# *Endoscopic ultrasound for evaluating pancreatic, gastric, oesophageal and hepatobiliary neoplasms*

**November 2006**

**MSAC application 1072**

**Assessment report**

**ISBN (Print)** **1-74186-199-3**

**ISBN (Online)** **1-74186-200-0**

**ISSN (Print)** **1443-7120**

**ISSN (Online)** **1443-7139**

**First printed** **November 2007**

**Paper-based publications**



**Internet sites**



Electronic copies of the report can be obtained from the Medical Service Advisory Committee's Internet site at http://www.msac.gov.au/

Printed copies of the report can be obtained from:

The Secretary
Medical Services Advisory Committee
Department of Health and Ageing
Mail Drop 106
GPO Box 9848
Canberra ACT 2601

Enquiries about the content of the report should be directed to the above address.

The Medical Services Advisory Committee (MSAC) is an independent committee which has been established to provide advice to the Commonwealth 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.***

This report was prepared by the Medical Services advisory Committee with the assistance of Dr Suzanne Dyer, Dr John Gillespie, Ms Meaghan Lynch, Mr Marc Bevan, Ms Jolie Hutchinson, Dr Amanda Ruth and Mr Dane Levison from the Medical Technology Assessment Group (M-TAG) a unit of IMS Health.
Ms Ann Jones of M-TAG edited the report. The Commonwealth Minister for Health and Ageing endorsed the report on 5 February 2007.

Publication approval number: P3-1287

# Contents

# Tables

# Figures

# Executive summary

## The procedure

Endoscopic ultrasound (EUS) uses an echoendoscope to place an ultrasound transducer close to the luminal surface of the gastrointestinal (GI) tract. This process allows the oesophageal, gastric and duodenal wall, and the pancreatic and extrahepatic biliary tract to be visualised. EUS first appeared in clinical practice in the 1980s and has become widely accepted. It is increasingly performed to evaluate a variety of GI disorders, including the diagnosis and staging of neoplasms of or near the GI tract.

This review evaluates EUS use with and without fine needle aspiration (FNA) in diagnosing and staging oesophageal, gastric, pancreatic, and extrahepatic biliary tract neoplasias.

EUS use has become accepted as a component of standard care for upper GI neoplasms as indicated by management guidelines developed in many industrialised nations. The United Kingdom's guidelines for oesophageal and gastric cancers management indicate that where metastatic disease is absent, preference should be given to using EUS to inform surgical assessment for resection. The UK National Health Service (NHS) guidelines recommend using EUS in staging oesophageal and gastric cancers in patients who do not present with evidence of metastases and who are suitable candidates to undergo radical surgery. It also recommends availability of EUS at cancer centres that provide services for patients with pancreatic cancer.

Endoscopic ultrasound has a potential positive impact on the health outcomes, (including quality of life), of patients by increasing diagnostic and staging accuracy of gastrointestinal (GI) neoplasms. EUS also has potential to reduce numbers of patients undergoing further diagnostic procedures. Improved diagnostic and staging techniques have significant positive potential impact to make more precise diagnoses at earlier stages of disease; with the consequent effect of increasing opportunities to better control GI malignancies. Accurate diagnosis of benign pathology may help to avoid invasive surgical procedures. Likewise, increased accuracy of staging and resectability may lead to fewer unnecessary surgical procedures performed for people with advanced disease.

Potential benefits in terms of patient quality of life, as well as economic benefits, are likely to result as further advancements in neoadjuvant therapies are made. Increased staging accuracy may provide improvements in the appropriate selection of patients for these treatments. This offers potential positive impact for chances of cure in people diagnosed at an apposite stage.

## Medical Services Advisory Committee—role and approach

The Medical Services Advisory Committee (MSAC) is a key element of a measure taken by the Australian Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Australian Government 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 the basis of decision making when funding is sought under Medicare. An advisory panel with expertise in this area evaluate the evidence and provide advice to MSAC.

The current review is concerned with comparative evidence for the value of EUS. The comparator is determined in relation to the technology's likely position in the clinical management pathway of current best practice in the Australian healthcare system. Therefore, the evidence included in this review is not comprehensive for all evidence available on the performance of EUS. Studies included in this review are those most relevant to the performance of EUS in relation to the specific research questions addressed.

## MSAC's assessment of endoscopic ultrasound

### Clinical need

There were 1,078 reported cases of oesophageal cancer diagnosed in Australia in 2001. In the same year, there were 1,039 deaths due to this disease, resulting in 6,553 person-years of life lost before the age of 75. Oesophageal cancer is a treatable disease but is only rarely curable. The overall five-year survival rate for oesophageal cancer in patients amenable to definitive treatment is in the range of 5 to 30 per cent. Treatment for oesophageal cancers is generally based on staging. Surgery is the standard treatment option for early stage tumours and palliative chemotherapy is provided for patients with advanced tumours. Almost a quarter (approximately 24%) of patients with oesophageal cancer will be deemed to be candidates for palliative care from diagnostic radiology.

In 2001, 1,902 new cases of gastric cancer and 1,209 deaths from this disease were reported in Australia. Deaths from gastric cancer resulted in 8,133 person-years of life lost before the age of 75. Gastric cancer treatment is generally based on staging, as determined by a number of diagnostic classification procedures. The prognosis for patients with gastric cancer is related to both the extent of the tumour and nodal involvement. The five-year survival of patients with localised distal gastric cancer is 50 per cent. Survival is lower (10–15%) for patients with localised proximal disease. Most patients present with regional or more distant involvement. There is negligible five-year survival among patients with disseminated disease.

Pancreatic cancer was the fifth most common cause of cancer-associated death in Australia in 2001—there were 1,811 deaths reported and 1,858 new cases diagnosed. Pancreatic cancer was the tenth most common neoplasm in both men and women (excluding non-melanocytic skin cancers). Pancreatic cancer is usually diagnosed late in

the course of the disease, and as a result, has an extremely poor prognosis. This is highly evident in the five-year relative survival rate—in Australia, this was approximately 5 per cent for the period 1992–1997.

There were 594 reported diagnoses of cancer of the gallbladder and other and unspecified parts of the biliary tract (including extrahepatic bile ducts) reported in Australia in 2001. The prognosis for patients with cancer of the gallbladder or extrahepatic bile ducts is poor. Bile duct cancer surgeries are usually extensive and have a high operative mortality (5–10%) and a low cure rate. In 2001, there were 351 deaths attributed to biliary tract cancer in Australia. Between 1994 and 2000, the five-year relative survival for patients with gallbladder cancer in NSW was 18.8 per cent. Surgery is not indicated for most patients with extrahepatic bile duct cancer—less than 10 per cent of all cases are considered surgically curable. Extrahepatic bile duct cancer that is not amenable to resection is generally incurable and treatment is palliative.

## Safety

Safety data relating to EUS use to diagnose and stage gastro-oesophageal cancers was obtained from reports that related to a total of 2,521 patients who received EUS and 565 patients who were subject to EUS-FNA. Perforation was a rare but serious adverse event that was reported in relation to eight patients receiving either EUS or EUS-FNA (8/3086, 0.26% of patients). Of patients undergoing EUS, 0.20 per cent experienced bleeding (5/2521), which was managed with endoscopic haemostatic methods. Among the 565 patients who underwent EUS-FNA, 15 (2.7 %) experienced minimal self-limited bleeding.

EUS safety data used to diagnose and stage pancreaticobiliary cancers were obtained from reports that related to a total of 2,240 patients who received EUS and 3080 patients undergoing EUS-FNA. Perforations were reported for two patients who received either EUS or EUS-FNA (0.04%).

In a comparison of the safety of EUS-FNA with CT-guided biopsy in patients with pancreaticobiliary lesions, the frequency of bleeding or pancreatitis did not differ (bleeding: 0.49% [95% CI: 0.27, 0.80] and 0.24% [95% CI: 0.03, 0.86]; pancreatitis: 0.42% [95% CI: 0.22, 0.72] and 0.72% [95% CI: 0.26, 1.55] respectively). The available studies generally did not incorporate adequate follow up to capture possible events related to peritoneal seeding.

The conclusions made about the safety of EUS used in diagnosis and staging gastrointestinal cancers are limited by inadequate and limited reporting of safety data in the identified studies and by insufficient follow up. Based on the available data, it is considered that the use of EUS in diagnosing and staging gastrointestinal cancers is associated with a very low risk of perforation and is generally a safe procedure. EUS-FNA is considered generally safe and equally as safe as CT-FNA/biopsy in the diagnosis of pancreatic cancers.

## Effectiveness

## Direct evidence

A single ongoing randomised controlled trial investigating the role of EUS in staging and managing patients with gastric and oesophageal cancers was identified (UK COGNATE). This trial was expected to end in January 2009.

Studies identified from a review of the literature reported survival only as a health outcome. No studies were identified that dealt with other health outcomes, such as quality of life. There were three studies found that provided level III-3 evidence regarding the impact of EUS on patient survival. Of these, two related to EUS used to stage oesophageal cancer and the other study investigated use in diagnoses of pancreatic cancer. The inadequate quality and inconsistent findings of the identified studies indicated that they did not provide direct evidence of patient survival benefit associated with EUS at that time.

In most cases, the potential value of EUS was not an increase in survival but a reduction in the number of inappropriate surgeries performed. Accordingly, the potential value of EUS on health outcomes for this indication is likely to be in quality of life measures.

## Linked evidence

### Is it accurate?

#### Systematic review

Harris et al (1998) systematically reviewed the use of EUS in gastro-oesophageal cancer based on data collected up until 1997. This review concluded that EUS is highly effective for the discrimination of stages T1 and T2 from T3 and T4, in both the oesophagus and the stomach. Performing EUS with lymph node staging was found to be less accurate than tumour staging. Staging metastases using EUS alone was not satisfactory.
The limited quantity of data available meant that conclusions could not be made about the comparative value of EUS versus computed tomography (CT) in relation to gastro-oesophageal cancer staging.

#### Oesophageal cancer staging

The research question addressed was
*"What additional benefit, in terms of safety, effectiveness and cost-effectiveness, does EUS ± FNA provide in the pre-operative staging of patients with oesophageal tumours (but no evidence of metastases) over and above the current clinical practice of using upper endoscopy, CT and PET (when available)?"*

There were 11 identified studies that provided information on the incremental value of EUS following CT and/or positron emission tomography (PET) in the group staging of oesophageal cancer. In three studies, determined to be medium to high quality, the combined use of CT + EUS increased the sensitivity for detecting late stage oesophageal cancer (stages IV or; III and IV; AJCC staging). Two studies that provided data on detection of distant node metastases similarly demonstrated increased sensitivity with a trade-off loss of specificity when EUS was used in addition to CT.

Evidence of the additional value of EUS over CT in tumour (T) staging was provided by four medium quality and limited applicability studies. In two of these four studies

combining EUS with CT to detect T3 or T4 tumours led to decreased specificity in one study and in the other, which was conducted in a small population with low prevalence, there was no change. In three of the four studies, CT combined with EUS to detect T4 tumours led to increased sensitivity. In two of the same three studies, this occurred with no loss of specificity; there was a small decrease in specificity in the remaining study, which was conducted in a population with a low prevalence of stage IV disease.

EUS accuracy data for locoregional lymph node (N) staging specific to the research question was provided by five studies deemed to be medium quality and limited applicability. The combination of CT and EUS for N-staging increased sensitivity compared with CT alone in all five studies. This occurred with a decrease in specificity of staging in all but one study. Three studies assessing N-staging reported the incremental value of EUS in addition to both CT and PET. These studies indicate that the incremental value of EUS over prior staging tests may be slightly decreased when PET is available.

Overall, the available evidence indicates that EUS use in addition to CT, or CT plus PET, increases sensitivity in late stage disease. Increase in sensitivity is likely to occur at the expense of a small trade-off in specificity.

A satisfactory body of evidence exists to support the additional value of EUS over and above CT or CT plus PET in oesophageal cancer staging.

**Gastric cancer staging**

The research question addressed was

*"What additional benefit, in terms of safety, effectiveness and cost-effectiveness, does EUS ± FNA provide in the staging of patients with gastric tumours (but no evidence of metastases) over and above the current clinical practice of using upper endoscopy, CT and PET (when available)?"*

Evidence supporting the incremental value of EUS over CT alone in staging gastric tumours was identified in one study classified to be high quality. This study did not determine group staging by CT and EUS using an either test positive approach which would likely be used in practice (positive test for either procedure considered as a positive result). This meant that the study provided limited applicability. Combining the results for American Joint Committee on Cancer (AJCC) group staging from EUS and CT in this study resulted in both greater sensitivity and specificity for late stage gastric cancer relative to CT alone. In practice, increased specificity does not occur where an either test positive approach for combined tests is used. Another two studies that provided high quality evidence for the replacement value of CT and EUS to stage gastric cancer were also included for review. Both studies had limited applicability. These replacement studies indicated that EUS was more accurate than CT to distinguish late from early stage tumours (T staging) and lymph node metastases.

The high quality studies reviewed provide supportive evidence that the combination of EUS and CT is likely to increase the sensitivity for late stage disease with a possible small trade-off in specificity.

**Gastric submucosal tumour diagnosis**

The research question addressed was
*"What benefit, in terms of safety, effectiveness and cost-effectiveness, does EUS ± FNA provide in the diagnosis and/or staging of patients with submucosal tumours, additional to the current clinical practice?"*

This review identified seven studies concerned with the accuracy of EUS in diagnosing suspected gastric submucosal tumours (SMTs) that were included for review. Of these seven, one small study designated as medium quality and limited applicability indicated that EUS (without FNA) was highly accurate in differentiating gastric SMTs from extramural compression.

