared to be more accurate (range: 50–97%) compared to CT, MRI or pooled CT and/or MRI data (range: 3–85%). However, most studies included only small numbers of patients (range: n=10 to n=71).

Change in management

9 studies indicated that PET offers additional information in the assessment of suspected residual or recurrent disease, which has the potential to affect patient management. It is likely that PET would avoid neck dissection or biopsy where CT or MRI incorrectly indicated recurrent disease. PET may also alter intent of management by detecting distant metastatic involvement or by distinguishing recurrent or residual disease from post-treatment tissue changes.

PET assisted in the detection of 29% of unknown primary tumours, which led to changes in planned clinical management in 81% of those where the primary tumour was detected by PET.

Health outcomes

No studies reported on the impact of PET on ultimate patient outcomes in residual/recurrent disease.

Detection of unknown primary disease:

Included studies

10 studies described the use of PET in detecting unknown primary tumours, 8 out of these provided some information on the accuracy of PET in the detection of unknown primary tumours.

Accuracy

PET is of value in detecting SCC unknown primary tumours in 8% to 35% of patients where conventional work-up had failed to identify the primary site. The majority of primary tumours identified in these studies were in the head and neck or in the lung.

Change in management

Based on 4 studies, PET assisted in the detection of 29% of unknown primary tumours, which led to changes in planned clinical management in 81% of those where the primary tumour was detected by PET.

Health outcomes

Three studies provided limited information regarding survival of patients diagnosed with unknown primary tumours. As only small numbers of patients had been analysed, there was not sufficient evidence to assess whether PET detection of occult primary tumours might improve survival or overall prognosis of patients.

Response to therapy:

Included studies

4 studies evaluating the role of PET in monitoring the response to therapy were identified.

Accuracy

The papers evaluating the role of PET in monitoring or evaluating the effects of therapy by detection of residual disease provided only limited information based on small, preliminary studies.

Appendix E PPICO tables

PPICO criteria and clinical questions for PET in newly diagnosed or recurrent head and neck cancer

Population	Prior tests	Intervention	Comparator	Reference standard	Outcomes
Patients with biopsy proven newly diagnosed or recurrent carcinoma of the head and neck Clinical stage T3/4 Nx or Tx N+ Suitable for definitive treatment on anatomical imaging	Panendoscopy ± biopsy CT of head/neck/ chest/upper abdomen +/– MRI	FDG–PET/CT plus standard conventional imaging	Prior tests without PET/CT	Pathology, or clinical follow-up (≥6 months)	Diagnostic accuracy: • sensitivity • specificity • additional TP & FP • ROC AUC, Q*, DOR Change in management: • Definitive treatment avoided (chemotherapy, radiotherapy, surgery) • Investigations avoided • Changed extent of radiotherapy field • Overall change • Change in intent from curative to palliative • Other changes occurring in ≥10% patients Patient outcomes: • overall survival • cancer-specific mortality • cancer progression • treatment morbidity/mortality • quality of life

Clinical questions
What is the value of the addition of PET/CT in the assessment of patients with biopsy-proven, clinical stage T3/4 Nx or Tx N+ newly diagnosed or recurrent carcinoma of the head and neck, considered suitable for definitive treatment on anatomical imaging?

PPICO criteria and clinical questions for PET in suspected residual head and neck cancer (including evaluation of response to therapy)

Population	Prior tests	Intervention	Comparator	Reference standard	Outcomes
Patients with residual carcinoma of the head and neck (suspicious lesion)	Physical examination CT +/– MRI	FDG–PET/CT plus prior tests and biopsy	Prior tests plus biopsy without PET/CT	Pathology, or clinical follow-up (≥ 6 months)	Diagnostic accuracy: • Sensitivity • Specificity • Additional TP & FP • ROC AUC, Q*, DOR Change in management: • Avoidance of salvage therapy (surgery, radiotherapy) • Salvage therapy instigated (surgery, radiotherapy) • Investigations avoided • Overall change • Change in intent from curative to palliative[a] • Other changes occurring in ≥ 10% patients Patient outcomes: • Overall survival • Cancer-specific mortality • Cancer progression • Treatment morbidity/mortality • Quality of life
Clinical questions What is the value of the addition of PET/CT to conventional staging in the assessment of patients with residual carcinoma of the head and neck (ie a suspicious lesion on prior tests)?					

[a] These are secondary outcomes and will only be extracted from studies included on the basis of reporting primary outcomes

PPICO criteria and clinical questions for PET in metastatic squamous cell carcinoma involving cervical nodes from unknown primary

Population	**Prior tests**	**Intervention**	**Comparator**	**Reference standard**	**Outcomes**
Patients with metastatic squamous cell carcinoma involving cervical nodes from an unknown primary site (no primary identified on conventional staging)	Physical examination CT MRI Panendoscopy Biopsy	FDG–PET/CT plus prior tests	Prior tests without PET/CT	Pathology, or clinical follow–up (≥ 6 months)	Diagnostic accuracy: • Sensitivity • Specificity • Additional TP & FP • ROC AUC, Q*, DOR Change in management: • Definitive treatment of primary instigated • Surgery and/or radiotherapy avoided • Modified curative therapy • Change in intent from curative to palliative • Other changes occurring in ≥ 10% patients Patient outcomes: • Overall survival • Cancer–specific mortality • Cancer progression • treatment morbidity/mortality • Quality of life

Clinical questions

What is the value of the addition of PET/CT to conventional staging in the assessment of patients with metastatic squamous cell carcinoma involving cervical nodes from an unknown primary site?

Appendix F Staging of head and neck cancer (AJCC, 2002)

Table 35 Stage grouping for all head and neck sites except the nasopharynx and thyroid

Stage group	T-stage	N-stage	M-stage
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0

Table 36 Stage grouping for tumours of the nasopharynx

Stage group	T-stage	N-stage	M-stage
0	Tis	N0	M0
I	T1	N0	M0
IIA	T2a	N0	M0
IIB	T1	N1	M0
	T2a	N1	M0
	T2b	N0	M0
	T2b	N1	M0
III	T1	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N0	M0
	T3	N1	M0
	T3	N2	M0
IVA	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
IVB	Any T	N3	M0
IVC	Any T	Any N	M1

Table 37 T-staging for tumours of the lip and oral cavity

Stage	Description
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3	Tumor more than 4 cm in greatest dimension
T4a	
Lip	Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face (ie chin or nose)*
Oral Cavity	Tumor invades through cortical bone, into deep [extrinsic] muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), maxillary sinus, or skin of face
T4b	Tumor involves masticator space, pterygoid plates, or skull base and/or encases internal carotid artery

