

***Positron emission
tomography for
oesophageal and
gastric 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 recommendations do not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

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Executive summary

The procedure

Positron emission tomography (PET) is a minimally invasive nuclear medicine imaging technique that uses short-lived radiopharmaceuticals to allow perfusion and metabolic activity in various organ systems to be detected and assessed. 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 in oncology relates to the greater uptake of glucose by many malignant tumours than by normal surrounding tissue. However, increased FDG uptake is not specific to malignant cells: inflammatory cells and some benign tumours also take up FDG, and thus inflammatory foci, sarcoidosis, and acute and chronic infections can be positive on PET imaging. FDG-PET alone does not distinguish between these benign conditions and uptake by malignancies. Where FDG-PET is being performed to stage a specific cancer, these findings are considered false-positives. The causes of increased uptake can be differentiated only 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 to provide more accurate anatomic localisation of the distribution of FDG and more efficient attenuation correction than is possible with standalone PET scanners. Standalone 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 oesophageal and gastric 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 oesophageal and gastric cancer (Medical Services Advisory Committee 2001). The previous assessment recommended interim funding for PET for the staging of proven oesophageal or gastric carcinoma, where curative surgery or chemo-radiation is planned. This report provides an assessment of evidence published since the 2001 review to December 2007 and provided in the report of the Australian data collection study (Chatterton 2006) initiated following the MSAC 2001 PET review.

This report assesses FDG-PET performed for the evaluation of oesophageal and gastric cancer. The specific research questions to be addressed are as follows:

1. What is the value of the addition of PET/CT in the assessment of patients with primary cancer of the oesophagus or the gastro-oesophageal junction (GEJ) considered suitable for definitive treatment as determined by conventional staging?
2. What is the value of PET/CT in the assessment of residual oesophageal or GEJ cancer following definitive chemo-radiation considered suitable for salvage surgery, (a) as a replacement for CT in staging biopsy-proven residual disease, or (b) in addition to endoscopy and biopsy where residual disease has not been confirmed?
3. What is the value of the addition of PET/CT in the assessment of patients with biopsy-proven primary gastric cancer considered potentially curable as determined by conventional staging including laparoscopy (with peritoneal cytology)?

A systematic review was conducted to identify evidence to December 2007 that would answer these questions. A recent high-quality health technology assessment (HTA) report from the UK National Coordinating Centre for HTA (NCCHTA) (Facey et al. 2007) was identified. The data from eligible studies provided in this HTA report were used as the basis of the assessment for oesophageal cancer. A systematic review was also undertaken to include more recent studies. No recent HTA report was identified that considered the role of PET in gastric cancer.

Clinical need

Oesophageal and gastric cancers are not common in Australia. In 2003, 1154 reported cases of oesophageal carcinoma were diagnosed in Australia, 765 in males and 389 in females. The overall age-standardised rate in 2003 was 5.6/100 000, an increase from 4.9/100 000 in 1983. Oesophageal cancer was responsible for 1147 deaths in 2005 (791 in men and 356 in women), equating to an overall age-standardised mortality in Australia of 5.3/100 000.

In 2003, 1873 new cases of gastric carcinoma were reported in Australia, 1216 in males and 657 in females. The overall age-standardised rate was 9.2/100 000, a decrease from 15.8/100 000 in 1983. Gastric cancer was responsible for 1090 deaths in 2005, equating to an overall age-standardised mortality in Australia of 5.0/100 000.

Safety

PET and PET/CT are considered safe procedures. Patients undergoing PET/CT will have additional radiation exposure (at low doses) to that from PET alone, 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 oesophageal and gastric cancer is in the exclusion of patients unlikely to benefit from therapy with curative intent or salvage surgery. The use of PET as an additional test may achieve this by detecting distant metastases that are likely to preclude definitive therapy.

Direct evidence

No direct evidence was found reporting the health outcomes of patients with oesophageal or gastric 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.

Accuracy

Oesophageal cancer primary staging

Data from the UK NCCHTA report (Facey et al. 2007) indicated that the sensitivity of PET for detecting distant metastases from oesophageal cancer is lower than that for other cancers but somewhat better than that of CT.

Four studies provided data on the incremental value of PET over that of CT in patient groups applicable to the clinical question of staging primary oesophageal cancer. Two studies were conducted in fewer than 50 patients, with positive PET results in only 4 and 6 patients. In the four studies, PET was positive (true- or false-positive) in 14 to 18 per cent of patients. One fair-quality study conducted in 189 patients (PET-positive in 34) indicated that the positive predictive value (PPV) for detecting additional metastases was 57 to 63 per cent. Another fair-quality study conducted in 199 patients (30 PET-positive) indicated that the PPV for detecting metastases from oesophageal cancer was 27 per cent, and synchronous neoplasms were also detected in 23 per cent of the patients with a positive PET result (3.5% of all patients).

The available evidence indicates that the addition of PET to the conventional staging pathway increases the detection of distant metastases from primary oesophageal cancer. However, this is also associated with an increase in the number of false-positive findings. PET/CT may have had a lower false-positive rate than PET alone, but no studies reporting the accuracy of PET/CT as an additional test were identified.

Oesophageal cancer residual disease

No studies reporting the accuracy of PET in assessing residual disease following definitive (not neoadjuvant) chemo-radiation were identified in the UK HTA report (prospective studies) or in the systematic review of primary prospective or retrospective studies published since August 2005.

Gastric cancer primary staging

Pre-PET staging of gastric cancer with CT will detect some hepatic metastases, distant nodal metastases and significant ascites that may indicate peritoneal metastases. Pre-PET staging with laparoscopy is expected to identify additional small-volume peritoneal and hepatic metastases from gastric cancer. The three most frequent sites of gastric cancer metastases are the liver, abdominal lymph nodes and peritoneum. Thus, the proportion of gastric cancer patients with stage IV disease and no metastases detected on laparoscopy or CT is expected to be small. No studies reporting the accuracy of PET or PET/CT following laparoscopy (with or without CT) were identified.

Impact on patient management

Oesophageal cancer primary staging

A prospective Australian data collection study (Chatterton 2006) provided information on the use of PET in 133 patients from 5 Australian PET facilities between 2004 and 2006. Patients with biopsy-proven cancer of the oesophagus or the GEJ and no distant metastatic disease found on conventional staging were included. PET detected distant metastases in 24 per cent of all patients (31/129; 95% CI 17%–32%).

This study reported that PET led to changed management plans in a total of 38 per cent (95% CI 30%–46%) of patients, 27 per cent (95% CI 20%–36%) due to a PET-positive result for regional or distant metastases. Surgery was avoided in 19 per cent (95% CI 12%–26%) of all patients, or 26 per cent (24/94; 95% CI 17%–36%) of those in whom surgery had been planned before PET. A positive PET result for regional or distant metastases led to a change in treatment intent from curative to palliative in 20 per cent (95% CI 14%–28%) of patients. Actual management at 6 months' follow-up was concordant with the post-PET management plan in 52 per cent, and was consistent with PET results in an additional 11 per cent.

Two smaller published studies identified in the systematic review reported that surgery was avoided in 2 and 6 per cent of patients (Duong et al. 2006a; McDonough et al. 2007). A retrospective cohort study with historical control reported that patients staged with CT and endoscopic ultrasound (EUS; in 1997) or CT+EUS+PET (during 1998–2002) underwent unnecessary explorations (including laparotomy and thoracotomy) in 50 per cent (18/36) and 21 per cent (13/61) of cases, respectively. However, studies of this design are prone to bias, making interpretation of these results difficult.

The identified studies provide evidence that the use of PET in patients with primary oesophageal cancer leads to changes in the management of a substantial proportion of patients. The most frequent major change was the avoidance of planned surgery. There is uncertainty regarding the magnitude of these effects due to inevitable biases inherent in studies of this type.

Oesophageal cancer residual disease

A single Australian study (Duong et al. 2006b) reported an impact of PET on treatment intent or modality in 36 per cent of patients following chemo-radiotherapy (CRT). The proportion of patients who had received definitive CRT was unclear. However, in the absence of evidence for the accuracy of PET for assessing residual disease, the proportion in whom the management change was based on a correct PET finding cannot be inferred.

Gastric cancer primary staging

No studies reporting the therapeutic impact of PET in staging patients with gastric cancer were identified.

Impact on health outcomes

Where the use of PET improves diagnostic accuracy, it should improve outcomes for patients if it results in more appropriate management. Evidence for the incremental accuracy of PET over conventional imaging for assessment of residual disease following definitive chemo-radiation for oesophageal cancer and for staging gastric cancer following CT and laparoscopy was not identified. Therefore, a case for linked evidence for an improvement of patient outcomes due to PET in these indications cannot be made.

Comparative studies of definitive versus palliative therapies for oesophageal cancer patients with PET-detected, CT-occult sites of metastatic disease (ie, PET-positive, CT-negative) were not identified.

The main role of PET for pretreatment staging of patients with primary oesophageal cancer otherwise considered curable is to identify other disease sites that would preclude definitive treatment. In lieu of definitive surgery and/or chemo-radiation, most patients will receive palliative chemo-radiation. Therefore the main treatment change likely to follow PET is the avoidance of oesophagectomy. In addition, patients are likely to receive less intensive regimens of chemo-radiation.

Patients avoiding oesophagectomy will avoid the risk of surgical complications and the impact of surgery on quality of life (pain, time in hospital, recovery after discharge) associated with resection that is unlikely to provide long-term benefit. In the absence of clinical trials comparing alternative therapies in these patients, it is not known whether the potential improvement in quality of life from avoiding surgery and instigating alternative management outweighs any potential benefit of surgery in providing local disease control.

Nevertheless, surgery is likely to be less beneficial in patients with additional metastases detected on PET than in patients with no additional sites of disease. Whilst there is no direct evidence of a benefit on patient outcomes, the expert opinion of the advisory panel was that aggressive surgical treatment is unlikely to be beneficial in these patients.

Economic considerations

A cost-consequence analysis was conducted to estimate the incremental costs and consequences (changes in management, health outcomes) associated with PET for staging primary oesophageal cancer.

The decision-analytic model was limited to an assessment of short-term costs and consequences of PET, instigated treatment and follow-up. The longer-term health outcomes and cost implications of PET were not investigated (eg, the costs associated with longer-term symptomatic management of unresected disease). Information on the cost of PET from an Australian PET cost data study (ANZAPNM 2007) was used in this analysis (median: \$1053; range: \$761–\$2067).

The decision-analytic model of PET in staging of patients with primary oesophageal cancer showed that PET would lead to the avoidance of radical treatment not considered to be of long-term benefit in an average of 6 per 100 patients (95% CL 4–9), which would include surgery (\pm [neo]adjuvant therapy) in 5 (95% CL 3–7). This leads to the avoidance of surgical complications in 2 (95% CL 1–3) patients per 100, and surgical mortality in 4 (95% CL 3–6) per 1000 patients. Conversely, PET may result in potentially detrimental health outcomes through incorrect upstaging in an average of 3 per 100 patients (95% CL 2–5), who would have missed the opportunity for potentially curative definitive treatment, and in 6 per 100 patients (95% CL 4–8), who would have had a delay in definitive treatment following restaging at follow-up biopsy. A proportion of these patients may have had a synchronous non-oesophageal neoplasm identified by PET.

The analysis showed that these health outcomes would be associated with lower costs of \$159 351 (95% CL \$348 730–\$13 125) per 100 patients. Sensitivity analysis considering a second PET scan in patients undergoing definitive treatment indicated a reduced cost saving of \$128 617 (95% CL \$328 135 to an additional \$23 200). True-positive and false-positive findings that are not proven on biopsy (35% of false-positives) are both associated with cost offsets through the avoidance of radical treatment.

Uncertainties exist around the extent of modelled health benefits and cost savings. The wide confidence limits around the results reflect the uncertainty in model input parameters. In particular, it is unclear whether the use of PET translates to overall health benefits in terms of quality-adjusted life years. Thus, an incremental cost-effectiveness ratio (ICER) allowing comparison of the cost-effectiveness of PET against other technologies could not be provided. Whilst PET is likely to be cost saving for these indications, there is uncertainty associated with the overall health outcomes.

The results of the decision-model analysis are comparable to data obtained for patients planned for definitive treatment enrolled in the Australian data collection study. Ninety-two per cent of patients were considered potentially curable before undergoing PET in this study. The cost and consequences of PET in patients planned for palliative treatment remain unknown. However, the cost-consequence profile of PET may be less favourable in this setting, as avoidance of treatment with curative intent is likely to provide the greatest cost offset.

Calculated estimates of net financial impact (costs to the total health care system) vary widely. Considering modelled incremental costs and the proportion of patients planned for definitive treatment in the Australian study, there are potential net cost savings to the health care system. Mean net financial cost savings range from approximately \$821 000 to \$1 539 000 depending on utilisation. The net financial impact in patients planned for palliative therapy remains unknown.

If PET were reimbursed in Australia according to the range of cost estimates from the Australian cost study, the potential annual total cost to the Medicare Benefits Schedule (MBS) could range between \$590 000 and \$1 106 000, depending on utilisation (estimated at between 560 and 1050 patients per year). This estimate does not include a forecast of future population growth or changes in incidence.

Conclusions

The use of PET in addition to conventional staging for patients with primary oesophageal cancer is considered

- safe
- to increase the detection of distant metastases from primary oesophageal cancer, in association with an increase in the number of false positive findings for metastatic disease
- to identify synchronous neoplasms
- to lead to changes in patient management, most commonly the avoidance of surgery
- to lead to the avoidance of surgical morbidity and mortality in patients who avoid oesophagectomy. Expert opinion is that this leads to improved patient outcomes in terms of quality of life, but definitive evidence for whether this outweighs any potential benefit of surgery is lacking
- cost saving in patients according to decision analytic modelling of short-term costs, due to the avoidance of treatments with curative intent following both true-positive and false-positive results.

Evidence for the use of PET in addition to conventional staging in the assessment of residual disease following definitive chemo-radiation is lacking.

Evidence for the use of PET in addition to conventional staging including laparoscopy in the staging of gastric cancer is lacking.

Advice

(i) MSAC has considered the safety, effectiveness and cost-effectiveness for positron emission tomography (PET) and PET/CT for the assessment of patients with primary cancer of the oesophagus or the gastro-oesophageal junction (GEJ) otherwise considered suitable for definitive treatment.

- MSAC finds PET is safe.

- MSAC finds that the addition of PET to the conventional staging of primary cancer of the oesophagus or the GEJ is clinically effective.
- MSAC finds that the addition of PET to the conventional staging of primary cancer of the oesophagus or the GEJ is likely to be cost saving.
- MSAC recommends public funding for the assessment of patients with primary cancer of the oesophagus or the gastro-oesophageal junction (GEJ) considered suitable by conventional staging for definitive treatment.

(ii) MSAC has considered the safety, effectiveness and cost-effectiveness for positron emission tomography (PET) and PET/CT for the assessment of residual oesophageal or GEJ cancer following definitive chemoradiation.

- MSAC finds PET is safe.
- MSAC finds that there are insufficient data to evaluate the effectiveness of PET for the assessment of residual oesophageal or GEJ cancer following definitive chemoradiation considered suitable for salvage surgery.
- A formal economic assessment was, therefore, not performed.
- MSAC does not recommend public funding for the use of PET in the assessment of residual oesophageal or GEJ cancer following definitive chemoradiation.

(iii) MSAC has considered the evidence for safety, effectiveness and cost-effectiveness for positron emission tomography (PET) and PET/CT in addition to conventional staging including laparoscopy for the assessment of patients with biopsy proven primary gastric cancer otherwise considered potentially curable.

- MSAC finds PET is safe.
- MSAC finds that there are insufficient data to evaluate the effectiveness of PET assessment of patients with biopsy proven primary gastric cancer considered potentially curable.
- A formal economic assessment was therefore not performed.
- MSAC does not recommend public funding for the use of PET in the assessment of patients with biopsy proven primary gastric cancer otherwise considered potentially curable.

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of positron emission tomography (PET), a non-invasive technology used for the diagnosis and staging of a variety of malignancies. MSAC evaluates new and existing diagnostic technologies and procedures for which funding is sought under the Medicare Benefits Scheme 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, based on reviews of the scientific literature and other information sources, including clinical expertise.

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

This report updates the previous assessment of evidence for FDG-PET imaging in oesophageal and gastric cancer (Medical Services Advisory Committee 2001). The previous assessment recommended interim funding for PET for the staging of proven oesophageal or gastric carcinoma, where curative surgery or chemo-radiation is planned. This report provides an assessment of evidence published since the 2001 review to December 2007 and provided in the report of the Australian data collection study (Chatterton 2006) initiated following the MSAC 2001 PET review.

Background

Positron emission tomography (PET)

PET is a minimally invasive nuclear medicine imaging technique that uses short-lived radiopharmaceuticals to allow perfusion and metabolic activity in various organ systems to be detected and assessed. 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 in oncology relates to the greater uptake of glucose by many malignant tumours than by 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. Semi-quantitative 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 or surface area), 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).

Increased FDG uptake is not specific to malignant cells: inflammatory cells and some benign tumours also take up FDG, and thus inflammatory foci, sarcoidosis, and acute and chronic infections can be seen as positive hot spots 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 cancer, these findings are considered false-positive results. The causes of increased uptake can be differentiated only 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 to provide both metabolic and anatomic information in a single examination. A recent UK National Coordinating Centre for Health Technology Assessment (NCCHTA) review of PET in multiple oncology indications found that PET/CT improved accuracy by 10 to 15 per cent over PET alone, resolving some equivocal images (Facey et al. 2007).

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

A more detailed description of these technologies 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 (HTA) report produced by the NHS in Scotland (Bradbury et al. 2002) canvassed patient views on the assessment of PET in Scotland. The considerations in that 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, and thus few patients had undergone a PET scan, and patient experience did not relate to undergoing a scan 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 Health Technology Board for Scotland's PET report (Bradbury et al. 2002) summarised the following major patient issues:

- PET imaging is likely to be just one part of the diagnostic work-up, so it is important to coordinate 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 of PET imaging, associated risks and counselling, and check that patients understand the information received. Carers also require this information.
- Leaflets with diagrams and clear explanation 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, 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 some patients value highly.

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

A Belgian PET HTA report (Agency KCE 2005) included the following statement in its 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 assesses FDG-PET performed for the evaluation of oesophageal and gastric cancer. The specific research questions to be addressed are as follows:

1. What is the value of the addition of PET/CT in the assessment of patients with primary cancer of the oesophagus or the gastro-oesophageal junction (GEJ) considered suitable for definitive treatment as determined by conventional staging?
2. What is the value of PET/CT in the assessment of residual oesophageal or GEJ cancer following definitive chemo-radiation considered suitable for salvage surgery, (a) as a replacement for CT in staging biopsy-proven residual disease, or (b) in addition to endoscopy and biopsy where residual disease has not been confirmed?
3. What is the value of the addition of PET/CT in the assessment of patients with biopsy proven primary gastric cancer that is considered potentially curable by conventional staging including laparoscopy (with peritoneal cytology)?

Clinical need

Oesophageal cancer

Oesophageal cancers are not common in Australia. The two most frequent types are squamous cell carcinoma (SCC) and adenocarcinoma (AC). Cancers of the GEJ originate from distal oesophageal AC, from carcinoma of the gastric cardia, or subcardially from gastric carcinoma.

A detailed description of the natural history and current treatments for oesophageal cancer is provided in the recent MSAC assessment of endoscopic ultrasound (EUS) (2006). The staging classification system for oesophageal cancer is provided in Appendix E (page 89).

Incidence and mortality

In 2003, 1154 reported cases of oesophageal carcinoma were diagnosed in Australia (AIHW 2007a). Of these, 765 were in males (resulting in an age-standardised rate for Australia of 8.2/100 000; standardised to Australian Standard Population 2001) and 389 were in females (3.4/100 000). The overall age-standardised rate in 2003 was 5.6/100 000 (AIHW 2007a), an increase from 4.9/100 000 in 1983 (AIHW and AACR 2004).

Oesophageal cancer was responsible for 1147 deaths in 2005 (791 in men and 356 in women), resulting in 6983 person-years of life lost before the age of 75 years. This equates to an age-standardised mortality of 8.1/100 000 for men and 2.9/100 000 for

women (standardised to Australian Standard Population 2001). The overall age-standardised mortality for Australia is 5.3/100 000. (AIHW 2007a).

Potential utilisation of PET

Interim funding service utilisation

Over the period 2002–2007, the number of PET scans for oesophageal cancer claimed annually in the seven reimbursed Australian centres (listed under ‘Current reimbursement arrangement’, page 15) increased from approximately 160 to 560 (Figure 1). In the first three quarters of 2007, there were 417 claims for PET scans for the staging of oesophageal carcinoma. These data equate to an estimated 556 scans for 2007.

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.

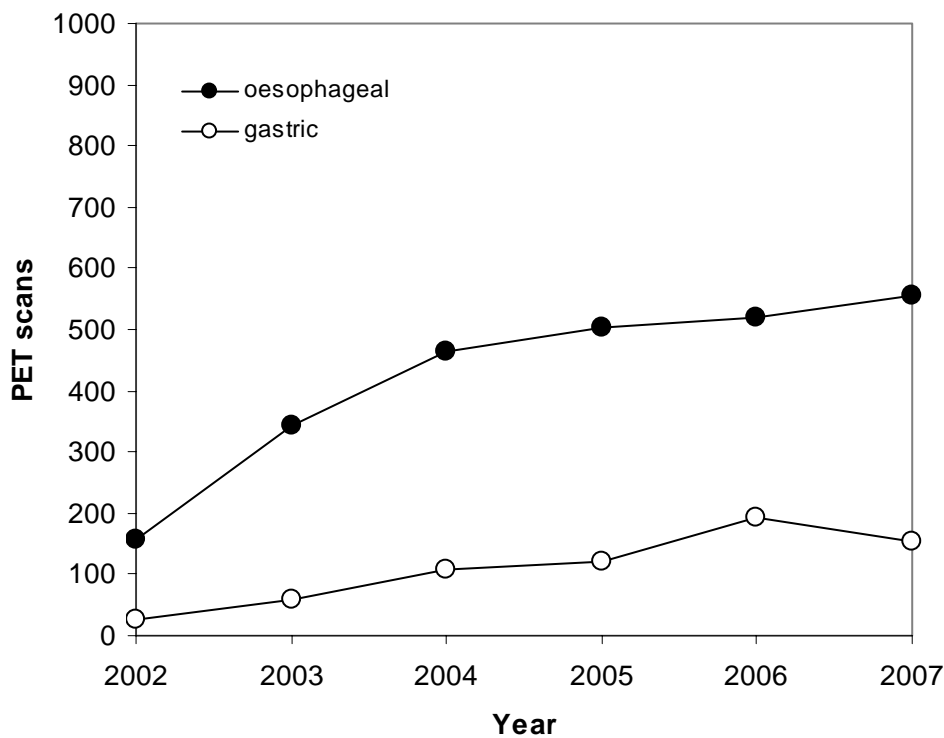


Figure 1 Annual Medicare Benefits Schedule item reimbursement for staging oesophageal cancer (MBS 61577, 61580) and gastric cancer (MBS 61583, 61586)

Epidemiological data

Primary oesophageal cancer staging

An alternative estimate of the potential utilisation of PET in patients with primary oesophageal cancer is presented in Table 1.

For the utilisation of PET in primary staging, the number of new cases of oesophageal cancer in Australia is used (see page 4), and the proportion of patients with distant metastases detected on conventional staging (CT), who are ineligible for PET, is subtracted from this number. Based on data provided in the projected utilisation estimate for EUS presented in the recent MSAC assessment (Medical Services Advisory Committee 2006), the proportion of patients with distant metastases detectable on CT is estimated to be 11.6 to 12.8 per cent. Using these values, the number of patients eligible for primary staging of oesophageal cancer with PET is estimated at approximately 1050 patients per year (Table 1).

Assessment of suspected residual disease

Table 1 also provides an estimate for patients undergoing a second PET scan for the assessment of residual disease after definitive chemo-radiation.

The maximum number of patients undergoing PET for assessment of residual disease would be all patients receiving definitive chemo-radiation (Table 1, line F). This is estimated as 200 to 225 patients annually. This estimate assumes that 14 to 24 per cent of patients undergoing PET are excluded from definitive treatment owing to the finding of distant metastases on PET, and that 25 per cent of patients undergoing definitive treatment undergo definitive chemo-radiation (advisory panel expert opinion).

Oesophageal cancer overall

For both oesophageal cancer indications, the overall estimate of potential PET utilisation ranges from approximately 1200 to 1300 (Table 1).

These estimates do not consider patients excluded from PET and/or definitive treatment owing to other medical reasons, personal preference or results of other diagnostic tests, nor do they consider the impact of forecasting of future population growth or changes in incidence.

Table 1 Estimated PET utilisation for assessment of oesophageal cancer

	Description	Source	Low PET utilisation estimate		High PET utilisation estimate	
			Calculation/ proportion	Patients	Calculation/ proportion	Patients
Patients eligible for PET for staging primary oesophageal cancer						
A	Incidence of oesophageal cancer 2008	2003 Australian age-standardised rate of oesophageal cancer × Australia's population ^a 2008	5.6/100 000 × 21 175 347	1186	5.6/100 000 × 21 175 347	1186
B	Patients with distant metastases identified on CT	MSAC (2006), citing Kato et al. (2005) and Parada et al. (2002)	12.8%	152	11.6%	138
C	Incidence of apparently localised oesophageal cancer 2008	A – B	1186 – 152	1034	1186 – 138	1048
Patients eligible for PET for assessment of residual disease						
D	Patients with distant metastases identified on PET	Yield of PET for distant metastases from studies included in systematic review ^b	24%	248	14%	147
E	Patients undergoing definitive treatment	C – D	1034 – 248	786	1048 – 147	901
F	Patients eligible for definitive chemo-radiation	E × percentage of patients eligible for definitive chemo-radiation if eligible for definitive treatment (25%) ^c	786 × 0.25	197	901 × 0.25	225
Patients eligible for PET for staging primary gastric cancer						
G	Incidence of gastric cancer 2008	2003 Australian age-standardised rate of gastric cancer × Australia's population ^a 2008	9.2/100 000 × 21 175 347	1948	9.2/100 000 × 21 175 347	1948
H	Patients with distant metastases identified on CT	MSAC (2006), citing Jong et al. (2002) and Kayaalp et al. (2002)	21%	409	9%	175
I	Patients with metastases identified on laparoscopy with peritoneal cytology	G × I (Burke et al. 1998) and (Lowy et al. 1996))	43%	838	23%	448
J	Incidence of apparently localised gastric cancer 2008	G – H – I (incidence gastric cancer – patients with stage IV disease identified before PET)	1948 – 409 – 838	701	1948 – 175 – 448	1325

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

a. Source: (ABS 2008)

b. Source: Chatterton et al. 2006, Meyers et al. 2007, Stahl et al. 2005, van Westreenen et al. 2007

c. Source: advisory panel expert opinion

Gastric cancer

Gastric cancer is the second most common cancer worldwide, with a particularly high prevalence in Asia and Latin America. However, it does not have a high prevalence in Australia (AIHW & AACR 2004).

A detailed description of the natural history and current treatments for gastric cancer is provided in the recent MSAC assessment of EUS (Medical Services Advisory Committee 2006). The classification system for staging gastric cancer is provided in Appendix E (page 89).

Incidence and mortality

In 2003, 1873 new cases of gastric carcinoma were reported in Australia (AIHW 2007). Of these, 1216 were in men (resulting in an age-standardised rate of 13.2/100 000; standardised to Australian Standard Population 2001) and 657 were in women (5.8/100 000). The overall age-standardised rate was 9.2/100 000, a decrease from 15.8/100 000 in 1983.

In 2005, gastric cancer was responsible for 1090 deaths (699 in men and 391 in women), resulting in 6805 person-years of life lost before the age of 75 years. This equates to an age-standardised mortality for Australia of 7.3/100 000 for men and 3.2/100 000 for women (AIHW 2007). The overall age-standardised mortality for Australia was 5.0/100 000.

Potential utilisation of PET

Interim funding service utilisation

Over the period 2002–2007, the number of PET scans for gastric cancer claimed in the seven reimbursed Australian centres (listed under ‘Current reimbursement arrangement’, page 15) has increased from approximately 30 to 155 (Figure 1). In the first three quarters of 2007, there were 116 claims for PET scans for the staging of gastric carcinoma. These data equate to an estimated 155 scans for 2007. Should the number of reimbursed services in Australia increase in the future, it is expected that utilisation would further increase.

Epidemiological data

The estimated use of PET for staging of gastric cancer is based on that described in the MSAC assessment of EUS (Medical Services Advisory Committee 2006) (Table 1). The use of PET will be equivalent to the Australian incidence of gastric cancer less the proportion of patients with M-stage disease at diagnosis, as identified on conventional staging.

In NSW between 1992 and 1996, before the introduction of PET, the proportion of patients diagnosed with distant disease was 21 per cent (Jong et al. 2002). Kayaalp et al. (2002) indicated that 9 per cent of gastric cancer patients had distant metastases diagnosed on ultrasound or CT. In addition to CT, laparoscopy with or without peritoneal cytology identified distant metastases in 23 per cent (Lowy et al. 1996) to 43 per cent (Burke et al. 1998). Based on these studies, the number of gastric cancer

patients eligible for staging with PET is estimated at approximately 700–1300 annually (Table 1).

Australian PET data collection study

Data were collected prospectively from five PET facilities in five states (NSW, WA, SA Victoria and Queensland) over the period 2004–2006 for patients with confirmed oesophageal or GEJ cancer with no or equivocal distant metastatic lesions on prior imaging (Table 2) (Chatterton 2006). Data were collected for 129 patients from 56 referring clinicians. PET/CT scans were used in 18 per cent of cases, and ‘standalone’ PET scans in the remainder. Mean patient age was 66 years, and most patients were male (81%). Inclusion criteria specified that patients have histologically confirmed cancer.

Seventy-three per cent of patients with oesophageal or GEJ cancer had a pre-PET management plan that included surgery; 26 per cent of these also had chemo- and/or radiotherapy (RT) included in their pretest management plan (Table 2). Non-surgical management with combined chemo-radiotherapy (CRT) was planned in 22 per cent before PET, whereas chemotherapy or RT alone or other management each accounted for fewer than 5 per cent.

Table 2 Characteristics of Australian patients undergoing PET for oesophageal cancer

Indication	N	Patient characteristics	Pretest (post-test) management plan
Initial staging of oesophageal and GEJ cancer in patients with	129	Age: mean 66 y (range 36–87)	Curative 92% (75%)
	5 centres	Males: 81%	Surgery only 47% (33%)
	2004–2006	Fit for radical treatment	Surgery, then chemo and/or radio: 9% (9%)
▪ histologically confirmed SCC or AC	56 referring clinicians	Basis for diagnosis:	Chemo and/or radio, then surgery: 17% (12%)
▪ no distant metastatic disease on CT or clinical examination, or	PET/CT 18%	▪ histology 100%	Radio & chemo: 22% (30%)
		▪ CT 85%	Chemotherapy: 2% (5%)
		▪ clinical examination: 27%	Radiotherapy: 3% (5%)
		▪ endoscopy: 88%	Other ± chemo or radio: 1% (4%)
		▪ EUS: 11%	Surgery + other: 1% (2%)
▪ equivocal lesions thought to be distant metastases but not readily accessible to FNA, on prior imaging		▪ MRI 1%	
		▪ US 1%	
		▪ other: 9%	

Abbreviations: AC = adenocarcinoma, chemo = chemotherapy, CT = computed tomography, EUS = endoscopic ultrasound, FNA = fine-needle aspiration biopsy, GEJ = gastro-oesophageal junction, MRI = magnetic resonance imaging, PET = positron emission tomography, SCC = squamous cell carcinoma, US = ultrasound
Source: (Chatterton 2006)

The Australian data collection study did not provide information on the characteristics of patients undergoing PET for staging of gastric cancer.