From the initial seven, five studies found that provided information about the performance of EUS to diagnose malignant SMTs used an outdated classification system. Data from these studies were not considered informative.

The final study considered from the initial group of seven, deemed medium quality and limited applicability, provided evidence about the performance of EUS for diagnosis of malignant gastric SMTs using current classification criteria. This study found that EUS was moderately sensitive in diagnosing malignant tumours, and highly specific in diagnosing benign tumours. The diagnostic odds ratio and likelihood ratios provide strong evidence to support the performance of EUS in differentiating malignant from benign gastric SMTs. There was insufficient evidence to determine if addition of FNA to EUS would improve diagnostic accuracy.

On the basis of evidence presented by two small studies, EUS can be considered highly accurate in differentiating malignant gastric SMTs from extramural compression, and is highly specific in diagnosing benign SMTs using current classification criteria.

**Diagnosis of pancreatic cancers**

***Pancreatic solid mass identified***

The research question addressed was
*"To what extent is EUS ± FNA (following abdominal ultrasound and CT) safe, effective and cost-effective in the diagnosis of pancreatic neoplasms in patients in whom a solid pancreatic mass has been identified by prior diagnostic tests (without any evidence of metastases), relative to CT-FNA/guided biopsy, over and above the current clinical practice of using abdominal ultrasound and CT?"*

*EUS versus no EUS (after CT)*

This assessment considered evidence provided by two replacement studies that reviewed EUS and CT efficacy in diagnosing causes of disease in identified pancreatic solid masses. These studies reported individual patient data that allowed the additional value of EUS to be calculated.

A medium quality study that was conducted in an applicable patient population investigated the diagnostic accuracy of EUS in a non-consecutive subgroup of patients who had pancreatic solid mass lesions. This subgroup was non-consecutive based on clinical presentation, which introduced potential for selection bias. This study did not report excluding patients with metastatic disease. The diagnostic accuracy of EUS and CT was greater than CT alone—sensitivity was increased from 78.9 per cent to 100 per cent—there was a small decrease in specificity from 88.2 per cent to 76.5 per cent.

The alternate study was deemed poor quality and of limited applicability. Quality deficits stemmed from the lack of clarity in reporting the basis for inclusion of patient records. Study inclusion was likely based on whether patients underwent exploratory laparotomy. It appears possible that only patients whose EUS or CT findings indicated surgical intervention were included in the study. Included patients were part of a surgical series, which limits the applicability of the study. EUS had no additional value to CT in diagnosing pancreatic masses. This finding should be considered in light of the study's low quality and limited applicability. The low patient numbers and high prevalence of malignancy (surgical series) in this study should also be considered when interpreting the results.

*EUS/EUS-FNA versus CT-guided biopsy*

There were no studies identified that compared EUS (without FNA) with CT-guided biopsy to diagnose malignant pancreatic solid masses. As a result, non-comparative studies that provided the highest level of evidence for diagnostic accuracy of these tests were included for review. A single level II non-comparative EUS study that used an echo-enhancing contrast agent demonstrated sensitivity of 94 per cent, and 100 per cent specificity. A second level III-1 study of EUS used without contrast agent reported 95 per cent sensitivity and 53 per cent specificity. Six level III-1 non-comparative studies of CT-FNA/guided biopsy indicated high specificity and variable sensitivity in malignant pancreatic mass diagnoses. The available data were insufficient in terms of quality and quantity to determine whether EUS (without FNA) was more accurate to diagnose malignant pancreatic solid masses than CT-guided biopsy.

Two comparative studies were identified that reported the accuracy of EUS-guided FNA and CT-guided biopsy to diagnose malignant pancreatic solid masses. Of these, one study was poor quality and of unknown applicability. In this study, tests were performed in different patient groups, rather than in a sequence of the same patients. The results of this study are considered to be uninformative. The second was a medium quality study conducted in a highly applicable patient population, which excluded patients with diagnoses of metastatic disease. In this study, EUS-FNA sensitivity was much greater than CT-guided biopsy (91% vs 6%, respectively), and both technologies demonstrated 100 per cent specificity.

On the basis of the limited available evidence, it can be interpreted that EUS-FNA has a greater sensitivity than CT-guided biopsy in the diagnosis of malignant pancreatic solid masses.

Two comparators— CT alone with no further tests, and CT-guided biopsy—were considered to assess the diagnostic value of EUS with or without FNA following CT to confirm malignancy in pancreatic solid masses. On the basis of one applicable medium quality study, the available data suggest that EUS offers a small increase in sensitivity compared with using CT alone in diagnosing malignant solid mass pancreatic tumours. This occurred with a small loss of specificity. This comparator pathway is considered to be the most applicable to current practice in Australia.

If EUS-FNA is considered a replacement test for CT-guided biopsy, EUS-FNA is much more sensitive in the diagnosis of malignant solid mass pancreatic tumours on the basis of one applicable study of medium quality. Both tissue sampling techniques had 100 per cent specificity in this study. It could not be determined if EUS (without FNA) was more

accurate than CT-guided biopsy in diagnosing malignant pancreatic solid masses because available data are qualitatively and quantitatively insufficient.

### *Pancreatic cystic lesion*

The research question addressed was
*"What additional benefit, in terms of safety, effectiveness and cost-effectiveness, does EUS ± FNA provide in the diagnosis of pancreatic neoplasms in patients in whom a cystic lesion has been identified, over and above the current clinical practice of using abdominal ultrasound and CT (without any evidence of metastases)?"*

No studies were identified that reported the incremental value of EUS over CT (without biopsy) used for diagnosing pancreatic cystic lesions. Four medium quality studies that reported the replacement value of CT and EUS used for diagnosing pancreatic cystic lesions (cystic masses, intraductal papillary or mucinous tumours) were reviewed.
Of these, three provided low quality comparisons of EUS and CT. These three studies did not apply both tests to all patients. These studies have high potential for bias in making comparisons, and their findings were inconsistent. In one study that provided a direct comparison of CT and EUS for all patients, EUS was found to be more sensitive and less specific than CT.

Based on this single study, the supportive evidence indicates that the addition of EUS to CT (without biopsy) in diagnosing IPMT is likely to increase the sensitivity of detecting malignancies with a trade-off loss of specificity.

### *No pancreatic mass identified on CT*

The research question addressed was
*"To what extent is EUS ± FNA safe, effective and cost-effective in the diagnosis of pancreatic neoplasms in patients with symptoms and biochemical evidence (CA 19-9 or neuroendocrine abnormalities) associated with pancreatic neoplasia, when abdominal ultrasound and CT have failed to identify an abnormality, relative to octreotide nuclear medicine scanning (somatostatin receptor scintigraphy, for suspected endocrine neoplasia), or relative to current clinical practice in the absence of EUS (for suspected exocrine neoplasia)?"*

Three studies were identified that provided evidence concerning the value of EUS in addition to CT in diagnosing exocrine pancreatic neoplasia in patients with no mass identified on the CT. Two studies that enabled determination of the incremental value of EUS performed only in patients with no mass identified by CT were reviewed. Of these, one study was considered to be medium quality and the other was poor quality. The applicability of the patients in the studies was considered to be limited. These studies provided evidence that the use of EUS (without FNA) in addition to CT may increase diagnostic sensitivity with a loss of specificity.

From the initial three studies identified, the remaining study was deemed poor quality. This study reported the value of using EUS-FNA in addition to CT and endoscopic retrograde cholangiopancreatography (ERCP) in diagnostically problematic patients with negative or equivocal CT results. On the basis of this study, it appears that EUS-FNA is associated with a similar increase in sensitivity to EUS alone. In contrast to the increase in sensitivity gained by the additional use of EUS, inclusion of EUS-FNA increased sensitivity with no loss of specificity.

Three limited applicability studies indicated that EUS (with or without FNA) used for patients with no mass identified on CT increased the sensitivity for diagnosing pancreatic cancer. The addition of FNA to EUS may result in no loss of specificity when the tests are used in combination.

### *Neuroendocrine tumours*

Four studies provided medium quality and limited applicability evidence concerning the comparative value of EUS and somatostatin receptor scintigraphy (SRS) in correct localisation of pancreatic neuroendocrine tumours. The comparative evidence on the performance of EUS and SRS to diagnose pancreatic neuroendocrine tumours has limited applicability to a patient group who has tested negative by CT. The available evidence indicates that EUS has greater accuracy in the correct localisation of pancreatic insulinomas than does SRS.

Clinical expert opinion indicates that correct localisation will frequently lead to less radical surgery in this patient group.

### Pancreatic cancer staging

The research question addressed was

*"What additional benefit, in terms of safety, effectiveness and cost-effectiveness, does EUS ± FNA provide in the pre-operative staging of pancreatic neoplasms (in patients with a malignant neoplasm identified by prior testing, but no evidence of metastases) over and above the current clinical practice of using clinical examination, serological testing, abdominal ultrasound and CT?"*

Four limited applicability studies were identified and included for review that provided data specifically on the incremental value of EUS in addition to CT for staging pancreatic cancer. Overall, the diagnostic accuracy of the combined use of CT and EUS in staging pancreatic cancer described in the included studies was greater than CT alone. The diagnostic accuracy of the test would depend on the prevalence of resectable disease in the study population. The four reviewed studies found that EUS + CT increased the sensitivity for determining unresectability compared with using CT alone. There may be a trade-off in terms of reduced specificity for resectability. The results of the reviewed studies were inconsistent for this outcome.

### Biliary tract cancer diagnosis

The research question addressed was

*"What additional benefit, in terms of safety, effectiveness and cost-effectiveness, does EUS ± FNA provide in the diagnosis and staging of biliary tract neoplasms in patients with a structural abnormality suggestive of biliary tract neoplasia, over and above the current clinical practice of using abdominal ultrasound, CT (with no evidence of metastases) and ERCP or MRCP?"*

Two studies that provided evidence concerning the value of EUS (without FNA) as an additional test following cholangiopancreatography were identified. Of these, one study was measured to provide poor quality evidence—accuracy outcomes were not reported clearly. This study was included in the absence of others that provided high quality data describing additional value of EUS performed in all patients. The other was medium quality designed as a replacement study of EUS, magnetic resonance cholangiopancreatography (MRCP), ERCP and CT. This study also reported data regarding the accuracy of the tests where both were in agreement. It appears that findings where both tests were in disagreement were excluded from the results. It was considered

that evidence was insufficient to determine whether EUS (without FNA) has additional value when used with cholangiopancreatography to diagnose biliary tract malignancy.

There was one high quality study identified that reported the accuracy of EUS with FNA in addition to ERCP, plus three tissue sampling methods, to diagnose malignant versus benign causes of biliary obstruction. This study appears likely to have underestimated the additional value of EUS-FNA. This study found that EUS-FNA added value in increasing the sensitivity and diagnostic accuracy for the detection of pancreaticobiliary malignancy when used in addition to ERCP-guided tissue sampling.

### Does it change patient management?

A literature search identified five studies reporting the effects of EUS on patient management as determined by the use of pre-test and post-test management plans. In all but one study, the referring clinicians completed management plans as applicable to clinical practice.

Of the five studies, one classified as high quality was performed in Australia. In general, EUS findings contributed to avoiding surgeries and other investigations, which reduced the number of complex procedures performed. EUS changed management in 24 to 74 per cent of patients among all indications. In relation to EUS-FNA, management changed in 31 to 43 per cent of patients. Use of EUS resulted in surgery being avoided in 10 to 18 per cent of patients, and further imaging or therapy was avoided in 14 to 57 per cent. These studies provide a high quality body of evidence on the use of EUS to diagnose and stage gastrointestinal neoplasms which reduces invasive patient interventions.

### Summary of evidence for effectiveness

The evidence available regarding EUS effectiveness, likely to be used in clinical practice in Australia, was reviewed. When used as an additional test, EUS is likely to result in an increase in sensitivity with a trade-off loss of specificity.

There was good or satisfactory evidence that EUS when used in addition to current Australian practice:

- alters patient management, including reducing the number of surgical and invasive procedures performed
- increases the accuracy of staging oesophageal cancer.

There was supportive or limited evidence that EUS, when used in addition to current Australian practice:

- increases the sensitivity for detection of late stage disease in gastric cancer
- is highly accurate in differentiating gastric submucosal tumours from extramural compression
- increases diagnostic sensitivity for pancreatic cancer in patients with no masses identified on CT. The use of FNA in this setting may increase sensitivity for diagnosis with a smaller loss of specificity

- provides a small increase in diagnostic sensitivity of malignant pancreatic solid masses in comparison with using CT alone
- has greater diagnostic sensitivity than CT-guided biopsy of malignant pancreatic solid masses when used in conjunction with FNA
- increases diagnostic sensitivity of malignant pancreatic intraductal papillary-mucinous tumours (IPMT)
- has a greater accuracy in the correct localisation of pancreatic insulinomas than achieved by somatostatin receptor scintigraphy (SRS)?
- increases sensitivity to determine resectability of pancreatic cancer
- with FNA increases the diagnostic accuracy of pancreaticobiliary malignancy when used in addition to ERCP-guided tissue sampling.

## Cost-effectiveness

The cost-effectiveness and financial impact of EUS and EUS-FNA was evaluated for indications where there was clinical evidence that the procedure was more accurate than the comparator. An economic analysis was not performed for indications with relatively small eligible populations, such as endocrine pancreatic tumours and biliary tract neoplasia. An economic evaluation was not performed if there was insufficient evidence to provide information on the effect of EUS or EUS-FNA on the management of the condition, such as was the case for gastric submucosal tumours.