Table 38 T-staging for tumours of the pharynx

Stage	Description
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Nasopharynx	
T1	Tumor confined to the nasopharynx
T2	Tumor extends to soft tissues
T2a	Tumor extends to the oropharynx and/or nasal cavity without parapharyngeal extension*
T2b	Any tumor with parapharyngeal extension*
T3	Tumor involves bony structures and/or paranasal sinuses
T4	Tumor with intracranial extension and/or involvement of cranial nerves, infratemporal fossa, hypopharynx, orbit, or masticator space
Oropharynx	
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3	Tumor more than 4 cm in greatest dimension
T4a	Tumor invades the larynx, deep/extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible
T4b	Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery
Hypopharynx	
T1	Tumor limited to 1 subsite of hypopharynx and 2 cm or less in greatest dimension
T2	Tumor invades more than 1 subsite of hypopharynx or an adjacent site, or measures more than 2 cm but not more than 4 cm in greatest diameter without fixation of hemilarynx
T3	Tumor measures more than 4 cm in greatest dimension or with fixation of hemilarynx
T4a	Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, esophagus, or central compartment soft tissue
T4b	Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures

Table 39 T-staging for tumours of the larynx

Stage	Description
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Supraglottis	
T1	Tumor limited to one subsite of supraglottis with normal vocal cord mobility
T2	Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (eg, mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx
T3	Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, preepiglottic tissues, paraglottic space, and/or minor thyroid cartilage erosion (eg, inner cortex)
T4a	Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T4b	Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures
Glottis	
T1	Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility
T1a	Tumor limited to one vocal cord
T1b	Tumor involves both vocal cords
T2	Tumor extends to supraglottis and/or subglottis, or with impaired vocal cord mobility
T3	Tumor limited to larynx with vocal cord fixation
T4a	Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)
T4b	Tumor invades prevertebral space, encases carotid artery or invades mediastinal structures
Subglottis	
T1	Tumor limited to the subglottis
T2	Tumor extends to vocal cord(s) with normal or impaired mobility
T3	Tumor limited to larynx with vocal cord fixation
T4a	Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)
T4b	Tumor invades prevertebral space, encases carotid artery, or involves mediastinal structures

Table 40 T-staging for tumours of the nasal cavity and paranasal sinuses

Stage	Description
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Maxillary sinus	
T1	Tumor limited to the maxillary sinus mucosa with no erosion or destruction of bone
T2	Tumor causing bone erosion or destruction including extension into the hard palate and/or middle nasal meatus, except extension to posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa, ethmoid sinuses
T3	Tumor invades any of the following: bone of the posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa, ethmoid sinuses
T4a	Tumor invades anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid or frontal sinuses
T4b	Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve V_2, nasopharynx, or clivus
Nasal cavity and ethmoid sinus	
T1	Tumor restricted to any one subsite, with or without bony invasion
T2	Tumor invading two subsites in a single region or extending to involve an adjacent region within the nasoethmoidal complex, with or without bony invasion
T3	Tumor extends to invade the medial wall or floor of the orbit, maxillary sinus, palate, or cribriform plate
T4a	Tumor invades any of the following: anterior orbital contents, skin of nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses
T4b	Tumor invades any of the following: orbital apex, brain, middle cranial fossa, cranial nerves other than V_2, nasopharynx, or clivus

Table 41 T-staging for tumours of the major salivary glands

Stage	Description
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 2 cm or less in greatest dimension without extraparenchymal extension*
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension without extraparenchymal extension*
T3	Tumor more than 4 cm and/or tumor having extraparenchymal extension*
T4a	Tumor invades skin, mandible, ear canal, and/or facial nerve
T4b	Tumor invades skull base and/or pterygoid plates and/or encases carotid artery

Table 42 N-staging for all head and neck sites except the nasopharynx and thyroid

Stage	Description
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N2a	Metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph more than 6 cm in greatest dimension

Table 43 M-staging for head and neck tumours

Stage	Description
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Source: American Joint Committee on Cancer. *AJCC Cancer Staging Manual.* Greene, F.L., Page, D.L., et al (Eds.), 2002, Lippincott Raven Publishers, USA

Appendix G Existing HTA reports

Organisation and year	Title
Australia Medical Services Advisory Committee (MSAC) 2001 (search up to March 2001)	*Positron emission tomography* *[Part 2(ii)]*
Canada Institute for Clinical Evaluative Sciences (ICES) 2001 (latest update April 2004)	*Health technology assessment of positron emission tomography (PET) — a systematic review*
Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AÉTMIS) 2001	*Positron emission tomography in Quebec*
Belgium Health Care Knowledge Centre (KCE) Belgium 2005 (search up to April 2005)	*Positron emission tomography in Belgium*
United Kingdom National Coordinating Centre for HTA (NCCHTA) 2007 (search to August 2005)	*Overview of the clinical effectiveness of positron emission tomography (FDG–PET) imaging in selected cancers*
Poland Agency for Health Technology Assessment Poland (AHTAPol) 2006 (search to March 2006)	*Cost-effectiveness analysis of PET–CT positron emission tomography and the diagnostic technologies financed from public sources in oncological diagnostics in Poland. Clinical and epidemiological aspects*

Appendix H Quality assessment of excluded AHTAPol report

Author (year)	Objective of report	Number and publication dates of included studies	Population considered in included studies Test comparison	Summary/Conclusions	Quality assessment
Agency for Health Technology Assessment Poland (AHTAPol) (2006)	A clinical and epidemiological analysis, as part of a comparative cost-effectiveness analysis of PET–CT with diagnostic technologies financed in Poland from public sources in oncological diagnostics. 12 cancers were investigated, including head and neck cancer	English and Polish language articles included: Overall, 16 primary studies, published 1998 to March 2006 were included 3 HTAs were identified but not analysed (2 non-English/Polish; 1 not freely available) Head and neck cancer: 932 primary studies identified Four studies in head and neck cancer included: *Diagnostic efficacy:* 1 study (Branstetter 2005 [included in UK review]) *Detection of bone infiltration of oral cancer:* 1 study (Goerres 2005) *Treatment revisions:* 2 studies (Koshy 2005 [included in UK review], Wild 2006)	PET/CT for diagnostic efficacy (1 study [n=65]): *Population* Patients w primary head and neck cancer, recurrence following therapy or unknown primary site *Test comparison* PET/CT versus CT PET/CT for detection of bone infiltration by oral cancer (1 study [n=34]): *Population* Patients w oral cancer, involvement of lower and upper jaw suspected based on clinical picture *Test comparison* PET/CT versus SPECT/CT and CT. Impact of PET/CT on treatment revisions (2 studies [n=36 and 21]): *Population* Patients w head and neck cancer. *Test comparison* PET/CT versus CT, MRI, clinical examination	For diagnostic efficacy, ‘ the accuracy was rated 94% for PET–CT (95% CI: 89;98) and 74% for CT (95% CI: 66;82) The difference is statistically significant.’ ‘The differences in accuracy, sensitivity and specificity or PET–CT, CT and SPECT/CT tests in the diagnostics of local involvement of bones by oral cavity cancer are not statistically significant.’ ‘In *Wild 2005*, PET–CT findings triggered revisions of treatment suggested based on conventional imaging in 43% patients, while in *Kosy 2005* the value was 25%, which produced a total of 32% cases (95% CI: 21;44).’	Quality: low Explicit review questions: no (no PICO) Explicit and appropriate eligibility criteria: yes Explicit and comprehensive search strategy: no (not comprehensive, may miss PET–CT studies) Quality of included studies appraised: yes Methods of study appraisal reproducible: yes Heterogeneity between studies assessed: N/A Summary of main results clear and appropriate: no (interpretation of superiority of PET based on low level evidence) Given the low quality of this report, results were not extracted in detail