Current treatment

Perioperative chemotherapy

Since publication of the MSAC assessment of EUS (Medical Services Advisory Committee 2006), the results of the UK National Cancer Research Institute's Medical Research Council Adjuvant Gastric Infusional Chemotherapy randomised trial of perioperative chemotherapy in resectable gastric cancer have been published (Cunningham et al. 2006). That study demonstrated a benefit from administering perioperative epirubicin, cisplatin and infused fluorouracil in patients with resectable AC of the stomach, GEJ or lower oesophagus. The chemotherapy regimen improved overall survival (hazard ratio [HR] 0.75; 95% CI 0.60–0.93), 5-year survival (36% vs 23%) and progression-free survival (HR = 0.66, 95% CI 0.53–0.81) by comparison with surgery alone. It has recently been suggested that this treatment regimen should now be considered standard treatment for patients with resectable gastric cancer (Chua & Cunningham 2007).

A recent meta-analysis has also demonstrated a survival benefit of preoperative CRT versus surgery alone in patients with oesophageal carcinoma (all-cause mortality HR 0.81; 95% CI 0.70–0.93; $P = 0.002$) (GebSKI et al. 2007). A similar benefit was seen for different histological tumour types (AC HR 0.75, 95% CI 0.59–0.95, $P = 0.02$; SCC HR 0.84, 95% CI 0.71–0.99, $P = 0.04$). A significant survival benefit was also seen for neoadjuvant chemotherapy in patients with oesophageal AC compared with surgery alone (HR 0.78; 95% CI 0.64–0.95; $P = 0.014$), but not in patients with oesophageal SCC (HR 0.88; 95% CI 0.75–1.03; $P = 0.12$).

Existing procedures

Existing procedures used in the diagnosis and staging of oesophageal and gastric cancer in Australian include endoscopy, CT, laparoscopy and EUS. Descriptions of CT and EUS technologies are provided in the recent MSAC assessment of EUS (Medical Services Advisory Committee 2006). Brief descriptions of endoscopy and laparoscopy are provided below.

Endoscopy

Endoscopy is a commonly used minimally invasive diagnostic technique for viewing the lumen of internal body structures. During inspection of the upper gastrointestinal tract, an endoscope is passed through the oesophagus and stomach (gastroscopy) and sometimes as far as the duodenum (oesophagogastroduodenoscopy). Endoscopy can be used as an initial diagnostic tool to identify tumours or other lesions and to guide biopsy, but it does not provide any staging information on tumours identified.

Endoscopy can also be used for conducting minimally invasive therapeutic procedures, in which instruments for local treatments such as dilatation, ablation or resection can be passed down a channel within the endoscope.

Laparoscopy

Laparoscopy is an endoscopic procedure for inspection of the abdominal or pelvic cavity. During laparoscopy an endoscope is passed through a small incision in the abdominal wall. Laparoscopy is useful in staging intra-abdominal malignancies such as gastric cancer and is a sensitive test for detecting peritoneal and other abdominal metastases (reviewed by Conlon & Johnston 2004).

Laparoscopic peritoneal lavage may be used to stage gastric cancer. Saline (200–400 mL) is inserted into the abdominal cavity, agitated and then aspirated before laparoscopic examination (Conlon & Johnston 2004). The fluid is then examined cytologically for the presence of malignant cells. Some clinicians consider that patients with positive cytology may be considered as having stage IV disease, even if peritoneal disease is not detected macroscopically (Burke et al. 1998). However, there is no consensus that positive peritoneal washings indicate incurable disease (advisory panel expert opinion).

Potential impact of PET on patient outcomes

The main potential impact of PET in patients with oesophageal and gastric cancer is in the exclusion of patients unlikely to benefit from therapy with curative intent or salvage surgery.

In patients with primary oesophageal or gastric cancer considered curable, the addition of PET for pretreatment staging is expected to increase the sensitivity of detecting additional metastases that would preclude definitive treatment. In patients with confirmed residual disease following definitive chemo-radiation for oesophageal cancer, who are considered suitable for salvage surgery, the addition of PET is also expected to increase the sensitivity of detecting additional metastases. In all of these patients, the addition of PET is expected to improve patient outcomes through reduced treatment morbidity and improved quality of life by avoiding non-beneficial interventions and guiding selection of optimal management.

In patients with suspected residual disease following definitive chemo-radiation for oesophageal cancer, the addition of PET is expected to increase the sensitivity of detection of residual disease. The addition of PET is therefore expected to improve patient outcomes by providing salvage surgery to patients who otherwise would have had a delayed or missed opportunity for therapy.

Patients proceeding to PET for these indications should do so only if they have consented to undertake definitive treatment or salvage surgery. Thus, a negative PET result for lesions beyond known sites of disease is used to ensure that such therapy can proceed with the highest prospect of success. A positive PET scan that detects previously unsuspected sites of incurable disease allows the patient to avoid radical therapy which is unlikely to be of long-term benefit.

Reference standard

Pathologic confirmation (histopathology or cytopathology) and clinical follow-up of at least 6 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 conventional staging against conventional staging alone (shown later in clinical flow charts, Figure 3 to Figure 5).

The comparator for PET in patients with primary oesophageal cancer eligible for definitive treatment is conventional staging including CT.

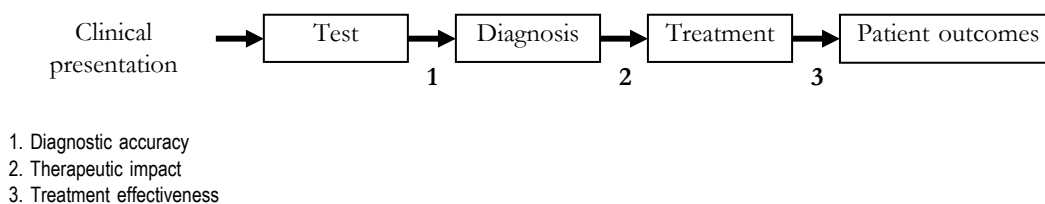
In patients considered eligible for salvage surgery following definitive chemo-radiation for oesophageal cancer, when suspected residual disease is not confirmed on biopsy, the comparator for PET is endoscopy with biopsy; when residual disease is biopsy proven, PET is considered as a replacement for CT (as a direct comparator).

The comparator for PET in patients with primary gastric cancer is conventional staging including CT and laparoscopy with peritoneal cytology, with or without EUS.

Methodological issues

The clinical value of a test depends on whether its use improves patient outcomes. 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



If randomised controlled trials are not available to assess whether adopting a new test improves patient outcomes compared with 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, 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 or treatment does not by itself provide evidence of effectiveness. Therefore, therapeutic impact studies need to be carefully designed to answer 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 (eg, improved patient outcomes through reduction of invasive testing, increase in effective treatment, 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 MSAC in 2001 reviewed the clinical effectiveness of PET for five indications, including oesophageal, gastric and gastro-oesophageal cancer (Medical Services Advisory Committee 2001). 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 87).

Twelve studies reporting the diagnostic accuracy of PET in oesophageal cancer were included for review. Four studies reporting the accuracy of PET for staging gastric and gastro-oesophageal cancer before initial treatment were reviewed. On the basis of these studies, PET had comparable accuracy to CT for the detection of nodal involvement and similar or better sensitivity, but the results varied widely across different studies. PET had greater sensitivity than CT for detecting distant metastases, but it was unclear how many PET-detected metastases were within the area imaged by CT (ie, the incremental value was uncertain).

MSAC drew the following conclusions on the role of PET in oesophageal cancer:

- PET appeared to offer additional useful information in the staging and treatment of patients.
- PET had the potential to affect patient management, particularly in the avoidance of inappropriate surgical intervention in patients with previously unsuspected distant disease.

- Generally, PET appeared to be as sensitive as or more sensitive than CT for the detection of local nodal disease, but both have low sensitivity for detecting low-volume nodal disease.
- Compared with CT, EUS and CT + EUS, PET had higher specificity for ruling out nodal disease. The sensitivity of PET for detecting nodal involvement may vary, however, depending on the anatomic location of involved nodes.
- PET appeared to be more sensitive than CT, EUS and CT + EUS for detecting stage IV disease. Specificities were comparable (and reasonably high) among these imaging modalities. PET had higher diagnostic accuracy than CT for detecting distant metastases.
- It was unclear, at that time, how changes in management may affect ultimate patient outcomes.
- The role of PET in restaging of patients after neoadjuvant therapy remained unclear, although potentially improved diagnostic accuracy in primary staging may also be applicable in this setting.
- PET might also provide useful prognostic information in some patients.

MSAC drew the following conclusions on the role of PET in gastric and gastro-oesophageal cancer:

- For the diagnosis of stage IV disease, PET appeared to offer superior diagnostic accuracy than either CT or EUS alone or CT + EUS.
- The accuracy of PET at determining resectability/non-resectability appeared to be superior to that of CT. PET alone correctly prevented a higher proportion of patients from undergoing inappropriate surgical intervention than would have been determined by CT alone.
- In patients considered inoperable, in whom neoadjuvant treatment was considered, PET might be of value. It was unclear at that stage, however, whether neoadjuvant therapy before surgery was better than surgery alone. The results of ongoing randomised trials addressing this question were awaited.
- The diagnostic accuracy of PET was comparable to CT for the detection of nodal involvement. As would be expected, however, both PET and CT had a low sensitivity for the detection of low-volume or micrometastatic disease, and laparoscopy might be appropriate in patients with negative PET before committing to surgery.
- The role of PET in the restaging of patients after neoadjuvant therapy required further evaluation, although potentially improved diagnostic accuracy in primary staging might also be applicable to this setting.

There was no direct evidence available at the time to demonstrate that improvements in diagnostic accuracy provided by PET, and any subsequent management changes, led to improvements in health outcomes for patients.

Thus, interim funding was provided for four clinical scenarios, including:

- staging of patients with proven oesophageal carcinoma in whom curative surgery or chemo-radiation is planned
- staging of patients with proven gastric cancer in whom curative surgery is planned

on the basis that the evidence suggested that FDG-PET is safe, has good accuracy and is potentially clinically effective and potentially cost-effective.

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 NSW; 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 Westmead hospital was not.

The recommendation of MSAC's original review of PET (Medical Services Advisory Committee 2001) was for funding to be made available on an interim basis contingent on the collection of data relating to PET's clinical effectiveness and/or cost-effectiveness. The results of the data collection are described in this report.

The following items are reimbursed under the Medicare Benefits Schedule (MBS) interim funding arrangement:

MBS 61577	Whole-body FDG-PET study, performed for the staging of proven oesophageal carcinoma, where curative surgery or chemo-radiation is planned	\$953.00
MBS 61580	Whole-body FDG-PET study, performed for the staging of proven oesophageal carcinoma, where curative surgery or chemo-radiation is planned, with catheterisation of the bladder	\$975.00
MBS 61583	Whole-body FDG-PET study, performed for the staging of proven gastric carcinoma, where curative surgery is planned	\$953.00
MBS 61586	Whole-body FDG-PET study, performed for the staging of proven gastric carcinoma, where curative surgery is planned, with catheterisation of the bladder	\$975.00

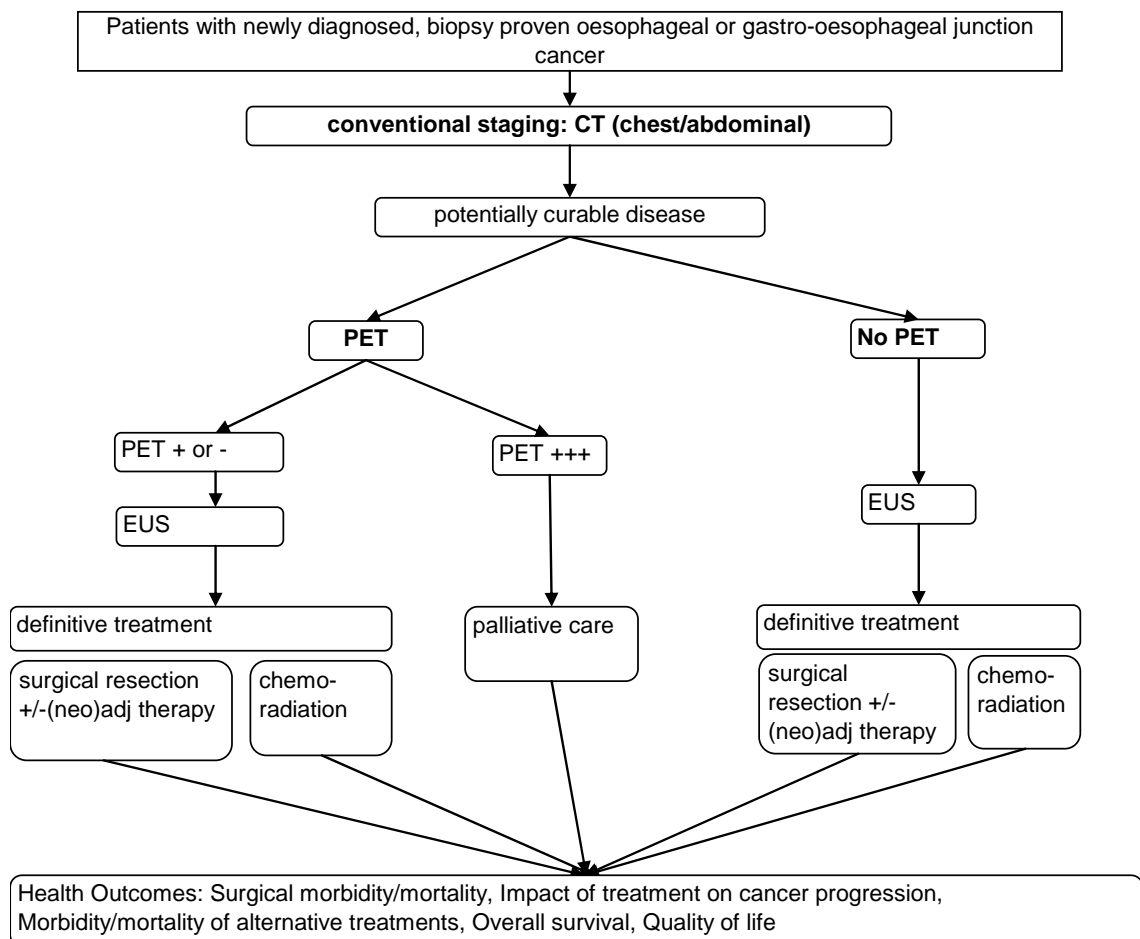
Approach to assessment

Research questions

The evaluators, in consultation with members of the advisory panel, developed specific research questions on the value of PET as a diagnostic test for the assessment of oesophageal and gastric cancer. These questions were formulated *a priori* based on information about the characteristics of oesophageal and gastric cancer, current practice, and the intended purpose of the test by using the ‘PPICO’ (Population, Prior tests, Intervention, Comparator, Outcomes) criteria (Richardson et al. 1995).

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

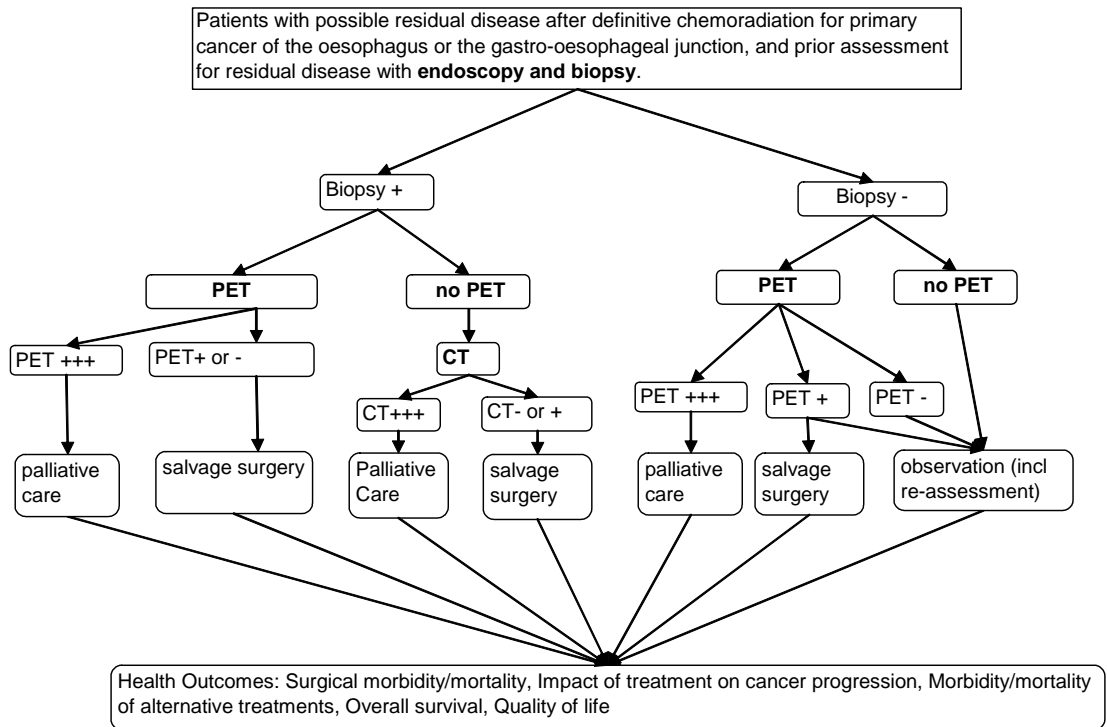
Figure 3 Clinical flow chart for role of PET in primary staging of oesophageal cancer



PET - negative for disease
 PET+ positive for disease, but negative for distant metastases
 PET +++ positive for distant metastases (stage IV disease)

Abbreviations: CT = computed tomography, EUS = endoscopic ultrasound, PET = positron emission tomography

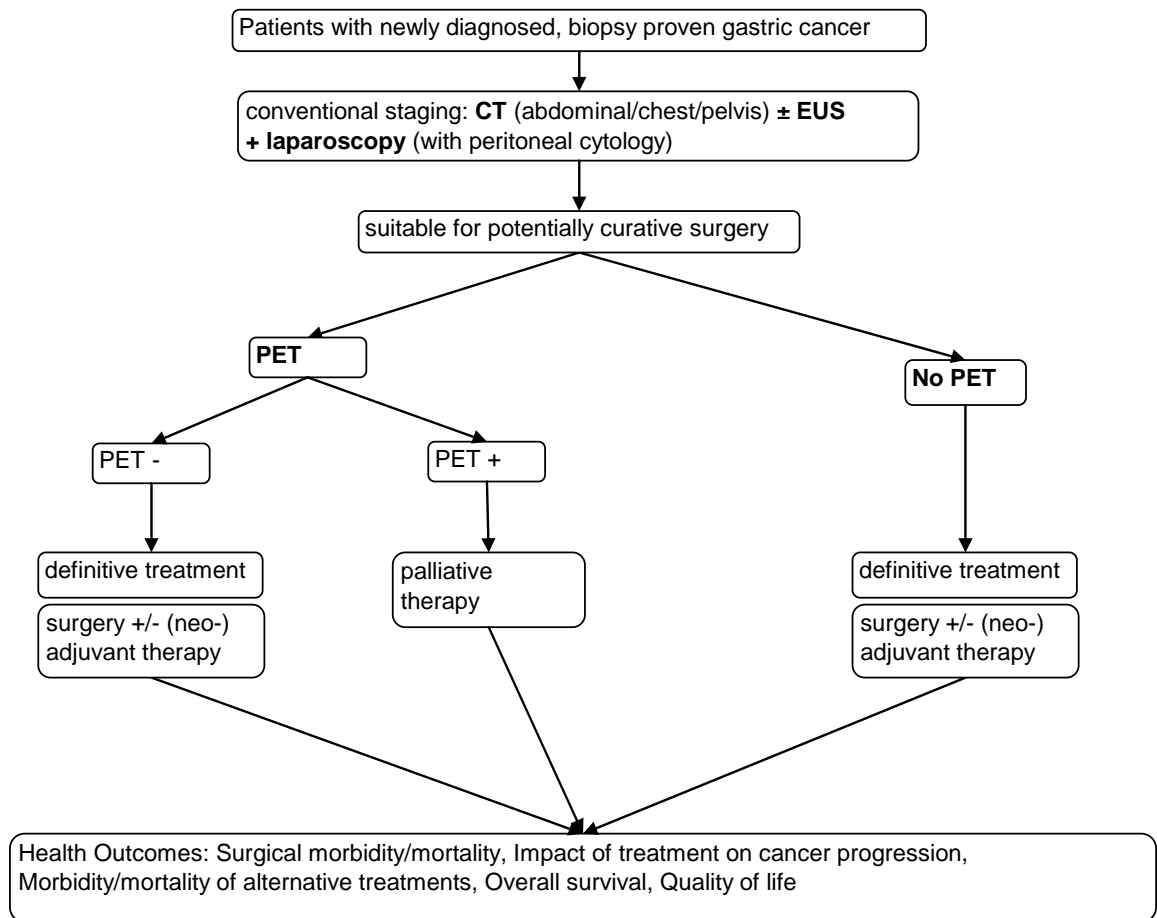
Figure 4 Clinical flow chart for role of PET in assessment for residual disease after definitive chemoradiation for oesophageal cancer



CT/PET - negative for disease
 CT/PET+ positive for disease, but negative for distant metastases
 CT/PET +++ positive for distant metastases (stage IV disease)

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

Figure 5 Clinical flow chart for role of PET in staging gastric cancer



PET + positive for stage IV disease
 PET - negative for stage IV disease

Abbreviations: CT = computed tomography, EUS = endoscopic ultrasound, PET = positron emission tomography

The research questions are as follows:

1. What is the value of the addition of PET/CT in the assessment of patients with primary cancer of the oesophagus or the GEJ considered suitable for definitive treatment as determined by conventional staging?
2. What is the value of PET/CT in the assessment of residual oesophageal or GEJ cancer following definitive chemo-radiation considered suitable for salvage surgery, (a) as a replacement for CT in staging biopsy-proven residual disease, or (b) in addition to endoscopy and biopsy where residual disease has not been confirmed?
3. What is the value of the addition of PET/CT in the assessment of patients with biopsy-proven primary gastric cancer considered potentially curable as determined by conventional staging including laparoscopy (with peritoneal cytology)?

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 management on health outcomes.

Review of the literature

A systematic review of the medical literature was conducted to identify relevant studies. Websites of international HTA agencies were searched for existing HTA reports (Appendix C, page 85), and electronic databases of published research (Table 3) were searched for original research papers, including systematic reviews.

A search of clinical trial databases (Table 4), the American College of Radiology Imaging Network database, and the UK NHS's HTA Programme database was undertaken, supplemented by information provided by the applicant, to identify ongoing studies.

Table 3 Electronic databases searched

Database	Period covered
<i>Oesophageal cancer</i>	
EMBASE.com (includes EMBASE and MEDLINE)	January 2005 – December 2007
PreMEDLINE	January 2005 – December 2007
Current Contents	January 2005 – December 2007
Cochrane Library Controlled Clinical Trials Registry	Issue 3, 2007
<i>Gastric cancer</i>	
EMBASE.com (includes EMBASE and MEDLINE)	January 2001 – December 2007
PreMEDLINE	January 2001 – December 2007
Current Contents	January 2001 – December 2007
Cochrane Library Controlled Clinical Trials Registry	Issue 3, 2007

Table 4 Databases searched to identify ongoing studies

http://www.controlled-trials.com/
http://clinicaltrials.gov/
http://www.anzctr.org.au/
http://www.acrin.org/
http://www.cancer.gov/search/clinical_trials/
http://www.nchta.org/project/
http://www.who.int/trialsearch/

Search strategy

Separate search strategies were developed for gastric and oesophageal cancer, using the key elements of the clinical question. The search strategy shown in Table 5 was used to

identify papers in 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 (oesophageal cancer)	1 'esophagus cancer'/syn
	2 *esophag*: ti,ab [in Field search]
	3 tumo*r OR cancer OR *carcinoma OR neoplasm: ti,ab [in Field search]
	4 2 AND 3
	5 1 OR 4
Population (gastric cancer)	1 'stomach cancer'/syn
	2 stomach OR gastric: ti,ab [in Field search]
	3 tumo*r OR *carcinoma OR neoplasm: ti,ab [in Field search]
	4 2 AND 3
	5 1 OR 4
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 relevant citations.

Existing health technology assessment reports

Four HTA reports on the value of PET for the investigation of oesophageal and/or gastric cancer published between 1999 and 2007 were identified (see Appendix G, page 94). No HTA report or systematic review of the value of PET in gastric cancer published since the MSAC 2001 report was identified, so a systematic review was undertaken to identify relevant primary studies published since 2001.

The two most recent HTA reports on PET in oesophageal cancer came from the NCCHTA (Facey et al. 2007) and AHTAPol (Agency for Health Technology Assessment in Poland 2006). The HTA report from Poland includes the most recent literature search (up to March 2006), but the review is considered to be of low quality (see Appendix H). The UK NCCHTA report (shown later in Table 12) was considered a high-quality systematic review. Therefore, the current assessment of PET in oesophageal cancer takes the approach of summarising and updating the UK HTA report (Facey et al. 2007).

No additional data extraction or re-appraisal of the quality or applicability of individual studies included in the UK HTA report was undertaken. A systematic review was

undertaken to include studies published since the UK systematic review (ie, since August 2005).

Eligibility criteria for studies

The search strategy for oesophageal cancer retrieved a total of 465 non-duplicate citations. One additional study was identified through hand-searching (van Westreenen et al. 2007a). The search strategy for gastric cancer retrieved a total of 435 non-duplicate citations.

The eligibility of citations for inclusion in the review was assessed by two reviewers according to the criteria outlined in Table 6. Discrepancies were resolved by discussion and the involvement of a third reviewer as necessary.

On the basis of these criteria, 456 citations identified in the oesophageal cancer search and 480 citations identified in the gastric cancer search were excluded from the review. QUOROM (Quality of Reporting of the Results of Meta-analyses) flow charts (Figure 6 and Figure 7) summarise the results of the literature searches and the application of the study exclusion criteria.

Table 6 Inclusion criteria for identification of relevant studies

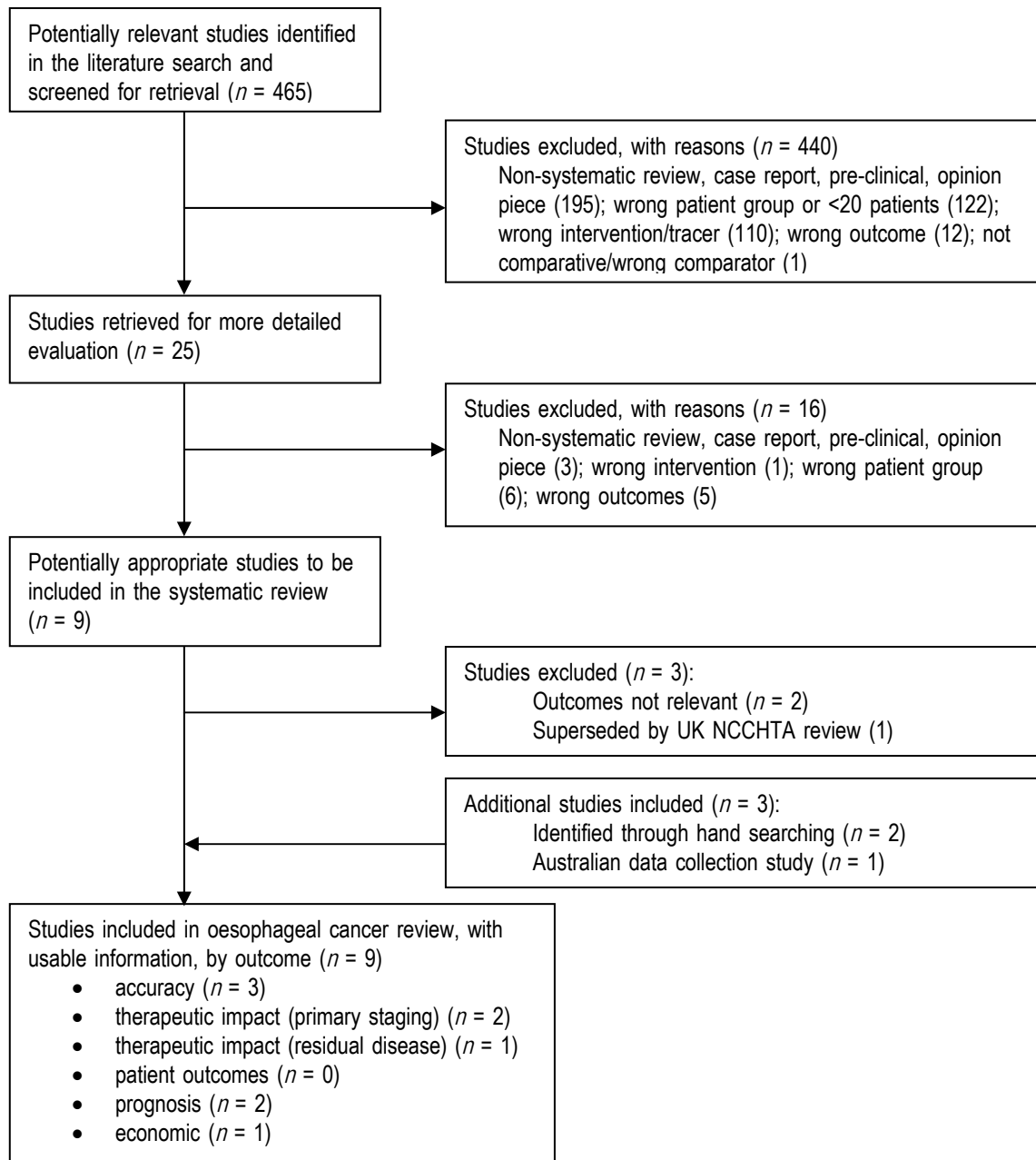
Characteristic	Inclusion criteria
Publication type	<p>Clinical studies included. Non-systematic reviews, letters, editorials; animal, <i>in vitro</i>, laboratory studies; conference abstracts and technical reports excluded</p> <p>Systematic reviews</p> <p>Systematic reviews that have been superseded will be excluded</p> <p>Primary studies</p> <p>Primary studies published during the search period of included systematic reviews will be excluded</p> <p>Accuracy studies excluded if:</p> <ul style="list-style-type: none"> ▪ patients were selected for inclusion based on their known disease (case-referent, case-control studies) <p>Change-in-patient-management studies will be excluded if:</p> <ul style="list-style-type: none"> ▪ change in therapeutic impact is not determined by comparison with 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 <p>Prognostic studies of survival outcomes will be included if:</p> <ul style="list-style-type: none"> ▪ 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	<p>≥ 70% of patients with one of the following indications:</p> <p>Oesophageal</p> <ul style="list-style-type: none"> ▪ primary cancer of the oesophagus or of the GEJ considered for definitive treatment as determined by biopsy and conventional staging ▪ possible residual disease following definitive chemo-radiation ^a for primary cancer of the oesophagus or GEJ, and biopsy for residual disease <p>Studies assessing response to neoadjuvant chemo-radiation will be excluded</p> <p>Gastric</p> <ul style="list-style-type: none"> * apparently resectable and potentially curable biopsy-proven primary gastric cancer ▪ gastrointestinal stromal tumour and gastric lymphoma excluded <p>Studies with <20 patients undergoing PET for the indication of interest are excluded</p>
Intervention/test	FDG-PET or FDG-PET/CT plus prior tests
Comparator	<p>Oesophageal</p> <p>Standard prior tests without PET:</p> <ul style="list-style-type: none"> ▪ including endoscopy, CT scan of chest/abdomen ▪ including endoscopy and biopsy <p>Gastric</p> <p>Standard prior tests including CT scan of chest/abdomen/pelvis and laparoscopy</p>
Outcome	<p>Studies must report on at least one of the following outcomes:</p> <ul style="list-style-type: none"> ▪ 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

Abbreviations: CT = computed tomography, FP = false-positive, GEJ = gastro-oesophageal junction, PET = positron emission tomography, Q* = Q statistic, ROC = receiver operating characteristic, TP = true-positive

a. Definitive chemo-radiation is characterised by at least 5 weeks of radiation therapy of at least 50 Gy, and 2–4 cycles of chemotherapy with cisplatin and fluorouracil.