The current capacity to perform EUS and EUS-FNA in Australia is limited by the availability of EUS equipment and the number of technically trained experts able to perform the procedure. The present estimate is that there are 11 centres in Australia with EUS equipment. According to expert opinion, approximately 1,320 EUS procedures can be performed in Australia each year. This assumes that each centre has the equipment to perform 200 procedures annually, but because of the expertise and technical training required, current capacity of each centre is limited to an estimated average of 120 procedures per year. Hence, the annual cost for the first three years following listing is estimated to be $1,098,600 for EUS and $2,279,010 for EUS-FNA.

### Oesophageal cancer staging

The use of EUS to determine oesophageal cancer staging is not expected to alter survival but may lead to an improvement in health outcomes. Advanced disease is normally considered unresectable, and its detection obviates surgical needs. For this reason, a cost-minimisation analysis was applied to assess the net cost of introducing EUS relative to CT for oesophageal cancer staging. The analysis revealed an incremental cost of $206.62 per patient receiving EUS following CT.

It is estimated that approximately 814 patients would be eligible to receive EUS procedures during the first year following listing on the Medicare Benefits Schedule (MBS), increasing to approximately 828 patients by the end of the third year of use. Excluding limitations in capacity and expertise needed to perform the procedure, the aggregate expenditure through the MBS is estimated to be $677,285 in the first year, rising to $689,438 in the third year following listing.

### Gastric cancer staging

A cost-minimisation analysis of the introduction of EUS relative to CT for gastric cancer staging indicates that there is lower total healthcare costs overall, with an estimated saving of between $1,506.50 and $2,845.14 per patient.

It is estimated that approximately 1,719 patients would be eligible for EUS procedures in the first year following listing on the MBS, increasing to approximately 1,750 patients by the end of the third year of use. Excluding limitations in capacity and expertise needed to perform the procedure, the aggregate expenditure through the MBS is estimated to be $1,430,796 in the first year, rising to $1,456,471 in the third year following listing.

### Pancreatic cancer staging

A cost-minimisation analysis to assess the use of EUS relative to CT to stage pancreatic cancer reveals that there are lower total healthcare costs overall, with a cost saving of $2149.95 per patient.

It is estimated that approximately 1,326 patients would be eligible for EUS procedures following the first year of listing on the MBS, increasing to approximately 1,350 patients by the end of the third year of use. Not accounting for limitations in capacity and expertise needed to perform EUS in Australia, the aggregate expenditure through the MBS is estimated to be $1,103,400 in the first year, rising to $1,123,200 in the third year of listing.

### Pancreatic cancer diagnosis

Approximately 3,062 patients would be eligible for EUS or EUS-FNA in the first year of listing on the MBS for diagnoses of pancreatic cancers. This is estimated to increase to approximately 3,117 patients by the end of the third year of use. Excluding consideration of limitations in capacity and expertise needed to perform the procedure, the aggregate expenditure on EUS through the MBS is estimated to be $2,548,774 in the first year, rising to $2,594,510 in the third year of listing. The aggregate expenditure on EUS-FNA through the MBS is estimated to be $5,287,348 in the first year, rising to $5,382,227.

### Pancreatic exocrine tumours

A cost-effectiveness analysis was conducted to assess value for money of performing EUS and EUS-FNA relative to CT alone to diagnose pancreatic exocrine tumours. The incremental cost of performing EUS is estimated to be $23,347 per life year gained. The evaluation of EUS-FNA following CT, versus CT alone, produced an incremental cost of $35,766 per life year gained.

### Pancreatic solid mass

An economic evaluation comparing EUS following CT versus CT alone to diagnose pancreatic solid masses produced an incremental cost of $29,089 per life year gained.

### Pancreatic intraductal papillary-mucinous tumours

A cost-minimisation approach was used to assess the value of performing EUS following CT versus CT alone to diagnose pancreatic intraductal papillary-mucinous tumours (IPMTs). The incremental cost of performing EUS following CT versus CT alone is estimated to be between $520 and $720 per patient.

## Recommendation

MSAC recommended that on the strength of evidence pertaining to endoscopic ultrasound, public funding should be supported for the staging of oesophageal, gastric and pancreatic cancer; with or without fine needle aspiration in the diagnosis of pancreatic, biliary and gastric submucosal tumours.

—The Australian Government Minister for Health and Ageing accepted this recommendation on 5 February 2007—

# Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of endoscopic ultrasound for the diagnosis and staging of upper gastrointestinal neoplasms. 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 at **Appendix A**. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

This report summarises the assessment of current evidence for the use of endoscopic ultrasound for the diagnosis and staging of upper gastrointestinal neoplasms.

# Background

## Endoscopic ultrasound

### The procedure

Diagnostic sonography is a technique that uses pulses of high-frequency sound waves (ultrasound) to image internal body structures. Conventional ultrasound enables obtaining images of internal anatomical structures by placing an ultrasound probe, containing the transducer, on the skin surface. Endoscopic ultrasound (EUS) uses an echoendoscope to place the ultrasound transducer close to the luminal surface of the gastrointestinal (GI) tract. The close proximity of the transducer to the target organ provides high-resolution images of the individual layers of the wall of the GI tract. In most cases, the echoendoscope can be introduced as far as the descending duodenum and ultrasound imaging is performed as the instrument is withdrawn. The gastric and duodenal wall, as well as the pancreatic and extrahepatic biliary tract, can be visualised through this process. EUS first appeared in clinical practice in the 1980s and has become widely accepted (Fusaroli and Caletti 2005). It is increasingly performed to evaluate a variety of GI disorders, including the diagnosis and staging of neoplasms of, or in close proximity to, the GI tract.

EUS transmission is improved by inflating a water-filled balloon at the instrument tip. Reducing the amount of air between the transducer and the GI wall by filling the stomach with water also improves imaging. Compared with conventional ultrasound, EUS minimises the amount of adipose tissue between the transducer and the imaged structure, which further improves transmission. EUS also avoids difficulties that can arise when intervening calcified structures are encountered.

A variety of EUS probes with transducers operating in the range 5–20 MHz are available. Probes operating at higher frequencies provide images at higher resolution, but are associated with a reduced viewing depth. There are two basic types of echoendoscopes: those with radial or linear scanners. Linear scanners provide limited (100–180$^{o}$) viewing along the direction of insertion, and may be used for EUS-guided tissue sampling. Biopsy can be performed with EUS-guided standard fine needle aspiration (FNA) using 22 or 19 gauge needles (EUS-FNA), or Trucut (19 gauge) needles. Linear echoendoscope probes may also have a colour Doppler facility for enhanced vascular imaging. In comparison, radial scanners provide 270–360$^{o}$ viewing perpendicular to the direction of insertion.

A recent advance in EUS technology has been the development of small calibre ultrasound miniprobes (ultrasound catheters), which can be passed through the biopsy channel of a standard endoscope. These probes are approximately 2 mm in diameter. Miniprobes operate at a higher frequency than standard EUS probes (12–30 MHz) and may offer an advantage over standard probes for the study of superficial or small GI lesions. For example, one of the limitations of EUS is non-traversability, that is, the inability of the scope to pass through a GI stricture. Miniprobes may resolve this limitation. Miniprobes can also be passed through the ampulla of Vater into the biliary tract to evaluate pancreatic and biliary tract disorders. This technique is known as intraductal ultrasonography (IDUS). Less commonly, IDUS may also be performed via

the percutaneous transhepatic route or through biliary drainage sites. This review excludes the use of IDUS.

Specifically trained medical practitioners, with competency in upper endoscopy, perform EUS. It is a highly specialised skill, carried out by a limited number of practitioners in Australia. EUS is performed as a separate episode of care to surgical treatment.

The American Society for Gastrointestinal Endoscopy has developed guidelines for training in the use of EUS. In order to be accepted for EUS training, the applicant must have two years experience in performing routine endoscopic procedures. Training involves performing a large number of suitably supervised EUS procedures that are fully documented to assess the development of expertise in EUS procedures. At the completion of training, the surgeon should be able to interpret EUS to an accuracy level found in published reports (American Society for Gastrointestinal Endoscopy 2005). In Australia, a joint committee of the Royal Australasian College of Surgeons, Royal Australasian College of Physicians and the Gastroenterological Society of Australia is currently developing professional training guidelines for the use of EUS (2006).

The use of EUS has become accepted as a component of standard care as indicated in management guidelines developed in other industrialised nations. UK guidelines for the management of oesophageal and gastric cancers indicate that in the absence of metastatic disease, EUS should preferably be used in the assessment of resectability of cancer (Allum et al 2002). The National Health Service (NHS) guidelines (NHS 2001) also recommend using EUS in the staging of oesophageal and gastric cancers in patients without evidence of metastases and who are capable of undergoing radical surgery. The guidelines further recommend that EUS be made available at cancer centres offering services to patients with pancreatic cancer.

According to the American Society of Gastrointestinal Endoscopy (American Society for Gastrointestinal Endoscopy et al 2005) EUS is indicated for:

- staging tumours of the gastrointestinal tract, pancreas, bile ducts and mediastinum
- evaluating abnormalities of the GI tract wall or adjacent structures
- tissue sampling of lesions within, or adjacent to, the wall of the GI tract
- evaluating abnormalities of the pancreas, including masses, pseudocysts and chronic pancreatitis
- evaluating abnormalities of the biliary tree
- providing endoscopic therapy under ultrasonographic guidance.

EUS is generally not indicated when:

- the results will not alter patient care
- staging tumours that have been shown to be metastatic by other imaging methods (unless the results are the basis for therapeutic decisions).

## Intended purpose

EUS and EUS-FNA are proposed to assist in diagnosing and staging GI neoplasms. This review evaluates the use of EUS in four clinical areas: oesophageal, gastric, pancreatic, and (extrahepatic) biliary tract neoplasms.

Improvements in diagnosis and staging may lead to improved management (curative and palliative treatment planning) and potentially to improved survival and quality of life.

## Complications

Most clinical practitioners consider EUS a safe procedure. Haemorrhage (sometimes requiring transfusion) and perforation (which could require surgical repair) are serious adverse events that have occasionally been associated with EUS procedures. The chances of perforation or haemorrhage occurring as complications of EUS are minimal for most patients. Perforation risk is considered to be higher for lesions in the oesophagus because of the narrow access for the endoscope. This risk is heightened when tumour stenoses occur. Stenoses often require dilation to be traversable by the EUS instrument. Some stenoses remain non-traversable following dilation. Because of the invasive nature of the FNA technique, EUS-FNA is thought to have a higher risk of complications than EUS alone. Colour Doppler used to identify and avoid vasculature along the needle tract during EUS-FNA minimises perforation and bleeding risks (Varadarajulu et al 2004).

If metastasis occurs as a result of needle tract seeding of malignant cells during the FNA procedure, unresectable disease and poor survival could potentially result.
EUS-FNA is associated with a low risk of peritoneal seeding according to Erickson (2002), who reported knowledge (via personal communication) of only one case of documented EUS-FNA peritoneal seeding after a cystadenocarcinoma was aspirated.
A study by Micames et al (2003) reported a lower incidence of peritoneal carcinomatosis after EUS-FNA was applied to investigate pancreatic cancers (1/46) than following percutaneous FNA for the same indication (7/43). Analysis of peritoneal washings revealed malignant cells in 2/32 of patients with pancreatic adenocarcinoma undergoing EUS-FNA, and 2/26 percutaneous FNA patients. The authors reported that EUS-FNA has the advantage of a short needle tract (compared with percutaneous FNA) and a lower theoretical risk of seeding of malignant cells.

Barawi et al (2001) studied the incidence of infection associated with EUS-FNA in 100 patients with lesions proximal to the GI tract, excluding cystic lesions. No procedural-related complications were found. The risk of infection has been reported to be higher for cystic lesions if prophylactic antibiotics are not used (Catalano et al 1997). A study by Janssen et al (2004) investigated the need for antibiotics following EUS-FNA of the upper GI tract to evaluate existing lesions/masses, choledocholithiasis and pancreatitis. They found that 2/100 patients had significant bacteraemia, but neither developed clinical signs of infection. The patients with bacteraemia had a pancreatic cyst and a mediastinal mass respectively. Intravenous antibiotics during aspiration, followed by a few days of oral antibiotics, are routinely administered for EUS-FNA of cystic pancreatic lesions to avoid infection (Erickson 2002). Using antibiotics for EUS-FNA of cystic lesions has become routine practice in recent years. Sedlack et al (2002) reported consistent use of antibiotics from 1998. Many patients who present with pancreaticobiliary neoplasia have associated pancreatitis or abdominal pain which is likely to limit the accuracy of estimated rates of complications occurring as a consequence of

the procedures. Procedure-related pancreatitis has been reported to occur more frequently in patients evaluated for recurrent pancreatitis and in instances where the FNA needle is passed through more than 2–3 cm of healthy pancreas (Erickson 2002).

## The reference standard

Investigation of novel diagnostic test accuracy requires comparison of diagnoses made using the new test with the true disease status. It is often not feasible to determine a patient's disease status unequivocally. In many disease states, a proxy measure—such as another diagnostic test or clinical judgement—must be used. The best available measure of disease is known as the reference standard.

The reference standard for diagnosing neoplasia is histological examination. This may be conducted on specimens obtained during surgery or on biopsies. In the case of negative diagnostic findings for neoplasia, measured in terms of the index test or comparator, long-term clinical follow up is an acceptable alternative reference standard.

The reference standard to assess the level of malignant neoplasms is surgical staging. This requires laparotomy and resection with pathological and histological examination of the resected specimen. Long-term clinical follow up is an acceptable alternative reference standard in situations where patients are not considered for surgery because of advanced disease and/or co-morbidity.