Appendix I Studies included in the review

Accuracy studies

Newly diagnosed or recurrent carcinoma of the head and neck

Author (year) Country Setting N	Study objective and design	Study population	Results	Study quality and applicability
Murakami et al. (2007) Japan Single centre Dec 2004–Jan 2006 N=23	Objective To evaluate impact of PET/CT on nodal staging for HNSCC Study design Accuracy study with information on incremental value of PET/CT • Method 1: CWU (physical and endoscopic examination, CT and MRI) • Method 2: CWU + PET/CT (visual information only) • Method 3: PET/CT alone (including SUV data) *Index test:* FDG–PET/CT • Whole-body 3D PET scanner • Skull base to pelvis • Non-contrast-enhanced CT (3.75 mm slice thickness)	Inclusion criteria Patients who had undergone pre-treatment evaluation for HNSCC, had PET and CT and went on to resection of primary tumour were included (N=23 of 54) Patient characteristics Mean age 66.9 years, range 26–82 20 males, 3 females T1: 1, T2: 6, T3: 9, T4: 7 N0: 8, N1: 8, N2b: 6, N2c: 1 All went on to resection of primary tumour • 1 laryngeal • 3 mesopharyngeal • 7 hypopharyngeal • 12 oral cavity	Correct nodal staging in 23 patients, two observers CWU: 14/23 and 17/23 CWU + PET/CT: 17/23 and 19/23 PET/CT: 19/23 and 20/23 Average of two raters CWU: TP: 13.5, FP: 2, TN: 6, FN: 1.5 Sens 90%, Spec 75% CWU + PET/CT: TP: 13.5, FP: 0.5, TN: 7.5, FN: 1.5 Sens 90%, Spec 94% Accuracy of nodal level staging, two observers, at 112 levels CWU: 100/112 and 104/112 CWU + PET/CT: 105/112 and 107/112 PET/CT: 108/112 and 108/112	Quality: fair *Patient selection:* Prospective: no Consecutive: NR Explicit selection criteria: no *PET protocol: yes* *Reference standard:* • Valid: yes • Applied to all participants: yes *Test interval in days/weeks:* • Reference standard: NR • Comparator: NR *Tests reported blinded to ref standard: NR* *Ref standard reported blinded to tests: NR*

	• Scans obtained on same day • PET and CT images fused *Comparator test:* Conventional work-up • Ultrasound • Contrast-enhanced CT • MRI *Reference standard:* Biopsy from neck dissection • Decision to perform selective or radical neck dissection based on clinical TNM stage and patient performance status • Pathologic findings on lymph nodes recorded at each anatomic level • Retropharyngeal lymph nodes excluded from study (not sampled by neck dissection)		Average of two raters CWU: TP: 14, FP: 5, TN: 88, FN: 5 Sens 74%, Spec 95% CWU + PET/CT: TP: 14, FP: 1, TN: 92, FN: 5 Sens 74%, Spec 99%	*Routine clinical data available: yes* *Analysis:* Uninterpretable/intermediate results reported: no Study withdrawals explained: no Sufficient data for 2 x 2 table: yes Applicability: applicable *Applicable population: yes* *Applicable comparator: yes* *Applicable intervention: yes*

Author (year) **Country** **Setting** **N**	**Study objective and design**	**Study population**	**Results**	**Study quality and applicability**
Ng et al. (2006) Taiwan Single centre	Objective To assess clinical usefulness of PET, CT/MRI and their visual correlation in oral SCC patients with palpably negative neck	Inclusion criteria Clinical diagnosis of SCC in oral cavity, no palpable lymph node, scheduled for surgery Exclusion criteria	Accuracy of nodal level staging, at 457 levels CT/MRI Sens 21.6 (11.3–35.3) Spec 97.5 (95.5–98.8)	Quality: fair *Patient selection:* Prospective: yes Consecutive: unclear Explicit selection criteria: yes

Jan 2003–Dec 2005 N=134	Study design Prospective accuracy study *Index test:* FDG–PET • Vertex to upper thighs *Comparator test:* CT • Contrast axial scans 5 mm • Contrast coronal scans 3 mm MRI • Axial 5 mm, sagittal 4 mm *Reference standard:* Histopathology of neck dissections performed based on imaging results	Other severe medical comorbidities, known distant metastases, second primary tumour Patient characteristics Mean age 52.1 years, range 26–82 129 males (96%), 5 females T1: 30, T2: 65, T3: 15, T4: 24 All patients underwent primary tumour resection • Level I to III: 125 • Level I to IV: 6 • Level I to V: 3	Acc 89.1 (85.8–91.8) PPV 52.4 (29.8–74.3) NPV 90.8 (87.7–93.4) CT/MRI + PET Sens 47.1 (32.9–61.5) Spec 98.0 (96.2–99.1) Acc 92.3 (89.5–94.6) PPV 75.0 (56.6–88.5) NPV 93.6 (90.9–95.8) Accuracy on patient basis, in 134 patients CT/MRI TP: 11, FP: 8, TN: 91, FN: 24 Sens 31.4 (16.9–49.3) Spec 91.9 84.7–96.4) Acc 76.1 (68.0–83.1) PPV 57.9 (33.5–79.7) NPV 79.1 (70.6–86.1) CT/MRI + PET TP: 20, FP:4, TN: 95, FN:15 Sens 57.1 (39.4–73.7) Spec 96.0 (90.0–98.9) Acc 85.8 (78.7–91.2) PPV 83.3 (62.6–95.3) NPV 86.4 (78.5–92.2)	*PET protocol: yes* *Reference standard:* • Valid: yes • applied to all participants: yes *Test interval in days/weeks:* • Reference standard: 2 weeks • Comparator: NR *Tests reported blinded to ref standard: yes* *Ref standard reported blinded to tests: NR* *Routine clinical data available: unclear* *Analysis* Uninterpretable/intermediate results reported: no Study withdrawals explained: no Sufficient data for 2 x 2 table: yes Applicability: applicable *Applicable population: yes* *Applicable comparator: yes* *Applicable intervention: yes*