QUOROM flow charts

Figure 6 Identification of primary studies of PET in oesophageal cancer published since August 2005



Adapted from Moher et al. (1999)

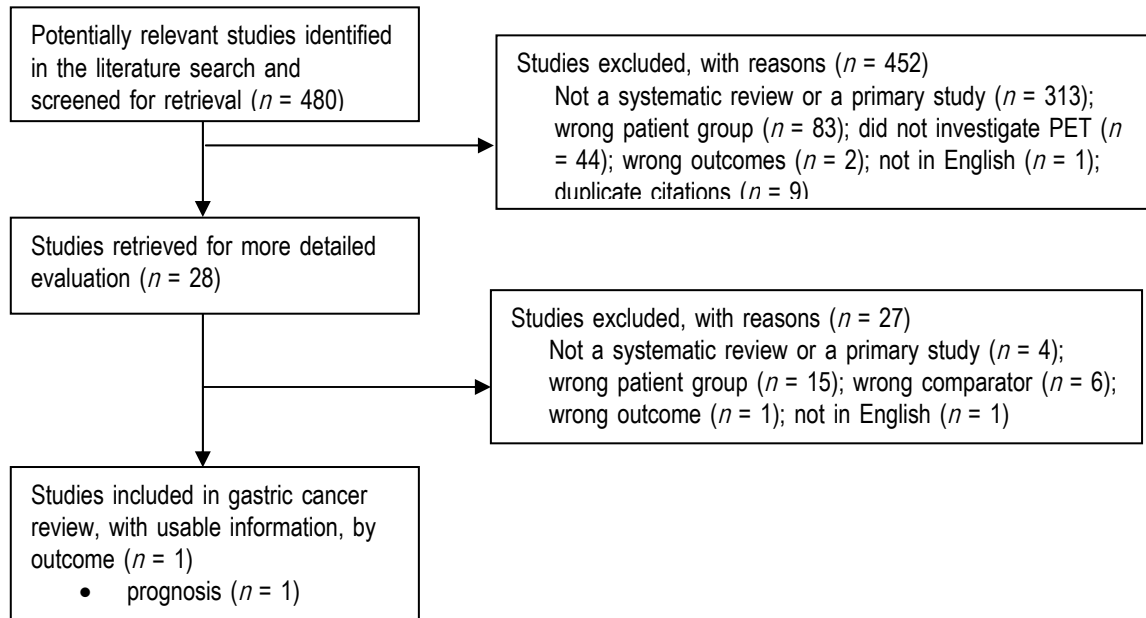
The nine primary studies published since August 2005 that were included in the oesophageal cancer review comprised:

- three studies of diagnostic test accuracy (primary staging)
- the Australian data collection study
- two additional therapeutic impact studies (primary staging)
- one therapeutic impact study (residual disease)
- one study providing supportive prognostic evidence (primary staging)

- one economic study.

Including the UK NCCHTA report, ten studies in total were included in the current review.

Figure 7 Identification of primary studies of PET in gastric cancer published since 2001



Adapted from Moher et al. (1999)

One study reporting the prognostic value of PET in gastric cancer was identified. No studies of PET accuracy meeting the predefined inclusion criteria were identified. Although some studies reporting the accuracy of PET in comparison to CT were identified, none provided information on the accuracy of PET in comparison or in addition to laparoscopy.

Evidence appraisal

Assessment of eligible studies

The evidence presented in the selected studies was appraised and classified using the NHMRC Dimensions of Evidence (NHMRC 2008) and the MSAC Diagnostic Test Guidelines (MSAC 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

Type of evidence	Definition
precision ⁱⁱ	
Thee evidence	The study design used, as an indicator of the degree to which bias has been eliminated by design (see Table 8)
Level	The methods used by investigators to minimise bias within a study design
Quality	The <i>P</i> -value or, alternatively, the precision of the estimate of the effect; it reflects the degree of certainty about the existence of a true effect
Statistical precision	
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

Adapted from NHMRC 1999 and 2008.

The three subdomains (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 8.

Table 8 Designations of levels of evidence

Level	Intervention	Diagnosis	Prognosis
I	A systematic review of level II studies	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	A prospective cohort study
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	All or none
III-2	A comparative study with concurrent controls: <ul style="list-style-type: none"> ▪ 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	Analysis of prognostic factors among untreated control patients in a randomised controlled trial
III-3	A comparative study without concurrent controls: <ul style="list-style-type: none"> ▪ historical control study ▪ two or more single-arm studies ▪ interrupted time series without a parallel control group 	Diagnostic case-control study	A retrospective cohort study
IV	Case series with either post-test or pretest/post-test outcomes	Study of diagnostic yield (no reference standard)	Case series, or cohort study of patients at different stages of disease

Source: (NHMRC 2008)

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 by using a checklist of 12 items adapted from the QUADAS (Quality Assessment of Diagnostic Accuracy Studies) tool developed by Whiting *et al.* (2003) (Table 9). This tool was developed recently 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 9). In addition, only prospective studies of diagnostic test accuracy were assessed as high quality. Studies that did not use a valid reference standard in all patients were classified as low quality.

Table 9 Criteria used to assess the quality of diagnostic accuracy studies—QUADAS tool

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?

Adapted from Whiting *et al.* 2003

High quality: Yes to 1, 3, 4, 5, 10, 11; other items required to be either Yes or Unclear

Low quality: No/Unclear for either 4 or 5

Other studies are assessed as fair quality

Seven criteria were used to assess the quality of systematic reviews, as outlined in Table 10. 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 10 Criteria used to assess the quality of effectiveness studies

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 estimates and measure of variability reported for the primary outcome?

Adapted from NHMRC 2000 and CRD 2001

* High quality: Yes or N/A to all seven criteria

Low quality: ≤ 4 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 in the target test population; document what proportion of consecutive eligible patients was 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; and 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 11).

Table 11 Criteria used to assess the quality of therapeutic impact studies

Item	Criteria
1	Was the study designed and conducted prospectively?
2	Did explicit eligibility criteria reflect specific presentation or clinical problem?
3	Consecutive recruitment of all patients eligible for testing?
4	Did referring clinician determine management plan?
5	Was test accuracy documented concomitantly?
6	Was pretest plan independently assessed?
7	Blinding to study test results at pretest measurement?
8	Was association between management change and study test result independently assessed?
9	Were management changes reported for specific test use and patient presentation?
10	Were management changes reported in adequate detail? (eg, surgery avoided, additional investigations)
11	Was descriptive information about patient outcomes reported?
12	Was physician experience reported?

Adapted from Guyatt et al. 1986

Applicability was assessed according to the patient population, prior tests and outcomes. Studies of high-applicability met all three criteria, fair-applicability two, low-applicability one or none.

Data analysis

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

Ninety-five per cent confidence intervals were calculated if these were not presented. Proportions were compared using Pearson's χ^2 test.

Measurement of test accuracy

The accuracy of a test is determined by comparison of its ability to identify the target condition with a reference standard test that is used as a proxy for true disease status. Subjects who test positive by 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 8.

Figure 8 Two-by-two table displaying the data used to determine test accuracy

		Reference standard	
		disease +	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 positives (TP). Subjects without the target condition who test negative by both tests were recorded as true negatives (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 disease is high. However, high specificity is particularly important if a false positive result can harm the patient.

$$\text{Sensitivity} = \text{TP}/(\text{TP} + \text{FN})$$

$$\text{Specificity} = \text{TN}/(\text{TN} + \text{FP})$$

Positive and negative predictive values

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.

$$\text{PPV} = \text{TP}/(\text{TP} + \text{FP})$$

$$\text{NPV} = \text{TN}/(\text{TN} + \text{FN})$$

Data extraction

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

Statistical methods

The PPV and yield from different studies were pooled by the inverse-variance pooling method. This is a weighted average of the individual study parameter estimates. The weights are the inverse of the corresponding study variance estimates for the quantity of interest.

Expert advice

An advisory panel with expertise in nuclear medicine, medical and radiation oncology, head and neck surgery, gastro-intestinal surgery, and consumer interests was established to evaluate the evidence and advise MSAC from a clinical perspective. In selecting members for advisory panels, MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations, and consumer bodies for nominees. Membership of the advisory panel is listed in Appendix B (page 84).

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 from 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

The four HTA reports published between 1999 and 2007 that consider PET in the assessment of oesophageal cancer are listed in Appendix G. No HTA reports that consider the role of PET in gastric cancer were identified.

The characteristics and quality assessment of the recent UK HTA report (Facey et al. 2007) are presented in Table 12. This report was considered a high-quality systematic review. The data from eligible studies provided in it were used as the basis of this assessment. A systematic review was also undertaken to include more recent studies.

Table 12 Characteristics and appraisal of NCCHTA report

Author (Year) Country	Objective & methods	Included studies	Quality assessment of review
UK NCCHTA (Facey et al. 2007) United Kingdom	<p>Objective: To assess the clinical effectiveness of PET to aid management decisions relating to diagnosis, staging/restaging, recurrence, treatment response, and RT planning for 8 indications, including oesophageal cancer</p> <p>Literature review:</p> <p><u>Databases:</u></p> <p><i>Time period:</i> to August 2005; systematic reviews since 1966, primary studies from 2000</p> <p><u>Inclusion/exclusion criteria:</u></p> <p><i>Study design:</i> systematic reviews and prospective primary accuracy studies (or retrospective for PET/CT); >12 patients (or 6 for management studies)</p> <p><i>Population:</i> one cancer of interest, pathway similar to Australia</p> <p><i>Intervention:</i> FDG-PET or PET/CT</p> <p><i>Outcomes:</i> accuracy, change in management or clinical outcomes</p> <p><i>Language:</i> English and Western European foreign language articles</p>	<p>Oesophageal and GEJ cancer:</p> <p><i>Diagnosis:</i></p> <p>1 systematic review (MSAC 2001)</p> <p><i>Staging:</i></p> <p>2 systematic reviews (2002, 2004)</p> <p>4 primary studies (2004) (3 accuracy, 1 prognosis ^a)</p>	<p>Quality: HIGH</p> <p>Explicit review questions: YES</p> <p>Explicit & appropriate eligibility criteria: YES</p> <p>Explicit & comprehensive search strategy: YES</p> <p>Quality of included studies appraised: YES</p> <p>Methods of study appraisal reproducible: YES</p> <p>Heterogeneity between studies assessed: N/A</p> <p>Summary of main results clear and appropriate: YES</p>

Abbreviations: CT = computed tomography, FDG = (2-fluoro-2-deoxy-D-glucose), GEJ = gastro-oesophageal junction, N/A = not applicable, PET = positron emission tomography

a. The study of prognosis was not considered in this assessment as it did not meet inclusion criteria (patients did not receive same treatment following PET, regardless of result).

Direct evidence

The current systematic review did not identify any studies comparing the health outcomes of patients with oesophageal or gastric 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 in patients staged with PET versus conventional testing alone, and therefore conclusions about the impact of adopting PET on patient outcomes cannot be made on this type of evidence. However, these studies may provide some supportive evidence for a role of PET. Information from studies reporting patient prognosis following PET is discussed under ‘Prognosis following PET’ (see page 55).

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). It also explains that although some studies make survival predictions and assess disease progression in follow-up, they are difficult to judge outside a randomised setting owing to potential confounding by other factors.

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

Indirect evidence

Included studies—oesophageal cancer

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.

The UK NCCHTA report provided data from four studies comparing the accuracy of PET for staging primary oesophageal cancer: three prospective primary studies and one systematic review.

The UK NCCHTA also reviewed the role of PET in assessing treatment response following neoadjuvant therapy, but not in assessing residual disease following definitive chemo-radiation.

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

One systematic review of PET in oesophageal cancer (Westerterp 2006) that included only studies published before the UK HTA search period was identified and excluded. One primary study assessing the accuracy of PET at identifying locoregional lymph node metastases was excluded as data were reported on a per-lesion basis only.

In total, eight additional primary studies in patients with oesophageal cancer met pre-defined eligibility criteria and were included for review:

- three studies of PET accuracy incremental to conventional staging of primary cancer on a per-patient basis
- two therapeutic impact studies
- one study providing supportive evidence of prognostic value and therapeutic impact in primary oesophageal cancer, and one study providing evidence of the prognostic value of PET following definitive CRT
- one cost study.

No studies that clearly met inclusion criteria for PET accuracy or therapeutic impact in the assessment of residual disease after definitive chemo-radiation for oesophageal cancer were identified. Therefore, a single Australian study (Duong et al. 2006b) reporting the therapeutic impact of PET following radical or palliative chemo-radiation, but not clearly reporting the proportion of patients receiving definitive chemo-radiation, was included for review.

In addition to the published literature, this review includes data from the Australian data collection study (Chatterton 2006), initiated following the MSAC 2001 PET review

(Medical Services Advisory Committee 2001). Unpublished analyses of these data were made available for this report.

Full details of the characteristics and appraisal of these eight additional primary studies reviewed in addition to the UK NCCHTA report are provided in Appendix H. The key characteristics of these studies are discussed below.

Study characteristics & appraisal

Accuracy studies

The characteristics of studies included in the UK NCCHTA report (Facey et al. 2007) that provided comparative data relevant to staging patients with primary oesophageal cancer and included in the current review are summarised in Table 13. No relevant data on PET for the assessment of residual disease after definitive CRT were provided.

Table 13 Characteristics of studies of PET for primary staging of oesophageal cancer from UK NCCHTA report

Author (Year) Country	Design	N	Population	Test comparison	Outcomes
BCBS 2002 United States	Systematic review	9 studies (3 for distant mets)	Patients with biopsy-proven oesophageal cancer (SCC, AC)	PET vs CT, EUS, CT+EUS	Accuracy (comparative) Locoregional lymph nodes Distant lymph nodes (CT only) All lymph nodes Distant sites (other than lymph nodes)
Heeren 2004 The Netherlands	Accuracy study	74	Patients with resectable carcinoma of the thoracic oesophagus or GEJ (62 AC, 12 SCC)	PET in addition to prior tests (CT, US of neck, EUS in 54) vs CT, EUS, CT+ EUS	Accuracy (comparative) Nodal mets Distant nodal mets Combined distant node and organ mets (CT+EUS only)
Libérale 2004 Belgium	Accuracy study	58	Patients with <i>de novo</i> oesophageal or GEJ cancer (31 SCC, 26 AC)	pet In addition to prior tests (EUS, CT etc.) vs CT, CT+EUS (n = 24)	Accuracy (comparative) Primary tumour Distant nodal mets (CT+EUS) Distant mets (CT)
Sihvo 2004 Finland	Accuracy study (w survival calculations [n.r.]	55	Patients w AC of oesophagus (20) or GEJ (35) considered eligible for resection	PET + CT, EUS vs CT, EUS, CT+ EUS	Accuracy (incremental) Primary tumour Locoregional nodal mets Distant mets

Abbreviations: AC = adenocarcinoma, BCBS = Blue Cross Blue Shield, CT = computed tomography, EUS = endoscopic ultrasound, GEJ = gastro-oesophageal junction, mets = metastases, n.r. = not reported, PET = positron emission tomography, vs = versus, SCC = squamous cell carcinoma, US = ultrasound

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 confirmed primary oesophageal cancer. The characteristics and appraisal of these studies are summarised in Table 14. Primary accuracy studies published since August 2005 reporting the value of PET as a replacement test for CT (rather than as an additional test) were not included for review.

One accuracy study was conducted in patients with confirmed AC or SCC of the oesophagus or the GEJ (Meyers et al. 2007) who were candidates for surgery, of whom 39 per cent were planned for neoadjuvant therapy. Van Westreenen et al. (2007b) included patients with confirmed cancer of the thoracic oesophagus (75%) or the GEJ (25%). The third study included patients with locally advanced AC of the distal oesophagus who were planned for neoadjuvant therapy (Stahl et al. 2005). The studies of Stahl et al. (2005) and van Westreenen et al. (2007b) included EUS as a prior test before PET. Although this does not directly reflect the suggested clinical pathway in Australia (Figure 3), it may not greatly limit the applicability of data on the accuracy of PET for detecting distant metastases, as the role of EUS is in staging regional, rather than distant, spread of disease.

All studies were of fair quality and were conducted in consecutive patient populations. One study was retrospective (Stahl et al. 2005). In all studies, a valid reference standard was not applied to every patient, introducing potential verification bias and limiting the quality of the study.

Two accuracy studies also provided data on the number of operations avoided (Meyers et al. 2007; van Westreenen et al. 2007b). However, these studies provide a lower level of data on therapeutic impact than the Australian data collection study and other dedicated studies of therapeutic impact, as they do not include an assessment of the suitability of patients for surgery before PET. For example, in Meyers et al. (2007), seven patients refused surgery following assessment by PET. Therefore, these data are not included as providing evidence of therapeutic impact in this review.

In total, four studies provided data on the incremental accuracy of PET in staging patients with primary oesophageal cancer. Two of these studies were highly applicable, and were conducted in patients with primary oesophageal cancer who were considered candidates for definitive treatment after relevant prior staging (Meyers et al. 2007; Sihvo et al. 2004). Two studies included applicable patient populations, but included EUS as a prior test, limiting the applicability of this study to the Australian clinical pathway (Stahl et al. 2005; van Westreenen et al. 2007b). However, as EUS is unlikely to upstage patients to incurable disease status, this limitation is considered minor. The applicability of data from Stahl et al. (2005) may further be limited, as PET scans were undertaken from the neck to the abdomen only.

Two studies and one systematic review also reported the comparative accuracy of PET and conventional imaging. The systematic review (BCBS 2002) assessed PET in patients with biopsy-proven oesophageal cancer in comparison with CT (and CT+EUS). The primary studies of comparative accuracy were conducted in an applicable patient population (biopsy-proven oesophageal or GEJ cancer) and assessed PET in addition to prior testing (including EUS, and ultrasound in one study) and in comparison with CT. One study further limited inclusion to patients with resectable disease on prior staging (Heeren et al. 2004).

One accuracy study (Meyers et al. 2007) reported adverse events from confirmatory procedures conducted following PET for staging primary oesophageal cancer. These data are not considered relevant to the safety of PET *per se*, but are provided in Appendix H for completeness.

Table 14 Characteristics and appraisal of primary accuracy studies in patients with primary oesophageal cancer

Author (Year) Setting	N	Test comparison	Population	Outcomes	Accuracy, quality & applicability
Meyers et al. (2007) United States 23 sites 2/2000–7/2004	189	Whole-body FDG-PET (excl. skull) upper/mid neck to upper thigh <i>in addition to</i> conventional staging by <ul style="list-style-type: none"> ▪ contrast-enhanced chest & abdominal CT ▪ bone scintigraphy and CT (if indicated) ▪ brain MRI (if indicated) 	Confirmed AC or SCC of oesophagus or GEJ; surgical candidates 39% planned for neoadj therapy (CRT in 36% of these) Stages T1–3, N0–1, M0–1a M0: 99% 63 ± 11 y; 85% males 84% AC, 13% SCC Prevalence: n.r.	Incremental accuracy for M-stage disease on basis of PET & CT concordance (per patient) Adverse events associated with confirmatory procedures Operations avoided	NHMRC level of evidence: level III-2 Quality: FAIR Applicable Not all patients received ref standard; some induction chemo before ref standard
Stahl et al. (2005) Germany Single centre Period n.r.	40	FDG-PET (neck, thorax abdomen only) <i>in addition to</i> conventional staging by <ul style="list-style-type: none"> ▪ contrast-enhanced chest & abdominal CT ▪ EUS 	Locally advanced AC of distal oesophagus 100% planned for neoadj therapy Stages T3/4, N0/+ on EUS Age, % males: n.r. Prevalence M-stage: 28%	Accuracy for staging additional (discrepant to CT) M-stage disease on PET on per-patient basis Operations avoided	NHMRC level of evidence: level III-2 Quality: FAIR Applicability: limited (prior tests [EUS], no whole-body PET) Retrospective; not all patients received ref standard
Van Westreenen et al. (2007b) The Netherlands 3 sites 10/2002 – 8/2004	199	Whole-body FDG-PET (from mid-skull) <i>in addition to</i> negative conventional staging by <ul style="list-style-type: none"> ▪ contrast-enhanced neck, chest & upper abdominal CT ▪ EUS ± FNA ▪ US of neck ± FNAC ± bronchoscopy 	Proven cancer of thoracic oesophagus or GEJ; w/o evidence of distant mets or locally unresectable disease Distal 67%, proximal 8%, GEJ 25% 64 y (29–82); 83% males Prevalence M-stage: 9%	Accuracy for staging M-stage disease on PET on per-patient basis Operations avoided	NHMRC level of evidence: level III-2 Quality: FAIR Applicability: limited (prior tests [EUS, US]) Not all patients received ref standard

Abbreviations: AC = adenocarcinoma, CRT = chemo-radiotherapy, CT = computed tomography, EUS = endoscopic ultrasound, FDG = 2-fluoro-2-deoxy-D-glucose, FNA = fine-needle aspiration, FNAC = fine-needle aspiration cytology, GEJ = gastro-oesophageal junction, mets = metastases, MRI = magnetic resonance imaging, neoadj = neoadjuvant, n.r. = not reported, PET = positron emission tomography, ref = reference standard, SCC = squamous cell carcinoma, US = ultrasound, vs = versus, w/o = without

Published therapeutic impact studies

Two published studies reporting the therapeutic impact of PET in patients with primary oesophageal cancer were included in the review. Another study assessing the therapeutic impact of PET for the assessment of residual disease was included. The characteristics and appraisal of these studies are presented in Appendix I (Table 32, page 112).

A study reporting the prognostic value of PET also reported data on the number of patients with primary oesophageal cancer undergoing unnecessary operations when staged with and without PET (van Westreenen et al. 2005, see below).

Published PET prognostic studies

Oesophageal cancer

One study providing information on the prognostic value of PET was identified (van Westreenen et al. 2005). This retrospective cohort study reported survival and the number of cases of abandoned resection in 203 patients with cancer of the oesophagus or the GEJ staged with versus without PET using a historical control group. Studies of this design are likely to contain a high number of confounding factors and are prone to bias. Patients were staged preoperatively with CT alone between 1992 and 1996 ($n = 106$), with CT and EUS in 1997 ($n = 36$), and with CT, EUS and PET between 1998 and 2002. CT was performed as single-detector-row CT from the neck to the upper abdomen including the liver; EUS was conducted with a radial scanner with fine-needle aspiration (FNA) biopsy of suspected lymph node metastases. Whole-body PET was conducted from the skull to the knees. The current review includes data on patients staged with CT and EUS compared with CT, EUS and PET, which provide information on the incremental value of PET. Resection was abandoned in 78 (38%) of all patients owing to M1 disease ($n = 59$), locally unresectable tumours (T4, $n = 14$) or metastatic spread with local unresectability ($n = 5$). Patients staged as having resectable disease proceeded to surgery and underwent an initial laparotomy and thoracic exploration to excluded distant metastases. If the tumour was assessed as curable, extended resection was performed. Palliative oesophagectomy was not performed. Survival analysis of patients undergoing resection was presented, but the number of censored patients was not reported.

Two studies reporting the prognostic value of the baseline SUV of the primary tumour (Hong et al. 2005; Rizk et al. 2006) or the number of locoregional PET abnormalities (Hong et al. 2005) before treatment for survival outcomes were excluded as not being directly relevant to the research question under review.

One study reporting the prognostic value of PET/CT following definitive CRT was identified (Konski et al. 2007). This retrospective study included a group of 37 patients who did not undergo surgery because of advanced disease, medical contraindications or patient refusal. Twenty-five of them (68%) underwent PET/CT after CRT. The prognostic value of the post-treatment SUV in predicting disease-specific survival on univariate analysis was reported, in addition to the results of a multivariate analysis. The variables included in the multivariate model were not clearly reported. In addition, the completeness of follow-up was not reported.

Gastric cancer

One study reporting the prognostic value of the SUV of the primary tumour in gastric cancer was identified and included for review (Mochiki et al. 2004). It reported the survival of 85 patients undergoing PET before radical gastrectomy with curative intent without neoadjuvant treatment. A comparison of the 2-year survival of patients with a positive versus negative PET finding for the primary tumour (at an SUV threshold of 4) was performed using a log-rank test. The number of censored patients in the

analysis was not reported and therefore the quality of these data is uncertain. These data are also not relevant to the standard use of PET for the identification of metastases from gastric cancer. In current practice, the SUV of the primary tumour is not used as a determinant of patient management.

Australian data

In addition to the published literature, this review includes unpublished data from the prospective Australian study (Chatterton 2006) initiated following the MSAC 2001 PET review. Analyses of the data were made available for this report. This study is included in this review as a report of the impact of PET on patient management (see page 47). A discussion of the interpretation and potential biases in therapeutic impact studies is included on page 27. The data reported on prognosis following PET are presented and discussed on page 57. The study characteristics and appraisal are summarised in Table 15.

This unpublished, prospective Australian multicentre study provides data on the impact of PET on management plans for patients with biopsy-proven cancer of the oesophagus or the GEJ with no distant metastatic disease found on conventional staging. In addition, it includes oesophageal cancer patients with equivocal metastatic lesions (35 lesions) that were not readily accessible to FNA. The number of patients with equivocal lesions is not reported. Patients undergoing staging of gastric cancer were not included.

The study provides data that are highly applicable to the patient population undergoing PET for staging primary of oesophageal cancer, and it directly reflects the population and clinical practice in Australia. The population may also include some patients undergoing assessment for residual disease after definitive chemo-radiation, but this is not clearly specified. In addition, this is the largest study identified reporting change in management in this patient population.

The study prospectively enrolled 133 patients. Clear inclusion criteria specifying prior diagnosis and staging of oesophageal cancer were described. The inclusion criteria specify that no or only equivocal metastatic lesions must be present, and that patients must be fit for radical treatment. Pre- and post-PET management plans were documented for all patients. Confirmation that assessment of eligibility for surgery was completed before the pre-PET management was determined and that the pre-PET plan was completed before the PET results were obtained was not reported. The study collected information on the therapeutic management plans and did not specifically request information on further diagnostic investigations. It also reported agreement of the actual patient therapy with the post-PET management plan at 6 months' follow-up. Only the data from those patients with complete pre- and post-PET management plans and confirmation that management plans were initiated were eligible for analysis. On this basis, 4 patients were excluded from the data analysis as they either died (3) or were lost to follow-up (1) before actual post-PET management could be confirmed, leaving 129 patients in the analysis. This approach provides a potential source of selection bias in the results; all patients undergoing PET should be included.

This report also provides detailed information about the spectrum of patients tested, the type of management received, and patient outcomes at 12 months. These findings are summarised on pages 9 ('Australian PET data collection study') and 57 (under

‘Prognosis following PET’). Data on the sensitivity of CT, PET and EUS for the primary tumour were also provided. However, these data are excluded from this review, which is concerned with the accuracy of PET for staging biopsy-proven primary oesophageal cancer.

Table 15 Characteristics and appraisal of Australian data collection project report

Author (Year) Setting	N	Test comparison	Population	Outcomes	Management
(Chatterton 2006) Australia Multicentre March 2004 – June 2006 (prospective data collection project)	129	PET/CT 18% PET 82% <i>in addition to</i> CT (85%), clinical exam (27%), endoscopy (88%), EUS (11%), other (11% [US, MRI, other])	Biopsy-confirmed cancer of oesophagus or GEJ (77% AC, 19% SCC, 4% other) Fit for potential radical treatments (surgery, neo-adjuvant chemo + surgery, or radical radio-chemo) No distant mets at presentation, CT and endoscopy or Equivocal metastatic lesions, not accessible to FNA 66 y (range 36–87) 81% male	PET detection of additional sites of disease (poor accuracy analysis) Change in management, proportion up- and downstaged, curative vs palliative intent Progression-free survival	Prospective: YES Explicit criteria: YES Consecutive patients: NO Referring clinician: YES Accuracy: n.r. Plans independently assessed: NO Blinding to study results: UNCLEAR Explicit outcomes: YES Patient outcomes: YES Physician experience: n.r.

Abbreviations: AC = adenocarcinoma, chemo = chemotherapy, CT = computed tomography, EUS = endoscopic ultrasound, FNA = fine-needle aspiration, GEJ = gastro-oesophageal junction, mets = metastases, MRI = magnetic resonance imaging, n.r. = not reported, PET = positron emission tomography, SCC = squamous cell carcinoma, vs = versus, US = ultrasound

Is it accurate?

Many studies report the comparative accuracy of PET and conventional imaging tests. They provide data on the value of PET as a replacement for conventional imaging. However, the current assessment addresses clinical questions concerned with the value of PET as an additional test. The accuracy of PET in providing incremental information over that of CT is the most relevant measure to answer these clinical questions. This information can be obtained only from studies reporting:

- 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)
- the accuracy of PET plus conventional imaging versus conventional imaging alone (ie, PET+CT vs CT alone) or
- discordant test results (or individual patient data) where both tests are performed in all patients (the discordant positive PET results for advanced disease are those where PET is positive and CT is negative).

Oesophageal cancer primary staging

PET is proposed for use in patients with biopsy-proven oesophageal cancer which is negative for distant metastases on CT. PET is then used to identify distant metastatic disease which would preclude definitive treatment. Therefore, data on the accuracy of

PET for M-stage disease (distant lymph node or organ metastases) are presented and discussed here in preference to data on N-staging. Detection of lymph node metastases may also aid in the selection of appropriate therapy for patients; where such data are reported in the included studies they are provided in Appendix H.

Comparative accuracy

Data from the UK NCCHTA report indicated that the sensitivity of PET for detecting distant metastases from oesophageal cancer is lower than that for other cancers but somewhat better than CT (Facey et al. 2007).

Incremental accuracy

Four studies provided data on the incremental value of PET over that of CT in a patient group applicable to the research question of staging primary oesophageal cancer. No studies reporting the incremental value of PET/CT were identified. Two studies were conducted in fewer than 50 patients, with positive PET results in only 4 and 6 patients.

Among studies of the value of PET in detecting additional distant metastases in patients with primary oesophageal cancer:

- four studies indicated that PET was positive in 14 to 18 per cent of patients
- one fair-quality study indicated that the PPV for detecting metastases with a high-quality reference standard was 63 per cent, and that the PPV for all metastases was 58 per cent
- another fair-quality study indicated that the PPV for detecting metastases from oesophageal cancer was 27 per cent, with synchronous neoplasms also detected in 23 per cent of the patients with a positive PET result (3.5% of all patients)
- in the two larger studies (conducted in 189 and 199 patients), PET was true-positive in 4 and 5 per cent of patients.

PET/CT may have had a lower false-positive rate than PET alone, but no data were available to permit this to be quantified.

Incremental accuracy

The incremental accuracy of PET in detecting distant metastatic disease over that of conventional staging in patients with potentially curable primary oesophageal cancer is shown in Table 16 and Table 17.

Data in Table 16 come from four studies identified in the current systematic review that report the accuracy of PET-positive results for distant metastases (M-stage disease). The yield of PET in identifying M-stage disease ranged between 14 and 18 per cent.

In one study (Meyers et al. 2007) the PPV of PET was 63 per cent for histopathologically confirmed M1a or M1b disease. Histopathological confirmation took place at the time of operation for some patients, in some cases following

induction chemotherapy. For M1a disease there were one true-positive and one false-positive finding. The remaining 15 patients were upstaged to M1b disease status. The PPV for PET-detected metastases with any reference standard (including imaging) was 58 per cent. The PPV for detecting organ metastases only (M1b disease) in patients staged M0 or M1a on CT was 55 per cent (with any reference standard).