## Existing tests

### Oesophageal and gastric neoplasia

Where appropriate, gastroscopy with biopsy is the first-line procedure to diagnose oesophageal or gastric neoplasia (Allum et al 2002).

Existing techniques used in staging gastrointestinal (GI) neoplasms include chest radiography (x-ray), computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), transabdominal ultrasound, exploratory laparotomy and laparoscopy.

#### Chest radiography (x-ray)

X-ray is a relatively non-invasive procedure that provides a two-dimensional image of the internal organs and is useful in metastatic staging. X-rays provide low resolution detail for tumour staging and low sensitivity for tumour visualisation.

#### Computed tomography (CT)

CT creates a two-dimensional cross-sectional image of the body from multiple x-ray images. The usefulness of CT in staging neoplasms is dependent on the size of the tumour and degree of mesenteric invasion, among other factors. A spiral contrast-enhanced scan with thin collimation (5 mm) is the optimal type of CT for staging gastro-oesophageal neoplasms (Allum et al 2002). CT cannot adequately delineate the component layers of the oesophageal wall and is unable to differentiate between T1

and T2 tumours. Inaccurate assessment of adjacent structures indicates that CT may not clearly differentiate between T3 and T4 tumours.

Complications associated with CT include contrast-induced renal impairment and allergic reactions to the contrast reagent and radiation exposure. Most reported complications relate to allergic/anaphylactic reactions to the contrast material. The most commonly used contrast media are non-ionic, monomeric agents that are well tolerated by most patients. Some patients experience mild or moderate adverse events and very occasionally, these can be severe. CT is also associated with a risk of radiation exposure similar to other forms of x-ray imaging.

CT can be used to guide sampling of suspected tumour tissue for diagnostic confirmation. Sequential CT scans are made as a needle is guided toward the suspected tumour until it penetrates the mass. Malignancies can be confirmed by microscopically examining tissue samples obtained using CT-guided FNA or conventional needle biopsy. Conventional needle biopsy generally uses a small gauge needle (14–20 gauge) to obtain a morphologically intact tissue sample. FNA uses a larger gauge needle (21–24 gauge) to obtain cellular aspirate. Needle biopsy, such as with a TruCut needle, can obtain tissue samples up to 13 mm long and less than 3 mm diameter. FNA is associated with a lower risk of procedure-related adverse events, such as bleeding, due to the smaller needle size, compared with needle biopsy.

### Magnetic resonance imaging (MRI)

MRI exploits the behaviour of unpaired hydrogen protons when biological tissue is subjected to a strong external magnetic field. Energy released by radiofrequency-excited protons is used to create cross-sectional and three-dimensional images of biological tissue. The timing and frequency of the radiofrequency pulse can be varied to obtain optimal tissue visualisation. MRI provides a high level of spatial resolution and can be used to stage cancers because it is able to map the vasculature and haemodynamic structures of relevant organs. This technique is extremely effective in identifying metastatic tumours.

### Positron emission tomography (PET)

The Medical Services Advisory Committee (MSAC) has previously assessed PET for multiple indications. The review concluded that this technology would receive interim funding for clinical scenarios relevant to this assessment: a planned whole body PET study performed for staging of a patient with proven oesophageal or gastric carcinoma where curative surgery or chemoradiation (oesophageal only) had failed (MSAC 2002).

PET is a non-invasive imaging procedure that provides metabolic rather than morphological information about tumours. It uses radioisotopes that decay quickly emitting positrons from the nucleus. When a positron collides with an electron, two high-energy photons are produced that travel in opposite directions. A toroid-shaped positron camera that encircles the patient detects photons and produces cross-sectional images. Because tumour cells tend to take up more glucose than normal cells, the glucose producing radionuclide 18F-FDG (2-[18F] fluoro-2-deoxyglucose) is particularly useful for tumour imaging. 18F-FDG is administered intravenously and the PET scanner tracks uptake.

### Surgical staging (exploratory laparotomy)

Exploratory surgical laparotomy is a highly invasive alternative for cancer staging. An offset benefit of this approach is that it provides opportunity for simultaneous identification and surgical excision of identified tumours. Laparoscopy, or visual examination of the abdominal structures through a laparoscope inserted through a small incision in the abdominal wall, is a slightly less invasive alternative. This technique also provides the option of resection, with or without conversion to open surgery.

The effectiveness of laparoscopy for the staging and treatment of malignant disease has not been clearly established.

## Pancreaticobiliary neoplasia

Existing techniques used to diagnose and stage pancreatic and biliary tract neoplasms include CT, selective venous angiography, arteriography, MRI, endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTC) and magnetic resonance cholangiopancreatography (MRCP). Serological testing options include measurement of carcinoembryonic antigen (CEA) and cancer antigen 19-9 (CA 19-9).

### Computed tomography (CT)

CT is useful in the detection of pancreatic malignancies, but in some patients it reveals only general pancreatic enlargement that cannot be differentiated from pancreatitis. The current preferred procedure for diagnosis and staging of pancreatic cancer is dual-phase multidetector CT employing thin section (3–5 mm) cuts and contrast enhancement (Takhar et al 2004). Complications associated with CT are described on page 5.

CT-guided biopsy/FNA can be used for cytological or histological diagnosis of pancreatic cancer, particularly when tumours are small and resectable. This technique is associated with possible risk of peritoneal and cutaneous cancer seeding along the needle track (Takhar et al 2004). The risk of seeding outweighs the benefits of using CT-guided biopsy/FNA techniques for patients with suspected resectable malignant lesions. CT-guided biopsy/FNA is inadvisable for patients with small resectable tumours who are likely to attain cure. This technology has potential to seed malignant cells (reviewed by the Pancreas Committee of the British Society of Gastroenterology 2005).

### Endoscopic retrograde cholangiopancreatography (ERCP)

Cholangiography uses x-rays and contrast medium to visualise the bile ducts. Pancreatic tumours and pancreatitis can be difficult to distinguish using ERCP, but this technique is generally the investigation of choice to visualise the biliary tree. ERCP can be performed in combination with EUS for diagnostic investigation of pancreatic tumours. This approach is associated with high levels of patient discomfort and prolongs procedure time. As a result, the procedures are generally performed separately.

ERCP is an invasive technique that requires sedation, administration of antiperistaltic agents and hospital admission. It is associated with risk of complications. ERCP can also provide therapeutic options such as lithotomy and biliary stent placement. CT scanning is the initial diagnostic intervention of choice when suspicion of malignancy is high.

Diagnostic and therapeutic ERCP can be associated with post-procedural mortality caused by haemorrhage (0.76–2% after sphincterotomy), cardiopulmonary complications (≤ 1% of cases) and cholangitis (≤ 1% of cases) (Reviewed by the American Society for Gastrointestinal Endoscopy Standards Practice Committee 2003).

Other adverse events associated with ERCP include acute pancreatitis (most common, 1–7% of cases), perforation (0.3–0.6% of cases), cholecystitis (0.2–0.5% of cases) and fever (Freeman et al 1996; Freeman et al 2001; Henson et al 1992; Masci et al 2001; Recine et al 2004). The selection of the patient population has been shown to affect the safety of ERCP.

It has been recommended that younger patients, those who have sphincter of Oddi dysfunctions (which increases risk of pancreatitis by 20–25%), prior history of ERCP-related pancreatitis, non-dilated ducts, or normal bilirubin levels, should be diagnostically tested using alternatives to ERCP, such as EUS (de Ledinghen et al 1999; Prat et al 1996; Prat et al 2001; Taylor et al 2002).

The level of risk associated with ERCP is also influenced by technique-related variables, including the use of access papillotomy, sphincter of Oddi manometry, pancreatic duct stents and electrocautery.

Less common complications reported in association with ERCP include: ileus, antibiotic-related diarrhoea, hepatic abscesses, pneumothorax, duodenal meatomas, portal venous air and impaction of therapeutic devices and pseudocyst infection (reviewed by the American Society for Gastrointestinal Endoscopy Standards Practice Committee 2003).

ERCP also involves exposure to potentially harmful ionising radiation from the contrast media and risk of allergic reaction. EUS is less invasive than ERCP and may reduce the risk of procedure-related complications.

### Percutaneous transhepatic cholangiography (PTC)

PTC allows visualisation of biliary blockages by injecting radiographic contrast medium via an ultrasound-guided transcutaneous needle into the liver. It can be used pre-operatively to delineate biliary anatomy, allow insertion of biliary stents and enable bile sampling for cytological tests.

### Magnetic resonance cholangiopancreatography (MRCP)

MRCP is a non-invasive technique for visualising the pancreaticobiliary system. In this technique, radiofrequency pulses are modified to enhance imaging of the fluid-filled bile and pancreatic ducts. These structures appear as intense white areas and the surrounding tissue and blood are dark.

MRCP allows diagnostic evaluation of the biliary tract, pancreatic duct and gallbladder without the administration of contrast media, or the use of instrumentation or radiation (Wiersema et al 1993). The procedure avoids complications such as pancreatitis, perforation and bleeding, that are associated with ERCP, EUS-FNA and CT-FNA/guided biopsy.

A recent MSAC review evaluated the safety of MRCP (MSAC 2005). The review of 43 studies reporting occurrence of adverse events in 1,618 patients who underwent MRCP, ERCP and CT found no reported events in relation to MRCP.

### Serological tumour markers

Serological markers that can be detected by monoclonal antibodies, such as carcinoembryonic antigen (CEA) and cancer antigen 19-9 (CA 19-9), are useful in the diagnosis and monitoring of pancreatic adenocarcinoma. They are not specific to pancreatic malignancy.

CA 19-9 is the most widely used serological marker for pancreatic cancer (Takhar et al 2004). Elevated levels of CA 19-9 have been detected in 75–85 per cent of patients with pancreatic cancer (Erickson 2004). CA 19-9 has limited sensitivity in the detection of small, early stage pancreatic cancers, although levels are commonly elevated in patients with pancreatic cancers that are at least 3 cm in diameter (Erickson 2004). This limits its use to detect potentially resectable tumours. Elevated levels of this serum marker may also be found in stomach, colon or biliary tree malignancies, as well as in benign conditions, such as pancreatitis. CA 19-9 is not specific for pancreaticobiliary tumours.

CEA levels are elevated in 40–45 per cent of patients with pancreatic cancer, but it has minimal application diagnosing this disease because other benign and malignant conditions can also contribute to elevated CEA levels (Erickson 2004).

### Angiography

Angiography studies are useful in staging tumours in the portal vein, mesenteric vein or hepatic artery because a key component to determine resectability of biliary tract malignancies shows evidence of vascular invasion into these anatomical structures. Angiography can also be useful in the diagnosis of some pancreatic endocrine tumours, given that these tend to be highly vascularised.

## Pancreatic neuroendocrine tumours

Additional techniques to diagnose pancreatic neuroendocrine tumours include biochemical tests and somatostatin receptor scintigraphy (SRS).

### Biochemical tests

Biochemical diagnosis of insulinomas is established in most patients during prolonged fasting. Tests include measurement of insulin, glucose and C-peptide levels (Radebold 2001).

Biochemical diagnosis of gastrinomas is based on three criteria (Nachimuthu 2002). During fasting, hypergastrinaemia is present; basal gastric acid output (BAO) is elevated (< 10 mEq/hour); and results from a secretin stimulation test are positive (eg 100% increase over baseline).

### Somatostatin receptor scintigraphy (SRS)

SRS involves the use of somatostatin analogues, including indium-111-labelled octreotide and pentetreotide, to bind to somatostatin receptors. The radioisotope concentrates in tissues containing these receptors and is a useful test for diagnosis and staging of pancreatic neuroendocrine tumours. The test sensitivity for neuroendocrine tumours depends on the density of somatostatin receptors in the tumour.

MSAC (1999) assessed Octreoscan scintigraphy for gastroenteropancreatic (GEP) neuroendocrine tumours which resulted in a positive recommendation for funding. The indications supported were: suspected GEP neuroendocrine tumour based on biochemical evidence with negative (or equivocal) conventional imaging or where a surgically amenable GEP neuroendocrine tumour has been identified based on conventional techniques, in order to exclude additional disease sites (MSAC 1999).

#### Complications associated with SRS

As part of the MSAC assessment of the use of Octreoscan for gastroenteropancreatic neuroendocrine tumours (MSAC 1999), 15 European multicentre trials were reviewed for safety. Of 482 patients, 12 reported adverse events (2.5%) nine of whom were included in the trials (there were two protocol violations and one patient did not have a neuroendocrine tumour). Adverse events reported included sweating, hypotension, headache, limb pain, fever, flushes, nausea, stomach spasms, weakness and dizziness. There were two reported fatal incidents that were considered unrelated to SRS. On the basis of these studies, it was concluded that the use of SRS was safe at the recommended dosages.

## Oesophageal neoplasia

### Clinical need

Squamous cell carcinoma and adenocarcinoma are the most common types of oesophageal cancer. Aetiology of squamous cell oesophageal carcinoma is linked to alcohol and tobacco consumption. Oesophageal adenocarcinoma is related to Barrett's oesophagus—the presence of chronic gastric reflux in association with intestinal metaplasia of the epithelium. Squamous cell oesophageal carcinomas arise from the inner lining of the oesophagus and are generally located in the upper third and middle of the oesophagus. Oesophageal adenocarcinomas arise from the gland/secretory cells, generally located in the lower part of the oesophagus.

Patients with oesophageal cancers can develop a number of signs and symptoms that adversely affect their quality of life. The initial features of the disease are weight loss and progressive dysphagia. Dysphagia progression can be associated with painful or difficult swallowing, regurgitation/vomiting or aspiration pneumonia. Some patients may develop tracheoesophageal fistulas which can greatly reduce patients' quality of life.
By the time patients develop noticeable symptoms of dysphagia, the cancer has usually infiltrated more than 60 per cent of the oesophageal circumference (Harrison 2005). The cancer generally progresses to adjacent and supraclavicular lymph nodes, lungs, liver and pleura.