Author (year) **Country** **Setting** **N**	**Study objective and design**	**Study population**	**Results**	**Study quality and applicability**
Liu et al. (2007) Taiwan Single centre April 2002–August 2005 N=300	Objective To compare the diagnostic efficacies of FDG–PET, conventional work-up and their combination for primary M-staging of nasopharyngeal carcinoma Study design Prospective accuracy study with information on diagnostic thinking *Index test:* FDG–PET *Comparator test:* CWU • chest radiography • abdominal ultrasonography • whole-body skeletal scintigraphy • MRI of head and neck for locoregional staging • CT at sites in question if CWU or FDG–PET suggestive for distant metastases	Exclusion criteria • History of previous or synchronous second malignancy • Tumour histology other than WHO type II or type III • Insufficient follow-up data Patient characteristics Mean age 50 years 210 males (70%), 90 females N0: 10.7% N1: 22.7% N2: 40.3% N3: 26.3%	Patient-based efficacy of FDG–PET compared with CWU CWU TP: 20, FP: 8 • Sens: 32.8% (20/61) • Spec: 96.7% (231/239) • Acc: 83.7% (251/300) CWU + PET TP: 51, FP: 15 • Sens: 83.6% (51/61) • Spec: 93.7% (224/239) • Acc: 91.7% (275/300) Efficacies of CWU + PET not superior compared with PET alone. Impact of PET on patient management PET had impact on management of 39 patients (13%). • 31 truly upstaged • 8 truly downstaged • 7 falsely upstaged • 1 falsely downstaged	Quality: fair *Patient selection:* Prospective: yes Consecutive: no Explicit selection criteria: yes *PET protocol: yes* *Reference standard:* • Valid: yes • Applied to all participants: yes *Test interval in days/weeks:* • Reference standard: ≤ 1 year • Comparator: ≤ 2 weeks *Tests reported blinded to ref standard: yes* *Ref standard reported blinded to tests: no* *Routine clinical data available: no* *Analysis:* Uninterpretable/intermediate results reported: no

	Reference standard: Within one year: • Histology • Unequivocal evidence of distant metastases in imaging studies with concordant clinical course • Equivocal evidence of distant metastases in imaging studies with subsequent histologic proof or clinical progression			Study withdrawals explained: yes Sufficient data for 2 x 2 table: yes Applicability: limited *Applicable population: unclear* *Applicable comparator: yes* *Applicable intervention: yes*

Suspected residual carcinoma of the head and neck (including response to therapy)

Author (year) Country Setting N	Study objective and design	Study population	Results	Study quality and applicability
Andrade et al. (2006) US Single centre NR N=28 N=23/11 (suspected residual disease)	Objective To assess use of FDG–PET/CT in detecting persistent disease after chemoradiotherapy Study design Accuracy study *Index test:* FDG–PET/CT *Comparator test:* • Clinical evaluation • CT (CT portion of PET/CT)	Inclusion criteria Patients with primary cancer treated by definitive chemoradiotherapy Patient characteristics Median age 58 years (range 43–71 years) 21 males (75%), 7 females Stage II 2 (7%) Stage III 8 (29%) Stage IV 18 (64%) All patients underwent post-treatment	Detection of residual disease CE and CT show suspected residual disease (n=11) PPV 100% (5 TP: 0 FP) NPV 83% (5 TN: 1 FN) Sensitivity and specificity 83%, 100%, LR+ NAN, LR– 0.17 CE or CT show suspected residual disease (n=23) PPV 100% (10 TP: 0 FP) NPV 85% (11 TN: 2 FN) Sensitivity and specificity 83%, 100%, LR+ NAN, LR– 0.17	Quality: fair *Patient selection:* Prospective: no Consecutive: no (states consecutive but retrospective) Explicit selection criteria: no *PET protocol: yes* *Reference standard:* • Valid: yes (median follow-up 17.6 months, range 4.5–33.6 months) • Applied to all participants: yes

	Reference standard: • Biopsy • Follow-up	PET/CT an average of 8 weeks (range 4–15.7 weeks) after completing chemoradiotherapy		*Test interval in days/weeks:* • Reference standard: yes • Comparator: yes *Tests reported blinded to ref standard: NR* *Ref standard reported blinded to tests: NR* *Routine clinical data available: yes* *Analysis:* Uninterpretable/intermediate results reported: yes Study withdrawals explained: n/a Sufficient data for 2 x 2 table: yes Applicability: applicable *Applicable population: yes.* *Applicable comparator: yes* *Applicable intervention: yes*

Author (year) **Country** **Setting** **N**	**Study objective and design**	**Study population**	**Results**	**Study quality and applicability**
Yao et al. (2005) US Single centre	Objective To assess the role of PET in decision- making for neck dissection after primary radiotherapy	Inclusion criteria Patients with primary cancer treated by definitive radiotherapy (with or without chemotherapy)	Detection of residual disease Patients with residual disease on CT/MRI and positive PET (n=7) 6/7 patients had neck dissection 1 patient had FNA	Quality: fair *Patient selection:* Prospective: no Consecutive: no Explicit selection criteria: no