The second larger study found that PET had a PPV for detecting metastases from oesophageal cancer (stage IV disease) of 27 per cent (van Westreenen et al. 2007b). However, seven patients (3.5% of total patient group) had synchronous neoplasms identified on PET (5 rectosigmoid adenomas, 1 Hürthle cell thyroid tumour, 1 colon AC). These 23 per cent (7/30) of patients with a PET-positive lesion were false-positive for oesophageal metastases, but true-positive for neoplastic disease, so that PET had a PPV of 50 per cent for detecting neoplastic disease. In this study all PET-positive lesions were confirmed by histology, cytology or other imaging where possible. When distant dissemination could not be confirmed preoperatively, the patients proceeded to surgery with intraoperative biopsy. Six months' follow-up was also used as a reference standard for any unconfirmed lesions.

In these two larger studies, additional true-positive findings were found by PET in 4 and 5 per cent of patients, and additional false-positive findings (for metastatic oesophageal cancer) in 3 and 11 per cent. The ratio of additional true-positive to false-positive findings ranged between 0.36 and 1.7.

Accuracy data from one study included in the UK NCCHTA report (Sihvo et al. 2004) are also summarised in Table 17. This study reports the sensitivity and specificity of PET plus conventional imaging versus that of conventional imaging alone. Inclusion of PET in the staging pathway increased the accuracy for M-staging over that of CT or CT+EUS, mostly by increasing the sensitivity. The specificity of all staging options with CT or CT+EUS, with or without PET, was high (97%–100%). Specificity was higher for PET+CT than for CT alone (100% vs 97% respectively), indicating that in at least one case a negative PET result was used to correct a false-positive CT finding. The PPV in this study was 100 per cent for the additional metastases detected by PET, as there were no false positives when PET was included for staging, but only six patients had additional metastases detected on PET (Table 16).

In the other smaller study (Stahl et al. 2005), when PET was read blind to CT, the PPV of PET for detecting additional metastases in four patients was 25 per cent. The true finding was a bone metastasis. When a consensus reading of PET and CT by a nuclear medicine physician and a radiologist was performed, the three false-positive findings were corrected. The small number of patients involved limits the value of these data.

The studies of Stahl et al. (2005) and van Westreenen et al. (2007b) include EUS as a prior test before PET. Although this does not reflect the suggested clinical pathway in Australia (Figure 3), it may not limit the applicability of the data greatly, as the role of EUS is in staging regional, rather than distant, spread of disease.

In the study by van Westreenen et al. (2007b), all PET-negative patients, or those with unconfirmed metastases, underwent surgical exploration. The authors reported that at surgery, nine patients with distant metastases were found (false-negative PET). Thus,

the sensitivity of PET for detecting distant metastases occult on conventional staging was at most 47 per cent (8/17; see Appendix H). These data are of limited use in determining the value of PET in the absence of information on the specificity of PET, or on the sensitivity of a non-PET staging strategy. The most clinically relevant accuracy measure is the ratio of additional true-positive to false-positive results, as negative PET results will not modify patient management.

Pooled results

Combining the results of all four studies included in the systematic review which reported yield and PPV (using a fixed-effects model) gave a pooled yield of 16 per cent (95% CI 12%–19%) and a pooled PPV of 40% (95% CI 28%–53%). For the pooled yield, studies were not heterogeneous ($Q = 1.32$, $P = 0.86$), whereas for the pooled PPV, studies showed statistically significant heterogeneity ($Q = 29.86$, $P < 0.0001$).

The two smaller studies (Sihvo et al. 2004; Stahl et al. 2005) had little impact on the pooled results. When they were excluded, the pooled PPV was 38 per cent (95% CI 25%–51%).

Table 16 Incremental value of PET in the assessment of primary oesophageal cancer (discordant positive PET results)

Author (Year)	N (% prev) / N prior negative disease	Population	Prior tests	Outcome	Incremental positive findings (distant metastases)					Quality & applicability
					Yield N (%)	TP N (%)	FP N (%)	PPV % (95% CI)	TP/FP	
Meyers et al. (2007)	189 (n.r.) / M0: 187	Confirmed AC or SCC of oesophagus or GEJ Surgical candidates	CT (bone scintigraphy, brain MRI if indicated)	M1a- or M1b-stage disease	34 (18)	10 (5%)	6 (3%)	63 ^{a, b}	1.7	Fair quality (poor-quality ref standard for all metastases) ^a Applicable (not PET/CT)
Stahl et al. (2005)	40 (28%) / CT-: 28	Confirmed, locally advanced AC of distal oesophagus planned for neoadjuvant therapy	CT EUS	M-stage disease (PET read blind to CT)	4 (14)	1 (4%)	3 (11%)	25	0.33	Fair quality (retrospective) Limited applicability (EUS prior)
				M-stage disease (consensus PET and CT reading)	1 (3)	1 (3%)	0 (0%)	–	–	
Van Westreenen et al. (2007b)	199 (9%)	Proven cancer of thoracic oesophagus or GEJ; resectable; no distant mets	CT EUS US of neck, ± FNAC, ± bronchoscopy	M-stage disease	30 (15)	8 (4%)	22 ^c (11%)	27 (10–43)	0.36	Fair quality Limited applicability (EUS prior)
Sivho et al. (2004)	48 CT- Incremental value	Patients w AC of oesophagus (20) or GEJ (35) considered eligible for resection CT-	Endoscopy, CT, EUS	M-stage disease	6 (13)	6 (13%)	0 (0%)	100	∞	From high-quality systematic review (prospective study)

Abbreviations: AC = adenocarcinoma, CI = confidence interval, CT = computed tomography, EUS = endoscopic ultrasound, FNAC = fine-needle aspiration cytology, FP = false-positive; GEJ = gastro-oesophageal junction, MRI = magnetic resonance imaging, n.r. = not reported, PET = positron emission tomography, PPV = positive predictive value; prev = prevalence; SCC = squamous cell carcinoma, TP = true-positive, US = ultrasound

a. PPV in 16 patients with histopathology reference standard (some patients may have undergone indication chemotherapy); confirmation with any ref standard (including imaging), PPV = 58% (15/26); confirmation with reference standard histopathology or clinical follow-up, PPV 57% (13/23).

b. Data for patients staged M0 on CT ($n = 187$); if 2 patients with CT-staged M1 are included ($n = 189$), PPV for M1b disease with a reference standard of histology or clinical follow-up = 55% (12/22).

c. 7 of 22 FP were synchronous non-oesophageal neoplasms.

Table 17 Accuracy studies of the incremental value of PET and CT compared to CT alone in primary oesophageal cancer staging

Author (Year)	N (% prevalence)	Population	Prior tests	Sensitivity % (95% CI)		Specificity % (95% CI)	
				M-stage		M-stage	
				PET + prior tests	Prior tests	PET + prior tests	Prior tests
Sivho et al. (2004)	55 (35%)	Patients w AC of oesophagus (20) or GEJ (35) considered eligible for resection	Endoscopy, CT, EUS	PET+CT 64 PET+CT+EUS 74	CT 32 CT+EUS 42	PET+CT 100 PET+CT+EUS 100	CT 97 CT+EUS 100

Abbreviations: AC = adenocarcinoma, CI = confidence interval, CT = computed tomography, EUS = endoscopic ultrasound, GEJ = gastro-oesophageal junction, PET = positron emission tomography

Comparative accuracy

The UK NCCHTA report presented data on the comparative accuracy of PET as a replacement for CT. These data are of limited use for estimating the incremental value of PET when it is added to the conventional staging pathway. Primary studies reporting the replacement value of PET and CT published since August 2005 are not included in this review, but the data provided in the UK NCCHTA report are summarised as providing supportive data for completeness.

Data from three studies relevant to primary oesophageal cancer, but reporting the replacement value of PET, are summarised in Table 18. The authors of the UK NCCHTA report concluded that the sensitivity of PET for detecting distant metastases from oesophageal cancer is lower than that for other cancers, at 67 per cent (sROC analysis), but somewhat better than that of CT (page 45 & 68, Facey et al. 2007). The conclusions on PET staging of lymph node metastases were similar: that the sensitivity is lower than for some other cancers, at approximately 50 per cent, but comparable to or a little better than that of CT.

Summary

The available evidence indicates that the addition of PET to the conventional staging pathway increases the detection of distant metastases from primary oesophageal cancer. However, this is also associated with an increase in the number of false-positive findings. PET was positive (including true-positive and false-positive findings) in 14 to 18 per cent of patients in four studies. One study (Meyers et al. 2007) indicated that the PPV for detecting distant metastases from oesophageal cancer was 57 to 63 per cent. The other large study (van Westreenen et al. 2007b) indicated that the PPV for distant metastases was 27 per cent, with an additional 23 per cent of positive findings due to synchronous non-oesophageal neoplasms. PET/CT may have had a lower false-positive rate than PET alone, but no data on the value of PET/CT as an additional test were available.

Table 18 Accuracy studies of the replacement value of PET staging of distant metastases in comparison to conventional imaging in primary oesophageal cancer (Facey et al. 2007)

Author (Year)	Population	Outcome	N (% prevalence)	Comparator	Sensitivity %		Specificity %	
					PET	Comparator	PET	Comparator
BCBS (2002)	Biopsy-proven oesophageal cancer (SCC, AC)	Distant lymph node mets	2 studies, <i>n</i> = 77 (16%–31%)	CT	25–77	0–46	90–96	69–100
		Distant organ mets	3 studies, <i>n</i> = 196 (17%–46%)	CT	69–100	41–50	90–93	74–95
Heeren et al. (2004)	Resectable carcinoma of the oesophagus or GEJ	Distant lymph node mets	<i>N</i> = 72 (33%)	CT	71	21	98	98
Liberale et al. (2004)	<i>De novo</i> oesophageal or GEJ cancer	Distant mets	<i>N</i> = 58 (28%)	CT	88	44	88	95

Abbreviations: AC = adenocarcinoma, CI = confidence interval, CT = computed tomography, GEJ = gastro-oesophageal junction, mets = metastases, PET = positron emission tomography, SCC = squamous cell carcinoma

Oesophageal cancer residual disease

PET is proposed to be used in assessing residual disease in patients who have received definitive chemo-radiation (see clinical flow chart, Figure 4, page 17). Where residual disease has been confirmed by biopsy, PET is then used as a replacement for CT to detect distant metastatic disease. Where residual disease has not been confirmed by biopsy, PET is used in addition to CT to detect active residual disease.

No studies reporting the accuracy of PET in assessing residual disease following definitive (not neoadjuvant) chemo-radiation were identified in the UK HTA report (prospective studies) or in the systematic review of primary (prospective or retrospective) studies published since August 2005.

Gastric cancer

PET is proposed to be used in patients with biopsy-proven gastric cancer eligible for curative surgery (stage I–III disease) on CT and laparoscopy (see clinical flow chart, Figure 5, page 18). PET is then used as a test to identify additional metastatic disease which would preclude definitive treatment.

No studies reporting the accuracy of PET following laparoscopy (with or without CT) were identified in the systematic review of primary studies published since 2001.

Pre-PET staging with laparoscopy is expected to identify most small volume peritoneal and hepatic metastases from gastric cancer that are not seen on abdominal CT. In gastric cancer, the three most frequent sites of metastases are the liver, abdominal lymph nodes and peritoneum (Hosokawa et al. 2007; Yoshida et al. 2004). These sites accounted for 89 per cent of metastases in 497 patients (Yoshida et al. 2004). Pre-PET staging with CT will detect some distant metastases. Thus, the proportion of gastric cancer patients with stage IV disease and no metastases detected on laparoscopy or CT is expected to be small.

Studies reporting the accuracy of PET in a different patient group would not be informative, because PET accuracy varies according to the anatomical location of the metastasis: ie, patients not staged by laparoscopy will have a different distribution of metastatic sites from patients staged after laparoscopy, and therefore estimates of PET accuracy will differ between these patient groups.

No studies reporting the incremental or comparative accuracy of PET versus CT for detecting extra-abdominal metastases from gastric cancer were identified.

Does it change patient management?

Additional positive results detected by PET can lead to changes in management, for example by identifying patients in whom attempted definitive treatment is unlikely to be beneficial, thus avoiding the associated risks of morbidity and mortality, and guiding the selection of optimal treatment for metastatic disease. However, the proportion of patients in whom definitive treatment will be avoided 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. In some patients with resectable disease, surgery may not in fact be planned owing to other contraindications or patient preference. In other patients, surgery may proceed despite the finding of additional foci on PET—for example, where a lesion cannot be confirmed by biopsy, or is considered on clinical grounds as unlikely to represent a metastasis.

Therefore, 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 disproved.

Australian data

The largest and most applicable study reporting the impact of PET on the management of patients with primary oesophageal cancer was the Australian prospective study by Chatterton (2006). PET detected distant metastases in 24 per cent of all patients (31/129; 95% CI 17%–32%). The following changes in management plans occurred after PET in patients with oesophageal cancer considered suitable for definitive treatment:

- Surgery was avoided in 19 per cent (95% CI 12%–26%) of patients; in particular, in 26 per cent (24/94; 95% CI 17%–36%) of patients for whom surgery had been planned before PET.
- Management was changed in a total of 38 per cent (95% CI 30%–46%) of patients, 27 per cent (95% CI 20%–36%) owing to a positive PET result for regional or distant metastases.
- Treatment intent was changed from curative to palliative owing to a positive PET finding of regional or distant metastases in 20 per cent (95% CI 14%–28%) of patients.
- Chemotherapy and/or RT were avoided (one or both modalities dropped) in 3 per cent of patients, and the intent of CRT was changed from curative to palliative CRT or RT in 5 per cent.

Actual management at 6 months' follow-up was in concordance with post-PET management plan in 52 per cent of patients, and was consistent with PET results in an additional 11 per cent.

The data in Australian prospective study of PET in oesophageal cancer (Chatterton 2006) are the most applicable to the study populations 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 this patient population. Only a minority of patients in this study had PET/CT (18%), limiting the applicability of the technology used to current Australian practice.

Table 19 presents the key therapeutic impact outcomes extracted from this report, as identified *a priori* in Table 6. The results of the Australian study are detailed in

Appendix H (page 95). The analysis included 129 patients with biopsy-proven oesophageal cancer.

The post-PET management plan included the avoidance of surgery in 19 per cent of all patients (24/129; 95% CI 12%–26%). However, before PET, only 94 patients (73%) were planned to have surgery. Surgery was avoided in 26 per cent (24/94; 95% CI 17%–36%) of those for whom it was planned. Intent of surgery was not recorded where there was no management change. Most surgery was avoided in patients initially scheduled to have surgery alone (14%); surgery in conjunction with (neo)adjuvant therapy was avoided in 5 per cent of all patients (32 per cent of those initially planned for surgery and [neo]adjuvant therapy).

Surgery was added to the post-PET treatment plan in 0.8 per cent (1 patient) of the total patient group (3% [1/35] of those in whom surgery was not planned before PET). This patient had a pre-PET plan of CRT with palliative intent.

Treatment planning after PET led to the avoidance of CRT (one or both modalities dropped) in 3 per cent (4/129) of patients, or 14 per cent of those for whom CRT without surgery was planned before PET. It is unclear whether the planned CRT was definitive or palliative in these cases. However, in an additional seven patients (5%), the intent of curative CRT was changed to palliative CRT or palliative RT.

On the other hand, post-PET treatment plans indicated that chemotherapy, RT or both were instigated (either one or both modalities added to the existing treatment plan) in 5 per cent (7/129) of all patients. Chemotherapy and/or RT was added to the post-PET plan for 75 per cent of patients who avoided surgery (18/24). Of those patients for whom chemotherapy plus radiation therapy had not been planned before PET (66%), 12 per cent of patients (16/129) had combined CRT planned after PET.

The management plan changed for a total of 38 per cent (95% CI 30%–46%) of patients, in 27 per cent (95% CI 20%–36%) owing to a PET result that confirmed equivocal or detected occult regional or distant metastases. The pre-PET treatment intent was curative for 92 per cent of patients. The total proportion of patients among whom PET led to a change in management plan was greater than the proportion benefiting from avoidance of planned surgery or other treatment. The treatment intent changed for 23 per cent (95% CI 16%–31%) of patients, including a change from curative to palliative intent in 20 per cent (95% CI 14%–28%) due to a positive PET finding of regional or distant metastases.

Avoidance of further investigations was reported for one patient who avoided laparoscopy, but the study did not specifically collect data on this outcome.

PET detected additional sites of distant disease in a higher proportion of patients than was indicated by the yield of PET in accuracy studies reporting the additional value of PET in the previous section ('Is it accurate?', Table 16, and Table 17). PET detected distant metastases in 24 per cent of all patients (31/129; 95% CI 17%–32%). This difference may be due to the inclusion of a selected sample of patients in the accuracy studies, or to differences in the spectrum of disease in the patient populations in the Australian study. The number of patients in whom additional metastases were detected was greater than the number in whom surgery was avoided. This exemplifies the

difficulties that may arise when attempting to infer management change from studies of diagnostic accuracy alone.

Table 19 Impact of PET on patient management in primary oesophageal cancer staging—Australian data collection

Author (Year)	N	Surgery avoided (%)	Chemo-radiation avoided ^a	Investigations avoided	Surgery instigated	Total % change (95% CI)	Other changes in >10% Type % (95% CI)	Yield Stage change % (95% CI)
(Chatterton 2006)	129	<u>Surgery alone</u> : 14% (30% of planned)	3% (14% of planned)	1% (laparoscopy)	1% (3% of non-surgical)	38 (30–46)	23 (16–31) treatment intent change	24% detection of distant mets in M0 CT (31/129)
	PET/CT 18%	<u>Surgery + chemo and/or RT</u> : 5% (32% of planned)	5% (7/129) definitive to palliative CRT or RT			Due to PET+ ^c : 27 (20–36)	20 (14–28) intent changed curative → palliative due to PET+ ^c	40% (51/129) detection of regional or distant mets
	PET 82%	<u>Any type</u> : 19% (26% of planned)					CRT instigated: ^a 12% (19% of those not planned before)	Upstaged to M-stage in 22% (28/128)

Abbreviations: chemo = chemotherapy, CRT = chemo-radiotherapy, CT = computed tomography, mets = metastases, PET = positron emission tomography, RT = radiotherapy

a. CRT refers to chemo + radiation therapy (consecutive, concurrent); changes to CRT are changes where either one or both modalities are added to the treatment plan; avoidance of CRT refers to changes where either one or both modalities are dropped.

b. Radio- or chemotherapy as single modality instigated

c. PET + for regional or distant metastases

The planned changes in patient management reported in this Australian study may overestimate actual management changes resulting from PET. In some cases the pre-PET management plan may not have accurately reflected actual clinical behaviour had PET been unavailable. For example, a stated intention to proceed to surgery before PET may not have reflected conventional planning for surgery in the absence of PET. It was reported that actual treatment was concordant with the predefined post-PET plan at 6 months' follow-up in 52 per cent (60/124) of patients. Reasons for discordance are provided in Table 20. In another 11 per cent (14/124) of patients, further review rated treatment as 'consistent' with the PET *results* (not the post-PET management plan). In these patients, it is unclear whether actual management changed from the pre-PET plan.

Actual management was not concordant with either the post-PET plan or the PET result in 37 per cent of patients. This indicates that the reported impact of PET on changing management plans many overestimate the impact in practice.

Table 20 Reasons for differences between post-PET treatment plan and actual management

	<i>N</i>	% total (/124)
Further review of treatment indicated consistent with PET findings	14	11.3%
Planned chemotherapy and/or RT regimen changed due to initial response, toxicity or patient deterioration	10	8.1%
More extensive disease than was detected on PET	8	6.5%
Other clinical reasons	7	5.6%
Insufficient information available	6	4.8%
Palliative treatment needed for symptom control	5	4.0%
Different surgical findings (tumour found to be unresectable at operation, clear margins not requiring any further treatment, incomplete dissection requiring additional treatment)	4	3.2%
Patient declined treatment as planned	3	2.4%
A second opinion indicated a different therapeutic approach	2	1.6%
Additional treatment for disease progression	1	0.8%
Total	60	48.4

Source: (Chatterton 2006)

Clinicians rated the impact of PET as high (ie, the treatment modality or intent was changed owing to the PET result) in 35 per cent (95% CI 27%–43%) of patients. The impact of PET was rated as none or low in 62 per cent (95% CI 54%–71%) of patients.

Evidence from published literature

Primary oesophageal cancer

Evidence from published studies provides supportive evidence of the impact of PET on the management of patients with primary oesophageal cancer in Australia.

The systematic review identified two therapeutic impact studies which provide information on the therapeutic impact of PET for staging of patients with primary

oesophageal cancer. The characteristics and quality assessment of these studies are summarised in Appendix I (Table 32). These studies were conducted in highly applicable patient populations. One study was of PET (Duong et al. 2006a), the other of PET and CT fusion (McDonough et al. 2007). In these two studies PET led to the avoidance of surgery in 6 and 2 per cent of patients, respectively. These data are summarised in Appendix I (Table 33, page 113).

In addition, the study by van Westreenen et al. (2005) provided information on the number of unnecessary explorations performed in patients with cancer of the oesophagus or the GEJ undergoing staging with or without PET using historical controls (see Appendix H). Patients undergoing preoperative chemotherapy or RT were excluded. In the study, 'unnecessary explorations' were defined as abandoned resections due to locally unresectable tumours or M1 disease, discovered at operation. The surgical procedures included laparotomy and thoracotomy with exploration. In patients staged with CT+EUS (during 1997) or CT+EUS+PET (during 1998–2002), unnecessary explorations were conducted in 50 per cent (18/36) and 21 per cent (13/61), respectively. However, studies of this design are prone to bias, making interpretation of results difficult.

Residual disease

One Australian therapeutic impact study of 53 patients undergoing PET for the assessment of residual disease after CRT was identified (Duong et al. 2006b). The characteristics and results of this study are summarised in Appendix I (Table 32 and Table 33, from page 111).

Patients with locally advanced disease (T3–4 or N1) received a 'radical' CRT regimen. Patients with M1a disease received a shorter course of treatment, which appeared to be a palliative CRT regimen. Details of the CRT regimens used are provided in the data extraction table in Appendix H. Pre-PET management plans are not reported, and it is unclear how many patients received PET after definitive ('radical') CRT and how many after the shorter course of chemo-radiation.

The study reported a high-impact management change (change in treatment intent or modality) in 36 per cent of patients (19/53).

Post-PET plans indicated a change in treatment modality in 14 patients (26%); avoidance of surgery or additional chemotherapy and change to observation in 9 patients (17%); and avoidance of surgery in 3 patients (6%) with minimal response to CRT and persistent bulky locoregional disease who received further courses of chemotherapy instead. In two patients (4%), PET was positive for CT-occult residual disease, and management plans changed from observation to surgery.

A change in treatment intent was reported from curative to palliative in 7 per cent (3/53) of all patients, and from palliative to curative in 4 per cent (2/53).

The authors reported that the treatment delivered corresponded to the post-PET management plan for all patients.

Primary gastric cancer

No studies reporting the therapeutic impact of PET in patients with gastric cancer were identified.

Summary

The identified studies provide evidence that the use of PET in patients with primary oesophageal cancer leads to changes in the management of a substantial proportion of patients. The most frequent major change in management following PET was the avoidance of planned surgery: in 19 per cent of patients in the Australian data collection study. A positive PET result for regional or distant metastases was associated with a change in management in 27 per cent (95% CI 20%–36%) and a change in treatment intent from curative to palliative in 20 per cent (95% CI 14%–28%). However, in that study, the post-PET plan differed from actual management of 48 per cent of patients. Surgery was avoided in 2 and 6 per cent of patients in two smaller studies (Duong et al. 2006a; McDonough et al. 2007).

A single study (Duong et al. 2006b) reported an impact of PET on treatment intent or modality in 36 per cent of patients following CRT. The proportion of patients who had received definitive CRT was unclear. However, in the absence of evidence for the accuracy of PET for assessing residual disease, the proportion in whom the management change was based on a correct PET finding cannot be inferred.

There is uncertainty regarding the magnitude of these effects due to inevitable biases inherent in studies of this type.

Does change in management improve patient outcomes?

Where the use of PET improves diagnostic accuracy, it should improve outcomes for patients if it results in more appropriate management.

Existing evidence indicated that the addition of PET improves the detection of distant metastases in patients with primary oesophageal cancer (see ‘Is it accurate?’, page 39).

Evidence for the incremental accuracy of PET over conventional imaging for assessment of residual disease following definitive chemo-radiation for oesophageal cancer, and for staging gastric cancer following CT and laparoscopy, was not identified. Therefore, a case for linked evidence for an improvement of patient outcomes due to PET in these indications cannot be made.

The main role of PET for pretreatment staging of patients with primary oesophageal cancer otherwise considered curable is to identify other disease sites that would preclude definitive treatment. In lieu of definitive surgery, chemo-radiation or both, the majority of patients will receive palliative chemo-radiation. Therefore, the main treatment change likely to follow PET is the avoidance of oesophagectomy. In addition, patients are likely to receive less-intensive regimens of chemo-radiation.

Appendix J (page 114) summarises the complication rates associated with oesophagectomy, and indicates that surgery is associated with mortality in

approximately 9 per cent of patients and with adverse events in approximately 35 to 70 per cent.

Patients avoiding oesophagectomy will avoid the risk of surgical complications and the impact of surgery on quality of life (pain, time in hospital, recovery after discharge) associated with resection that is unlikely to provide long-term benefit.

A randomised controlled clinical trial of attempted curative therapy versus palliative therapy in this patient group would be needed to demonstrate that the adoption of palliative therapy leads to improved outcomes (Bossuyt et al. 2000). However, comparative studies of curative versus palliative therapies for patients with PET-detected CT-occult sites of metastatic disease (ie, PET-positive, CT-negative) were not identified in this assessment (although a systematic review addressing this question has not been performed). Clinician and patient preference is likely to play an important role in treatment selection that may reduce the feasibility of conducting randomised trials.

Current treatments for patients with more widespread metastatic disease are based upon trials among patients with metastases detected by conventional imaging, rather than PET-detected, CT-occult disease. Patients with metastatic disease detected by PET but not by CT could conceivably be at an earlier stage of disease progression than those with metastases detected by CT alone. Whether additional disease sites detectable only by PET progress at a rate that negates any benefit from resection of the primary tumour has not been demonstrated in clinical trials.

In the absence of clinical trials comparing alternative therapies in these patients, it is not known whether the potential improvement in quality of life from avoiding surgery and instigating alternative management outweighs any potential benefit of surgery in reducing disease progression and local symptoms. Nevertheless, surgery is likely to be less beneficial in patients with additional metastases detected by PET than in patients with no additional sites of disease. The expert opinion of the advisory panel was that aggressive surgical treatment is not warranted in these patients.

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 therefore detect patients with a different spectrum of disease from 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 (with or without EUS), but it is possible their prognosis may still be better than that of patients with widespread metastatic disease detectable by CT \pm EUS. 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 in patients staged with PET versus conventional

testing alone, and therefore conclusions about the impact of adopting PET on patient outcomes cannot be made on the basis of this type of evidence. However, well designed studies may provide some supportive evidence for a role of PET.

Information from studies reporting the prognosis of patients with oesophageal and gastric cancer following PET is discussed below.

Published literature—systematic review

A retrospective cohort study reporting survival of patients with oesophageal or GEJ cancer staged with versus without PET using a historical control group was identified (van Westreenen et al. 2005). It reported that patients who underwent resection following staging by PET in addition to CT and EUS survived longer than those staged by CT+EUS alone (median survival 48.2 months [$N = 48$] versus 25.6 months [$N = 18$]; the authors reported no significant difference between these groups or a CT-alone group by log-rank test $P = 0.34$). However, the number of censored patients in the analysis is not reported. In such historical comparisons the inherent bias makes interpretation of findings difficult (see page 37).

A study of the use of PET following CRT reported findings in a group of 37 patients who did not undergo surgery owing to advanced disease, medical contraindications or patient refusal (Konski et al. 2007). Twenty-five (68%) underwent PET after CRT. The authors reported that neither mean post-treatment SUV nor mean percentage decrease in SUV predicted the site of failure. Univariate analysis found that post-treatment SUV significantly predicted disease-free survival; a single unit increase in the post-treatment SUV increased disease-specific mortality by 30 per cent ($P = 0.01$). However, no variables were significant on multivariate analysis, indicating that the finding from the univariate analysis was likely to be due to confounding by other factors.

Theoretically, studies demonstrating better outcomes for patients selected for surgery on the basis of PET would indicate that PET assists in selecting the group with the best prognosis for surgery. Those excluded from surgery would appear to have a less favourable prognosis. The morbidity and associated quality of life implications of surgery may be more important for those with a shorter life expectancy—median survival in patients undergoing surgical exploration without curative oesophagectomy was 8.8 months (van Westreenen et al. 2005). Also, surgical morbidity rates may be higher in patients with a worse prognosis. However, such prognostic data do not prove that these patients might not have achieved some benefit from surgery in comparison with palliative therapy alone.

Similarly, studies comparing the prognosis of patients undergoing *the same therapy* regardless of PET results could provide information about the prognostic value of PET. Studies in which all patients underwent surgical resection might be expected to show that patients positive for metastases on PET have a worse postoperative survival than PET-negative patients and thus confirm the prognostic value of PET. However, such studies would not provide data on the relative benefits of treatment alternatives (ie, the benefit of palliative vs attempted curative therapy) for patients at a given stage of disease.

One study reporting the prognostic value of PET in primary gastric cancer was also identified in the systematic review (Mochiki et al. 2004). This study reported the survival of 85 patients undergoing radical gastrectomy with curative intent without neoadjuvant treatment. Patients with PET-positive primary tumours had a significantly shorter survival than patients with PET-negative tumours (2-year survival approximately 66% [$n = 64$] versus 94% [$n = 21$] respectively; $P = 0.046$, log-rank test). This study may indicate that PET provides some information on the aggressiveness of PET-positive gastric cancer, but knowledge of the SUV of the primary tumour is not currently used as a determinant of the management of the patient. The study provided no information on the prognostic value of using PET to detect gastric cancer metastases.

Australian data

The Australian data collected from the five PET facilities between 2004 and 2006 provide some information on patient prognosis following PET (Table 21) (Chatterton 2006). The study was not designed to compare patient survival or disease progression in patients staged with PET versus conventional testing alone, and therefore valid conclusions about the direct impact on patient outcomes of adopting PET cannot be made.

The study demonstrated that patients with PET-detected metastatic oesophageal or GEJ cancer not apparent on prior imaging have a higher risk of disease progression at 12 months than those without PET-detected extra sites of disease (relative risk [RR] = 1.69, 95% CI 1.07–2.72). The results also show that patients classified by PET as potentially curable have a lower risk of disease progression than those classified as incurable; ie, ‘palliative’ (palliative progression RR = 1.69, 95% CI 0.94–2.71). However, these patient groups received treatment modified by their PET findings, and thus this information does not provide evidence for the prognostic value of PET alone, as it also captures the effects of different treatments on disease progression.

Table 21 Prognosis following PET-selected therapy for oesophageal cancer in Australian patients

PET classification	Disease progression by 12 months <i>n/N</i> (%)	Relative risk (95% CI)	Risk difference (%) (95% CI)	χ^2 test <i>P</i>
Curable	27/78 (35)	1.69 (0.94–2.71)	24 (17–33)	<0.05
Incurable ('palliative')	13/22 (59)			
No occult disease	20/37 (54)	1.69 (1.07–2.72)	22 (15–31)	<0.02
Occult disease	20/63 (32)			

What are the economic considerations?

Economic evaluation of new health care technologies is particularly important when the new technology offers health benefits at additional cost. It is clear that there will always be a limit to the additional cost which would willingly be paid for a given health gain. Economic evaluation is generally aimed at determining whether such incremental costs represent value for money.

The usual process for an economic evaluation is first to consider the additional benefits accrued with the new device or procedure relative to the comparator (ie, the incremental effectiveness), and then to proceed with determining 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, then an incremental cost-effectiveness ratio (ICER) can be determined.

There are situations where capturing health outcomes into a single effectiveness measure is difficult or inadequate. This might be the case when various morbidity and mortality outcomes exist and if trade-offs between multiple health gains and detriments exist between two technologies (for example, if one technology offers benefits in terms of quality of life at reduced safety than the standard technology). In these cases, conducting a cost-consequence analysis may be the preferable approach. In a cost-consequence analysis, the incremental costs of the proposed technology over its main comparator are compared with an array of outcomes measured in their natural units rather than as a single representative outcome (Drummond et al. 2005).