#### Incidence and mortality

Although oesophageal cancers are uncommon in Australia, incidence has increased over time. The age-standardised rate increased from 4.9/100,000 in 1983 to 5.6/100,000 in 2001 (Australian Institute of Health and Welfare [AIHW] and Australasian Association of Cancer Registries [AACR] 2004).

There were 1,078 reported cases of oesophageal carcinoma diagnosed in Australia in 2001 (Australian Institute of Health and Welfare [AIHW] and Australasian Association of

Cancer Registries [AACR] 2004). Of these 1,078 new cases, 704 occurred in males (age-standardised rate for Australia of 8.0/100,000) and 374 were in females (age-standardised rate for Australia of 3.4/100,000). The overall age-standardised rate for Australia was 5.6/100,000.

Application of the age-standardised rate from 2001 to the Australian population in 2005 gives an estimated incidence of 1,141 reported cases (calculated from current projected Australian population of 20,375,000; Australian Bureau of Statistics 2005).

Oesophageal cancer was responsible for 1,039 deaths in 2001 (698 male and 341 female), resulting in 6,553 person-years of life lost before the age of 75. This equates to an age-standardised mortality for Australia of 8.1/100,000 for men and 3.1/100,000 for women (Australian Institute of Health and Welfare [AIHW] and Australasian Association of Cancer Registries [AACR] 2005). The overall age-standardised mortality for Australia is 5.4/100,000.

There were 4,362 separations for oesophageal cancer in 2001; the average length of stay for most patients was 6.8 days, resulting in 29,853 patient-days in hospital. The *Australian Refined Diagnosis Related Groups* (AR-DRG version 5.1) classification indicates the following for stomach, oesophageal plus duodenal surgical procedures for malignancy for 2001: 1,244 separations, an average length of stay of 16.1 days and a total of 20,002 patient-days in hospital (Australian Institute of Health and Welfare [AIHW] 2005b).

### Eligible population

The use of EUS for staging oesophageal cancer can be estimated by subtracting the proportion of patients considered unsuitable for EUS from the Australian incidence rate of oesophageal cancer. This proportion has been estimated using two methods.

Associate Professor Mark Smithers (personal communication, 26 September 2005) provided data from an Australian database of oesophageal cancer patients for the first estimation. This database prospectively included all patients (1,157) seen at a combined upper gastrointestinal oncology clinic from 1987 to 2005. The proportion deemed suitable for palliative care from radiology, and who were not eligible for EUS staging of oesophageal cancer, was 24.4 per cent. An additional 21.5 per cent of patients included in the database were considered unsuitable for surgery and unlikely to receive EUS. Using these values and the projected Australian incidence of oesophageal cancer for 2005, the number of patients eligible for EUS for staging of oesophageal cancer is estimated at 617 patients per year. The calculation of this figure is provided under estimate 1 in **Table 1**. These data represent the best estimate available for EUS use in the staging of oesophageal cancer in Australia.

The second estimate used a proportion of patients diagnosed with distant metastases by CT to represent those ineligible for EUS. From a recent study in Japan (Kato et al 2005) and a meta-analysis on the resource utilisation of EUS (Parada et al 2002), the proportion of patients with distant metastases detected by CT is estimated to be 11.6–12.8 per cent. Using these values, the number of patients eligible for EUS staging of oesophageal cancer is 995–1,009 patients per year (estimate 2, **Table 1**). This second estimate assumes that following exclusion for distant metastases based on CT results, all remaining patients would be eligible for EUS. It does not consider patients who are subsequently excluded from EUS due to other medical reasons, or results of other diagnostic tests (such as

abdominal ultrasound), as does estimate 1. This estimate can be considered to equate with an upper limit of the maximum possible number of patients eligible for EUS.

**Table 1 Projected EUS use to stage oesophageal cancer**

| | | Estimate 1 | Estimate 2 |
|---|---|---|---|
| **A:** | Australian age-standardised rate of oesophageal cancer (2001) | 5.6/100,000 | 5.6/100,000 |
| **B:** | Current estimate of Australia's population[a] (2005) | 20,375,000 | 20,375,000 |
| **C:** | Estimated number of cases of oesophageal cancer in 2005 (A × B) | 1141 | 1141 |
| **D:** | Percentage of patients excluded because of distant metastases or other medical reasons (%) | 45.9[b] | 11.6–12.8[c] |
| **E:** | Number of patients per year not considered for EUS for staging (C × D/100) | 524 | 132–146 |
| **F:** | Number of patients per year eligible for EUS for oesophageal cancer staging (C–E) | 617 | 995–1009 |

Abbreviation: EUS, endoscopic ultrasound
[a] Source: Australian Bureau of Statistics 2005
[b] Source: Personal communication from Associate Professor Mark Smithers
[c] Source: Kato et al 2005; Parada et al 2002

## Current treatment

Oesophageal cancer is a treatable disease but is only rarely curable. The overall five-year survival rate of patients with oesophageal cancers who are amenable to definitive treatment ranges between 5 and 30 per cent (National Cancer Institute 2004c). Patients diagnosed with early disease have the best chance of survival. Treatment for oesophageal cancers is generally based on disease staging, although precise pre-operative staging may be difficult. Patients with early stage tumours (T1–2) are usually surgically treated, while those with advanced tumours (T3 and N1) are usually treated with chemotherapy or chemoradiation. Patients not fit for surgery, but with potentially curable disease, will receive definitive radiotherapy combined with chemotherapy. Patients with unresectable disease or with metastases will receive palliative treatment.

Small asymptomatic tumours that are confined to the oesophageal mucosa or submucosa are generally detected by chance. Surgery is the treatment of choice for these small tumours. Once symptoms are present, indicated by dysphagia in most cases, oesophageal cancers have usually invaded the muscularis propria (T2) or beyond and have a higher potential for metastasis to lymph nodes or other organs (National Cancer Institute 2004c).

Although rarely diagnosed, stage 0 oesophageal cancer is treated by surgical resection (National Cancer Institute 2004c). Surgery is also the standard treatment for patients with stages I or IIa oesophageal cancer. Patients with stages IIb and III may receive neoadjuvant chemotherapy plus radiation therapy if the appropriate stratification can be done pre-operatively. There have been a number of randomised controlled trials assessing pre-operative chemotherapy or pre-operative chemoradiation.
Recent meta-analyses have suggested a 5–10 per cent benefit from these therapies (Fiorica et al 2004; Kaklamanos et al 2003).

There is no evidence that chemotherapy or radiation therapy after surgery improves overall survival benefit compared with surgery alone (National Cancer Institute 2004c). Further clinical assessment with better stratification for T and N stage is required to optimise patient care and improve patient survival.

Some patients with stage III oesophageal cancer (T3N1, T4 any N,) will be treated with surgery; the majority will be treated with definitive chemoradiation (see **Figure 18** in **Appendix G**). Other treatment options may include neoadjuvant chemoradiation followed by surgery or neoadjuvant chemotherapy followed by surgery. Patients who are not medically fit for potentially curative treatment may be managed with palliative therapy.

Following diagnosis by radiology, approximately 24 per cent of patients with oesophageal cancer will be deemed palliative (Associate Professor Mark Smithers, personal communication, 26 September 2005). A variety of palliative care treatments may be used to improve the quality of life for these patients: endoscopically placed stents; radiation therapy with or without intraluminal intubation and dilation; intraluminal brachytherapy, Nd:YAG endoluminal tumour destruction or electrocoagulation; or chemotherapy (National Cancer Institute 2004c). This group of patients has a poor survival rate and may be recommended for new treatments in clinical trials, such as those evaluating single-agent or combination chemotherapy.

In patients who have resectable disease, the operative mortality in specialist centres should be less than 5 per cent (National Cancer Institute 2004c). Definitive treatment with radiation plus chemotherapy has been investigated in an attempt to avoid this perioperative mortality and to relieve dysphagia. An overall survival rate of 22 per cent has been reported for patients with squamous cell carcinoma receiving chemoradiation therapy, after eight years of follow up (National Cancer Institute 2004c). It has been shown that chemoradiation therapy achieves better five-year survival than radiotherapy alone (National Cancer Institute 2004c).

# Gastric neoplasia

## Clinical need

### Gastric cancer

Gastric cancer is the second most common cancer worldwide, with a particularly high prevalence in Asia and Latin America. It does not have a high prevalence in the Australian population (Australian Institute of Health and Welfare [AIHW] and Australasian Association of Cancer Registries [AACR] 2004).

The precise aetiology of stomach cancer is unknown, but several risk factors have been identified such as long-term consumption of preserved foods with high concentrations of nitrates. The two other major identified risk factors are salt intake, and infection by the *Helicobacter pylori* bacterium, which causes chronic gastritis. If untreated, this infection may lead to mucosal hyperplasia, then dysplasia, and eventually carcinoma. Other risk factors for stomach cancer include advanced age, male gender, low dietary fibre intake, cigarette smoking and familial adenomatous polyposis.

Gastric cancers may present as submucosal tumours. These tumours are completely contained within the stomach lining and are more difficult to diagnose.

The most common form of gastric cancer is adenocarcinoma (National Cancer Institute 2004b). Incidence of adenocarcinoma is estimated to be 90–95 per cent of all gastric tumour types. Adenocarcinoma arises in the glands of the innermost layer of the stomach and can be classified under either of two categories based on their cell cohesion

characteristics: an intestinal type, characterised by generally having a distal stomach location and the presence of neoplastic cell cohesion which forms polyps; and a diffuse type, generally characterised by proximal location and a lack of cell cohesion, which prevents cells forming a discrete mass.

Intestinal type gastric cancer, as opposed to diffuse type gastric cancer, progresses through well-defined steps that include atrophic gastritis, intestinal metaplasia and dysplasia, and adenocarcinoma. As either of the two types of adenocarcinoma develops, cells can spread through the layers of the stomach wall to adjacent organs and lymph nodes and then metastasise through the circulatory or lymphatic systems to distant sites.

Early stage gastric cancers that are viable for surgical cure are seldom associated with specific symptoms. As tumours progress, patients' quality of life can be affected by symptoms such as abdominal pain and the manifestations of gastrointestinal bleeding.

Primary lymphoma is an uncommon tumour that accounts for less than 15 per cent of malignant gastric tumours. The stomach is the most frequent extranodal location for lymphoma and these tumours have been increasing in frequency. The most important aetiological factor for this tumour appears to be the presence of an *H. pylori* infection. These tumours arise in the lymphatic tissue of the stomach wall and are characterised by ulcerations of the stomach lining with a ragged, thickened mucosal pattern. Many gastric lymphoid tumours are non-Hodgkin's lymphoma. Hodgkin's disease is extremely uncommon. As the primary lymphoma develops, it spreads to regional lymph nodes from where it metastasises further.

### Gastric submucosal tumours

Gastrointestinal stromal tumour (GIST) is the most common type of gastric submucosal tumour. These tumours arise from the mesenchymal cells (as opposed to the other type of soft tissue tumour, leiomyosarcoma, which arises from smooth muscle tissue). Presentation of these lesions involves bleeding. They are also commonly found incidentally at upper gastrointestinal endoscopy. These tumours are not a subgroup of gastric cancer but are a histologic type of soft tissue sarcoma (American Joint Committee on Cancer 2002b; National Cancer Institute 2005). GISTs all have potential for malignant activity. The risk of malignancy relates to size and the number of mitoses per high power field seen on histological examination (Fletcher et al 2002). These tumours rarely spread to regional lymph nodes; metastasis is usually via the liver or peritoneum. Recent published findings indicate that many GISTs were previously misclassified as leiomyosarcomas (Nguyen 2004). The majority view of the GIST consensus workshop in 2001 was that the term 'GIST' should with very few exceptions, be applied to neoplasms displaying KIT (CD117) immunopositivity (Fletcher et al 2002). Rather than define strict criteria to separate benign from malignant tumours, it has been proposed that the risk of aggressive behaviour in a given GIST should be designated as low, intermediate or high according to size and mitotic count (Fletcher et al 2002).

### Incidence and mortality

#### Gastric cancer

In 2001, there were 1,902 new cases of gastric carcinoma reported in Australia (Australian Institute of Health and Welfare [AIHW] and Australasian Association of Cancer Registries [AACR] 2004). Of these, 1,202 cases occurred in males, making it the ninth most frequent notifiable cancer in men. The corresponding age-standardised rate

for gastric cancer among men in Australia was 13.8/100,000. In the same period 700 new cases were reported in women, resulting in an age-standardised rate for Australia of 6.5/100,000. The overall age-standardised rate was 9.8/100,000.

Application of this overall rate to the Australian population in 2005 gives an estimate of 1,997 cases of gastric carcinoma (based on a projected Australian population of 20,375,000 in 2005) (Australian Bureau of Statistics 2005).

In 2001, gastric cancer was responsible for 1209 deaths (753 in men and 456 in women), resulting in 8,133 person-years of life lost before the age of 75 years. This equates to an age-standardised mortality for Australia of 8.9/100,000 for men and 4.2/100,000 for women (Australian Institute of Health and Welfare [AIHW] and Australasian Association of Cancer Registries [AACR] 2005). The overall age-standardised mortality for Australia was 6.2/100,000.