1999–2004 N=53 (70 hemi-necks) N=28 (hemi-necks/patients with residual lymphadenopathy based on CT/MRI findings)	Study design Accuracy study *Index test::* FDG–PET *Comparator test:* • Clinical evaluation • CT • MRI *Reference standard:* • Biopsy • Neck dissection • Follow-up	Patient characteristics (n=53) Median age 55.5 years (range 35–77 years) 43 males (81%), 10 females All patients underwent post-treatment PET at a median of 15 weeks (range 5–29 weeks) after completing chemoradiotherapy	PET: TP 3, FP 4, PPV 43% Patients (hemi-necks) with residual disease on CT/MRI and negative PET (n=21) 4/21 had neck dissection 4/21 FNA 13/21 had clinical follow-up Sensitivity and Specificity 100%, 84%, PET: TN– 21, FN–0 NPV–100% LR+ 6.3, LR– 0 Unclear in the text when talking about hemi-necks and/or patients	*PET protocol: yes* *Reference standard:* • Valid: yes (median follow-up 26 months, range 12–57) • Applied to all participants: yes *Test interval in days/weeks:* • Reference standard: yes • Comparator: yes *Tests reported blinded to ref standard: NR* *Ref standard reported blinded to tests: NR* *Routine clinical data available: yes* *Analysis* Uninterpretable/intermediate results reported: yes Study withdrawals explained: n/a Sufficient data for 2 x 2 table: yes Applicability: applicable *Applicable population: yes, suspicious and non-suspicious lesions.* *Applicable comparator: yes* *Applicable intervention: yes*

Author (year) Country Setting N	Study objective and design	Study population	Results	Study quality and applicability
Yao et al. (2007) US Single centre NR N=23 (24 hemi-necks)	Objective To assess whether PET can predict the pathology status of residual lymph nodes in patients who have undergone definitive treatment Study design Accuracy study *Index test:* FDG–PET *Comparator test:* • Clinical evaluation • CT *Reference standard:* • Biopsy • Neck dissection • Follow-up	Inclusion criteria Patients with primary cancer treated by definitive radiotherapy (with or without chemotherapy); post-treatment PET and CT studies and at least one residual lymph node larger than 1.0 cm with pathological evaluation (neck dissection or FNA) Patient characteristics (n=23) Median age 52.5 years (range 35–77 years) 22 males (96%), 1 female All patients underwent post-treatment PET and CT at a median of 13 weeks (range 6–26 weeks) after completing radiation	Detection of residual disease Correlation of PET with pathology PET: TP 5, FP 6, PPV 45% TN 13, FN 0 NPV 100% Sensitivity and specificity 100%, 68%, LR+3.2, LR– 0 Secondary criteria SUV <3.0 (PET negative) PET: TP 5, FP 3, PPV 63% TN 16, FN 0 NPV 100% Sensitivity and specificity 100%, 84%, LR+ 6.3, LR– 0 Analysis based on number of hemi-necks rather than patients (one patient had bilateral disease)	Quality: fair *Patient selection:* Prospective: no Consecutive: no Explicit selection criteria: yes *PET protocol: no* *Reference standard:* • Valid: yes (median follow-up 26 months, range 12–57 • Applied to all participants: yes *Test interval in days/weeks:* • Reference standard: yes • Comparator: yes *Tests reported blinded to ref standard: NR* *Ref standard reported blinded to tests: NR* *Routine clinical data available: yes* *Analysis* Uninterpretable/intermediate results reported: yes Study withdrawals explained: n/a Sufficient data for 2 x 2 table: yes

				Applicability: applicable *Applicable population: yes* *Applicable comparator: yes* *Applicable intervention: yes*

Metastatic squamous cell carcinoma involving cervical nodes from an unknown primary site

Author (year) **Country** **Setting** **N**	**Study objective and design**	**Study population**	**Results**	**Study quality and applicability**
Silva et al. (2006) UK Single centre 1999 – 2003 N=25	Objective To assess use of FDG–PET in patients with unknown head and neck squamous primary Study design Accuracy study with incremental information of PET *Index test:* FDG–PET • GE Advance PET system *Comparator test:* • Clinical evaluation • Biopsy • CT or MRI *Reference standard:* • Biopsy	Inclusion criteria True unknown primary, with no evidence of any primary malignancy either radiographically (CT, MRI) or by clinical evaluation Patient characteristics NR	Incremential information of PET PET positive in 9/25 cases: • TP: 3/9 • FP: 6/9	Quality: fair *Patient selection:* Prospective: yes Consecutive: NR Explicit selection criteria: yes *PET protocol: yes* *Reference standard:* • Valid: yes (min follow-up period 10 months) • Applied to all participants: yes *Test interval in days/weeks:* • Reference standard: NR • Comparator: NR *Tests reported blinded to ref standard: NR* *Ref standard reported blinded to tests: NR* *Routine clinical data available: no* *Analysis*

	• Follow-up			Uninterpretable/intermediate results reported: no Study withdrawals explained: no Sufficient data for 2 x 2 table: yes Applicability: applicable *Applicable population: yes* *Prior tests:* yes *Applicable comparator: yes* *Applicable intervention: yes*

Author (year) **Country** **Setting** **N**	**Study objective and design**	**Study population**	**Results**	**Study quality and applicability**
Wartski et al. (2007) France Single centre 2002–2005 N=38	Objective To assess use of FDG–PET in patients with unknown head and neck squamous primary Study design Accuracy study with incremental information of PET (including some therapeutic information) *Index test:* FDG–PET/CT *Comparator test:* • Clinical evaluation • Biopsy	Inclusion criteria Patients with cervical metastases, with no evidence of any primary malignancy either radiographically (CT, MRI) or by panendoscopy, clinical evaluation (systematic palpation, fibre-optic laryngoscopy and nasopharyngoscopy) Patient characteristics Median age 57 years (range 36–80 years) 31 males (82%), 7 females Histology Squamous cell carcinoma (32) Undifferentiated carcinoma (4) Mucoepidermoid carcinoma (2)	Incremential information of PET PET positive in 26/38 cases: Pathological analysis of the potential primary site was only available in 17 patients Nine patients could not undergo a second panendoscopy due to health status • TP: 13/17 • FP: 4/17 Impact of PET on patient management In 23 patients, PET–CT provided additional information which altered the treatment plan	Quality: fair *Patient selection:* Prospective: no Consecutive: yes (states consecutive but retrospective so unclear) Explicit selection criteria: yes *PET protocol: yes* *Reference standard:* • Valid: yes • Applied to all participants: no (only 17 patients had histological verification) *Test interval in days/weeks:* • Reference standard: NR • Comparator: yes

	• CT or MRI • Panendoscopy *Reference standard:* • Panendoscopy (biopsy) • Follow-up		12/23 had targeted radiotherapy 8/23 had surgery 3/23 had palliative treatment In the group with confirmed histology (n=13) 8 had surgery 3 had targeted radiation 2 had palliative chemotherapy	*Tests reported blinded to ref standard: NR* *Ref standard reported blinded to tests: NR* *Routine clinical data available: yes* *Analysis* Uninterpretable/intermediate results reported: NR Study withdrawals explained: no Sufficient data for 2 x 2 table: no (because of reference standard) Applicability: applicable *Applicable population: yes* *Applicable comparator: yes* *Applicable index test: yes*