In the case of PET for the staging of primary oesophageal cancer, a cost-consequence analysis appears the most appropriate approach to capture potential trade-offs associated with using PET. Trade-offs between the potential health benefits associated with avoiding non-beneficial definitive therapy and the potential harms associated with falsely upstaging curable disease can then be captured. Thus, a cost-consequence analysis was undertaken to investigate the economic considerations for PET staging of primary oesophageal cancer; the results of this analysis are presented below.

In the case of PET for the staging of primary gastric cancer, a cost-consequence analysis was not undertaken, as evidence for clinical effectiveness was not identified. This lack of data (in particular the lack of information on the false-positive rate for PET applicable to the Australian clinical pathway) also precludes an assessment of the financial impact associated with public funding of PET for gastric cancer in the Australian health care system. The costs to the MBS of the provision of PET itself would not accurately capture the total financial impact. Similarly, the costs, consequences and financial impact of the provision of PET for assessing residual disease following definitive chemo-radiation for oesophageal cancer cannot be determined.

Existing literature

The UK NCCHTA report (Facey et al. 2007) identified one cost-effectiveness analysis of PET in staging of oesophageal cancer (Wallace et al. 2002). The systematic literature review identified one additional unpublished study of the cost of PET for staging oesophageal cancer (van Westreenen 2007a). Neither of these economic analyses was conducted in Australia. No economic analyses of PET in staging of gastric cancer were identified.

Wallace et al. (Wallace et al. 2002) assessed the cost-effectiveness (cost per life year saved / cost per QALY) of six strategies for staging oesophageal cancer, including the addition of PET to CT+EUS. The analysis used a decision-analytic model and is based

on the US Medicare setting. Utility values used for calculation of QALYs are based on expert opinion. In this analysis, CT+EUS was the least expensive option of all six staging strategies. In terms of life years saved, CT+EUS was more effective than PET+CT+EUS. However, both staging strategies had almost identical QALYs (0.9649 vs 0.9650).

The role of PET in the staging of patients with oesophageal cancer in this study is similar to that in the Australian pathway. PET is used if prior CT shows potentially resectable disease, and EUS is used only after a negative PET. However, this analysis is presented for the US health care system, which differs from the Australian system in how health care resources are used, and thus the analysis may not be applicable to this assessment. In addition, the results of this analysis need to be interpreted with caution: calculation of QALYs based on utility values for patients' health states that are derived from expert opinion is not considered appropriate, as estimates usually differ widely between experts and from patients' self-reported values.

The unpublished report by van Westreenen et al. (2007a) describes a prospective study in the Netherlands that aimed to determine the additional costs and value of adding PET to a conventional staging strategy for 199 patients with histologically proven cancer of the thoracic oesophagus or gastric cardia. The incremental accuracy data for PET from this study have recently been published and are included in the present systematic review (van Westreenen et al. 2007b).

Costs of PET and follow-up investigations which precede surgical resection (up to and including surgical exploration) were considered and were assessed from the Dutch hospital viewpoint. Costs of treatment (eg, surgical resection in 5 of 8 patients in their study) were excluded, as only staging costs were investigated. Conventional staging included multi-detector CT, EUS, ultrasound, MRI and bronchoscopy. The study found the costs of PET (€1463/patient) and additional investigations after positive PET (€45/patient), accrued by all 199 patients in the study, to be partly offset by the avoided costs of surgical explorations in 6 patients (€9330/patient), resulting in an additional cost of adding PET to the staging strategy of €1226 per patient. The authors state that it is likely that in practice, cost offsets would be higher given that the costs of oesophagectomy are much higher than palliative care costs. They argue that a fully comprehensive analysis of staging strategies should include the downstream consequences and consider survival and quality of life as ultimate patient outcome measures. However, they considered such an analysis beyond the scope of their study.

The cost of PET in Australia

As part of the PET data collection project, a costing study has been conducted at eight of the nine funded PET sites to assess the current 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) are available from all eight sites for costs of standard whole body scan and long whole body scan for 2005–06

(Appendix K Results of PET cost data study, page 116). Total costs for a standard whole-body PET scan (appropriate for primary oesophageal cancer) ranged between \$761 and \$2067 (mean [SD]: \$1265 [\$482]; median: \$1053).

Costs and consequences of PET in staging oesophageal cancer in Australia

General approach

A cost-consequence analysis was conducted to assess both costs and effects (consequences) of adding PET to the conventional staging pathway for patients with biopsy-proven oesophageal cancer. The analysis considered staging oesophageal cancer for primary treatment only.

Potential consequences of adding PET are changes in patient management (eg, avoidance of radical treatment not considered to be of long-term benefit) and health outcomes arising from the change in management (eg, improved quality of life and reduced surgical morbidity and mortality).

Costs captured in the analysis include the costs of PET and subsequent and alternative staging (EUS) and treatment, and any differences in costs associated with adding PET to the staging pathway.

A decision-analytic model and the information on change in management from the prospective Australian study (Chatterton 2006) were used to assess the costs and consequences of using PET in patients with oesophageal cancer.

Decision model of PET for primary staging of oesophageal cancer

The decision-analytic model assessed the costs and consequences of adding PET for staging patients with biopsy-proven oesophageal or GEJ cancer, who are considered curable on CT staging. In this scenario, PET is used to stage primary oesophageal cancer and will either (a) confirm staging and the decision that definitive treatment is appropriate, or (b) upstage disease (to stage IV) by detecting distant metastases which render the patient ineligible for definitive treatment.

The model has two arms, each of which follows one cohort of patients until final staging: one cohort in which PET is added to the clinical staging pathway and one without PET. The model is based on the proposed role of PET as identified in the clinical flow chart (Figure 3). Accuracy data identified in the systematic review are linked to information on the clinical pathway (follow-up diagnostic tests and treatment) following positive PET results and following conventional staging. The decision tree (Figure 9) is based on the clinical flow chart and expert advice. The distribution of treatments (surgery, surgery + CRT, RT and chemotherapy) in pre-PET management plans from the Australian management study (Chatterton 2006) was used as the model input for treatment distributions for curative treatment in the non-PET arm and in PET-negative patients. The outcomes of the decision analysis were then validated against the Australian patient management data.

The main variables in the model are listed in Table 22 (test characteristics, epidemiology, management of patients, health outcomes), Table 23 and Table 24 (resource use and costs).

Model assumptions

The following main assumptions underlie the decision model:

- The model considers patients with biopsy-proven primary oesophageal cancer which is apparently eligible for definitive treatment as determined by conventional imaging (chest and abdominopelvic CT).
- Curable disease is defined as oesophageal cancer that is amenable to definitive therapy.
- Incurable disease is defined as oesophageal cancer that is not amenable to definitive therapy.
- If disease is considered curable, patients proceed to EUS and then to definitive therapy.
- EUS guides definitive treatment selection, but does not detect any incurable disease.

The following assumptions apply to the group of patients that have **PET added to the conventional staging pathway**:

- A positive PET result is defined as the detection of distant metastases (stage IV disease), which renders the disease incurable.
- If incurable disease is identified on PET, palliative therapy is undertaken after confirmation of incurable disease on biopsy in 65 per cent of patients.
- At confirmation of incurable disease on biopsy, all false-positive PET results (curable disease falsely upstaged to incurable disease) will be corrected and definitive treatment will be instigated in these patients (delayed treatment).
- In patients with apparently incurable disease on PET who do not proceed to biopsy, incurable disease cannot be confirmed and the opportunity for definitive treatment is foregone. That is, false-positive PET results are assumed not to be corrected and/or patients have progressed to incurable disease.

Health outcomes

The main impact on health outcomes from adding PET to the conventional staging pathway in patients with primary oesophageal cancer is the outcome associated with the avoidance of treatment with mistakenly curative intent through the detection of distant metastases (upstaging):

- In this scenario, the outcomes are potential health benefits if PET correctly identifies distant metastases (true-positive for incurable disease), avoiding the quality of life detriment, and morbidity and mortality associated with surgery that is unlikely to be beneficial (see section ‘Does change in management improve patient outcomes?’ page 54).

- The outcomes are potential health detriments if PET results were false-positive for additional metastases, as the opportunity for definitive therapy would be delayed or lost.

In this analysis, only the morbidity and mortality associated with radical surgery are quantified (see Appendix J page 111 and Table 22). The other potential health outcomes are not quantified, but are discussed qualitatively as appropriate.

In patients being assessed for salvage surgery for residual disease after definitive chemo-radiation, detection of distant metastases by PET may likewise lead to improvements in quality of life or reduced morbidity, but these are not considered in the model. Similarly, health outcomes associated with the instigation of salvage surgery through the finding of residual disease after definitive primary therapy are not considered.

Costs

The decision-analytic model captures the costs associated with the addition of PET to the conventional staging pathway. The costs of staging and treatment initiated by staging were considered for both the PET and the non-PET arms of the model. For the time period after the initial treatment, the model considers any differences in costs associated with positive findings on PET.

Costs were estimated from a government perspective using the most recent MBS, Pharmaceutical Benefits Scheme and Diagnosis-Related Group costs (Department of Health and Ageing 2006; Department of Health and Ageing 2007; Department of Health and Ageing 2008) and were not discounted. Resource use estimates were based on information from the literature and expert advice provided by the advisory panel. Resource use, unit costs and total costs of all cost items used in the model are listed in Table 25 and Table 26.

The cost of PET used in the cost-consequence analysis is taken from the information in the recent PET cost data report (ANZAPNM 2007). Given the limitations of the cost estimates reported (see page 59), the full range of reported costs (\$761–\$2067) was used in the modelled analysis.

For the estimation of the resource use in patients undergoing definitive treatment, the following assumptions were made (Table 23 provides details of costing):

- All patients undergo EUS (15% with FNA) and then proceed to definitive treatment.
- Definitive treatment consists of definitive chemo-radiation in 25 per cent of patients, surgery alone in 50 per cent and surgery + neo ± adjuvant therapy in 25 per cent.
- Neo ± adjuvant therapy consists of chemo-radiation in 50 per cent and chemotherapy alone in 50 per cent of patients.
- One third (33%) of patients have GEJ cancer, so treatment regimens reflect a ratio of 2:1 oesophageal to GEJ cancer patients.

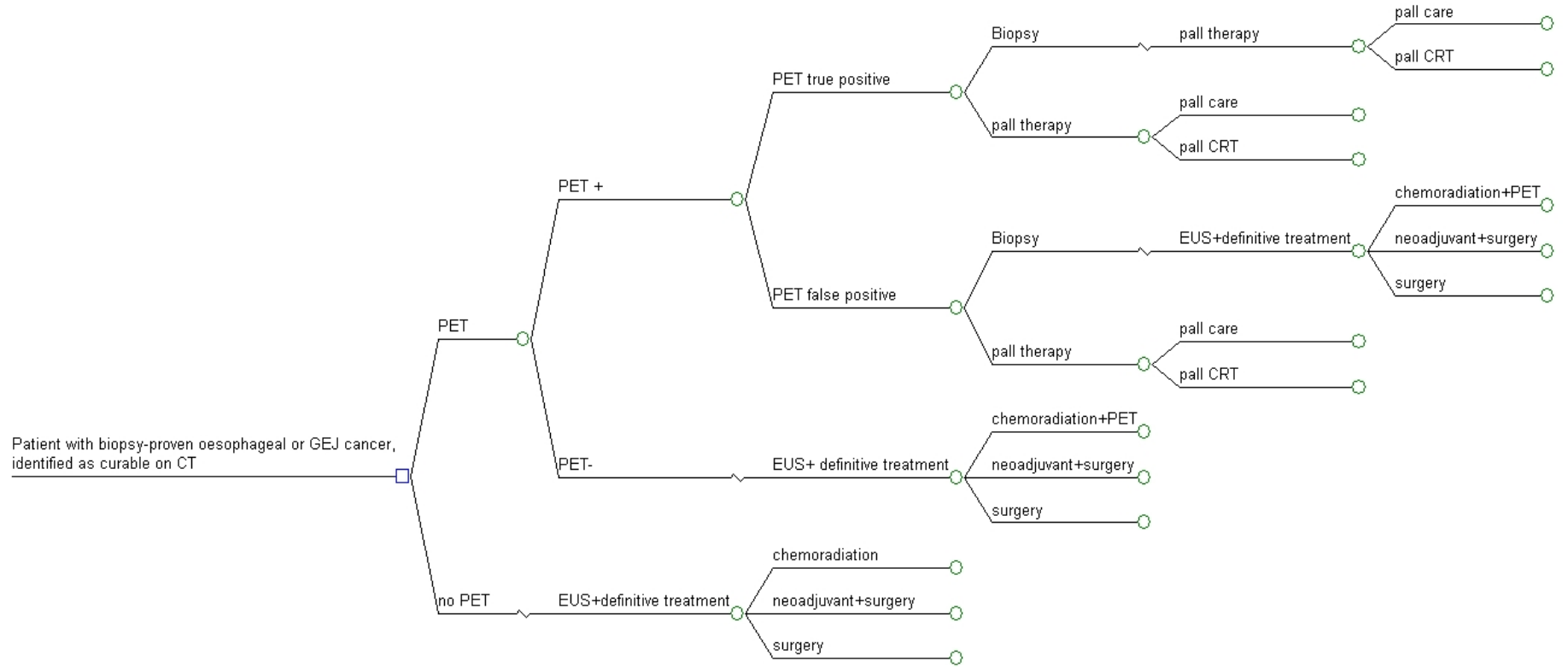
After the initial treatment period, both model arms are costed together: only differences in costs between the PET and the non-PET arms are considered. It is assumed that these differences arise because:

- in patients in whom the false-positive PET result is corrected on biopsy and definitive treatment is initiated with delay, there are additional costs of biopsy and costs of definitive treatment
- in patients in whom the false-positive PET result is not corrected (biopsy not undertaken), patients 'save' the costs of definitive treatment, but accrue the cost of palliative therapy instead.

Palliative therapy consists of:

- palliative chemo-radiation in 80 per cent
- palliative oesophageal stent in 20 per cent
- palliative supportive care for all patients.

Figure 9 Simplified tree structure of decision-analytic model of PET versus no PET in patients with biopsy proven oesophageal cancer



PET+ = PET positive for stage IV disease
 PET- = PET negative for stage IV disease

Table 22 Variables (test characteristics, epidemiology, management) used in economic model of PET vs no PET for primary staging of oesophageal cancer

Variable	Base Mean value	Low-high value (Range/CI)		Distribution	Source
Test characteristics of PET					
Positive yield for detection of distant metastases	0.16	0.12	0.19	Beta (alpha=73.1, beta=389.2)	Systematic review (Meyers, Sivho, Stahl, van Westreenen)
PPV of PET for distant metastases	0.40	0.28	0.53	Beta (alpha=22.2, beta=32.7)	Systematic review (Meyers, Sivho, Stahl, van Westreenen)
Management of patients					
Proportion of patients undergoing FNA with EUS	0.15			Beta (alpha=15, beta=85)	Expert opinion
Proportion of patients undergoing biopsy after PET+	0.65			Beta (alpha=65, beta=35)	Expert opinion
<i>Definitive treatment</i>					
Proportion of patients undergoing surgery	0.50			Beta (alpha=50, beta=50)	Chatterton 2006
Proportion of patients undergoing definitive chemoradiation	0.25			Beta (alpha=25, beta=75)	Chatterton 2006
Proportion of patients undergoing neo±adjuvant therapy	0.25			Beta (alpha=25, beta=75)	Chatterton 2006
Proportion of patients undergoing neo±adjuvant therapy that receive neo±adjuvant chemoradiation	0.50			Beta (alpha=50, beta=50)	Expert opinion
<i>Palliative treatment</i>					
Proportion of patients undergoing supportive care	1.00			fixed	
Proportion of patients undergoing palliative chemoradiation	0.80			Beta (alpha=80, beta=20)	
Proportion of patients undergoing palliative stenting	0.20			Beta (alpha=20, beta=80)	
Health outcomes					
Surgical morbidity	0.37			Beta (alpha=260, beta=446)	See Appendix J
Surgical mortality	0.09			Beta (alpha=2674, beta=27370)	See Appendix J

Abbreviations: CI = confidence interval, EUS = endoscopic ultrasound, FNA = fine-needle aspiration, PET = positron emission tomography, PPV = positive predictive value

Table 23 Resource use, unit costs and total costs of diagnostic tests and therapies associated with PET used in economic model of primary oesophageal cancer

Cost item	MBS/DRG/PBS Item ^a	Unit costs	No	total costs/item	Distribution	Source
PET scan	N/A			\$1,265 (SD: \$482; median: \$1,053)	Uniform (\$761-\$2,067)	PET cost data report (ANZAPNM 2007)
EUS	MBS 30688	\$329.55	1	\$329.55	fixed	
EUS + FNA	MBS 30690	\$508.70	1	\$508.70	fixed	
Oesophagectomy ± complications						
Stomach, oesophageal and duodenal procedures with malignancy	G03A			\$26,478.00	Gamma (alpha = 19.1656; beta = 1381.5356)	DRG cost weights
Definitive chemoradiation					fixed	
5-6 weeks of RT, 4 cycles of chemo (weeks 1 and 5 of RT, 2 weeks after RT)						
<i>Costs of chemotherapy</i>						
Cisplatin + Fluorouracil		\$155.12	4	\$620.50		
Administration of chemotherapy:						
Injection <1 h (once per cycle)	MBS 13915	\$58.75	4	\$235.00		
Injection 2 h infusions	MBS 13918	\$88.40	4	\$353.60		
implantable device loading (once per cycle)	MBS 13939	\$88.40	4	\$353.60		
5HT3 receptor antagonist (2 packs per cycle)	PBS 8225X	\$58.01	8	\$464.08		
Hospital stay for administration of Cisplatin (1 night per cycle)		\$728.59	4	\$2,914.36		
<i>Radiation therapy for 5 weeks</i>						
50-60 Gy in 25-30 fractions in 5-6 weeks						
Dosimetry for 3D conformal RT of level 3 complexity	MBS 15562	\$990.35	1	\$990.35		
Simulation for 3D conformal RT (w/o iv contrast)	MBS 15550	\$581.95	1	\$581.95		
Radiation oncology treatment (1 field) (5.5 weeks on average)	MBS 15254	\$53.90	27.5	\$1,482.25		
Radiation oncology treatment (fields 2-4) (@ \$34.25 per field)	MBS 15269	\$102.75	27.5	\$2,825.63		
EPI once a week - chest (lung fields) by direct radiograph (1/field)	MBS 58503	\$47.15	22	\$1,037.30		
<i>PEG in 1/3 of patients</i>						
Percutaneous gastrostomy (initial procedure), including any associated	MBS 30481	\$322.45	0.33	\$107.48		

Cost item	MBS/DRG/PBS Item ^a	Unit costs	No	total costs/item	Distribution	Source
imaging services						
Anaesthetist: Initiation of management of anaesthesia for upper gastrointestinal endoscopic procedures	MBS 20740	\$89.50	0.33	\$29.83		
Anaesthetist: Time (5 basic units)	MBS 23051	\$89.50	0.33	\$29.83		
PEG tube	Prosthesis list NF001/2, PO 003/4	\$147.50	0.33	\$49.17		median of four types listed on prosthesis list
Overnight hospital stay		\$728.59	0.33	\$242.86		
<i>Total cost for definitive chemoradiation treatment</i>				<i>\$12,317.79</i>		
Neo ± adjuvant Chemoradiation					fixed	
3 weeks of RT, 3.33 cycles chemo						
(average 2.33 cycles of chemo neoadjuvant [= 2/3 patients x 2 cycles for oesophageal cancer + 1/3 patients x 3 cycles for GEJ cancer] + 1 cycle adjuvant [1/3 patients x 3 cycles GEJ cancer])						
<i>Costs of chemotherapy</i>						
Cisplatin + Fluorouracil		\$155.12	3.33	\$516.56		
Administration of chemotherapy						
Injection <1 h (once per cycle)	MBS 13915	\$58.75	3.33	\$195.64		
Injection 2 h infusions	MBS 13918	\$88.40	3.33	\$294.37		
Implantable device loading (once per cycle)	MBS 13939	\$88.40	3.33	\$294.37		
5HT3 receptor antagonist (2 packs per cycle)	PBS 8225X	\$58.01	6.66	\$386.35		
Hospital stay for administration of Cisplatin (1 night per cycle)		\$728.59	3.33	\$2,426.20		
<i>Radiation therapy for 3 - 5 weeks (on average 4 weeks)</i>						
40 Gy in 20 fractions (5 fractions/week for 4 weeks)						
Dosimetry for 3D conformal RT of level 3 complexity	MBS 15562	\$990.35	1	\$990.35		
Simulation for 3D conformal RT (w/o iv contrast)	MBS 15550	\$581.95	1	\$581.95		
Radiation oncology treatment (1 field)	MBS 15254	\$53.90	20	\$1,078.00		
Radiation oncology treatment (fields 2-4) (@ \$34.25 per field)	MBS 15269	\$102.75	20	\$2,055.00		
EPI once a week - chest (lung fields) by direct radiograph (1/field)	MBS 58503	\$47.15	16	\$754.40		
<i>Total cost for neo ± adjuvant chemoradiation treatment</i>				<i>\$9,573.19</i>		
Neo ± adjuvant Chemotherapy					fixed	

Cost item	MBS/DRG/PBS Item ^a	Unit costs	No	total costs/item	Distribution	Source
Costs of chemotherapy (cisplatin + Fluorouracil + Epirubicin), 3.33 cycles (average 2.33 cycles of chemo neoadjuvant [= 2/3patients x 2 cycles for oesophageal cancer + 1/3 patients x 3 cycles for GEJ cancer] + 1 cycle adjuvant [1/3 patients x 3 cycles GEJ cancer]) <i>Administration of chemotherapy</i>		\$813.58	3.33			
Injection <1 h (once per cycle)	MBS 13915	\$58.75	3.33	\$195.64		
Injection 2 h infusions	MBS 13918	\$88.40	3.33	\$294.37		
implantable device loading (once per cycle)	MBS 13939	\$88.40	3.33	\$294.37		
5HT3 receptor antagonist (2 packs per cycle)	PBS 8225X	\$58.01	6.66	\$386.35		
Hospital stay for administration of Cisplatin (1 night per cycle)		\$728.59	3.33	\$2,426.20		component cost for Ward Medical/Nursing, allied health, Pharmacy, Supplies, Hotel (from DRG G03A)
<i>Total cost for neo ± adjuvant chemotherapy treatment</i>				\$6,306.15		
Biopsy for confirmation of stage IV disease detected on PET					fixed	
Biopsy (MBS item for lymph node biopsy used)	MBS 52027	\$135.20	1	\$135.20		
CT guidance	MBS 57341	\$470.00	1	\$470.00		
Examination of complexity level 4 biopsy material with 1 or more tissue blocks	MBS 72823	\$97.95	1	\$97.95		
Initiation of patient episode associated with MBS 72823	MBS 73924	\$14.75	1	\$14.75		
<i>Total costs of biopsy</i>				\$717.90		
Palliative therapy					fixed	
<i>Supportive Care</i>						
Prednisone (2 x 30 tablets @ 25mg)	PBS 1936	\$10.42	2	\$20.84		
Morphine (2 x 20 tablets @ 10g)	PBS 8669 G	\$14.04	2	\$28.08		
<i>Total cost for supportive care</i>				\$48.92		
<i>Palliative chemoradiation (in 80%)</i>						
Palliative Chemotherapy (cisplatin + Fluorouracil), 3 cycles		\$89.76	2	\$179.52		
<i>Administration of chemotherapy</i>						
Injection <1 h (once per cycle)	MBS 13915	\$58.75	2	\$117.50		

Cost item	MBS/DRG/PBS Item ^a	Unit costs	No	total costs/item	Distribution	Source
Injection 2 h infusions	MBS 13918	\$88.40	2	\$176.80		
Implantable device loading (once per cycle)	MBS 13939	\$88.40	2	\$176.80		
5HT3 receptor antagonist (2 packs per cycle)	PBS 8225X	\$58.01	4	\$232.04		
Hospital stay for administration of Cisplatin (1 night per cycle)		\$728.59	2			component cost for Ward Medical/Nursing, allied health, Pharmacy, Supplies, Hotel (from DRG G03A)
				\$1,457.18		
RT: 30-40 Gy in 10-20 fractions over 2-4 weeks (average 3 weeks)						
Dosimetry for 3D conformal RT of level 3 complexity	MBS 15562	\$990.35	1	\$990.35		
Simulation for 3D conformal RT (w/o iv contrast)	MBS 15550	\$581.95	1	\$581.95		
Radiation oncology treatment (1 field)	MBS 15254	\$53.90	15	\$808.50		
Radiation oncology treatment (fields 2-3) (@ \$34.25 per field)	MBS 15269	\$68.50	15	\$1,027.50		
EPI once a week - chest (lung fields) by direct radiograph (1/field)	MBS 58503	\$47.15	9	\$424.35		
<i>Total cost for palliative CRT</i>				<i>\$6,172.49</i>		
<i>Oesophageal stent (in 20%)</i>						
Procedure - insertion of oesophageal prosthesis, including endoscopy and dilatation	MBS 30490	\$475.35	1	\$475.35		
Prosthesis (Polyflex oesophageal stent)	BS102	\$2,040.00	1	\$2,040.00		
Anaesthetist: Initiation of management of anaesthesia for all closed-chest procedures (incl. rigid oesophagoscopy or bronchoscopy) (6 basic units)	MBS 20520	\$107.40	1	\$107.40		
Anaesthetist: Time	MBS 23062	\$107.40	1	\$107.40		
Bed day charge (1 night)		\$728.59	1	\$728.59		component cost for Ward Medical/Nursing, allied health, Pharmacy, Supplies, Hotel (from DRG G03A)
<i>Total cost for oesophageal stent</i>				<i>\$3,458.74</i>		

Abbreviations: chemo = chemotherapy, CRT = chemo-radiotherapy, CT = computed tomography, DRG = Diagnosis-Related Group, EPI = Electronic portal imaging, EUS = endoscopic ultrasound, FNA = fine-needle aspiration, iv = intravenous, MBS = Medicare Benefits Schedule, mets = metastases, N/A = not applicable, PBS = Pharmaceutical Benefits Scheme, PEG = percutaneous endoscopic gastrostomy, PET = positron emission tomography, RT = radiotherapy

a. MBS November 2007, PBS November 2007, DRG 2006 Round 9 (2004–05) (Department of Health and Ageing 2006; Department of Health and Ageing 2007; Department of Health and Ageing 2008)

Table 24 Details of resource use associated with chemotherapy costs used in economic model of PET in primary oesophageal cancer

Cost items	Source	Unit cost (per mg)	Dose mg/m ²	BSA (70 kg; 1.75 m ²)	Average mg/cycle	Total \$/cycle
Costs per cycle of chemotherapy (as part of definitive or neo ± adjuvant chemo-radiation)						
Cisplatin (25 mg/m ²) iv over 1 h, days 1–3	dispensed price/mg PBS 2579R	\$0.5502	75	1.91	143.3	\$78.82
Fluorouracil 1000 mg/m ² /day iv by 24-h infusions on days 1–4	dispensed price/mg PBS 9005Y	\$0.0100	4000	1.91	7640.0	\$76.31
<i>Total costs per cycle</i>						\$155.12
Costs per cycle of chemotherapy (neo ± adjuvant chemo)						
Cisplatin (60 mg/m ²) iv, day 1	dispensed price/mg PBS 2579R	\$0.5502	60	1.91	114.6	\$63.05
Fluorouracil 200 mg/m ² /day iv, 1 week	dispensed price/mg PBS 9005Y	\$0.0100	1400	1.91	2674.0	\$26.71
Epirubicin 50 mg/m ² by iv infusion, day 1	dispensed price/mg PBS 1377L	\$4.9747	50	2.91	145.5	\$723.82
<i>Total costs per cycle</i>						\$813.58
Costs per cycle of chemotherapy (as part of palliative chemo-radiation)						
Cisplatin (60 mg/m ²) iv, day 1	dispensed price/mg PBS 2579R	\$0.5502	60	1.91	114.6	\$63.05
Fluorouracil 200 mg/m ² /day iv, 1 week	dispensed price/mg PBS 9005Y	\$0.0100	1400	1.91	2674.0	\$26.71
<i>Total costs per cycle</i>						\$89.76

Abbreviations: BSA = body surface area, iv = intravenous, PBS = Pharmaceutical Benefits Scheme, PET = positron emission tomography

Sensitivity analysis

A probabilistic sensitivity analysis was conducted to determine the overall influence of uncertainty within the model. A probabilistic structure (prior distributions) for the major model variables was used, and a second-order Monte-Carlo simulation was performed for all model parameters simultaneously. In this simulation, a cohort of 1000 patients was run through the model and values were picked randomly (using a random number generator) from the pre-defined distributions (see Table 22 and Table 23).

Sensitivity analyses were also conducted to assess the impact on results of considering the following scenarios:

- The use of PET for the assessment of residual disease. In this sensitivity analysis the additional cost of a second PET scan for assessment of residual disease in all patients undergoing definitive CRT is included in the costs of definitive CRT.
- The higher yield of PET results that are positive for distant metastases from the Australian data collection study (Chatterton 2006) is used (24%), instead of the pooled yield from the accuracy studies identified in the systematic review (16%). The PPV comes from the pooled accuracy studies. *Note:* PPV and yield depend on prevalence, which may differ between Chatterton (2006) and the accuracy studies in the systematic review.

Results of cost-consequence analysis

Table 25 summarises the costs and consequences resulting from the modelled decision analysis of adding PET to the conventional staging pathway in patients with biopsy-proven oesophageal cancer. The confidence limits reflect the overall uncertainty tested in probabilistic sensitivity analyses.

The modelled analysis resulted in an average of 84 of 100 patients undergoing definitive treatment (median: 84 [95% CL 81–87]) in the PET arm, compared to all (100 patients) in the non-PET arm, indicating the avoidance of definitive treatment in 16 patients (16 [13–19]). This value includes correct and incorrect avoidance of treatment with curative intent (ie, considers both true-positive and false-positive PET results).

Among patients avoiding definitive treatment in the PET arm, 6 of 100 patients (median 6.4; 95% CL 4.3-9.0, Table 25) would have avoided treatment correctly. In 5 of 100 patients (median 4.8; 95% CL: 2.9-7.2), the avoided definitive treatment would include surgery (surgery \pm [neo]adjuvant therapy), and in 2 of 100 patients (median 1.6; 95% CL: 1.0 to 2.6), the avoided treatment was definitive CRT.

As a result of correct avoidance of surgery, surgical complications would have been avoided in an average of 2 of 100 patients (median 2; 95% CL 1–3) following PET. Surgical mortality would have been avoided in 4 of 1000 patients (median 4; 95% CL 3–6).

Potential health detriments associated with adding PET to the staging pathway would have occurred in 3 of 100 patients (median 3 [95% CL 2–5]) who had false-positive PET results and did not undergo biopsy confirmation. These patients would have

missed the opportunity for definitive treatment through overstaging of disease. A further 6 of 100 patients (median 6 [95% CL 4–8]) would have had a delay in definitive treatment following restaging by follow-up biopsy to evaluate additional abnormalities detected on PET. A missed opportunity for, or a delay in, curative treatment may lead to disease progression and reduced quality of life and survival in these patients. However, in a proportion of these patients, the false-positive PET result may have been due to the detection of a synchronous non-oesophageal neoplasm. In either case, additional costs of evaluation would be incurred, but exploration of the costs and consequences of these findings is beyond the scope of this decision-analytic model.