Between 1991 and 2001, the incidence of gastric cancer in men and women fell by an average of 2.3 per cent and 1.6 per cent, respectively, per annum. Between 1991 and 2001, the mortality associated with gastric cancer in men and women fell by an average of 3.4 per cent and 3.6 per cent, respectively, per annum (Australian Institute of Health and Welfare [AIHW] and Australasian Association of Cancer Registries [AACR] 2004).

There were 5,429 separations for gastric cancer in 2001, and the average length of stay for most patients was 7.8 days. This resulted in 42,136 patient-days in hospital (Australian Institute of Health and Welfare [AIHW] 2005b).

### Gastric submucosal tumours

Gastrointestinal stromal tumour (GIST) is the most common of the gastric submucosal tumour types. GIST incidence reported in Western countries is 14.5 per million of the population (Fletcher et al 2002). The incidence in countries such as Korea and Japan, which offer gastric cancer screening programs, has been reported in the range of 40–60 per million of the population. Most GISTs (50–70%) occur in the stomach (Nguyen 2004). The annual incidence of gastric GISTs in the stomach is estimated at 7.0–9.8 per million of the population. This may underestimate the rate because there is confusion about the GIST definition and likelihood of misclassification as other tumour types.

## Eligible population

EUS use for gastric cancer staging in Australia can be estimated by subtracting the proportion of patients with distant metastases at diagnosis from the population's gastric cancer incidence rate.

The proportion of patients diagnosed with distant disease in NSW between 1992 and 1996 was 21 per cent (Jong et al 2002). Using this value as an estimate for the proportion of patients with distant metastases, the number of patients eligible for EUS for staging of gastric cancer is estimated to be 1,578 patients per year (estimate 1 **Table 2**).

Recent studies by Chen et al (2003) and Kayaalp et al (2002) and a meta-analysis by Parada et al (2002) on EUS resource utilisation indicate that the proportion of gastric cancer patients with distant metastases was estimated in the range of 7.0–9.0 per cent. Using these values, the estimated number of patients eligible for EUS for staging of gastric cancer is 1,817–1,857 patients per year (estimate 2 **Table 2**). These data represent

the best estimate available in the public domain for EUS use in the staging of gastric cancer in Australia.

**Table 2 Projected EUS use to stage gastric cancer**

| | | Estimate 1 | Estimate 2 |
|---|---|---|---|
| **A:** | Australian age-standardised rate of gastric cancer (2001) | 9.8/100,000 | 9.8/100,000 |
| **B:** | Current estimate of Australia's population[a] (2005) | 20,375,000 | 20,375,000 |
| **C:** | Estimated number of cases of gastric cancer in 2005 (A × B) | 1997 | 1997 |
| **D:** | Percentage of patients excluded because of distant metastases (%) | 21[b] | 7.0–9.0[c] |
| **E:** | Number of patients per year not considered for EUS for staging (C × D/100) | 419 | 140–180 |
| **F:** | Number of patients per year eligible for EUS for gastric cancer staging (C–E) | 1578 | 1817–1857 |

Abbreviations: EUS, endoscopic ultrasound
[a] Source: Australian Bureau of Statistics 2005
[b] Estimated from the percentage of patients with distant spread of disease (Jong et al 2002)
[c] Source: Chen et al 2003; Kayaalp et al 2002; Parada et al 2002

## Current treatment

### Gastric cancer

Treatment for gastric cancer is generally based on its staging and relies on appropriate stratification. The prognosis for patients with gastric cancer is related to both tumour extent and nodal involvement. Estimated five-year survival among patients with localised distal gastric cancer is 50 per cent. The rate is lower (10–15%) among patients with localised proximal disease (National Cancer Institute 2004b). Most patients present with regional or more distant involvement. The five-year survival is almost zero in patients with disseminated disease.

Radical surgery is the standard form of treatment with curative intent. High failure rates associated with this approach has led to adjuvant therapy being considered for advanced disease; chemoradiation has shown a survival benefit (National Cancer Institute 2004b).

The treatment of choice for patients with stage I and II gastric cancer is surgical resection incorporating regional lymphadenectomy (National Cancer Institute 2004b). Surgical approach varies depending on the anatomical location of the tumour and level of diffusion. Distal subtotal gastrectomy is appropriate if the tumour is not in the fundus or at the cardioesophageal junction. If the tumour involves the cardia, proximal subtotal gastrectomy or total gastrectomy with distal oesophagectomy is performed. Total gastrectomy is appropriate if the tumour involves the stomach diffusely or arises in the gastric corpus and extends to within 6 cm of the cardia or involves the stomach diffusely or extensively.

Regional lymphadenectomy is recommended with all of these procedures for stage I and II disease.

Postoperative chemoradiation may also be considered for patients with stage IB or II disease. Although the US National Cancer Institute regards postoperative chemoradiation as a standard option for stage IB and stage II gastric cancer patients, such use is uncommon for patients with stage IB disease in Australia.

All patients with resectable stage III tumours should undergo surgery. Up to 15 per cent of selected stage III patients can be cured by surgery alone, particularly if lymph node involvement is minimal (less than seven lymph nodes) (National Cancer Institute 2004b). Curative resection procedures are confined to patients who, at the time of surgical exploration, do not have extensive nodal involvement (National Cancer Institute 2004b). Postoperative chemoradiation may also be considered for patients with stage III gastric cancer because it appears to confer a survival benefit (National Cancer Institute 2004b).

A recent trial of pre-operative and postoperative therapy reported a 15 per cent improvement in survival (Cunningham et al 2005). This will increase the need for pre-operative stratification of patients aiming to treat patients with T3 N0, N1 tumours.

Chemotherapy may provide substantial palliation and occasional durable remission among patients with stage IV disease who have haematogenous or peritoneal metastases, but does not prolong life. Other palliative treatment options include endoscopic laser therapy or endoluminal stent placement (useful in patients whose tumours have occluded the gastric inlet) and radiation therapy (which may alleviate bleeding, pain and obstruction). Palliative resection should be reserved for patients with continued bleeding or obstruction.

Patients with stage III and IV gastric cancer may be considered candidates for clinical trials.

Neoadjuvant chemoradiation therapy is under clinical evaluation for patients with stage I–III gastric cancer, as well as those with stage IV disease, who do not have distant metastases (National Cancer Institute 2004b).

#### Gastric submucosal tumours

The present recommendation is that all submucosal tumours 3 cm or greater should be resected. This recommendation relates to the risk of malignancy increasing as the tumour reaches 5 cm (Anonymous 2004; Dematteo et al 2002). The recent recognition of this entity indicates that there are presently no guidelines from well-conducted trials. Growth rates of tumours less than 3 cm should be monitored under endoscopic surveillance.

## Pancreatic neoplasia

### Clinical need

Factors associated with increased risk of pancreatic neoplasia include smoking, prior gastric surgery, exposure to radiation or chemicals such as chlorinated hydrocarbon solvents. Predisposing conditions associated with pancreatic tumours include chronic pancreatitis and recent onset of diabetes mellitus (DiMagno 1999).

Most pancreatic tumours (90–95%) develop in the exocrine region, which produces pancreatic juice; tumours that develop in the endocrine, hormone producing region, account for the remaining 5–10 per cent of tumours. About 75 per cent of pancreatic carcinomas occur in the head or neck of the pancreas, 15–20 per cent in the pancreas body, and 5–10 per cent in the tail (Erickson 2004).

Most exocrine tumours are ductal adenocarcinomas which account for 90 per cent of all pancreatic tumours (Keogh et al 1999). Less common exocrine tumours include neoplastic cysts and carcinomas of the ampulla of Vater.

Most pancreatic cystic lesions are pseudocysts (80–90%) with neoplastic cysts accounting for the remainder. Neoplastic cysts include serous cystic neoplasms and mucin-producing tumours of which there are two types: intraductal papillary-mucinous tumours (IPMT) and mucinous cystic neoplasms (MCN). The degree of epithelial dysplasia is used to classify IPMT and MCN into benign, borderline and malignant tumours (Falconi et al 2001; Zamboni et al 1999). Despite this classification, all IPMT and MCN are regarded as potentially malignant (Conlon 2005; Levy et al 2004).

IPMTs predominantly occur in the head of the pancreas and are characterised by cystic dilation of the pancreatic ducts and intraductal papillary growth (Conlon 2005).

Mucinous cystadenomas and cystadenocarcinomas (MCNs) are usually located in the body and tail of the pancreas and contain copious amounts of mucin in a cyst encapsulated by a thick fibrous wall. These cysts are not connected to the pancreatic duct structure. MCNs are rare, accounting for only 2–5 per cent of all exocrine pancreatic tumours (Zamboni et al 2000).

Carcinomas of the ampulla of Vater (the point where the pancreatic and bile ducts merge and exit into the duodenum) can arise in pancreatic ductal epithelial cells. Tumours originate from these cells and usually invade the body of the pancreas. Carcinoma of the ampulla of Vater is uncommon; in the USA, ampullary neoplasia accounts for 0.2 per cent of all GI tract malignancies (Chaturvedi et al 2004). Most of these tumours are resectable for cure at diagnosis; the five-year survival rate is low (40%) (Chaturvedi et al 2004).

Pancreatic endocrine tumours are described as functional when they produce hormones that cause a distinct clinical syndrome. These tumours may occur sporadically or in association with multiple endocrine neoplasia type 1 (MEN-1), a condition involving the pituitary gland, parathyroid glands and pancreatic islet cells. Patients with non-functional endocrine tumours typically present later in the course of the disease with symptoms arising due to the tumour mass. Endocrine tumours are often multiple and occur in both the pancreas and duodenum.

The most common types of pancreatic endocrine tumours are gastrinomas and insulinomas. Insulinomas are characterised by overproduction of insulin or proinsulin which can cause hypoglycaemia. These may be presumptively diagnosed on the basis of blood insulin and glucose levels. It has been estimated that insulinomas account for about 50 per cent of islet cell tumours (Radebold 2001). Most insulinomas are benign; about 10 per cent are designated as malignant (National Cancer Institute 2003b; Radebold 2001).

Gastrinomas may occur sporadically or in association with Zollinger-Ellison syndrome, a severe form of stomach and duodenal ulceration. Biochemical detection of gastrinomas may be based on elevated basal and secretin stimulated gastric acid and serum gastrin levels. About 25 per cent of gastrinomas are related to MEN-1 (Nachimuthu 2002). At diagnosis, 60–75 per cent of gastrinomas associated with MEN-1 are found to be malignant with evident metastases (National Cancer Institute 2003b).

### Incidence and mortality

In 2001, pancreatic neoplasia was the fifth most common cause of cancer-associated death (n = 1811; 946 in men, 865 in women) in Australia, equating to an age-standardised mortality of 11/100,000 and 7.8/100,000 for men and women respectively. The poor prognosis of pancreatic neoplasia is highly evident in the five-year relative survival figures. In Australia between 1992 and 1997, the five-year relative survival was 5.4 per cent for males and 5.2 per cent for females (AIHW and AACR 2005).

There were 1,858 new diagnoses in that year: 958 occurred in men and 900 in women. Age standardised rates were 11/100,000 and 8.2/100,000 in men and women, respectively (Australian Institute of Health and Welfare [AIHW] and Australasian Association of Cancer Registries [AACR] 2004). The overall Australian age-standardised incidence of pancreatic neoplasia was 9.6/100,000. This disease was the tenth most frequent neoplasm that occurred in both men and women (excluding non-melanocytic skin cancers). The lifetime risk of pancreatic neoplasia is 1 in 133 for men and 1 in 207 for women (AIHW and AACR 2004).

Application of the overall age-standardised incidence to the Australian population in 2005 provided an estimate of 1,956 new diagnoses of pancreatic neoplasms (projected Australian 2005 population of 20,375,000) (Australian Bureau of Statistics 2005).

In 2002–2003, there were 3,400 non-same-day and 799 same-day hospital separations for malignant pancreatic neoplasms, equating to a total of 38,593 patient-days in hospital (AIHW 2005b). These figures include data for malignant neoplasms of the endocrine pancreas; in 2002–2003 there were 34 non-same-day and 13 same-day hospital separations for this subset of tumours, equating to a total of 403 patient-days in hospital.

MSAC has previously assessed the use of Octreoscan scintigraphy for gastroenteropancreatic (GEP) neuroendocrine tumours (MSAC 1999). Clinically significant pancreatic endocrine tumours were reported to have an estimated incidence of 3.6–4 per million of population annually. In the 2001, 2002 and 2003 financial years, there were respectively 211, 251, and 237 claims for indium-labelled octreotide studies (Medicare Benefits Schedule item number 61369) for '…a suspected GEP endocrine tumour, based on biochemical evidence, with negative (or equivocal) conventional imaging; or a surgically amenable GEP endocrine tumour identified based on conventional techniques, in order to exclude additional disease sites'.

### Eligible population

#### Pancreatic cancer diagnosis

The estimated number of patients undergoing EUS to confirm pancreatic cancer diagnoses was based on the assumption that all patients with suspected cancer, without CT-identified metastases (see Clinical pathway, **Figure 4**), would be examined using EUS. The estimate was calculated by subtracting the proportion of patients with distant metastases at diagnosis from the incidence of pancreatic cancer in Australia. This corrected incidence underestimates the eligible population because the number of patients with suspected malignancies referred for EUS would be greater than the number of patients with final pancreatic cancer diagnoses. The estimated incidence was further corrected by assigning an estimate of the ratio of patient numbers with suspicion and the diagnosis of pancreatic cancer.

The percentage of patients with distant metastases who would be excluded based on CT results (and not considered for EUS) was estimated by using the percentage of patients diagnosed with distant spread of disease. The NSW estimate between 1992 and 1996 was 29.8 per cent (Jong et al 2002). It was estimated that 29.8 per cent of pancreatic cancer patients would not be considered eligible for EUS to confirm diagnoses.