Author (year) **Country** **Setting** **N**	**Study objective and design**	**Study population**	**Results**	**Study quality and applicability**
Miller et al. (2008) US Single centre Recruitment period: NR N=31	Objective To assess PET/CT in primary tumour identification in patients with cervical lymph node metastases of unknown primary site Study design Accuracy study	Inclusion criteria Cervical lymph node metastases of unknown primary site Patient characteristics Mean age 60.5 years, range 39–81 years 27 males (87%), 4 females	Detection of primary tumour (biopsy confirmed) PET: 9/31 (28%) It is reported that there is one false-positive PET study (1/31). Five additional patients with a negative PET scan had the primary detected on panendoscopy	Quality: fair *Patient selection:* Prospective: NR Consecutive: yes Explicit selection criteria: yes *PET protocol: no* *Reference standard:*

	Index test: Whole-body FDG–PET/CT *Comparator test:* Tumour work-up • CT • MRI • Chest x-ray • Endoscopic exploration *Reference standard:* Biopsy	All patients had PET prior to panendoscopy	PET + panendoscopy 14/31 (45%)	• Valid: yes • Applied to all participants: yes *Test interval in days/weeks:* • Reference standard: NR • Comparator: NR *Tests reported blinded to ref standard: NR* *Ref standard reported blinded to tests: NR* *Routine clinical data available: yes (PET read in conjunction with panendoscopy)* *Analysis* Uninterpretable/intermediate results reported: NR Study withdrawals explained: yes Sufficient data for 2 x 2 table: yes Applicability: limited *Applicable population: no* *Prior tests*: PET prior to panendoscopy *Applicable comparator: no* *Applicable intervention: yes*

Therapeutic impact data

Author (year) Country Setting N	Study objective and design	Study population	Results	Study quality and applicability
Ha et al. (2006) US Single centre July 2000–January 2005 N=36	Objective To assess whether the addition of PET–CT, compared with CT or MRI alone, contributed to the treatment planning process Study design Therapeutic impact study Treatment plans generated using clinical information (physical examination, conventional diagnostic testing). Then, PET–CT results were revealed, and new PET–CT-informed clinical assessments and treatment plans were generated *Index test:* • FDG–PET/CT *Comparator test:* • Clinical examination • Contrast-enhanced CT or MRI *Reference standard:* • Histopathology (in 18 patients)	Inclusion criteria Patients initially seen for evaluation of suspected head and neck squamous cell cancer Exclusion criteria • Non-squamous cell malignancies • Previous treatment for the suspected lesions Patient characteristics 28 males (78%), 8 females Patients with confirmed treatment (n=25): Mean age 58.3 years, range 17–81 years Patients with altered treatment (n=11): Mean age 59.2 years, range 40–80 years	PET–CT findings • Detection of additional pathologic neck lymphadenopathy: 7 • Identification of unknown primary: 1 Impact of PET on patient management In 11 (31%) patients, PET–CT provided additional information which altered the treatment plan 6/11 had disease upstaged Treatment plan alterations included addition of chemotherapy or radiotherapy so that multimodality approach was favoured In 4 of 8 early-stage and in 7 of 28 advanced-stage lesions, initial stage was altered	Prospective: no Explicit criteria: yes Consecutive patients: no Referring clinician: no Accuracy: no Plans independently assessed: no Blinding to study results: yes Management change independent: unclear Specific test use: yes Explicit outcomes: no Patient outcomes: no Physician experience: no Applicability: limited *Applicable population:* unclear *Applicable comparator: yes* *Applicable intervention: yes*

Author (year) Country Setting N	Study objective and design	Study population	Results	Study quality and applicability
Connell et al. (2007) Australia Single centre January 2002–December 2003 N=76 (TI information for n=35 patients with PET/CT for primary staging of head and neck cancer included)	Objective To prospectively determine the incremental value of PET/CT over standard assessment, in 3 clinical scenarios: staging, post-treatment assessment of response, ongoing follow-up Study design Therapeutic impact study (including some accuracy information) Prospective documentation of pre-PET TNM classification and intended management plans. PET/CT results read in concert with all available information (including CT or MRI) *Index test:* FDG–PET/CT • Neck, thorax, abdomen, pelvis *Comparator test:* • History, physical exam, fiberoptic endoscopy • CT or MRI (in71/76 patients) *Reference standard:* • Histopathology, but commonly not obtained	Inclusion criteria • Primary head and neck squamous cell carcinoma • Contemporaneous conventional assessment • Minimum follow-up 12 months after PET/CT Exclusion criteria • Nasopharyngeal cancer Patient characteristics 70% males, median age 59 years (range 21–83 years) (only reported for all 76 patients)	PET–CT findings • 12/35 (34%) patients with change in TNM classification • 2 patients downstaged (N-staging) • 10 patients upstaged (one T-staging, 8 N-staging, 1 M-staging) Impact of PET on patient management • High impact in 4/35 (11%) patients: changed treatment modality • Medium impact in 10/35 (29%) patients: treatment modality unchanged, but RT planning technique or dose altered: - 7/35 patients: increase in high-dose volume due to nodal or primary upstaging - 1/35 patient: reduction in volume due to nodal downstaging - 1/35 patient: parallel-opposed field (parotid) irradiated due to nodal upstaging - 1 patient: unilateral RT due to exclusion of contralateral nodes	Quality: fair Prospective: no Explicit criteria: yes Consecutive patients: no Referring clinician: yes Accuracy: no Plans independently assessed: no Blinding to study results: yes Management change independent: no Specific test use: yes Explicit outcomes: yes Patient outcomes: no Physician experience: no Applicability: applicable *Applicable population: unclear* *Applicable comparator: yes* *Applicable intervention: yes*