The modelled analysis resulted in mean total costs of diagnostic testing and management associated with staging in the PET arm of \$2 322 127 (median: \$2 270 009 [95% CL \$1 590 270—\$3 311 440]) per 100 patients (Table 25), compared to \$2 481 478 (\$2 420 430 [95% CL \$1 638 739–\$3 644 510]) per 100 patients in the non-PET arm. This results in mean cost savings for PET of \$159 351 (median: \$150 813) per 100 patients. The probabilistic sensitivity analysis that considers the overall uncertainty in the model gives wide confidence limits, but there is nearly a 99 per cent probability that the use of PET is cost-saving compared with a staging strategy without PET.

Table 25 Costs and consequences associated with addition of PET in cohort of 100 patients with primary oesophageal cancer

Costs	PET	No PET	PET vs no PET
	Total in AU\$		Cost savings in AU\$
Average	2,322,127	2,481,478	159,351
(Median)	(2,270,009)	(2,420,430)	(150,813)
[95% CL]	[1,590,270–3,311,440]	[1,638,739–3,644,510]	[13,125–348,730]
Consequences			
Outcomes	Average incremental value		
	Mean (median [95% CL])		
Associated with possible health benefit of PET:			
Correctly avoided EUS and definitive treatment	6.4 (6.4 [4.3–9.0])		
Of these:			
▪ correctly avoided surgery (± [neo]adjuvant therapy)	4.8 (4.8 [2.9–7.2])		
▪ correctly avoided definitive chemo-radiation	1.6 (1.6 [1.0–2.6])		
Associated with correctly avoided surgery:			
▪ surgical complications avoided	1.8 (1.8 [1.1–2.6])		
▪ surgical mortality avoided	0.4 (0.4 [0.3–0.6])		
Associated with possible health detriment of PET:			
Missed definitive treatment	3.3 (3.2 [2.2–4.8])		
Delayed definitive treatment following biopsy	6.1 (6.1 [4.2–8.3])		
▪ potential impact on quality of life through disease progression			

Abbreviations: CL = confidence limits, EUS = endoscopic ultrasound, PET = positron emission tomography

Additional univariate sensitivity analyses

Cost results did not vary greatly when the cost of CRT (considering a second PET scan during follow-up of patients) and the yield of PET were tested in additional sensitivity analyses (Table 26).

When the cost of a second PET scan for assessment of residual disease following definitive CRT was added to the modelled analysis, mean costs were \$2 352 862 in the PET arm and \$2 481 478 in the non-PET arm, resulting in cost-savings of \$128 617 per 100 patients associated with PET for the staging of primary oesophageal cancer. The probability of this scenario being cost saving was 93 per cent. In this scenario, consequences do not differ from the base case analysis, but total costs associated with PET were higher, so cost savings were lower.

Table 26 Incremental costs associated with addition of PET in cohort of 100 patients with primary oesophageal cancer—additional univariate sensitivity analyses

	PET	No PET	PET vs no PET
Including cost of PET following definitive CRT:			
	Total costs in AU\$		Cost savings in AU\$
Average	2,352,862	2,481,478	128,617
(Median)	(2,301,779)	(2,420,430)	(119,904)
[95% CL]	[1,619,379–3,344,681]	[1,638,739–3,644,510]	[328,135 to –23,200]
Including yield of PET from Chatterton (2006):			
	Total costs in AU\$		Cost savings in AU\$
Average	2,169,168	2,481,478	312,309
(Median)	(2,133,338)	(2,420,430)	(300,206)
[95% CL]	[1,485,861–3,121,198]	[1,638,739–3,644,510]	[632,168–101,663]

When the yield of PET was increased to 24 per cent (from 16%), cost savings increased to an average of \$312 309. If this is associated with the same PPV as that from the studies in the systematic review, this would be associated with avoidance of definitive treatment based on a correct PET result in 9 of 100 patients, and potentially detrimental health outcomes due to false-positive PET results in 15 of 100 patients. However, both yield and PPV depend on prevalence, which is unknown in the patient population in the Australian data collection study (Chatterton 2006). Therefore, this yield may not be associated with the same PPV of PET derived from the studies included in the systematic review.

Consequences of PET compared to Australian data collection study

Data from the Australian data collection study (Chatterton 2006) provide estimates of management changes in standard Australian practice. These data are likely to overestimate actual changes in management (see page 48), but provide highly applicable data for comparison with the model output. Ninety-two per cent of patients were considered potentially curable before undergoing PET.

The patient group for whom surgery (\pm radio-/chemotherapy) is included as part of the pre-PET plan ($n = 94$, 73% of all patients) is the patient group of most relevance to that considered in the cost-consequence analysis. Another 22 per cent (28) of

patients are considered for chemo-radiation: some of these are likely to have been considered for curative treatment and are relevant to the modelled population.

The major changes in management from pre-PET plan to post-PET plan in the Australian study indicate that among 100 patients undergoing PET after conventional staging who are considered for surgery (\pm radio-/chemotherapy), the plan for surgery for 19 patients would be abandoned after PET scanning.

If changes in both surgery (\pm radio-/chemotherapy) and chemo-radiation are considered, based on Chatterton (2006), 11 patients would have their pre-PET treatment abandoned.

Comparing the data from the Australian study to the outcomes of the cost-consequence model based on yields from the systematic review, the proportion of patients avoiding operation are comparable (model outcome: 12% [median: 12%; 95% CL 9%–15%]; Australian management study: 19% [95% CI 13%–26%]). In the Australian study it is unclear what proportion of operations avoided had curative intent. As expected, where the yield from Chatterton (2006) was used in the modelled sensitivity analysis, the proportion of patients avoiding surgery was equivalent (model outcome: 18% [18 (12–25)]), validating the model.

It is important to note that it is not possible from the data in the Australian study to draw conclusions about whether the health outcomes following the management change would have been beneficial or detrimental for the patient. In particular, it is not known what proportion of operations avoided were based on correct vs incorrect PET results.

Data from the systematic review of accuracy indicate that up to approximately 60 per cent of distant metastases found on PET may be true-positive (pooled PPV of 40 per cent for incremental positive findings). It is assumed that avoiding surgery in these cases is associated with positive health outcomes, but evidence for this is lacking. Conversely, at least approximately 40 per cent of the 19 per cent of patients avoiding surgery would have beneficial operations avoided or delayed; ie, a minimum of 8 per cent of patients.

Summary and discussion

The decision-analytic model indicated that staging with PET in patients with primary oesophageal cancer is associated with both potentially beneficial and detrimental health outcomes. The model resulted in the avoidance of radical treatment not considered to be of long-term benefit in an average of 6 per 100 patients (95% CL 4–9), 5 (95% CL 3–7) of which would receive surgery (\pm [neo]adjuvant therapy), resulting in the avoidance of surgical complications in 2 (95% CL 1–3) patients per 100, and surgical mortality in 4 (95% CL 3–6) per 1000 patients. Conversely, PET may result in potentially detrimental health outcomes through incorrect upstaging in an average of 3 per 100 patients (95% CL 2–5) who would have missed the opportunity for potentially curative definitive treatment, and in 6 per 100 patients (95% CL 4–8) who would have had a delay in definitive treatment after restaging at follow-up biopsy. A proportion of these patients may have had a synchronous non-oesophageal neoplasm identified by PET.

The modelled results indicate that it is uncertain whether the use of PET in upstaging primary oesophageal cancer leads to health benefits overall. Data on the long-term impact of PET are not available. In particular, it is unclear how the avoidance of operations translates to health benefits for the patient in terms of quality of life or survival (see page 54). Whether the trade-off between potential health gains from true-positive PET results and the potential health detriments from false-positive PET results gives an overall net gain in health outcomes across the population is not known. This limits interpretation of the analysis, as health outcomes could not be expressed as a single summary measure. Thus, an ICER could not be calculated.

These health consequences were associated with a mean cost saving of \$159 351 (95% CL \$348 730–\$13 125) per 100 patients. Sensitivity analysis considering a second PET scan in patients undergoing definitive treatment indicated a lower cost saving of \$128 617 (95% CL \$328 135 to additional \$23 200). True-positive findings and false-positive findings that are not proven to be so on biopsy (35% of false-positives) are both associated with cost offsets through the avoidance of radical treatment.

The validity of these findings is dependent on the key model assumptions that:

- all differences in health outcomes and costs are incurred for PET-positive patients only (ie, PET-negative results do not modify patient management)
- all differences in costs due to the use of PET are incurred through the avoidance of EUS and definitive treatment of patients with distant metastases detected on PET
- the PPV of PET for detecting distant metastases is 40 per cent (95% CI 28%–53%)
- the costs of definitive treatment are \$26 478 for oesophagectomy, \$9573 for neo ± adjuvant CRT and \$6306 for chemotherapy, and \$15 232 for definitive chemo-radiation; and the cost of palliative CRT is \$6172.

The modelled analysis is applicable to the majority of patients with primary oesophageal cancer undergoing PET in Australia, as 92 per cent of patients enrolled in the Australian patient management study were planned for curative treatment.

Although PET is likely to be cost saving for this indication, there is uncertainty associated with the overall health outcomes. Economic implications are irrelevant if the procedure does not provide a health outcome equivalent to or better than the alternative.

Financial implications

The financial implications of the use of PET for primary oesophageal cancer were estimated. Both the total costs to the Federal Government (not discounted for the 75 to 85 per cent rate of MBS reimbursement to patients) and the net impact on health care expenditure were considered using estimates of 'Potential utilisation of PET' provided above (page 5).

Patient uptake of PET for oesophageal cancer has continually 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 of between 560 and 1050 patients for primary oesophageal cancer (see pages 5–7).

If PET were reimbursed in Australia at the median value from the PET cost data report (\$1053) (ANZAPNM 2007), the total annual cost to the MBS for primary oesophageal cancer could range between \$590 000 and \$1 106 000, depending on utilisation. When the full range of costs in the Australian cost study is applied (\$761–\$2067), the annual total cost to the MBS could range between \$426 000 and \$2 170 000.

Although PET as an additional test for primary oesophageal cancer is expected to incur costs to the MBS within these ranges, the net financial impact on health care expenditure associated with PET is not considered in these numbers.

For oesophageal cancer, the economic analysis (Table 25) indicates that the costs of PET are likely to be more than offset through the avoidance of definitive treatment. Considering the modelled incremental costs and the proportion of patients with oesophageal cancer planned for curative treatment in the Australian study (92%), there is a range of possible net financial implications to the health care system. Mean net annual cost savings ranged from approximately \$821 000 to \$1 539 000 depending on utilisation (Table 27).

These estimates need to be interpreted within the context of the assumptions and limitations of the modelled analysis. The net financial impact of PET in a population not planned for definitive treatment is unknown, but it may be less favourable, as the modelled analysis for primary oesophageal cancer patients considered for definitive treatment is likely to represent the subgroup of patients in whom PET has the most favourable cost profile.

Table 27 Net financial impact of PET for patients with primary oesophageal cancer

PET cost (AU\$)	Patient subgroup	Modelled cost savings/ 100 patients mean (median) [95% CL]	Net financial implications—potential cost savings/year mean (median) [95% CL] ^a	
			low usage estimate ^b	high usage estimate ^c
ANZAPNM median: \$1,053 (range): \$761–\$2,067	Patients planned for definitive treatment—92%	\$159,351 (\$150,813) [\$13,125–\$348,730]	\$820,975 (\$776,986) [\$67,620–\$1,796,656]	\$1,539,328 (\$1,456,849) [\$126,788–\$3,368,731]
	Patients planned for palliative treatment—8%	Unknown	Unknown	Unknown

Abbreviations: CL = confidence limits

a. Values rounded to nearest \$1000

b. Low usage estimate: 560 scans/year 92% planned for surgery

c. High usage estimate: 1050 scans/year 92% planned for surgery

As discussed previously (Medical Services Advisory Committee 2007), the number of reimbursed PET sites may have implications for total health care expenditure owing 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 the Medicare benefit. From this perspective, the total cost of PET would primarily be determined by total patient throughput at all sites.

A detailed assessment of how the number of reimbursed centres may affect 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, the question of equity of access needs to be considered when decisions are made about public funding of PET.

Conclusions

The main potential impact of PET in patients with oesophageal and gastric cancer is in the exclusion of patients unlikely to benefit from therapy with curative intent or salvage surgery. The use of PET as an additional test may achieve this by detecting distant metastases that are likely to preclude definitive therapy.

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

There were three specific research questions for this review:

1. What is the value of the addition of PET/CT in the assessment of patients with primary cancer of the oesophagus or the GEJ considered suitable for definitive treatment as determined by conventional staging?
2. What is the value of PET/CT in the assessment of residual oesophageal or GEJ cancer following definitive chemo-radiation considered suitable for salvage surgery, (a) as a replacement for CT in staging biopsy-proven residual disease, or (b) in addition to endoscopy and biopsy where residual disease has not been confirmed?
3. What is the value of the addition of PET/CT in the assessment of patients with biopsy-proven primary gastric cancer that is considered potentially curable as determined by conventional staging including laparoscopy (with peritoneal cytology)?

Diagnostic accuracy

Oesophageal cancer primary staging

The sensitivity of PET for detecting distant metastases from primary oesophageal cancer is lower than that for other cancers but somewhat better than that of CT.

Existing evidence indicates that PET detects additional abnormal distant sites (true-positive or false-positive) in 14 to 18 per cent of patients, with a PPV for metastatic disease of 27 to 63 per cent. Some false-positive findings are due to synchronous non-oesophageal neoplasms.

The available evidence indicates that the addition of PET to the conventional staging pathway increases the detection of distant metastases from primary oesophageal cancer. However, this is also associated with an increase in the number of false-

positive findings. No studies reporting the incremental accuracy of PET/CT were identified.

Oesophageal cancer residual disease

No prospective studies reporting the accuracy of PET or PET/CT in assessing residual disease following definitive chemo-radiation were identified in the UK HTA report, nor in the systematic review for primary prospective or retrospective studies published since August 2005.

Gastric cancer primary staging

No studies reporting the accuracy of PET or PET/CT following laparoscopy (with or without CT) were identified in a systematic review of primary studies published since 2001.

Impact on patient management

Oesophageal cancer primary staging

The prospective Australian data collection study (Chatterton 2006) reported that PET led to a change in management plan in a total of 38 per cent of patients, 27 per cent due to a positive PET result for regional or distant metastases. Surgery was avoided in 19 per cent of all patients, 26 per cent of those for whom surgery had been planned. A positive PET result for regional or distant metastases led to a change in treatment intent from curative to palliative in 20 per cent of patients. In two smaller published studies, surgery was avoided in a smaller proportion of patients (2% and 6%). A retrospective cohort study with historical controls reported a 29 per cent reduction in the number of patients who underwent unnecessary exploration after staging with PET.

These data provide evidence that the use of PET in patients with primary oesophageal cancer leads to changes in the management of a substantial proportion of patients. The most frequent major change in management following PET is the avoidance of planned surgery. There is uncertainty regarding the magnitude of these effects due to inevitable biases inherent in studies of this type and the discrepancies between post-PET management plans and actual management.

Oesophageal cancer residual disease

A single Australian study reported an impact of PET on treatment intent or modality in 36 per cent of patients following CRT. However, the proportion of patients who had received definitive (rather than palliative) CRT was unclear.

Gastric cancer primary staging

No studies reporting the therapeutic impact of PET in staging patients with gastric cancer were identified.

Impact on health outcomes

The main treatment change likely to follow PET in the staging of primary oesophageal cancer is the avoidance of oesophagectomy. In addition, patients are likely to receive less-intensive regimens of chemo-radiation.

Patients avoiding oesophagectomy will avoid the risk of surgical complications and the impact of surgery on quality of life (pain, time in hospital, recovery after discharge) associated with resection that is unlikely to provide long-term benefit. In the absence of clinical trials comparing alternative therapies in these patients, it is not known whether the potential improvement in quality of life from avoiding surgery and the instigation of alternative management outweigh any potential benefit of surgery in providing local disease control.

Nevertheless, surgery is likely to be less beneficial in patients with additional metastases detected on PET than in patients with no additional sites of disease. Although there is no direct evidence of a benefit on patient outcomes, the expert opinion of the advisory panel was that aggressive surgical treatment is unlikely to be beneficial in these patients.

Evidence for the incremental accuracy of PET over conventional imaging for the assessment of residual disease following definitive chemo-radiation for oesophageal cancer and for staging gastric cancer following CT and laparoscopy was not identified. Therefore, a case for linked evidence for an improvement in patient outcomes due to PET in these indications cannot be made.

Economic considerations

The decision-analytic model of PET in staging of patients with primary oesophageal cancer showed that PET would lead to the avoidance of radical treatment not considered to be of long-term benefit in an average of 6 per 100 patients (95% CL 4–9), including surgery (\pm [neo]adjuvant therapy) in 5 (95% CL 3–7). This leads to the avoidance of surgical complications in 2 (95% CL 1–3) patients per 100 and of surgical mortality in 4 (95% CL 3–6) per 1000 patients. Conversely, PET may result in potentially detrimental health outcomes through incorrect upstaging in an average of 3 per 100 patients (95% CL 2–5) who would have missed the opportunity for potentially curative definitive treatment, and in 6 per 100 patients (95% CL 4–8) who would have had a delay in definitive treatment following restaging at follow-up biopsy. Some of these patients may have had a synchronous non-oesophageal neoplasm identified by PET.

The analysis showed that these health outcomes would be associated with lower costs of \$159 351 (95% CL \$348 730–\$13 125) per 100 patients. Sensitivity analysis considering a second PET scan in patients undergoing definitive treatment indicated a reduced cost saving of \$128 617 (95% CL \$328 135 to an additional \$23 200). True-positive findings and false-positive findings that are not proven on biopsy (35% of false-positives) are both associated with cost offsets through the avoidance of radical treatment.

Uncertainties exist around the extent of modelled health benefits and cost savings. In particular, it is unclear whether the use of PET translates to overall health benefits in terms of QALYs. Thus, an ICER allowing comparison of cost-effectiveness of PET against other technologies could not be provided. Although PET is likely to be cost saving for this indication, there is uncertainty associated with the overall health outcomes.

If PET were reimbursed in Australia using the range of cost estimates from the Australian cost study, the potential annual total cost to the MBS could range between \$590 000 and \$1 106 000. This estimate does not include a forecast of future population growth or changes in incidence. Calculated estimates of net financial impact (costs to the total health care system) vary widely, but there are likely to be net cost savings to the health care system of \$821 000 to \$1 539 000 per annum depending on utilisation.

Conclusions

Evidence for the use of PET in addition to conventional staging in the assessment of residual disease following definitive chemo-radiation is lacking.

Evidence for the use of PET in addition to conventional staging including laparoscopy in the staging of gastric cancer is lacking.

The use of PET in addition to conventional staging in the staging of patients with primary oesophageal cancer is considered

- safe
- to increase the detection of distant metastases from primary oesophageal cancer, in association with an increase in the number of false positive findings for metastatic disease
- to identify synchronous neoplasms
- to lead to changes in patient management, most commonly the avoidance of surgery
- to lead to the avoidance of surgical morbidity and mortality in patients who avoid oesophagectomy. Expert opinion is that this leads to improved patient outcomes in terms of quality of life, but definitive evidence for whether this outweighs any potential benefit of surgery is lacking
- cost saving in patients according to decision analytic modelling of short-term costs, due to the avoidance of radical treatment with curative intent following both true-positive and false-positive results.

Advice

(i) MSAC has considered the safety, effectiveness and cost-effectiveness for positron emission tomography (PET) and PET/CT for the assessment of patients with primary cancer of the oesophagus or the gastro-oesophageal junction (GEJ) otherwise considered suitable for definitive treatment.

- MSAC finds PET is safe.
- MSAC finds that the addition of PET to the conventional staging of primary cancer of the oesophagus or the GEJ is clinically effective.
- MSAC finds that the addition of PET to the conventional staging of primary cancer of the oesophagus or the GEJ is likely to be cost saving.
- MSAC recommends public funding for the assessment of patients with primary cancer of the oesophagus or the gastro-oesophageal junction (GEJ) considered suitable by conventional staging for definitive treatment.

(ii) MSAC has considered the safety, effectiveness and cost-effectiveness for positron emission tomography (PET) and PET/CT for the assessment of residual oesophageal or GEJ cancer following definitive chemoradiation.

- MSAC finds PET is safe.
- MSAC finds that there are insufficient data to evaluate the effectiveness of PET for the assessment of residual oesophageal or GEJ cancer following definitive chemoradiation considered suitable for salvage surgery.
- A formal economic assessment was, therefore, not performed.
- MSAC does not recommend public funding for the use of PET in the assessment of residual oesophageal or GEJ cancer following definitive chemoradiation.

(iii) MSAC has considered the evidence for safety, effectiveness and cost-effectiveness for positron emission tomography (PET) and PET/CT in addition to conventional staging including laparoscopy for the assessment of patients with biopsy proven primary gastric cancer otherwise considered potentially curable.

- MSAC finds PET is safe.
- MSAC finds that there are insufficient data to evaluate the effectiveness of PET assessment of patients with biopsy proven primary gastric cancer considered potentially curable.
- A formal economic assessment was therefore not performed.
- MSAC does not recommend public funding for the use of PET in the assessment of patients with biopsy proven primary gastric cancer otherwise considered potentially curable.

Appendix A MSAC 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; and
- undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC) and report its findings to AHMAC.

The membership of the 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

Dr Stephen Blamey (Chair)
Professor Brendon Kearney (Deputy Chair)
Dr William Glasson (Second Deputy Chair)
Associate Professor John Atherton
Associate Professor Michael Cleary
Associate Professor Paul Craft
Dr Kwun Fong
Professor Richard Fox
Professor Jane Hall
Associate Professor Terri Jackson
Associate Professor Ray Kirk
Associate Professor Frederick Khafagi
Dr Ewa Piejko
Dr Ian Prosser
Mrs Sheila Rimmer
Dr Judith Soper
Professor Ken Thomson
Dr David Wood

Expertise or affiliation

general surgery
health administration and planning
ophthalmology
cardiology
emergency medicine
clinical epidemiology and oncology
thoracic medicine
oncology
health economics
health economics
health research
nuclear medicine
general practice
haematology
consumer health issues
radiology
radiology
orthopaedic surgeon

Appendix B Advisory panel

Member	Nomination / Expertise or Affiliation
Associate Professor Frederick Khafagi (Chair)	MSAC member Nuclear medicine
Dr Bryan Burmeister	Royal Australian and New Zealand College of Radiologists nominee Radiation oncology
Dr Gabrielle Cehic	MOGA nominee Oncology
Professor Glyn Jamieson	Co-opted member Upper gastrointestinal surgery
Professor Brendon Kearney	Deputy Chair MSAC Health administration and planning
Dr George Larcos	ANZAPNM nominee Nuclear medicine
Mr Bernard M. Lyons	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

Appendix C Electronic databases and HTA websites

1. International electronic databases

NHS Centre for Reviews and Dissemination databases / International Network of Agencies for Health Technology Assessment (INAHTA)

Economic Evaluation Database (EED)

Database of Abstracts of Reviews of Effectiveness (DARE)

Health Technology Assessment (HTA)

<http://www.york.ac.uk/inst/crd/>

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/open/asernip-s.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'Évaluation 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 Coordinating Office for Health Technology Assessment (CCHOTA) http://www.ccohta.ca/entry_e.html

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>

Institute for Clinical and Evaluative Studies (ICES) <http://www.ices.on.ca>

DENMARK

Danish Institute for Health Technology Assessment (DIHTA) http://www.dihta.dk/publikationer/index_uk.asp

FINLAND

FINOHTA <http://www.stakes.fi/finohta/e/>

FRANCE

Agence Nationale d'Accréditation et d'Évaluation en Santé (ANAES) <http://www.anaes.fr/>

GERMANY

German Institute for Medical Documentation and Information (DIMDI) / HTA <http://www.dimdi.de/en/hta/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 Centre for Health Technology Assessment (SMM)

<http://www.oslo.sintef.no/smm/Publications/Engsmdrag/FramesetPublications.htm>

SPAIN

Agencia de Evaluación de Tecnologías Sanitarias, Instituto de Salud 'Carlos III' / Health Technology Assessment Agency (AETS) <http://www.isciii.es/aets/>

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/admin/index.asp>

Center for Medical Health Technology Assessment <http://www.cmt.liu.se/English/Engstartsida.html>

SWITZERLAND

Swiss Network on Health Technology Assessment (SNHTA) <http://www.snhta.ch/>

UNITED KINGDOM

Health Technology Board for Scotland <http://www.htbs.org.uk/>

National Health Service Health Technology Assessment (UK) / National Coordinating Centre for Health Technology Assessment (NCCHTA) <http://www.hta.nhsweb.nhs.uk/>

National Institute for Clinical Excellence (NICE) <http://www.nice.org.uk/index.htm>

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>

US Blue Cross Blue Shield Association Technology Evaluation Center

(TEC) <http://www.bcbs.com/consumertec/index.html>

Author (Year)	Objective of report Databases & dates searched	Number & publication dates of included studies	Population considered in included studies Test comparison	Conclusions/recommendation	Quality assessment
Medical Services Advisory Committee 2001 Positron Emission Tomography Part 2(i) Reference 10	To assess the clinical effectiveness of PET for 5 indications including: Oesophageal cancer Primary: staging of patients before initial treatment Gastric and gastro-oesophageal cancer Primary: staging of patients before initial treatment to determine suitability for surgery or neoadjuvant therapy	Included articles published in English up to 2000 <i>Oesophageal cancer:</i> 12 accuracy studies published 1997–2000 <i>Gastric and gastro-oesophageal cancer:</i> 4 accuracy studies published 1997–2000 (included for oesophageal cancer as well)	Population <i>Oesophageal cancer:</i> Patients with oesophageal cancer <i>Gastric and gastro-oesophageal cancer:</i> Patients with gastric cancer Test comparison PET + conventional imaging versus conventional imaging alone	Overall conclusion FDG-PET is safe, has good diagnostic accuracy and is potentially clinically effective and cost-effective for the assessment of patients with oesophageal or gastric cancer Recommendation A whole-body PET study should be funded on an interim basis following initial therapy for: ▪ staging of a patient with proven oesophageal carcinoma where curative surgery or chemo-radiation is planned ▪ staging of a patient with proven gastric cancer where curative surgery is planned	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 [Note: assessment of heterogeneity and summary of main results were limited by lack of evidence identified]

Results

Included studies

12 accuracy studies were identified:

- 8 were studies of oesophageal cancer only ($n = 25-109$)—included for oesophageal cancer indication
- 3 were studies of oesophageal and gastro-oesophageal cancer ($n = 16-74$ overall; of these: $n = 13-31$ gastro-oesophageal)—included for oesophageal and gastric/gastro-oesophageal cancer (from 1 study it was not possible to extract results for the 2 indications separately)
- 1 was a study of oesophageal and gastric cancer ($n = 16$ overall; of these: $n = 2$ gastric cancer, $n = 1$ gastric lymphoma)—included for oesophageal and gastric/gastro-oesophageal cancer.

Oesophageal cancer:

Staging accuracy

The sensitivity of PET in detecting primary disease appears to be high, but may vary with the T-stage of the disease.

Generally, PET appeared to have comparable or higher sensitivities than CT for the detection of local nodal disease but both have low sensitivity for detection of low volume nodal disease.

The sensitivity of PET for detecting nodal involvement may vary, depending upon anatomic location of nodes.

In the detection of distant metastases, PET had higher diagnostic accuracy than CT, EUS and CT + EUS.

Change in management

PET appears to offer additional useful information in the staging and treatment of patients.

PET has the potential to affect patient management, particularly in the avoidance of surgical intervention with curative intent in patients with previously unsuspected distant disease.

Health outcomes

It is unclear, as yet, how changes in management may affect ultimate patient outcomes.

Other uses of PET in oesophageal cancer:

Restaging of patients after neoadjuvant therapy (0 studies): 'The role of PET in restaging of patients after neoadjuvant therapy remains unclear, although potentially improved diagnostic accuracy in primary staging may also be applicable in this setting.'

Prognosis of patients (2 studies): 'PET can also provide useful prognostic information in some patients.'

Gastric and gastro-oesophageal cancer:*Staging accuracy*

The diagnostic accuracy of PET was comparable to CT for the detection of nodal involvement.

PET had lower sensitivity but higher specificity and comparable or higher accuracy than EUS for the detection of local lymph node involvement.

For the diagnosis of stage IV disease, PET appeared to offer superior diagnostic accuracy than either CT or EUS alone, or the combination of CT + EUS.

As would be expected, both PET and CT have low sensitivity for the detection of low-volume or micrometastatic disease, and laparoscopy may be appropriate in patients with negative PET before formal surgery.

The accuracy of PET to determine resectability/non-resectability of patients appeared to be superior to that of CT.

Change in management

PET alone appeared to correctly prevent a higher proportion of patients from undergoing inappropriate surgical intervention than would the results of CT alone.

Health outcomes

No studies reported on the impact of PET on ultimate patient outcomes. It is less clear at this stage whether PET-directed downstaging or changes in management of patients deemed inoperable by CT and/or EUS might affect ultimate patient outcomes.

In patients considered inoperable, and in whom neoadjuvant treatment is considered, PET may be of value. It is unclear at this stage, however, whether neoadjuvant therapy before surgery is better than surgery alone. There are ongoing randomised trials addressing this question.

Other uses of PET in gastric or gastro-oesophageal cancer:

The role of PET in the restaging of patients after neoadjuvant therapy requires further evaluation, although potentially improved diagnostic accuracy in primary staging may also apply to this setting.

Appendix E Staging classification ¹

The most widely accepted system for the staging of pathological cancer is the TNM (tumour, node, metastasis) classification system. Cancer staging involves defining the extent of the primary tumour, spread to regional lymph nodes, and the presence or absence of metastases. Accurate cancer staging is essential to well-informed clinical management decisions. The increasing range of surgical, non-surgical and palliative treatment options has increased clinical emphasis on cancer staging.

Anatomically, the walls of the oesophagus and stomach consist of the external muscular, middle areolar, and internal mucous layers. The stomach has an additional external serous layer that is derived from the peritoneum and covers the entire surface except the greater and lesser curvatures. The muscular layer is further subdivided into two layers in the oesophagus and three in the stomach.

Gastric polyps are a relatively common finding upon gastroscopic examination. They occur sporadically in people who have average risk, and more frequently in association with polyposis syndromes such as familial adenomatous polyposis coli. Gastric polyps may be neoplastic or non-neoplastic; hamartomatous; related to polyposis syndromes; derived from heterotopic tissue; or reactive. Neoplastic polyps can be differentiated by pathological interpretation of biopsied tissue taken during gastroscopy.

The TNM classification for oesophageal and gastric cancer is shown in Table 28, and the stage classification is shown in Table 29. The Japanese staging system is different from the American Joint Committee on Cancer staging system.

Malignant gastrointestinal stromal tumours are not currently classified using TNM nomenclature (American Joint Committee on Cancer 2002a).

¹ Reproduced from the MSAC endoscopic ultrasound assessment report (Medical Services Advisory Committee 2006).

Table 28 TNM classification of oesophageal and gastric cancer

Classification	Oesophagus	Gastric
Tumour		
TX	Primary tumour cannot be assessed	Primary tumour cannot be assessed
T0	No evidence of primary tumour	No evidence of primary tumour
Tis	Carcinoma in situ	Carcinoma in situ: intraepithelial tumour without invasion of the lamina propria
T1	Tumour invades lamina propria or submucosa	Tumour invades lamina propria or submucosa
T2	Tumour invades muscularis propria	Tumour invades muscularis propria or subserosa
T2a	–	Tumour invades muscularis propria
T2b	–	Tumour invades subserosa
T3	Tumour invades adventitia	Tumour penetrates serosa (visceral peritoneum) without invasion of adjacent structures
T4	Tumour invades adjacent structures	Tumour invades adjacent structures
Node		
NX	Regional lymph nodes cannot be assessed	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis	No regional lymph node metastasis
N1	Regional lymph node metastasis	Metastasis in 1–6 regional lymph nodes
N2	–	Metastasis in 7–15 regional lymph nodes
N3	–	Metastasis in >15 regional lymph nodes
Metastasis		
MX	Distant metastasis cannot be assessed	Distant metastasis cannot be assessed
M0	No distant metastasis	No distant metastasis
M1	Distant metastasis	Distant metastasis
<i>Tumours of the lower thoracic oesophagus</i>		
M1a	Metastasis in coeliac lymph nodes	
M1b	Other distant metastasis	
<i>Tumours of mid thoracic oesophagus</i>		
M1a	Not applicable	
M1b	Non-regional lymph nodes and/or other distant metastasis	
<i>Tumours of upper thoracic oesophagus</i>		
M1a	Metastasis in cervical nodes	
M1b	Other distant metastasis	

Sources: Esophagus. In: American Joint Committee on Cancer. AJCC Staging Manual. 6th ed. New York, NY: Springer, 2002, pp 91–8. Stomach. In American Joint Committee on Cancer. AJCC Staging Manual. 6th ed. New York, NY: Springer, 2002, pp 99–106.