A US study of projected EUS use found that approximately 27 per cent of EUS procedures for suspected pancreatic malignancy resulted in cancer diagnoses (Parada et al 2002). This suggests that the incidence corrected for the proportion of patients with distant metastases would account for 27 per cent of potential EUS use for pancreatic cancer diagnoses. Adjusting for the proportion of patients with distant metastases and accounting for all patients with suspected pancreatic malignancy, an estimate of the number of patients who would potentially receive EUS for pancreatic cancer diagnosis is 5,085 patients per year (estimate 1, **Table 3**).

Another estimate of the number of patients who would be considered for EUS to diagnose pancreatic cancer was derived from the total number of patients whose presentation raised suspicion of pancreatic cancer. Using data from the AIHW Interactive National Hospital Morbidity Database for the period 1998 to 2004 (AIHW 2005b), and using the total number of same-day and non-same-day separations (episodes of care) as an estimate of patient numbers, translated to an estimated 5,823 patients who would be investigated for pancreatic cancer diagnoses using EUS annually (estimate 2, **Table 3**).

**Table 3 Projected EUS use to diagnose pancreatic cancer**

| **Estimate 1** | |
|---|---|
| **A**: Australian age-standardised rate of pancreatic cancer (2001) | 9.6/100,000 |
| **B**: Current estimate of Australia's population[a] (2005) | 20,375,000 |
| **C**: Estimated number of cases of pancreatic cancer in 2005 (A×B) | 1956 |
| **D**: Percentage of patients not considered for EUS because of distant metastases (%) | 29.8[b] |
| **E**: Number of patients per year not considered for EUS for diagnosis (C×D/100) | 583 |
| **F**: Number of potential patients per year diagnosed by EUS (C–E) | 1373 |
| **G**: Percentage of EUS procedures for suspected pancreatic malignancy resulting in cancer diagnosis | 27[c] |
| **H**: Annual number of patients eligible for EUS for suspected pancreatic malignancy [F/(G/100)] | 5085 |
| **Estimate 2** | |
| **Hospital separation code** | **Number of same-day and non-same-day separations 1998–2004[d]** |
| **A**: Malignant neoplasm of pancreas | 23,707 |
| **B**: Cyst of pancreas | 680 |
| **C**: Pseudocyst | 1605 |
| **D**: Other chronic pancreatitis | 8169 |
| **E**: Disease of pancreas, unspecified | 774 |
| **F:** Total patients potentially eligible for EUS (A + B + C + D + E) | 34,935 |
| **G**: Number of patients per year eligible for EUS for suspected pancreatic malignancy (F/6) | 5823 |

Abbreviation: EUS, endoscopic ultrasound

[a] Source: Australian Bureau of Statistics 2005

[b] Estimated from the percentage of patients with distant spread of disease (Jong K. et al 2002)

[c] Source: Parada et al (2002)

[d] Source: AIHW Interactive National Hospital Morbidity Database (Australian Institute of Health and Welfare [AIHW] 2005b)

### Pancreatic cancer staging

The use of EUS for pancreatic cancer staging was estimated by subtracting the proportion of patients with distant metastases at diagnosis from the incidence of pancreatic cancer in Australia. Using the percentage of patients with distant spread of disease as an estimate for the proportion of patients with distant metastases the estimated use of EUS for pancreatic cancer staging is 1,373 patients per year (estimate 1, **Table 4**).

The proportion of CT-identified distant metastases is estimated at 21–44 per cent based on data provided in a study by Freeny et al (1993) and a meta-analysis conducted by Parada et al (2002). These proportions provided the means to estimate that the projected use of EUS for pancreatic cancer staging is 1,095–1,545 patients per year (estimate 2, **Table 4**).

**Table 4 Projected EUS use to stage pancreatic cancer**

| | | Estimate 1 | Estimate 2 |
|---|---|---|---|
| **A**: | Australian age-standardised rate of pancreatic cancer (2001) | 9.6/100,000 | 9.6/100,000 |
| **B**: | Current estimate of Australia's population[a] (2005) | 20,375,000 | 20,375,000 |
| **C**: | Estimated number of cases of pancreatic cancer in 2005 (A×B) | 1956 | 1956 |
| **D**: | Percentage of patients excluded because of distant metastases (%) | 29.8[b] | 21–44[c] |
| **E**: | Number of patients per year not considered for EUS for staging (C×D/100) | 583 | 411–861 |
| **F**: | Number of patients per year eligible for EUS for pancreatic cancer staging (C–E) | 1373 | 1095–1545 |

Abbreviation: EUS, endoscopic ultrasound

[a] Source: Australian Bureau of Statistics 2005

[b] Estimated from the percentage of patients with distant spread of disease (Jong et al 2002)

[c] The proportion of computed-tomography identified distant metastases (Freeny et al 1993; Parada et al 2002)

## Current treatment

Pancreatic carcinoma is usually diagnosed late in the course of the disease and as a result, has an extremely poor prognosis. The presenting symptoms usually include jaundice, pain, weight loss, dark urine, clay-like stools and pruritus. The poor prognosis associated with pancreatic carcinoma is clearly demonstrated in the standardised incidence and mortality rates reported previously.

Surgical resection is the only effective treatment for pancreatic neoplasia; only 15 to 20 per cent of patients present with disease is readily resectable (ie no evidence of local advancement) (Erickson 2004). The five-year survival rate among these patients following resection is 15 to 20 per cent (Erickson 2004).

The American Joint Committee on Cancer (AJCC) staging of pancreatic neoplasia is presented in **Appendix F**. Management of pancreatic neoplasia is described in **Appendix G**. The most effective treatment for patients with early stage disease is surgical excision of the tumour. Adjuvant chemotherapy and radiotherapy with the aim of preventing recurrence may follow, but this is currently applied only in clinical trial settings. These postoperative treatments may confer a survival advantage through decreased local recurrence of disease. A Cochrane review was in progress (2005–2006) to assess the effect of chemotherapy, radiotherapy or chemoradiation on overall survival in people with pancreatic carcinoma (Yip et al 2000).

Management is directed at palliation of symptoms for patients whose pancreatic neoplasia is surgically unresectable. Jaundice may be relieved by biliary stent procedures or surgical biliary bypass. These treatments may be followed by chemotherapy, sometimes with radiotherapy, aimed to alleviate pain and prolong survival.

Management of advanced metastatic pancreatic neoplasia involves supportive care, chemotherapy and/or pain relieving procedures with the intention of improving the patient's quality of life.

The treatment of cystic pancreatic lesions is determined by the nature of the lesion. Pseudocysts (benign) and serous cystic neoplasms (with very low malignancy potential) are managed conservatively by observation and surveillance (Levy et al 2004). Resection may be required if symptoms or complications, such as compression of adjacent organs, occur.

The malignant potential of IPMT and MCN indicates that surgical resection is recommended in medically fit patients (Levy et al 2004). The surgical resection approach for patients with MCN may be influenced by diagnosis: cystadenomas may be managed using a conservative approach to resection; cystadenocarcinomas generally require a more aggressive resection (Partensky 2004). Following resection of IPMT, five-year survival rates of 77–100 per cent for non-invasive carcinoma and 43–80 per cent for invasive carcinoma have been reported (Conlon 2005). Following resection of mucinous cystadenomas, five-year survival rates of over 95 per cent have been reported (Levy et al 2004). Estimated five-year survival rates following resection for mucinous cystadenocarcinoma vary widely between studies—the lowest reported was 17 per cent (Levy et al 2004).

Initial treatment for patients with pancreatic endocrine neoplasms is aimed at addressing the clinical conditions caused by hormone overproduction. The management of these effects is balanced with the management of symptoms related to tumour bulk.

Overproduction of insulin causes hypoglycaemia in patients with insulinomas which is counteracted by pharmacological intervention. Gastric acid hypersecretion causes symptoms similar to common peptic ulcer disease in gastrinoma patients. Symptoms are managed using antisecretory medications such as proton pump inhibitors or $H_2$-blocking agents.

Surgical management is similar for different types of pancreatic endocrine neoplasms and is determined by tumour size, position and number of lesions (National Cancer Institute 2003b). Single tumours in the head of the pancreas can be enucleated. Surgery achieves cure in 90 per cent of patients with insulinomas (Radebold 2001). Surgery for localised disease in patients with gastrinomas leads to a complete cure without any recurrence in 20–25 per cent of cases (Nachimuthu 2002).

Chemotherapy may be used to treat symptoms resulting from tumour bulk or excess hormone production in patients whose conditions cannot be managed by surgery or other treatments.

# Biliary tract neoplasia

## Clinical need

Cancers of the gallbladder, intrahepatic or extrahepatic bile ducts can be collectively classified as biliary tract neoplasms. The current review concerns only neoplasms of the gallbladder and extrahepatic bile ducts. Gallbladder cancers are uncommon in the Australian population, but they are the fifth most common neoplasm of the GI tract in the USA (Murr 2005). More than 80 per cent of patients with gallbladder cancer have gallstones (Murr 2005) but there is no general agreement about whether this represents cause and effect or is a common risk factor. Carcinoma of the extrahepatic bile duct is also very rare. Possible predisposing factors for extrahepatic bile duct cancer include parasitic infections, sclerosing cholangitis and chronic ulcerative colitis (Harrison 2005).

Most malignant tumours of the gallbladder are adenocarcinomas. Squamous cell carcinoma, cystadenocarcinoma and adenoacanthoma also occur. Papillomas, adenomyomas, cystadenomas and cholesterol polyps occur as benign gallbladder tumours. Other types of gallbladder polyps include adenomas, adenomyomatous and malignant polyps. Larger polyps carry higher risk of becoming malignant. At present, there is no imaging test that can differentiate neoplastic and non-neoplastic gallbladder polyps.

Most extrahepatic bile duct carcinomas are adenocarcinomas. Extrahepatic bile duct tumours include papillomas, adenomas and cystadenomas, but these are all very rare. The term cholangiocarcinoma can be applied to define any primary neoplasm—intrahepatic, perihilar and distal extrahepatic—in the bile ducts. Cholangiocarcinoma was originally applied only to primary tumours of intrahepatic bile ducts.

### Incidence and mortality

In 2001, there were 594 reported cases of cancer of the gallbladder and other and unspecified parts of the biliary tract (including extrahepatic bile ducts) in Australia[1] (AIHW and AACR 2004). Of these, 261 occurred in men, and 333 were detected in women. Australian age-standardised rates were 3.0/100,000; and 3.1/100,000 in men and women, respectively (AIHW and AACR 2004). The overall Australian age-standardised rate of biliary tract neoplasia in 2001 was 3.1/100,000, with 1.5/100,000 cases accounted for by gallbladder cancer (AIHW 2005a). The remaining 1.6/100,000 cases were accounted for by other and unspecified parts of the biliary tract (AIHW 2005a). Separate incidence data were not reported for extrahepatic bile ducts.

Application of the overall rate of biliary tract neoplasia to the Australian population in 2005 gives an estimate of 632 cases of biliary tract neoplasia (projected Australian 2005 population of 20,375,000 [Australian Bureau of Statistics 2005]).

---

[1] Australian incidence data for gallbladder is described by *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (ICD-10) codes C23–C24 (AIHW and AACR 2004). According to the ICD-10 classification, code C23 is 'malignant neoplasm of gallbladder' and code C24 is 'other and unspecified parts of the biliary tract' (World Health Organization 2003). Code C24 covers 'extrahepatic bile ducts' (C24.0), 'ampulla of Vater' (C24.1), 'overlapping lesion of biliary tract' (C24.8) and 'biliary tract, unspecified' (C24.9). Code C24 excludes 'intrahepatic bile duct' (C22.1).

The prognosis for patients with cancer of the gallbladder or extrahepatic bile ducts is poor. In 2001, there were 351 deaths caused by biliary tract cancer in Australia, 144 in men and 207 in women (AIHW and AACR 2004). This equates to an age-standardised mortality for Australia of 1.7/100,000 for men and 1.9/100,000 for women. During the period 1994–2000, the five-year relative survival of patients with gallbladder cancer in NSW was 18.8 per cent (Yu et al 2003). Five-year survival rates of up to 40 per cent have been reported after complete resection of distal cholangiocarcinoma of the extrahepatic biliary tract (Fong et al 2001).

In 2002–2003, there were 455 non-same-day and 48 same-day hospital separations for malignant gallbladder neoplasms, equating to a total of 4555 patient-days (Australian Institute of Health and Welfare [AIHW] 2005b). For malignant neoplasms of other parts of the biliary tract, there were 479 non-same-day and 126 same-day hospital separations, equating to a total of 6,011 patient-days. For malignant neoplasms of the ampulla of Vater, there were 210 non-same-day and 68 same-day hospital separations, equating to a total of 2,863 patient-days.

### Eligible population

The estimated number of patients who would receive EUS to diagnose non-gallbladder extrahepatic biliary tract neoplasms was based on the assumption that all patients with suspected cancer, without CT-identified metastases, would undergo EUS.

The percentage of patients with distant metastases who would be excluded by CT (and not considered for EUS) can be estimated using the percentage of patients with distant spread of disease. In a review by Malka et al (2002), more than 95 per cent of biliary tract neoplasms were found to be adenocarcinomas, and of these, between 10 and 20 per cent had distant metastases. Therefore, these biliary tract cancer patients would not be considered for EUS. Based on 2001 Australian incidence, this approximates to between 0.16 and 0.32/100,000 patients, resulting in 1.28–1.44/100,000 patients eligible for EUS.