Author (year) Country Setting N	Study objective and design	Study population	Results	Study quality and applicability
Ware et al. (2004) Australia Single centre October 1996–August 1999 N=53	Objective To examine the use of PET in the evaluation of patients after definitive therapy for head and neck SCC Study design Therapeutic impact study (including some accuracy information) Prospective documentation of pre-PET TNM classification and intended management plans for 40 patients (75%). In 13 patients the pre-PET plan was left blank and was determined by the authors in conjunction with clinical evidence and protocols *Index test:* FDG–PET/CT *Comparator test:* • Clinical examination • CT or MRI *Reference standard:* • Histopathology biopsy follow-up	Inclusion criteria • Primary head and neck squamous cell carcinoma • Completed definitive therapy • PET was performed more than 6 weeks after surgery and more than 2 months after radiotherapy Patient characteristics NR	Impact of PET on patient management • High impact in 21/53 patients: changed treatment modality Pre-PET 17 patients were planned to have surgery Post-PET - 14 were observed - 1 invasive diagnosis - 1 palliative chemotherapy - 1 supported care In this group all 14 patients who avoided surgery had a negative PET scan. Pre-PET 2 patients were planned to have invasive diagnosis or surgery and radiotherapy Post-PET - 2 were observed Pre-PET 2 patients were planned to have radical or palliative radiotherapy Post-PET - 1 was observed - 1 radical radiotherapy • Low impact (consistent—not changed) in 17/53 patients No impact (PET inconsistent—no change) 15/53 patients	Quality: fair Prospective: no Explicit criteria: yes Consecutive patients: no Referring clinician: yes in 75% of patients. Accuracy: yes Plans independently assessed: yes but only in subset Blinding to study results: yes Management change independent: yes Specific test use: yes Explicit outcomes: yes Patient outcomes: yes Physician experience: no Applicability: applicable *Applicable population: yes* *Prior tests*: yes *Applicable comparator: yes* *Applicable intervention:yes*

Appendix J Results from Australian data collection

Author (year) Country Setting N	Objectives	Study population	Management quality and applicability
Scott et al. (2007) Australia 3 sites: Victoria, New South Wales, South Australia 32 referring clinicians December 2003–December 2006	Primary objective: To determine the impact of PET in changing initial management plans in patients with head and neck cancer Secondary outcomes: • To document the effect on treatment outcomes • To confirm the importance of PET in staging and follow-up of patients with head and neck cancer • To determine the incremental information provided by PET in staging patients with head and neck cancer	Inclusion criteria: • Previously untreated carcinoma of the nasal cavity, nasopharynx, oral cavity, oropharynx, hypopharynx or larynx, *or* metastatic disease involving cervical lymph nodes from an unknown primary • ECOG performance status of ≤ 2 • Able to undergo study procedures/treatment • ≥ 18 years of age • Available for follow-up for at least 12 months after treatment • Able to provide informed consent Exclusion criteria: • Previous surgical resection for head and neck cancer • Previous radiotherapy for head and neck cancer • Concurrent active cancer, except treated non-melanoma skin cancer or carcinoma in situ of the cervix. (In general, patients with previously treated cancers that had been in remission for ≥ 5 years were eligible.) • Symptomatic or radiological evidence of distant metastatic disease • Concurrent treatment with any other anti-cancer therapy • Uncontrolled diabetes mellitus • Pregnant at the time of PET scan/s • Unable to provide informed consent	Prospective: yes Explicit criteria: yes Consecutive patients: NR Referring clinician: yes Accuracy: no Plans independently assessed: NR Blinding to study results: no Explicit outcomes: yes Patient outcomes: yes Physician experience: NR

RESULTS:

Patients with known primary tumour (n=56)

Before PET

RT planned: 51/56 patients (91%)

ChT planned: 31/56 patients (55%)

Surgery planned: 12/56 patients (21%)

Treatment intent: curative in 55/56 patients (98%)

TNM staging

		N stage						
		0	1	2	2b	2c	X	Total
T stage	1	2	3	2	0	0	1	8
	2	12	1	5	1	0	0	19
	3	4	2	2	0	1	0	9
	4	5	6	1	2	2	0	16
	X	2	0	1	0	0	1	4
	Total	25	12	11	3	3	2	56

		Frequency	Per cent
M stage	0	49	87.50
	1	1	1.79
	X	6	10.71

After PET—all patients (n=56)

PET detected additional lesions in 20/56 patients (36%). A total of 31 additional lesions were detected, of these 2 were second primary tumours (in 2 patients), 22 lymph node metastases (15 patients), 7 distant metastases (5 patients).

Treatment intent changed from curative to palliative in 6/56 patients (11%; 95% CI: 4–22%), from palliative to curative in 1 patient (2%; 95% CI: 0–10%).

Overall, management plans changed in 18/56 patients (32%; 95% CI: 20–46%)..

After PET—patients with additional lesions detected (n=20)

In the 20 patients where PET detected additional lesions, treatment intent changed from curative to palliative in 4/20 (20%; 95% CI: 6–44%), from palliative to curative in 1/20 (5%; 95% CI: 0–25%).

TNM staging

- T-staging unchanged in 19/20 cases (from TX to T3 in one case)
- N-staging unchanged in 11/20 cases (changed from N0 to N1 in 4 cases; N0 to N2 in 2 cases; N0 to N2c in 1 case; N1 to N2 in 1 case; N2 to N1 in 1 case)
- M-staging unchanged in 14/20 cases (changed from MX to M0 in 3 cases; MX to M1 in 1 case; M1 to M0 in 1 case; M0 to M1 in 1 case).

Management changes

In the 20 patients where PET detected additional lesions, management plans changed in 14/20 patients (70%; 95% CI: 46–88%; P<0.001 Fisher's exact test vs no additional lesions):

- RT was added in 2 cases (instead of surgery in one case)
- RT *dose* was decreased in 3 cases, and increased in 1 case
- RT *field* was decreased in 2 cases and increased in 6 cases
- RT *dose or field* were changed in 8/20 patients (40%, P=0.02 Fisher's exact test vs no additional lesions)
- ChT was abandoned in 2 cases, but added in 3 cases
- Surgery was abandoned in 2 cases, added in 1 case and changed in 1 case (local resection of tongue base extended to neck dissection).

Distant metastases

In the 5 patients with additional distant metastases, the primary tumour was located in the tongue (2 patients), hypopharynx, vocal cord and supraglottic larynx.

Treatment intent was changed from curative to palliative in 2 cases (surgery abandoned/RT instead; RT field and dose decreased/CT added).

In one instance ChT was added, one case was further investigated (lung surgery), in one case treatment was not changed.

After PET—no additional lesions detected (n=36)

In the 36 patients with no additional lesions, treatment intent was changed from curative to palliative in 2/36 patients (6%; 95% CI: 1–19%).

TNM staging

- T-staging unchanged in 33/36 cases (changed from T2 to T1 in 1 case, T3 to T4 in 1 case, T4 to TX in 1 case)
- N-staging unchanged in 33/36 cases (changed from N2 to N1 in 1 case, N2 to N3 in 1 case, NX to N1 in 1 case)
- M-staging remained unchanged in 34/36 cases (all M0), MX to M0 in 2 cases.