Table 29 Oesophageal and gastric cancer staging by TNM grouping

Stage	Oesophagus	Gastric
0	Tis, N0, M0	Tis, N0, M0
I	T1, N0, M0	T1, N0, M0
IA		T1, N1, M0
IB		T2a, N0, M0 T2b, N0, M0
II	T2, N0, M0 T3, N0, M0	T1, N2, M0
IIA	T1, N1, M0 T2, N1, M0	T2a, N1, M0
IIB		T2b, N1, M0 T3, N0, M0
III	T3, N1, M0 T4, any N, M0	T2a, N2, M0
IIIA		T2b, N2, M0
IIIB		T3, N1, M0 T4, N0, M0 T3, N2, M0
IV	Any T, any N, M1	T4, N1–3, M0
IVA	Any T, any N, M1a	Any T1, N3, M0
IVB	Any T, any N, M1b	Any T, any N, M1

Sources: Esophagus. In: American Joint Committee on Cancer. AJCC Staging Manual. 6th ed. New York, NY: Springer, 2002, pp 91–8.
Stomach. In American Joint Committee on Cancer. AJCC Staging Manual. 6th ed. New York, NY: Springer, 2002, pp 99–106. Note: See Table 28 for explanation of T, N and M notation.

Appendix F PPICO criteria

The clinical questions for review were defined based on the PPICO (Population, Prior tests, Intervention, Comparator, Outcomes) criteria. The detailed PPICO criteria defined *a priori* for each indication are shown in Table 30 and Table 31.

Table 30 PPICO criteria and clinical question for PET in primary oesophageal cancer

Population	Prior tests	Intervention	Comparator	Reference standard	Outcomes
<p>Patients with biopsy-proven potentially curable oesophageal cancer (including GEJ cancer) considered for:</p> <p>1. definitive treatment (surgery ± neoadjuvant therapy, or chemo-radiation)</p> <p>2. salvage surgery of residual disease following definitive chemo-radiation</p>	<p>1. Endoscopy (and Biopsy) for primary disease, and CT (chest and abdomen)</p> <p>2. Endoscopy (and biopsy) for residual disease (2a = biopsy confirmed ; 2b = unconfirmed)</p>	<p>1. & 2a. FDG-PET/CT plus prior tests (standard conventional imaging)</p> <p>2b. FDG-PET/CT alone</p>	<p>1. Prior tests (standard conventional imaging) without PET/CT</p> <p>2a. Biopsy confirmed residual disease: CT</p> <p>2b. Unconfirmed residual disease: prior tests without PET/CT</p>	<p>Pathology, or clinical follow-up (≥6 months)</p>	<p>Diagnostic accuracy</p> <ul style="list-style-type: none"> ▪ sensitivity ▪ specificity ▪ additional TP & FP ▪ ROC AUC, Q*, DOR <p>Change in management</p> <ul style="list-style-type: none"> ▪ definitive treatment (surgery or chemo-radiation) avoided ▪ definitive treatment instigated (salvage surgery) ▪ investigations avoided ▪ overall change ▪ change in intent from curative to palliative ^a ▪ upstaging to stage IV ^a ▪ other changes occurring in ≥10% patients <p>Patient outcomes</p> <ul style="list-style-type: none"> ▪ overall survival ▪ cancer-specific mortality ▪ cancer progression ▪ treatment morbidity/mortality ▪ quality of life
<p>Clinical question</p> <p>What is the value of the addition of PET/CT in the assessment of patients with primary cancer of the oesophagus or the oesophageal junction considered suitable for definitive treatment as determined by conventional staging?</p> <p>What is the value of PET/CT in the assessment of residual disease following definitive chemo-radiation considered suitable for salvage surgery, (a) as a replacement for CT in staging biopsy proven residual disease, or (b) in addition to endoscopy and biopsy where residual disease has not been confirmed?</p>					

a. These are secondary outcomes and will be extracted only from studies included on the basis of reporting of primary outcomes. Abbreviations: AUC = area under the curve, CT = computed tomography, DOR = diagnostic odds ratio, FP = false-positive, GEJ = gastro-oesophageal junction, PET = positron emission tomography, Q* = Q statistic, ROC = receiver operating characteristic, TP = true-positive

Table 31 PPICO criteria and clinical question for PET in primary gastric cancer

Population	Prior tests	Intervention	Comparator	Reference standard	Outcomes
Patients with biopsy-proven, potentially curable primary gastric cancer planned for definitive therapy (surgery ± (neo)adjuvant therapy)	CT (abdominal/ chest/ pelvis) ± EUS Laparoscopy with peritoneal cytology	FDG-PET/CT plus prior tests (standard conventional imaging)	Prior tests without PET/CT	Pathology, or clinical follow-up (≥6 months)	<p>Diagnostic accuracy</p> <ul style="list-style-type: none"> ▪ sensitivity ▪ specificity ▪ additional TP & FP ▪ ROC AUC, Q*, DOR <p>Change in management</p> <ul style="list-style-type: none"> ▪ surgery avoided ▪ investigations avoided ▪ overall change ▪ change in intent from curative to palliative ^a ▪ upstaging to stage IV ^a ▪ other changes occurring in ≥10% patients <p>Patient outcomes</p> <ul style="list-style-type: none"> ▪ overall survival ▪ cancer-specific mortality ▪ cancer progression ▪ treatment morbidity/mortality ▪ quality of life
<p>Clinical question</p> <p>What is the value of the addition of PET/CT in the assessment of patients with biopsy proven primary gastric cancer that was potentially curable as determined by conventional staging including laparoscopy (including peritoneal cytology)?</p>					

Abbreviations: AUC = area under the curve, CT = computed tomography, DOR = diagnostic odds ratio, EUS = endoscopic ultrasound, FP = false-positive, PET = positron emission tomography, Q* = Q statistic, ROC = receiver operating characteristic, TP = true-positive
a. These are secondary outcomes and will be extracted only from studies included on the basis of reporting primary outcomes.

Appendix G Existing HTA reports 1999–2007

Organisation	Year	Title Indications
Medical Services Advisory Committee (MSAC) Australia	2001	Positron emission tomography <ul style="list-style-type: none"> ▪ oesophageal ▪ gastric and gastro-oesophageal
NHS R&D NCCHTA Programme United Kingdom	2007	Overview of the Clinical Effectiveness of Positron Emission Tomography (FDG-PET) Imaging in Selected Cancers <ul style="list-style-type: none"> ▪ oesophageal
Health Care Knowledge Centre (KCE) Belgium	2005	Positron emission tomography in Belgium <ul style="list-style-type: none"> ▪ oesophageal ▪ other (including gastric [HTA/sys reviews only; not presented in detail])
Agency for Health Technology Assessment Poland (AHTAPol)	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 <ul style="list-style-type: none"> ▪ oesophageal

HTA REPORTS					
Author/Year	Objective of report	Number & publication dates of included studies	Population considered in included studies Test comparison	Summary/conclusions	Quality assessment
<p>Agency for Health Technology Assessment Poland (AHTAPol) 2006</p>	<p>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 oesophageal and gastric</p>	<p>English and Polish language articles included</p> <p>Overall, 16 primary studies published 1998 to March 2006 were included</p> <p>3 HTAs were identified but not analysed (2 non-English/Polish; 1 not freely available)</p> <p>Oesophageal and gastric cancer:</p> <p>393 primary studies identified</p> <p>Two studies in oesophageal cancer included:</p> <p><i>Restaging</i>: 1 study (Certfolio 2005 [included in UK review])</p> <p><i>Tumour diagnosis</i>: 1 study (Kula 2005, Polish language?)</p>	<p>PET for restaging (1 study [<i>n</i> = 48]):</p> <p><i>Population</i></p> <p>Patients w oesophageal cancer in whom disease is restaged after neoadjuvant chemo-radiation</p> <p><i>Test comparison</i></p> <p>PET/CT versus CT, EUS</p> <p>PET for staging of primary cancer (1 study [<i>n</i> = 12]):^b</p> <p><i>Population</i></p> <p>Patients w confirmed primary or suspected recurrent oesophageal cancer</p> <p><i>Test comparison</i></p> <p>PET/CT versus CT</p>	<p><i>Summary</i></p> <p>'In summary, in restaging esophageal cancer, and in determining complete response to treatment, PET-CT imaging demonstrates higher diagnostic efficacy than CT or trans-oesophageal ultrasound-guided biopsy.'</p> <p>'Based on studies accessible, PET-CT is characterized by higher sensitivity (100%) in comparison to CT (92%) in detecting esophageal cancer.'</p>	<p>Quality: LOW</p> <p>Explicit review questions: NO (no PICO)</p> <p>Explicit & appropriate eligibility criteria: YES</p> <p>Explicit & comprehensive search strategy: NO [not comprehensive, may miss PET-CT studies]</p> <p>Quality of included studies appraised: YES</p> <p>Methods of study appraisal reproducible: YES</p> <p>Heterogeneity between studies assessed: N/A</p> <p>Summary of main results clear and appropriate: NO [interpretation of superiority of PET based on low-level evidence]</p> <p>Given the low quality of this report, results were not extracted in detail.</p>

PRIMARY STUDIES			
Author & Year Setting, <i>N</i>	Study objective Study design	Study population	Study quality and applicability
ACCURACY STUDIES			
<p>Meyers et al. (2007)</p> <p>American College of Surgeons Oncology Group Z0060 trial</p> <p>United States</p> <p>23 sites</p> <p>February 2000 – July 2004</p> <p><i>N</i> = 189</p>	<p>Objective</p> <p>To ascertain whether FDG-PET could detect metastatic lesions that would preclude oesophageal resection in patients believed to be surgical candidates after standard imaging procedures</p> <p>Study design</p> <p>Prospective diagnostic accuracy study</p> <p><i>Index test: FDG-PET</i></p> <p>Full-ring dedicated PET scanners; no PET/CT</p> <p>Upper/mid neck to upper thigh</p> <p>Interpreted by experienced nuclear physician</p> <p>Blinded and unblinded interpretation (to comparator), unblinded used in analysis</p> <p><i>Comparator</i></p> <p>Chest & abdominal CT: from thoracic inlet to inferior tip of liver, with iv contrast, 4th generation scanners</p> <p><i>Prior tests</i></p> <p>Bone scintigraphy and CT/ MRI brain, if indicated</p> <p>Within 30 days before study</p> <p><i>Reference standard</i></p> <p>Confirmation of additional disease detected by PET</p> <ul style="list-style-type: none"> ▪ hepatic lesion: biopsy or FNA cytology ▪ benign cysts or hemangiomas: MRI, US ▪ adrenal lesions: biopsy ▪ osseous abnormalities: imaging or biopsy or both ▪ multiple lesions: biopsy at least at one site ▪ laparotomy or thoracotomy if not otherwise 	<p>Inclusion criteria</p> <p>Histologically confirmed AC or SCC of oesophagus or GEJ</p> <p>Tumours ≥ 20 cm from incisors</p> <p>Stages T1–3 N0–1 M0–1a</p> <p>Free of metastatic disease after clinical and radiologic screening (non-calcified lung lesions ≤4 mm, liver cysts accepted)</p> <p>Medically fit for staging or oesophagectomy</p> <p>No recurrence of previous cancers ≥5 y</p> <p>Aged ≥18 y</p> <p>Exclusion criteria</p> <p>Poorly controlled diabetes mellitus</p> <p>Previous PET, unable to tolerate PET</p> <p>Patients planned for neoadjuvant therapy before 2001 (20% enrolled before amendment)</p> <p>Patient characteristics (<i>n</i> = 189)</p> <p>AC: 84%, SCC: 13%</p> <p>On CT: T0–T2: 51%, N0:88%, M0 99%</p> <p>Mean age (SD; range): 63 (11; 36–89)</p> <p>Female: 15%</p> <p>39% planned for neoadjuvant therapy (36% of these chemo-radiation)</p> <p>Prevalence distant mets: n.r.</p> <p>38.6% underwent induction chemo and/or RT after PET</p>	<p>NHMRC level: III-2</p> <p>Quality: fair</p> <p>Patient selection</p> <ul style="list-style-type: none"> ▪ Prospective: YES ▪ Consecutive: NO (non-evaluable pat excluded) ▪ Explicit selection criteria: YES <p>Test performance & interpretation PET protocol: YES</p> <p>Reference standard</p> <ul style="list-style-type: none"> ▪ Valid: YES ▪ Applied to all participants: NO <p>Test interval within days/weeks</p> <ul style="list-style-type: none"> ▪ Reference standard (n.r.): UNCLEAR ▪ Comparator (30 days): YES <p>PET reported blinded to ref std: YES</p> <p>Ref std reported blinded to PET: n.r.</p> <p>Routine clinical data available: YES</p> <p>Analysis</p> <ul style="list-style-type: none"> ▪ Uninterpretable/intermediate results reported: YES ▪ Study withdrawals explained: YES ▪ Data for 2 × 2 table reported: YES (incremental) <p>Applicable</p> <p>Applicable population</p> <ul style="list-style-type: none"> ▪ Presentation: YES ▪ Prior tests: YES

PRIMARY STUDIES			
Author & Year Setting, <i>N</i>	Study objective Study design	Study population	Study quality and applicability
	accessible; follow-up (6 mo) Others (17/35) received diagnostic f/up		Applicable intervention: YES Relevant outcome: YES
<p>Incremental accuracy</p> <p>Nodal disease (N-stage): additional disease (+ yield): 27% (45/166); accuracy n.r.</p> <p>Metastatic disease (M-stage):</p> <p>M-disease in M0 (+ yield M1a/M1b in M0): 18% (34/187); 10 TP, 6 FP, 18 unconfirmed (10 of these confirmed on f/up or imaging); PPV w ref standard histopathology: 63% (10/16); PPV w any ref standard (incl imaging): 58% (15/26); PPV w ref std histo or clin f/up 57% (13/23).</p> <p>M1b distant mets in M0 or M1a patients: 17% (33/189); 9 TP, 6 FP, 19 unconfirmed (3 of these confirmed on f/up imaging); PPV w ref standard histopathology: 60% (9/15); PPV w any ref standard (incl imaging): 56% (14/25); PPV w ref std histo or clin f/up 55% (12/22).</p> <p>Histopathological confirmation took place at the time of operation for some patients, in some cases following induction chemotherapy.</p> <p>Therapeutic impact</p> <p>Information on the number of patients avoiding surgery or resection was reported and included patients undergoing surgery during which confirmation of PET-detected M1 disease avoided resection. When confirmatory tests suggested or proved a false-positive PET result, patients proceeded to surgery. No pre-PET assessment of suitability.</p> <p>PET avoided surgery due to detection of M1 disease in 9 patients (5%). 2 patients proceeded to surgery but resection was avoided due to M1 disease identified on PET but not confirmed before (total avoiding resection 11, 6%).</p> <p>7 patients avoided resection due to M1 disease found at exploration but not on PET (liver, peritoneum and lung), 10 patients avoided surgery due to decline or death and 7 patients refused surgery. The latter indicates that that patient agreement for surgery was not established before enrolment.</p> <p>5 patients avoided surgery due to unresectable tumour at exploration and 2 due to extensive N1 disease (unclear if identified at surgery or before).</p> <p>Adverse events</p> <p>7 patients underwent confirmatory procedures due to FPs, 1 adrenalectomy (surgical morbidity & therapy for adrenal insufficiency), 1 grade 3 wound complication from confirmatory procedure.</p>			
Stahl et al. (2005) Germany 1 site period n.r. <i>n</i> = 40 patients	<p>Objective</p> <p>To assess in patients with locally advanced AC of the distal oesophagus (ADE): (i) how often staging changed in pat w locally advanced ADE by the addition of PET to CT, (ii) whether these changes are clinically relevant, (iii) whether clinically relevant changes are correct, (iv) diagnostic impact of independent vs concomitant reading of PET and CT</p> <p>Study design</p> <p>Retrospective diagnostic accuracy study, with</p>	<p>Inclusion criteria</p> <p>Histologically proven locally advanced AC of the distal oesophagus (T 3/4, N0/+ on EUS)</p> <p>Planned for neoadjuvant therapy</p> <p>Exclusion criteria</p> <p>Diabetes mellitus</p> <p>Previous anticancer therapy</p> <p>Patient characteristics (<i>n</i> = 40)</p>	<p>NHMRC level: III-2</p> <p>Quality: fair</p> <p>Patient selection</p> <ul style="list-style-type: none"> ▪ prospective: NO ▪ consecutive: YES <p>Explicit selection criteria: YES</p> <p>Test performance & interpretation PET protocol: YES</p>

PRIMARY STUDIES			
Author & Year Setting, <i>N</i>	Study objective Study design	Study population	Study quality and applicability
	<p>diagnostic thinking information</p> <p><i>Index test: FDG-PET</i></p> <p>PET scanners</p> <p>Neck, thorax, abdomen</p> <p>Interpreted independently by 2 nuclear med physicians, blinded to CT, consensus reading between 2 readers if discordant results</p> <p><i>Comparator</i></p> <p>Helical CT of chest & abdomen w iv contrast; read by one experienced radiologist</p> <p>If PET and CT discordant, reassessment with concomitant reading of PET and CT</p> <p><i>Prior tests</i></p> <p>EUS</p> <p><i>Reference standard</i></p> <p>Patho-histology of surgical specimen; biopsy of suspicious lesion; additional diagnostic imaging (in particular MRI); clinical follow-up over at least 6 months including imaging studies</p> <p>Some patients no ref std. Concordant findings on PET and CT, considered as true if neg or if further confirmation not available (eg, distant lymph node or organ mets) ('extended gold standard')</p>	<p>Mean age (range): n.r.</p> <p>Female: n.r.</p> <p>Prior staging: EUS</p> <p>Prevalence M-stage: 28% (11/40)</p> <p>After PET: 18% surgery alone (7/40), 50% preop chemo + surgery (20/40), 33% palliative therapy (chemo ± radio ± stenting (13/40)</p> <p>Enrolled in prospective phase II therapy trial</p>	<p>Reference standard</p> <ul style="list-style-type: none"> ▪ Valid: YES ▪ Applied to all participants: NO <p>Test interval within days/weeks</p> <ul style="list-style-type: none"> ▪ Reference standard (n.r.): UNCLEAR ▪ Comparator (n.r.): UNCLEAR <p>PET reported blinded to ref std: YES</p> <p>Ref std reported blinded to PET: NO</p> <p>Routine clinical data available: YES (consensus reading)</p> <p>Analysis</p> <ul style="list-style-type: none"> ▪ Uninterpretable/intermediate results reported: YES ▪ Study withdrawals explained: NONE ▪ Data for 2 × 2 table reported: YES (positives) <p>Applicability: limited</p> <p>Applicable population:</p> <ul style="list-style-type: none"> ▪ Presentation: NO (locally advanced only) ▪ Prior tests: NO (EUS prior) <p>Applicable intervention: YES</p> <p>Relevant outcome: YES</p>
<p>Incremental accuracy</p> <p>M-stage disease (distant lymph nodes, organ mets):</p> <p>Positivity rate (+ yield): 14% of all patients with CT– for M-stage (4/28); TP = 1; FP = 3; PPV = 25%. Consensus reading of PET and CT corrected all 3 FP results, giving PPV = 100% (1/1) of incremental value of PET for consensus reading.</p> <p>Diagnostic thinking:</p> <p>2.5% of all patients (1/40) had discordant positive findings (PET+/CT–) that were clinically relevant (change from curative to palliative clinical concept) and correct, but clinical relevance was not determined for all patients.</p>			

PRIMARY STUDIES			
Author & Year Setting, <i>N</i>	Study objective Study design	Study population	Study quality and applicability
Van Westreenen et al. (2007b) Netherlands 3 sites October 2002 – August 2004 <i>N</i> = 199	Objective To assess the additional value of FDG-PET in patients with oesophageal cancer after other diagnostic investigations Study design Diagnostic accuracy study Therapeutic impact information <i>Index test: FDG-PET</i> PET scanners; no PET/CT Mid-skull to mid-femur Interpreted independently by 2 exp nuclear physicians, 3rd reviewer if disagreement CT available for localisation, blinded to other data <i>Comparator (prior conventional staging)</i> Fitness assessment for surgery Multidetector CT of neck, chest, upper abdomen, w oral & iv contrast EUS of oesophagus: radial scanner, ± small-calibre probe if stenotic tumour, ± FNA; incomplete in <i>n</i> = 16 US of neck ± FNA Bronchoscopy if carcinoma at or above carina (<i>n</i> = 14) All tests within 2 weeks <i>Reference standard</i> PET+: Histological, cytological examination, or other imaging (skeletal radiology (<i>n</i> = 3), bone scan (4), further CT (5), US (4), MRI (7), colonoscopy (9), bronchoscopy (1), laparoscopy (1)). Unconfirmed to surgery + intraoperative biopsy. Progression of unconfirmed during 6 mo f/up considered proof of	Inclusion criteria Histologically proven cancer of the thoracic oesophagus or GEJ, without evidence of distant metastases or locally unresectable disease based on conventional evaluation Aged ≥ 18 Exclusion criteria Patients unable to undergo major surgery Malignancy in previous 5 y Uncontrolled diabetes mellitus Pregnancy Patient characteristics (<i>n</i> = 199) AC: 80%, SCC: 20% GEJ: 25%, distal thoracic: 67%, proximal thoracic: 8% On conventional staging: Stage I/II/III/IV: 7%/ 32%/ 53%/ 8% Mean age (range): 64 (29–82) Female: 17% Prevalence distant mets: 9% (17/199)	NHMRC level: III-2 Quality: FAIR Patient selection <ul style="list-style-type: none"> ▪ Prospective: YES ▪ Consecutive: YES Explicit selection criteria: YES Test performance & interpretation PET protocol: YES Reference standard <ul style="list-style-type: none"> ▪ Valid: YES ▪ Applied to all participants: NO (not all valid) Test interval within days/weeks <ul style="list-style-type: none"> ▪ Reference standard (2 w): YES ▪ Comparator (2 w): YES PET reported blinded to ref std: YES Ref std reported blinded to PET: NO Routine clinical data available: partially (CT YES, other NO) Analysis <ul style="list-style-type: none"> ▪ Uninterpretable/intermediate results reported: YES ▪ Study withdrawals explained: YES ▪ Data for 2 × 2 table reported (PPV only): YES Applicability: limited Applicable population <ul style="list-style-type: none"> ▪ Presentation: YES ▪ Prior tests: NO (includes EUS, US)

PRIMARY STUDIES			
Author & Year Setting, <i>N</i>	Study objective Study design	Study population	Study quality and applicability
	malignancy No oesophagectomy if distant dissemination confirmed		Applicable intervention: YES Relevant outcome: YES
<p>Incremental accuracy</p> <p>Metastatic disease (M-stage):</p> <p>Positivity rate for distant mets (+ yield): 15% (95% CI 10.1–19.9) (30/199); 27% (8/30; 95% CI 10.4%–43.0%): 8 TP [8 TP mets], 22 FP (15 FP, 7 synchronous neoplasms [rectosigmoid (5), thyroid, colon; all resected subsequently]; PPV (distant malignancy) = 50% (15/30).</p> <p>PET FN (distant mets) = 9; PET sensitivity (distant mets): 47% (8/17[9+8]), based on transthoracic or trans-hiatal surgical approach only.</p> <p>Therapeutic impact</p> <p>In absence of confirmation of dissemination, or if confirmation not possible, patients proceeded to surgery. No pre-PET assessment of suitability.</p> <p>3% avoided unnecessary surgery (6/199; 6 of 8 TP).</p> <p>13% (25/199) avoided surgical resection (but underwent surgical exploration; resection abandoned during exploration); due to T4 tumour (14), distant mets: (11; 2 identified on PET).</p>			
CHANGE IN MANAGEMENT STUDIES			
Duong et al. (2006a) Australia 1 site October 1996 – March 2002 <i>N</i> = 68	<p>Objective</p> <p>To assess whether incremental FDG-PET findings affect the management plan of patients undergoing primary staging for oesophageal cancer</p> <p>Study design</p> <p>Change in management; survival analysis [not reported here]</p> <p>Prospective, consecutive patients</p> <p>Management plans:</p> <ul style="list-style-type: none"> ▪ pre-PET plan: recorded in database ▪ by 2 surg independently ▪ 1 surgeon with PET info (CT+EUS+PET), 1 surgeon no PET info (CT+EUS) <p><i>Index test:</i></p> <p>FDG-PET, with/without attenuation correction</p> <p>Lower neck, thorax and abdomen to iliac crest</p>	<p>Inclusion criteria</p> <p>Biopsy-proven oesophageal cancer and PET scan as part of primary staging</p> <p>Exclusion criteria</p> <p>Unresectable systemic metastases (stage IVb) that had been confirmed on biopsy, or unequivocally documented on conventional imaging</p> <p>Patient characteristics (<i>n</i> = 68)</p> <p>AC: 50%, SCC: 49%, small cell carcinoma: 1%</p> <p>GEJ: 22%; lower-third: 43%, mid-third: 24%</p> <p>Equivocal metastatic lesions on conventional imaging: <i>n</i> = 11</p> <p>Mean age (range): 68 (43–88)</p> <p>Female: 26% (18/68)</p> <p>Prevalence (conventional staging): stage I–III: 84% (57/68), stage IV: 16% (11/68)</p>	<p>Prospective: YES</p> <p>Explicit criteria: YES</p> <p>Consecutive patients: YES</p> <p>Referring clinician: UNCLEAR</p> <p>Accuracy: NO</p> <p>Plans independently assessed: NO (at weekly multidisciplinary meeting)</p> <p>Blinding to study results: NO (YES for staging, NO for plan)</p> <p>Explicit outcomes: NO (pre-PET not reported in adequate detail)</p> <p>Patient outcomes: YES</p> <p>Physician experience: YES</p> <p>Applicability: LIMITED</p> <p>Applicable population</p>

PRIMARY STUDIES			
Author & Year Setting, <i>N</i>	Study objective Study design	Study population	Study quality and applicability
	<p>One experienced nuclear med physician, independent assessment of second specialist if difficult case to ascertain consensus</p> <p>Not blinded to previous imaging result, but blinded to pre-PET management plan and outcome</p> <p>Within 2 weeks of conventional staging</p> <p><i>Comparator (conventional staging):</i></p> <p>CT (chest/abdomen), iv contrast</p> <p>EUS ± FNA (<i>n</i> = 12)</p> <p>Before PET</p> <p><i>Reference standard</i></p> <p>Surgical exploration</p> <p>Positive lesion: serial imaging, lesion resolved at treatment (TP); negative lesion: clinical f-up (12 mo)</p> <p>Verification in 76% (52/68), and of those, PET findings were correct in 87% (45/52); post-PET stage correct in 19 of 20 (of 22 with high-impact management change) (However, verification not reported in detail; ie, not for upstaging to stage IV, so can't be used for accuracy)</p>		<ul style="list-style-type: none"> ▪ Presentation: YES ▪ Prior tests: NO (includes EUS) <p>Applicable intervention: YES</p> <p>Relevant outcome: YES</p>
<p>Change in management:</p> <p>Change in treatment modality: Surgery avoided (surgery to induction chemo-radiation): 6% of all patients (4/68); definitive chemo-radiation avoided or surgery added: 3% (2/68).</p> <p>Overall change: 40% of all patients (27/68).</p> <p>Diagnostic thinking: Stage change from stage I–III to stage IV: 21% (12/57), 10.5% to stage IVa (coeliac or supraclavicular nodal involvement), 10.5% to stage IVb (liver and lung mets). 100% correct (of at least <i>n</i> = 10 [10 = 12–2, 2: 2 of 22 in whom management plan was sign altered were not confirmed] in whom post-PET stage was confirmed).</p> <p>Change in treatment intent: curative to palliative: 18% of all patients (12/68) (can be assumed these are patients who were upstaged post-PET); palliative to curative: 4% (3/68).</p> <p>Additional results:</p> <p>Synchronous cancers in 6 patients (3 additional oesophageal tumours, 1 soft palate tumour, 1 lung cancer, 1 colon cancer).</p>			
Duong et al. (2006b)	Objective	Inclusion criteria	

PRIMARY STUDIES			
Author & Year Setting, <i>N</i>	Study objective Study design	Study population	Study quality and applicability
Australia 1 site October 1996 – March 2002 <i>N</i> = 53	To study the impact of FDG-PET on treatment selection after completion of CRT and subsequent survival of oesophageal cancer patients Study design Change in management; survival analysis [not reported here]) Prospective, consecutive patients Management plans: Pre-PET plan: prospectively indicated on routine PET request form Post-PET plan: medical record, or direct contact with treating clinicians; in weekly multidisciplinary meeting <i>Index test:</i> FDG-PET (dose: 70–120 MBq), with and without attenuation correction Lower neck, thorax and abdomen to iliac crest One experienced nuclear med physician, independent assessment by second specialist if difficult case to ascertain consensus Not blinded to previous imaging result, blinding to pre-PET management plan unclear Within 2 weeks of conventional staging <i>Comparator (conventional staging):</i> CT (chest/ abdomen), with contrast, 4–5 weeks after completion of CRT <i>Disease classification:</i> Residual disease: positive/negative, according to RECIST criteria <i>Follow-up:</i> min of 12 months (median: 19 [range: 1–52])	Patients referred for PET evaluation of tumour response to CRT Exclusion criteria Patients with systemic mets (stage M1b) at baseline investigation were excluded Patient characteristics (<i>n</i> = 53) Study included patients undergoing radical CRT and some with reduced course of CRT Radical CRT: external beam RT: total dose of 50 Gy in 25 fractions (5 fractions per week for 5 weeks); chemo: Cisplatin (75 mg/m ²) iv over 1 h, 5-fluorouracil 1000 mg/m ² /day iv by 24 h infusion on days 1–4 inclusively, 2 cycles in weeks 1 and 5 of RT, and additional 2 after RT in some who tolerate treatment Shorter 3-week course of CRT (in M1a): 35 Gy in 15 fractions, chemo concurrently during first week of RT % radical CRT: unclear AC: 45%, SCC: 51%, small cell carcinoma: 4% GEJ: 26%; lower-third: 34%, mid-third: 23%, upper third: 17% Median age (range): 64 (39–97) Female: 30% (16/53) CMR of tumour on PET after completion of CRT: 43%	Prospective: YES Explicit criteria: YES Consecutive patients: YES Referring clinician: UNCLEAR Accuracy: NO Plans independently assessed: UNCLEAR (pre-PET unclear, post-PET YES [at weekly multidisciplinary meeting]) Blinding to study results: YES Explicit outcomes: NO (Pre-PET not reported in adequate detail) Patient outcomes: YES Physician experience: YES Applicability: Limited applicable Applicable population <ul style="list-style-type: none"> ▪ Presentation: NO (proportion with definitive CRT unclear) ▪ Prior tests: YES Applicable intervention: YES Relevant outcome: YES