Management changes

In the 36 patients with no additional lesions, management plans were changed in 4/36 patients (11%; 95% CI: 3–26%), including:

- ChT abandoned, in combination with RT dose decrease in 2 cases
- RT field increased in one case

- RT field decreased in one case
- RT dose or field were changed in 4/36 patients (11%, P=0.02 Fisher's exact test vs no additional lesions).

Patients with unknown primary tumour (n=15)

Before PET
RT planned pre-PET: 9 patients (60%).
Surgery planned: 10 patients (67%).
ChT planned: 4 patients (27%).

After PET—all patients (n=15)
PET detected additional lesions in 53% (8/15) patients. Of the 12 additional lesions detected, 7 were primary tumours, 5 lymph node metastases.
T-staging was unchanged in 12 cases (80%), changed from X to T1 in 3 cases.
N-staging was unchanged in 13 cases (87%), one case changed from X to N1, one case was downstaged from N2 to N1.
M-staging was unchanged in 14 patients (93%), one case was downstaged from N1 to N0.

Management plans changed in 47% (95% CI: 21–73%) of all patients (7/15). Treatment intent was unchanged in all 15 patients (all curative).

After PET—primary tumour detected (n=7)
In the 7 patients where PET detected the primary tumour, management plans changed in 71% (5/7).

- RT field was increased in 3 cases (in one of these cases, surgery was abandoned)
- RT was added in one case
- In 1 case, further investigation (bronchoscopy) changed to surgery (limited neck dissection).

After PET—no primary tumour detected (n=8)
In the 8 patients with no primary tumour detected, management plans were changed in 25% (2/8)

- RT field was decreased
- parotidectomy was planned in addition to biopsy.

Abbreviations: ChT = chemotherapy, RT = radiotherapy, PET = positron emission tomography

Appendix K Morbidity and mortality of definitive treatments

The morbidity and mortality of head and neck cancer treatment (attributed to surgery and radiotherapy) is described below. Note that these studies were not identified by systematic review.

Surgical morbidity and mortality

Literature addressing the adverse events associated with surgery for head and neck cancers is 'all retrospective and quite sparse' (Trotti 2000). Although surgical complications are not easily quantifiable, due to non-standardised, often ad hoc reporting, they include: dehiscence of incisions, infection, major bleeding, flap/soft tissue/bone necrosis, fistula, stricture, chyle leaks, chronic aspiration/pneumonia and edema. Severe complications (grade 3–4) are expected to occur in 5–10% of patients, and minor complications (grade 1–2) in 10–30% of patients. It is to be noted that salvage neck dissection is associated with a lower complication rate than primary site resection (+/– neck dissection), planned neck dissections (within 3 months of RT) are considered to carry a lower risk than delayed dissections, and previously irradiated patients are expected to have complication rates 2–3 times higher than those who undergo surgery alone (Trotti 2000).

Radiotherapy morbidity and mortality

Radiotherapy for head and neck cancers is associated with toxicity and several adverse outcomes for patients. Specifically, treatment intensification and dose accumulation are associated with severe (grade 3 and 4) adverse events such as: mucositis, weight loss, pain, and dermatitis (Trotti et al. 2003). The addition of chemotherapy is expected to result in worsening of these adverse events including dysphagia (Palazzi et al. 2008; Trotti et al. 2003). Radiation is expected to have a negative impact on patient functioning, notably swallowing (Robbins 2002). Radiotherapy is associated with a reduction in salivary flow which can lead to xerostomia, increased risk of dental caries, oral candidiasis, and difficulty chewing, swallowing and speaking (Bussels et al. 2004). Parotid sparing is used when possible to allow patients to retain some of this functioning post-radiotherapy (Advisory Panel expert advice). Irradiation of the thyroid is associated with an increased risk of thyroid dysfunction (hypo- and hyper-thyroidism) and thyroid cancer (Advisory Panel expert advice).

Appendix L Results of PET cost data study

Results of the recent Australian PET cost data study (ANZAPNM 2007) are summarised in Table 44. Total costs per scan by labour and non-labour costs are reported by site for 2005–2006 for a standard whole body scan (used in staging of recurrent ovarian cancer) and long whole body scan.

Table 44 Standard and long whole body PET scan costs

Site	Standard whole body scan Costs per scan in A$ for 2005–2006			Long whole body scan Costs per scan in A$ for 2005–2006		
	Total	Non-labour	Labour	Total	Non-labour	Labour
A	958.47	565.53	392.93	1,437.70	848.3	589.4
B	1,878.37	922.64	955.73	2,295.78	1,127.67	1,168.11
C	1,451.56	808.74	642.82	2,903.12	1,617.48	1,285.65
D	1,100.00	668.0	432.0	1,834.00	1,113.00	720.0
E	1,006.14	646.46	359.68	1,175.98	749.49	426.49
F	761.19	559.76	201.42	1,096.11	806.06	290.05
G	2,066.64	1,369.24	697.4	3,718.95	2,463.97	1,254.98
H	899.55	582.12	317.43	1,729.91	1,119.47	610.44
Mean	1,265.24	765.31	499.93	2,023.94	1,230.68	793.14
Median	1,053.07	657.23	412.47	1,781.96	1,116.24	665.22
Std deviation	482.44	275.34	246.49	907.59	568.9	389.91
Maximum	2,066.64	1,369.24	955.73	3,718.95	2,463.97	1,285.65
Minimum	761.19	559.76	201.42	1,096.11	749.49	290.05
Mean+1SD	1,747.68	1,040.65	746.42	2,931.53	1,799.58	1,183.05
Mean–1SD	782.8	489.97	253.43	1,116.35	661.78	403.23
Mean+ 2SD	2,230.12	1,315.99	992.91	3,839.12	2,368.47	1,572.97
Mean– 2SD	300.36	214.63	6.94	208.77	92.89	13.31

Abbreviations

AIHW	Australian Institute of Health and Welfare
CE	Conventional examination
ChT	Chemotherapy
CI	Confidence interval
CL	Confidence limits
CT	Computed tomography
CWU	Conventional Work up
FDG	2-[^{18}F]fluoro-2-deoxy-D-glucose
FN	False-negative
FNA	Fine needle aspiration
FP	False-positive
HNC	Head and neck cancer
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
MBS	Medicare Benefits Schedule
MRI	Magnetic resonance imaging
MSAC	Medical Services Advisory Committee
NCCHTA	National Coordinating Centre for HTA
NHMRC	National Health and Medical Research Council
NPV	Negative predictive value
PET	Positron emission tomography
PPV	Positive predictive value
QALY	Quality adjusted life year
Sn	Sensitivity
Sp	Specificity
SUV	Standardised uptake value

TN	**True-negative**
TP	**True-positive**
US	**Ultrasound**

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