PRIMARY STUDIES			
Author & Year Setting, <i>N</i>	Study objective Study design	Study population	Study quality and applicability
	<i>Reference standard: n.r.</i>		
<p>Change in management: High-impact management change (change in treatment intent or modality) in 36% of patients (19/53). Change in treatment modality in 14 (26%), change in treatment intent in 5 patients (9%). Change in treatment modality (in <i>n</i> = 14 who were borderline or poor surgical candidates): Surgery or additional chemotherapy avoided (observation instead): 17% of all patients (9/53); surgery avoided (chemotherapy instead): 6% (3/53) patients with minimal response to CRT on PET and persistent bulky loco-regional disease (salvage chemotherapy?). Surgery instigated (from observation, CT-occult PET-positive for residual disease): 4% (2/53). Change in treatment intent: curative to palliative: 7% of all patients (3/53); palliative to curative: 4% (2/53). Treatment delivered corresponded to the post-PET management plan in all patients.</p> <p>Additional results: PET results verified in 91% (48/53) of patients; if verified, confirmed to be correct in 79% (38/48).</p>			
McDonough et al. (2007) USA 1 site December 2003 – March 2007 <i>N</i> = 50	<p>Objective To analyse if the addition of FDG-PET offers any additional information that affects the initial treatment stratification of patients with oesophageal cancer</p> <p>Study design Change in management study Prospective, consecutive patients</p> <p><i>Management plans:</i> By 2 surgeons independently, blinded to patient identifying info and demographics Determine for each patient: surgical resection, induction chemo + surgical resection, palliation 1 surgeon with PET info (CT+EUS+PET), 1 surgeon no PET info (CT+EUS), independently Treatment decisions of 2 surgeons compared: Kappa's coefficients of agreement between readers</p>	<p>Inclusion criteria Primary biopsy-proven oesophageal cancer</p> <p>Exclusion criteria Patients with GEJ tumours or another primary malignancy</p> <p>Patient characteristics (<i>n</i> = 50) AC: 86%, SCC: 14% On conventional staging: Stage I/II/III/IV: 7% / 32% / 53% / 8% Mean age (range): 63 (34–89) Female: 10% (5/50) Surgery alone: 19, chemo-radiation + surgery: 25, pall chemo-radiation: 6 Prevalence mets: n.r.</p>	Prospective: YES Explicit criteria: YES Consecutive patients: YES Referring clinician: YES Accuracy: NO Plans independently assessed: NO Blinding to study results: YES Explicit outcomes: NO Patient outcomes: NO Physician experience: NO Applicability: LIMITED Applicable population <ul style="list-style-type: none"> ▪ Presentation: YES ▪ Prior tests: NO (includes EUS) Applicable intervention: YES (PET & CT fusion)

PRIMARY STUDIES			
Author & Year Setting, <i>N</i>	Study objective Study design	Study population	Study quality and applicability
	<p><i>Index test:</i> FDG-PET/ non-contrast CT fusion n.r. where scan was done</p> <p><i>Comparator (conventional staging):</i> CT (chest/ upper abdomen), iv contrast EGD/EUS ± FNA: upper endoscopy before each EUS All tests within 1 month of consultation with a thoracic surgeon</p> <p><i>Reference standard:</i> Where surgical pathology available (<i>n</i> = 21)</p>		Relevant outcome: YES
<p>Accuracy: Nodal disease (N-stage) (in 21 patients undergoing surgery only): PET: yield = 14% (3/21), FP = 3; CT: yield = 5% (1/21), FP = 1, EUS: yield = 0.</p> <p>Change in therapy Treatment decision: surgery: <i>n</i> = 19 with PET, <i>n</i> = 19 without PET; surgery + neoadjuvant radiation: <i>n</i> = 24 with PET, <i>n</i> = 25 without PET (assumption); palliative: <i>n</i> = 7 with PET, <i>n</i> = 6 without PET (assumption). In 2% of patients (1/50), PET led to change in management from surgery + neoadjuvant chemo-radiation to palliative therapy. In 98% (49/50) of patients, both surgeons came to identical clinical management decisions independent of PET results (98% agreement, <i>k</i> = 0.97 (95% CI 0.93–0.99). In one case where treatment decision differed, EUS was incomplete secondary to high-grade stenosis.</p> <p>Adverse events: Complications of EUS-FNA: microperforation with pneumomediastinum without evidence of mediastinitis on CT.</p> <p>Additional results: <i>N</i> = 2 excluded due to second primary malignancy found during evaluation (4% of <i>n</i> = 52).</p>			
PROGNOSTIC STUDIES			
Van Westreenen et al. (2005) The Netherlands 1 site	<p>Objective To analyse the patients with oesophageal cancer who were suitable for potentially curative surgery after preoperative staging; identify number of unresectable</p>	<p>Inclusion criteria Diagnosis of cancer of the oesophagus or the GEJ Eligible for potentially curative surgery (tumours staged as T1–3, N0–1, M0)</p>	<p>Level III-3 Quality assessment</p> <ul style="list-style-type: none"> An inception cohort assembled: YES

PRIMARY STUDIES			
Author & Year Setting, <i>N</i>	Study objective Study design	Study population	Study quality and applicability
1992–2002 <i>N</i> = 203	<p>disease/ distant metastases during surgery; impact of different staging modalities on number of unnecessary explorations; estimate prognostic value of different combinations of staging for survival</p> <p>Study design</p> <p>Retrospective cohort with historical control</p> <p><i>Index test (since 1998):</i></p> <p>FDG-PET</p> <p>n.r. where scan was done</p> <p>Interpretation: n.r.</p> <p><i>Comparator (conventional staging):</i></p> <p>Single-slice spiral CT (neck to upper abdomen), iv and oral contrast</p> <p>EUS ± FNA (since 1997): radial scanner, small-calibre probe if stenotic tumour not traversable; performed by one well-trained endoscopist</p> <p>All tests within median of 2 weeks (range: 1–4 weeks) to the time of surgery</p> <p><i>Analysis</i></p> <p>Survival analysis using the Kaplan–Meier method, differences: log-rank test</p> <p>Logistic regression using forward stepwise regression</p>	<p>Exclusion criteria</p> <p>Patients with high-grade dysplasia, preoperative chemotherapy, RT</p> <p>Patients unfit for surgery</p> <p>Patient characteristics (<i>n</i> = 50)</p> <p>AC: 84%, SCC: 16%</p> <p>Mid oesophagus: 4%, distal oesophagus: 50%, GEJ: 45%</p> <p>Surgical staging: M0/Mx: 68% (139/203); M1: 32%(64/203)</p> <p>Median age (range): 62 (22–82)</p> <p>Female: 17%</p> <p>Prevalence M1 disease: 32% (64/203) (59 M1 + 5 mets and local unresectability)</p>	<ul style="list-style-type: none"> ▪ Patients at risk for expected clinical course: YES ▪ Referral pattern: n.r. ▪ Complete follow-up: n.r. ▪ Objective outcome criteria: YES ▪ Outcome assessment: blind N/A ▪ Adjustment procedure for extraneous prognostic factors: NO (survival) <p>Applicability: LIMITED</p> <p>Applicable population</p> <ul style="list-style-type: none"> ▪ Presentation: YES ▪ Prior tests: NO (includes EUS) <p>Applicable intervention: YES</p> <p>Relevant outcome: YES</p>
<p>Results</p> <p><u>Prognostic information:</u></p> <p>Median survival in patients undergoing surgical exploration vs curative oesophagectomy: 8.8 vs 36.4 months ($P < 0.001$).</p> <p>Median survival in patients undergoing resection ($n = 125$) selected with CT (1992–1996) vs CT+EUS ($n = 18$; 1997) vs CT+EUS+PET ($n = 48$; 1998–2002): 28 vs 25.6 vs 48.2 mo ($P = 0.34$).</p> <p><u>Therapeutic impact info:</u></p> <p>In patients staged with CT+EUS or CT+EUS+PET, unnecessary explorations were conducted in 50% (18/36) or 21% (13/61) of patients (surgical procedure included laparotomy and thoracic exploration to exclude distant metastases).</p>			

PRIMARY STUDIES			
Author & Year Setting, <i>N</i>	Study objective Study design	Study population	Study quality and applicability
Addition of PET to CT+EUS leads to avoidance of unnecessary explorations in 29% of patients. <u>Other results</u> Overall, resection abandoned/unnecessary explorations in 38% (78/203).			
Konski et al. (2007) USA 1 site 2002–2006 <i>N</i> = 37 (25 PET)	Objective To determine whether PET scans predict disease-free and overall survival in patients with oesophageal cancer undergoing definitive CRT Study design Retrospective cohort <i>Index test:</i> FDG PET-CT n.r. where scan was done Interpretation: a nuclear medicine physician obtained a maximal SUV; blinded to the clinical outcome <i>Comparator (conventional staging):</i> CT (apex of lung to mid abdomen), oral contrast EUS ± FNA: radial scanner, followed with curvilinear array ultrasound gastroscopie if coeliac lymphadenopathy was detected Time period between tests and CRT: n.r. <i>Analysis</i> Cox proportional hazards model using backward stepwise regression was used to investigate an association between disease-free survival and the selected variables	Inclusion criteria Patients with AC or SCC of the oesophagus Underwent PET-CT in addition to conventional staging before undergoing CRT Post-treatment PET Exclusion criteria n.r. Patient characteristics AC: 65%, SCC: 35% Cervical oesophagus: 3%; mid oesophagus: 32%; distal oesophagus: 32%; GEJ: 32% Median age (range): n.r. Female: 30% Prevalence (accurate staging in 27 patients): Stage II/III/IV: 26%/48%/26%	Level III-3 Quality assessment <ul style="list-style-type: none"> ▪ Inception cohort assembled: NO ▪ Patients at risk for expected clinical course: YES ▪ Referral pattern: n.r. ▪ Complete follow-up: n.r. ▪ Objective outcome criteria: YES ▪ Outcome assessment: blinded N/A ▪ Adjustment procedure for extraneous prognostic factors: YES Applicability: LIMITED Applicable population <ul style="list-style-type: none"> ▪ Presentation: YES ▪ Prior tests: NO (includes EUS) Applicable intervention: YES Relevant outcome: YES
Results <u>Prognostic information:</u> Univariate analysis: post-treatment SUV significantly predicted for disease-specific survival, with 1-unit increase in post-treatment SUV increasing disease-specific mortality by 30% ($P = 0.01$). No variables were significant on multivariate analysis (variables tested not clearly reported).			

PRIMARY STUDIES			
Author & Year Setting, <i>N</i>	Study objective Study design	Study population	Study quality and applicability
Mochiki et al. (2004) Japan 1 site 2000–2002 <i>N</i> = 85	<p>Objective</p> <p>To study the prognostic significance of FDG-PET in patients with gastric cancer</p> <p>Study design</p> <p>Retrospective cohort</p> <p><i>Index test (since 1998):</i></p> <p>FDG-PET</p> <p>From head to thigh</p> <p>Interpretation: evaluated by two experienced nuclear medicine physicians; blinded to CT results</p> <p><i>Prior tests:</i></p> <p>CT (from neck to the bottom of the pelvis), iv contrast EUS, gastric fluoroscopy and gastric endoscopy</p> <p><i>Analysis</i></p> <p>Survival analysis using the Kaplan–Meier method, differences: log-rank test</p>	<p>Inclusion criteria</p> <p>Patients undergoing surgical treatment for gastric cancer with curative intent</p> <p>Exclusion criteria</p> <p>Diabetes</p> <p>Previous anti-cancer therapy</p> <p>Patient characteristics (<i>n</i> = 50)</p> <p>AC: 89%, Signet-ring cell carcinoma: 11%</p> <p>Upper gastric: 29%; middle gastric: 44%; lower gastric: 27%</p> <p>Median age (range): 63 (36–85)</p> <p>Female: 36%</p> <p>Median follow-up time: 17 months (range 4–36 months)</p>	<p>Level III-3</p> <p>Quality assessment</p> <ul style="list-style-type: none"> ▪ Inception cohort assembled: NO ▪ Patients at risk for expected clinical course: YES ▪ Referral pattern: n.r. ▪ Complete follow-up: NO ▪ Objective outcome criteria: YES ▪ Outcome assessment: blind N/A ▪ Adjustment procedure for extraneous prognostic factors: NO <p>Applicability: LIMITED</p> <p>Applicable population</p> <ul style="list-style-type: none"> ▪ Presentation: YES ▪ Prior tests: NO (include EUS) <p>Applicable intervention: YES</p> <p>Relevant outcome: YES</p>
<p>Results</p> <p><u>Prognostic information:</u></p> <p>2-y survival rate was 72.1%.</p> <p>2-y survival rate for patients with SUV > 4 (50.6%; <i>n</i> = 31) was lower than for patients with SUV < 4 (81.3%; <i>n</i> = 34) (<i>P</i> < 0.05).</p> <p>2-y survival rate for patients with positive PET results (65.9%; <i>n</i> = 64); negative PET results (94.4%; <i>n</i> = 21); <i>P</i> = 0.046.</p> <p>Abbreviations: AC = adenocarcinoma, chemo = chemotherapy, CRT = chemo-radiotherapy, CT = computed tomography, EGD = oesophagogastroduodenoscopy, EUS = endoscopic ultrasound, FDG = 2-fluoro-2-deoxy-D-glucose, FN = false-negative, FNA = fine-needle aspiration, f/up = follow-up, GEJ = gastro-oesophageal junction, mets = metastases, MRI = magnetic resonance imaging, n.r. = not reported, pall = palliative, PET = positron emission tomography, PPV = positive predictive value, RECIST = Response Evaluation Criteria In Solid Tumours Response, RT = radiotherapy, SCC = squamous cell carcinoma, SUV = standardised uptake value, TP = true-positive, US = ultrasound, vs = versus, w = with</p>			

Australian Data Collection Report			
Study Setting	Study objectives	Study population Patient outcomes	Study quality and applicability
Chatterton 2006 Australia 5 sites: Vic, NSW (2), Qld, WA 56 referring clinicians March 2004 – June 2006	<ol style="list-style-type: none"> To evaluate the accuracy of PET and other imaging techniques for the initial staging of oesophageal and GEJ cancer compared with surgical pathology and to determine the sensitivity and specificity in patients submitted to surgery To determine the incremental information provided by PET in staging patients with oesophageal and GEJ cancer To determine the potential impact of PET staging on post-PET management of oesophageal and GEJ cancer, including change in prescribed radiation fields, and on prognosis To determine the impact of PET in retagging patients after neo-adjuvant CRT (optional) 	<p>Inclusion criteria:</p> <p>Histology-confirmed SCC or AC of oesophagus or GEJ</p> <p>Fit for potential radical treatments (surgery, neo-adjuvant chemo + surgery, or radical radio-chemo)</p> <p>No obvious distant metastatic disease at presentation as assessed by clinical examination, CT and endoscopy; or equivocal lesions possibly thought to be metastatic but too difficult for easy FNA</p> <p>Able to undergo study procedures and treatment</p> <p>ECOG performance status grade ≤ 2</p> <p>≥ 18 y</p> <p>Available for at least 12 months' follow-up</p> <p>Able to provide informed consent</p> <p>Exclusion criteria:</p> <p>Uncontrolled diabetes</p> <p>Pregnant</p> <p>Unable to provide informed consent</p> <p>Outcomes (objective):</p> <p>Sensitivity/specificity/accuracy of preoperative CT, PET and EUS compared with surgical pathology (1)</p> <p>Detection of N and M metastases with PET compared with CT and EUS (2)</p> <p>Clinical impact (= change in management) of confirmation of equivocal mets and/or detection of occult metastases (2)</p> <p>Potential impact of PET on RT fields/volume (no analysis conducted as info only for 5 patients) (3)</p> <p>Changes in management by PET after a course of neo-adjuvant therapy (no analysis as no info available) (4)</p>	<p>Quality</p> <p>Prospective diagnostic case series with explicit eligibility criteria reflecting intended test use</p> <p>Non-consecutive patient selection</p> <ul style="list-style-type: none"> Total number of potentially eligible patients in recruitment period not reported 13/204 (6%) of patients not included in analysis of therapeutic impact or patient prognosis due to death before treatment initiation or incomplete data about treatment initiated <p>Accuracy poorly reported</p> <p>Pretest plan not independently assessed</p> <p>Blinding to test results at pretest measurement NR</p> <p>Association between management change and PET result not independently assessed</p> <p>Descriptive information about patient outcomes reported</p> <p>Physician experience NR</p> <p>Applicability</p> <p>No comparison of survival or progression-free survival of patients staged by PET versus conventional testing</p> <p>All patients received management based on PET staging</p> <p>Comparisons of patient prognosis according to classification by conventional testing before versus after PET staging not valid due to confounding by treatment assigned based on PET results</p>

Australian Data Collection Report			
Results			
N & patient characteristics	Change in patient management	Other outcomes	Author Conclusions
<p>129</p> <p>Of $n = 74$: 77% AC; 19% SCC, 4% other</p> <p>Lymph node involvement: 39%</p> <p>PET/CT 18%</p> <p>Mean age 66 y (range 36–87)</p> <p>Males: 81%</p> <p>Prior tests for diagnosis:</p> <ul style="list-style-type: none"> ▪ histology 100% ▪ CT 85% ▪ clin exam: 27% ▪ endoscopy: 88% ▪ EUS 11% ▪ US: 1% ▪ MRI: 1% ▪ other 9% <p>Management plan intent (%): curative, 119 (92); palliative, 10 (8)</p>	<p>Pretest (post-test) management plan:</p> <p>Intent: curative 92% (75%)</p> <p>Post-PET palliative in pre-PET curative: 20%</p> <p>Post-PET curative in pre-PET palliative: 3%</p> <p>Any surgery: 73% (55%)</p> <p>Surgery only: 47% (33%)</p> <p>Surgery, chemotherapy and/or RT (consecutive or concurrent): 9% (9%)</p> <p>Chemo and/or RT, then surgery (consecutive or concurrent): 17% (12%)</p> <p>Surgery, then other: 1% (1%)</p> <p>Other, then surgery: 0% (1%)</p> <p>Chemotherapy: 2% (5%)</p> <p>RT: 3% (5%)</p> <p>RT & chemo: 22% (30%)</p> <p>Other \pm chemo or RT: 1% (5%)</p> <p>Changes in management plan (>10%):</p> <p>Overall change: 38% (49/129) (95% CI 30%–46%)</p> <p>Surgery avoided: 19% (24/129) (95% CI 13%–26%)</p> <p>Surgery alone avoided: 14% (30% of planned)</p> <p>Surgery + (neo)adjuvant avoided: 5% (32% of planned)</p> <p>Surgery avoided of those in whom surgery was planned: 25% (23/94)</p> <p>Surgery instigated in 0.08% (1/129) of patients (3% [1/35] in whom surgery not planned) (palliative to curative treatment intent)</p> <p>RT and chemo avoided (or one modality dropped, w/o surgery): 3% (4/129) (of those planned: 14% [4/28])</p> <p>RT and chemo instigated (or one modality added, w/o surgery): 12% (16/129) (in those not planned before: 16% (16/101))</p>	<p>Lesions before PET and PET-detected; PET-detected additional lesions; tumour detection</p> <p>Concordant/discordant results</p> <p>Detection of extra sites of disease</p> <p>41% (53/129) of pat: additional lesions</p> <p>26% (34/129) pat, lesions detected before PET were not detected by PET</p> <p>Compared to CT:</p> <p>24% (31/129) pat, distant mets on PET vs 0 on CT (yield) (48 lesions)</p> <p>70% (49/70) pat, regional mets on PET vs 57% (40/129) on CT</p> <p>40% (51/ 129) detection of regional or distant mets</p> <p>Compared to EUS:</p> <ul style="list-style-type: none"> ▪ 42% (5/12) pat, distant mets on PET vs 0 on EUS (yield) ▪ 33% (4/12) pat, regional mets on PET vs 67% (8/12) on EUS (not yield) <p>Accuracy data for primary tumour reported, but not retrieved (not relevant) (p 33)</p> <p>Disease progression</p> <ul style="list-style-type: none"> ▪ disease progression by treatment intent before and after PET ▪ additional lesions and time to progression <p><i>Disease progression by 12 months</i></p> <p>PET-staged curative: 27/78 (35%)</p> <p>PET-staged palliative: 13/22 (59%)</p> <p>χ^2 test $P \leq 0.05$</p>	<p>PET had significant impact on patient management decisions.</p> <p>“Patients who had equivocal metastases confirmed and/or additional lesions found on PET, when compared with conventional imaging, had a worse prognosis.”</p>

Australian Data Collection Report			
	<p>RT or chemo instigated (w/o surgery): 9% (11/129) (in those not planned before: 9%)</p> <p>Investigations avoided: 0.08% (laparoscopy)</p> <p>5% (7/129) changed from definitive CRT to palliative CRT or RT</p> <p>Diagnostic thinking:</p> <p>TNM classification (<i>N</i> = 128):</p> <p>T-stage: upstaged 4/128 pat (3%); downstaged 4/128 (3%); unchanged 120/128 (94%)</p> <p>N-stage: upstaged 20/128 pat (16%); downstaged 13/128 (10%); unchanged 93/128 (73%)</p> <p>M-stage: upstaged 28/128 pat (22%); downstaged 0/128 (0%); unchanged 94/128 (73%)</p> <p>20% (26/129; 95% CI 14%–28%) intent changed from curative to palliative due to PET+ for regional or distant metastases</p> <p>Change in patient management</p> <p>Of <i>n</i> = 124:</p> <p>60/124 (48%): actual treatment differed from post-PET management plan, due to:</p> <ul style="list-style-type: none"> ▪ Further review of treatment indicated consistent with PET findings: 23% ▪ Planned chemo-and/or RT regimen changed: 17% ▪ More extensive disease (FN on PET): 13% ▪ Other clinical reasons: 12% ▪ Insufficient information: 10% ▪ Palliative for symptom control: 8% ▪ Different surgical findings: 7% ▪ Patient declined treatment as planned: 5% ▪ Second opinion indicated a different therapeutic approach: 3% ▪ Additional treatment for disease progression: 2% 	<p>Log-rank test <i>P</i>: NR</p> <p>RR progression if classified as palliative = 1.69 (95% CI 0.94–2.71)</p> <p>RD = 24% (17%–33%)</p> <p><i>Disease progression by 12 months</i></p> <p>PET-detected occult disease: 20/37 (54%)</p> <p>No PET-detected occult disease: 20/63 (32%)</p> <p>χ^2 test <i>P</i> < 0.02</p> <p>Log rank test <i>P</i>: NR</p> <p>RR progression if PET-detected occult disease = 1.69 (95% CI 1.07–2.72)</p> <p>RD = 22% (15–31%)</p>	

Abbreviations: AC = adenocarcinoma, chemo = chemotherapy, CRT = chemo-radiotherapy, clin = clinical, CT = computed tomography, ECOG = Eastern Cooperative Oncology Group, EUS = endoscopic ultrasound, FN = false-negative, FNA = fine-needle aspiration, GEJ = gastro-oesophageal junction, mets = metastases, MRI = magnetic resonance imaging, NR = not reported, pat = patient, PET = positron emission tomography, RD = risk difference, RR = relative risk, RT = radiotherapy, SCC = squamous cell carcinoma, TNM = Tumour, Node, Metastasis, US = ultrasound, w/o = without

Appendix I PET therapeutic impact studies

Evidence from the published studies provides supportive information on the impact of PET on the management of patients with primary oesophageal cancer in Australia.

Two published studies reporting the therapeutic impact of PET in patients with primary oesophageal cancer were included in the review. One therapeutic impact study of PET for the assessment of residual disease was also included. The characteristics and appraisal of these studies are summarised in Table 32.

Data on the impact of PET on patient management are summarised in Table 33.

Table 32 Characteristics and appraisal of primary therapeutic impact studies in patients with oesophageal cancer

Author (Year) Setting	N	Test comparison	Population	Outcomes	Management quality & applicability
Primary staging					
Duong et al. (2006a) Australia Single centre Oct 1996 – March 2002	68	FDG-PET <i>in addition to</i> conventional staging by CT (iv contrast, chest & abdomen) EUS ± FNA (n = 12)	Biopsy-proven oesophageal cancer and PET scan as part of primary staging, no confirmed systemic metastases <ul style="list-style-type: none"> ▪ 68 years (43–88), 74% males ▪ GEJ: 22%; lower-third: 43%; mid-third: 24% ▪ 50% AC, 49% SCC, small cell carcinoma 1% ▪ on conventional staging: stages I–III: 84%, stage IV: 16% 	Therapeutic impact Diagnostic thinking (stage change)	Prospective: YES Explicit criteria: YES Consecutive patients: YES Referring clinician: UNCLEAR Accuracy: NO Plans independently assessed: NO Blinding to study results: NO Explicit outcomes: NO Patient outcomes: YES Physician experience: YES Limited applicability (includes EUS)
McDonough et al. (2007) USA Single centre Dec 2003 – Oct 2006	50	FDG-PET/CT fusion <i>in addition to</i> conventional staging by CT (iv contrast, chest/upper abdomen) EGD/EUS ± FNA	<ul style="list-style-type: none"> ▪ Primary biopsy-proven oesophageal cancer ▪ Excluded GEJ cancer or other primary malignancy ▪ 63 years (34–89), 90% males ▪ 86% AC, 14% SCC 	Accuracy (N-stage) Therapeutic impact	Prospective: YES Explicit criteria: YES Consecutive patients: YES Referring clinician: YES Accuracy: NO Plans independently assessed: NO Blinding to study results: YES Explicit outcomes: NO Patient outcomes: NO Physician experience: NO Limited applicability (includes EUS)
Assessment of residual disease					
Duong et al. (2006b) Australia Single centre Oct 1996 – March 2002	53	FDG-PET <i>in addition to</i> conventional staging by CT (contrast, chest/abdomen)	<ul style="list-style-type: none"> ▪ Patients referred for PET evaluation of tumour response to 4–5 weeks following CRT ▪ Proportion with definitive CRT unclear ▪ 64 years (39–97) ▪ GEJ: 26%; lower-third: 34%; mid-third: 23%; upper third: 17% ▪ 45% AC, 51% SCC, small cell carcinoma 4% ▪ Male: 70% 	Therapeutic impact	Prospective: YES Explicit criteria: YES Consecutive patients: YES Referring clinician: UNCLEAR Accuracy: NO Plans independently assessed: UNCLEAR Blinding to study results: YES Explicit outcomes: NO Patient outcomes: YES Physician experience: YES Limited applicability (proportion with definitive CRT unclear)

Abbreviations: AC = adenocarcinoma, CT = computed tomography, EGD = oesophagogastroduodenoscopy, EUS = endoscopic ultrasound, FDG = 2-fluoro-2-deoxy-d-glucose, FNA = fine-needle aspiration, GEJ = gastro-oesophageal junction, PET = positron emission tomography, SCC = squamous cell carcinoma

Table 33 Impact of PET for the assessment of oesophageal cancer on patient management

Author (Year)	<i>N</i>	Surgery avoided % (<i>n/N</i>)	Chemo-radiation avoided	Investigations avoided	Surgery instigated	Total % change (95% CI)	Other changes in >10% Type % (95% CI)	Yield Diagnostic thinking % (95% CI)
Primary staging								
Duong et al. (2006a)	68	6 (4/68)	3 (2/68)	–	3 (2/68)	40 (27/68)	18% change curative to palliative	21% (12/57) upstage to IV 11% upstage to M1a 11% upstage to M1b
McDonough et al. (2007)	50	2 (1/50)	–	–	–	–	–	–
Assessment of residual disease								
Duong et al. (2006b)	53	6 (3/53) ^a	11 (6/53)	–	4 (2/53)	High impact ^b 36 (19/53)	9% change in intent 26% change in modality	–

a. Due to lack of response to CRT

b. Change in treatment intent or modality

Abbreviations: CI = confidence interval

Appendix J Surgical morbidity and mortality associated with oesophagectomy

The morbidity and mortality rates associated with oesophagectomy are described below. These studies were not identified by systematic review.

In some patients, the CT-occult metastatic disease which would have been detectable by PET may not be apparent at thoracotomy, and the surgery avoided following PET is oesophagectomy. In these patients, palliative therapy will be instigated instead of radical surgery. It is assumed that the morbidity and mortality associated with surgery would be greater than those associated with palliative therapy in these patients.

Complication rates reported in the following sources are presented in Table 34.

Jamieson et al. 2004 conducted a systematic review of 312 papers (1999–2000) reporting postoperative mortality and anastomotic leakage following oesophagectomy, with any degree of radicality, with or without neoadjuvant therapy. The overall complication rates for patients in Western countries are presented below.

A systematic review by Fiorica et al. (2004) included six randomised controlled trials comparing surgery alone with surgery plus preoperative CRT in patients with histologically proven resectable oesophageal cancer without metastatic disease.

Blazeby et al. (2000) conducted a prospective study that collected morbidity data on 55 patients undergoing oesophagectomy between 1993 and 1995, five of whom received neoadjuvant chemotherapy.

Swisher et al. (2000) reported complication rates in 340 patients undergoing oesophagectomy between 1994 and 1996 in 13 US National Cancer Institutions and 88 community hospitals.

Table 34 Oesophagectomy complication rates

Complication	Rate (%)	Source
Overall postoperative adverse events	34.3 surgery alone	Fiorica et al. 2004
	39.4 surgery +CRT	
	55–57 major centres	Swisher et al. 2000
	68–70 small, low-volume centres	
Major complications (including death)	47.3	Blazeby et al. 2000
Postoperative mortality	8.9	Jamieson et al. 2004
	6.2 surgery alone	Fiorica et al. 2004
	11.9 surgery + CRT	
	16.4	Blazeby et al. 2000
	3.0–4.2 major centres	Swisher et al. 2000
	12.2–13.3 small, low-volume centres	
Respiratory complications	19.9	Fiorica et al. 2004
	7.3	Blazeby et al. 2000
Heart failure	6.9	Fiorica et al. 2004
Anastomotic leak	10.2	Jamieson et al. 2004
	6.9	Fiorica et al. 2004
	3.6	Blazeby et al. 2000
Wound haematoma/infection	3.6	Blazeby et al. 2000
Upper gastrointestinal bleed	1.8	Blazeby et al. 2000
Recurrent nerve palsy	3.6	Blazeby et al. 2000
Deep-vein thrombosis	3.6	Blazeby et al. 2000
Fistula/stricture	7.3	Blazeby et al. 2000

Appendix K Results of PET cost data study

Results of the recent Australian PET cost data study (ANZAPNM 2007) are summarised in Table 35. Total costs per scan by labour and non-labour costs are reported by site for 2005–2006 for standard whole-body scan (used in staging of primary oesophageal cancer) and long whole-body scan.

Table 35 Standard and long whole body PET scan costs

Site	Standard whole-body scan			Long whole-body scan		
	Costs per scan in AU\$ for 2005–2006			Costs per scan in AU\$ 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	432	1,834.00	1,113.00	720
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
SD	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 + 1 SD	1,747.68	1,040.65	746.42	2,931.53	1,799.58	1,183.05
Mean – 1 SD	782.8	489.97	253.43	1,116.35	661.78	403.23
Mean+ 2 SD	2,230.12	1,315.99	992.91	3,839.12	2,368.47	1,572.97
Mean – 2 SD	300.36	214.63	6.94	208.77	92.89	13.31

Abbreviations

AC	adenocarcinoma
CI	confidence interval
CL	confidence limits
CRT	chemo-radiotherapy
CT	computed tomography
DRG	Diagnosis-Related Group
EPI	electronic portal imaging
EUS	endoscopic ultrasound
FDG	2-[¹⁸ F]fluoro-2-deoxy-D-glucose
FN	false-negative
FNA	fine-needle aspiration
FNAC	fine-needle aspiration cytology
FP	false-positive
GEJ	gastro-oesophageal junction
HR	hazard ratio
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
PBS	Pharmaceutical Benefits Scheme
PEG	percutaneous endoscopic gastrostomy
PET	positron emission tomography
PPICO	Population, Prior tests, Intervention, Comparator, Outcomes
PPV	positive predictive value
QALY	quality-adjusted life year
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
QUOROM	Quality Of Reporting of the Results Of Meta-analyses
ROC	receiver operating characteristic
RR	relative risk
RT	radiotherapy
SCC	squamous cell carcinoma
SD	standard deviation
SUV	standardised uptake value
TN	true-negative
TNM	Tumour, Node, Metastasis
TP	true-positive
US	ultrasound

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