Because many patient referrals for EUS are due to suspicion of malignancy, it is expected that the number of patients who may be considered for EUS would be greater than 1.28–1.44/100,000. Rosch et al (2002b) conducted a study of EUS accuracy to diagnose pancreaticobiliary cancer which found that approximately 52 per cent of patients who were suspected of cancer had these diagnoses confirmed. This suggests that 1.28–1.44/100,000 patients (Australian incidence for 2001) would account for 52 per cent of potential EUS use for biliary tract cancer diagnosis. The number of patients who would potentially receive EUS to diagnose biliary tract cancer is estimated to be 1.28–1.44/0.52 per 100,000 = 2.46–2.77/100,000 patients per year. Using the current estimate of Australia's population of approximately 20,375,000 (Australian Bureau of Statistics 2005) and incidence data for 2001, the estimated use of EUS to diagnose biliary tract cancer is 501–564 patients per year.

## Current treatment

Cancers that arise in either the gallbladder or extrahepatic bile duct (biliary tract cancers) are uncommon. Typical presenting symptoms of these conditions are right upper quadrant abdominal pain and obstructive jaundice. Complete surgical resection remains the only means of cure for biliary tract cancer. Gallbladder tumours discovered incidentally have a reported cure rate of more than 80 per cent (National Cancer Institute 2003a). The management of biliary tract cancer is described in **Appendix G**.

Patients whose gallbladders are removed for other reasons, such as cholecystectomy for benign gallbladder disease, sometimes have tumours that are discovered incidentally. These cancers are often cured without further treatment. If it is suspected that cancer has spread beyond the mucosa of the gallbladder, it may be necessary to perform a follow up operation to resect adjacent liver, bile duct and local lymph nodes. Patients with symptoms suggestive of gallbladder cancer before surgery are usually found to have disease that has penetrated beyond the mucosa, with potential for cure in fewer than 5 per cent of patients (National Cancer Institute 2003a).

Patients who have gallbladder cancer that is unresectable cannot be cured and treatment is palliative. If symptoms (pruritus, hepatic dysfunction, and cholangitis) indicate a biliary blockage, treatment such as biliary bypass surgery can relieve obstruction. External-beam radiation therapy may also be used to relieve biliary obstruction and can supplement bypass procedures. Palliative chemotherapy is an option for some patients.

Surgery is not indicated for most patients with extrahepatic bile duct cancer. Fewer than 10 per cent of all diagnoses of extrahepatic bile duct cancer are curable by surgery (National Cancer Institute 2004a). Complete resection may be possible for patients whose disease is localised, but this occurs in a minority of occasions. Resection is more likely when the tumour is located in an accessible anatomical location and lesions are confined to the distal common bile duct (National Cancer Institute 2004a). Patients are advised that surgeries for bile duct cancer are usually extensive and have high operative mortality (5–10%) and a low cure rate (National Cancer Institute 2004a). Surgical resection may be used in conjunction with external beam radiation.

When extrahepatic bile duct cancer is non-resectable, patients cannot be cured and treatment is palliative. The aim of treatment is to relieve bile duct obstruction, which can cause symptoms that outweigh other cancer symptoms. Surgical palliation can be achieved by anastomosing the bile duct to the bowel or by inserting bile duct stents. Some patients may benefit from palliative radiation therapy.

## Potential impact of the test

Endoscopic ultrasound has a potential positive impact on health outcomes (including quality of life) of patients by increasing diagnostic accuracy and staging of gastrointestinal (GI) neoplasms. It also has potential to reduce the number of patients undergoing further diagnostic procedures.

Increased diagnostic accuracy potentially leads to earlier confirmation of diagnoses, which enhances likelihood of GI malignancy cures. This potential advantage is particularly important in diagnosing pancreaticobiliary malignancies, since confirming diagnosis is clinically challenging, and these cancers are associated with poor prognoses. EUS may provide a benefit over CT in the earlier detection of pancreatic neoplasia, particularly in small lesions. This potentially increases the proportion of patients eligible for curative treatment and possibly increases survival. In particular, EUS-guided FNA may be useful to confirm presumptive diagnoses of neoplastic lesions. Accurate diagnosis of benign pathology may result in the avoidance of invasive surgical procedures.

The application of EUS to stage identified neoplasms has an important potential positive impact on the management of patients with gastrointestinal malignancies. Increased accuracy of staging and resectability may contribute to a reduction in the number of

unnecessary surgical procedures performed for patients with advanced disease. Enhanced staging accuracy offers benefits in terms of patient quality of life and in economic benefits. As further advancements in neoadjuvant therapies are made, increased staging accuracy may amplify appropriate selection of patients for neoadjuvant therapies. This may have a potential positive impact on the likelihood of cure in patients diagnosed at an appropriate stage.

## Marketing status of the device/technology

EUS components are available from Phillips, Hitachi, Olympus and Aloca, which manufacture processors; and Pentax and Olympus that build endoscopes. These manufacturers offer a range of devices that enable radial, linear and curvilinear endosonography and fine needle aspiration (FNA) biopsy to be performed.

Pentax FG-32UA ultrasound endoscopes (radial and linear) are registered with the Therapeutic Goods Administration (TGA). The Australian Registry of Therapeutic Goods (ARTG) listing number is Aust L 13212. Hitachi ultrasound diagnostic scanners (various models) are also registered with the TGA (ARTG listing number Aust L 81013). Olympus endoscopic ultrasound equipment (various products) is listed with the TGA (ARTG listing number AUST L 71621). Toshiba and Hitachi endoscopic ultrasound products are not currently listed with the TGA; both manufacturers have general ultrasound equipment listed (Aust L 18113 and Aust L 81013, respectively).

EUS is listed with the US Food and Drug Administration (FDA) as a Class 2 medical device. The FDA-approved use is for diagnostic ultrasound imaging or fluid flow analysis of the human body, including: gastrointestinal tract, biliary, pancreatic duct and surrounding organs, intraluminal ultrasound for upper airways and tracheobronchial tree, urinary tract and female reproductive tract. EUS is currently reimbursed for the diagnosis/management/staging of oesophageal, gastric, pancreatic, biliary, and ampullary neoplasms by a number of private providers in the USA.

## Current reimbursement arrangement

EUS is not currently funded under the Medicare Benefits Schedule in Australia.

# Approach to assessment

## Management and health outcomes

Due to the large body of evidence, a separate search for management and health outcomes studies was conducted. This search was limited by outcomes and was combined with the diagnostic accuracy studies search.

### Assessment framework

A systematic review of the medical literature was undertaken to identify relevant studies concerning the value of EUS on management and health outcomes. Direct evidence about the impact of EUS on health outcomes was sought. In the absence of trials providing direct evidence, confirmation of the impact of EUS on clinical management and diagnostic accuracy was assessed. This indirect evidence was then combined with the evidence for treatment effectiveness to assess the impact of EUS on health outcomes.

### Review of the literature

The medical literature was searched to identify all relevant studies and reviews published up to 2005. Searches were conducted in the primary databases indicated in **Table 5**.

#### Search strategy

**Primary databases**

**Table 5 Electronic databases searched: use of EUS to evaluate management and health outcomes**

| Database | Period covered/date searched |
|---|---|
| Medline | 1966 to May, week 1, 2005 |
| EMBASE | 1980 to 2005, week 20 |
| PreMedline | To 13 May 2005 |
| Cochrane Library | Issue 3, 2005 (4 August 2005) |

The search terms included the following (as determined from the PPICO [target population, prior tests, index test, comparator, outcomes] criteria):

- endosonography, endoscopic ultrasound, echoendoscopy, interventional ultrasound
- decision-making, disease management, management plan, management change, survival, survival analysis, mortality, death, fatal outcome and prognosis.

Complete details of the literature searches performed within the Medline and EMBASE databases are presented in **Appendix D**.

**Secondary databases**

Searches of the following secondary databases/sites were also performed.

- American Society of Clinical Oncology (ASCO)

- British Columbia Office of Health Technology Assessment
- Canadian Coordinating Office for Health Technology Assessment (CCOHTA)
- Centre for Health Economics (Monash University, Australia)
- Current Controlled Trials metaRegister and ISRTCN Register
- Danish Centre for Evaluation and Health Technology Assessment (DACEHTA)
- Health Economics Research Group (Brunel University, UK)
- Health Information Research Unit (HIRU) internal database (McMaster University, Canada)
- National Health and Medical Research Council Australia (publication list)
- National Health Service (UK)
- NHS Centre for Reviews and Dissemination
- National Cancer Control Initiative (NCCI)
- National Information Center on Health Services Research and Health Care Technology (HSTAT database) (USA)
- Scottish Intercollegiate Guideline Network (SIGN)
- Swedish Council on Technology Assessment in Health Care (SBU)
- Blue Cross and Blue Shield Association (Technology Evaluation Center).

Advice from Australian experts regarding identification of unpublished relevant research was also sought. Additional searches were conducted to source epidemiological and economic information, as required.

### Selection criteria

Selection criteria for studies evaluating the impact of EUS on management and health outcomes are described below for each indication.

### Search results

Due to a high degree of overlap, the results from the management and health outcomes searches were pooled with the searches for studies on diagnostic accuracy of oesophageal and gastric neoplasia. Following deletion of duplicate references, 827 citations were retrieved.[2] Of these, 21 citations specifically relating to pancreatic or biliary indications were identified and transferred to the pancreatic and biliary search results.

[2] An additional study was in press at the time the literature search was undertaken. This study (Chong et al 2005) was recommended by a member of the advisory panel and has since been published.

To identify additional papers included, studies from the management and health outcomes search were used in a citation search using the Science Citation Index (SCI®).

The Quality of Reporting of Meta-analyses (QUOROM) flowcharts in **Figure 2** and **Figure 6** summarise the exclusion of studies from the safety and effectiveness review of EUS for oesophageal or gastric neoplasms and pancreatic or biliary neoplasms, respectively.

# Oesophageal neoplasia

## Research question

The PPICO criteria developed *a priori* for this application of endoscopic ultrasound (EUS) are given in **Table 6**.

**Table 6 PPICO criteria for EUS use in oesophageal neoplasia**

| Population | Prior tests | Index test | Comparator | Outcomes |
|---|---|---|---|---|
| Patients with an oesophageal tumour identified by prior imaging or endoscopy | Upper endoscopy<br>Computed tomography<br>Positron emission tomography | Endoscopic ultrasound for staging (± fine needle aspiration) | Current clinical practice in the absence of EUS | Change in clinical outcomes<br>Change in clinical management<br>Diagnostic accuracy |

Abbreviation: PPICO, target population, prior tests, index test, comparator, outcomes; EUS, endoscopic ultrasound

The research question for this indication, based on these criteria, is as follows.

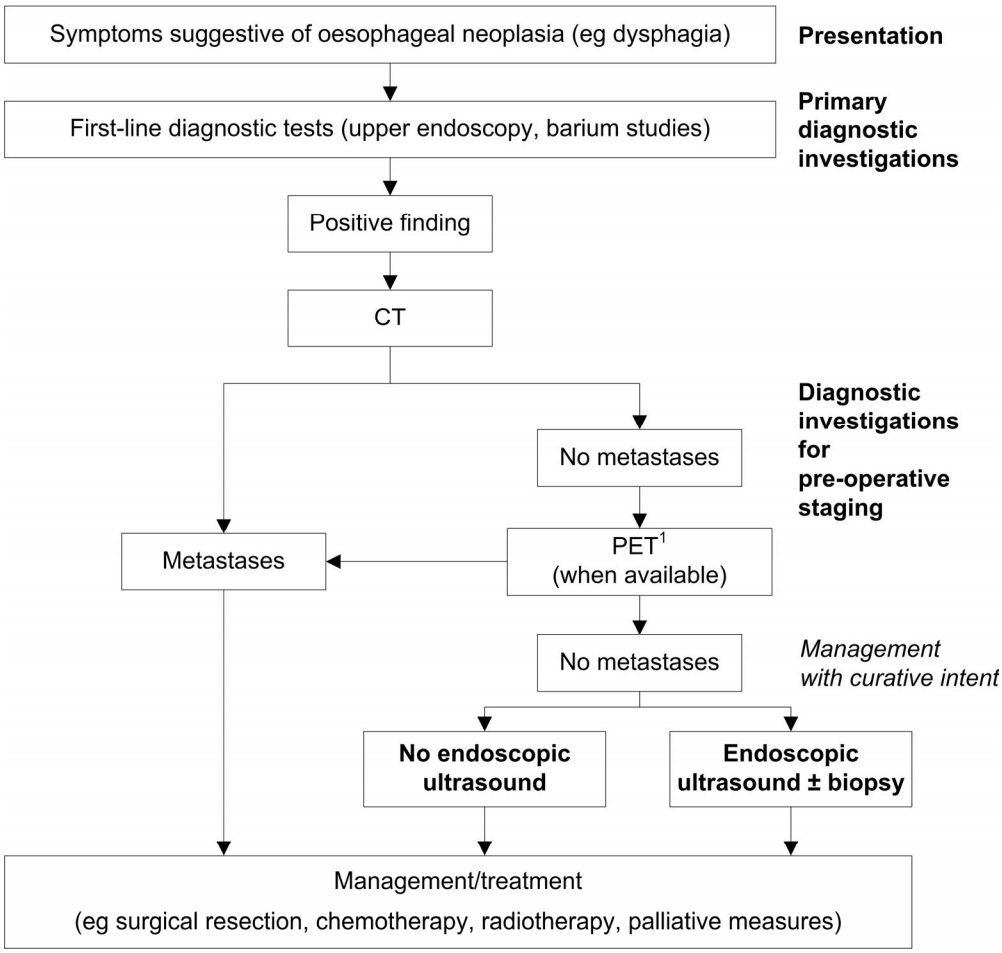
What additional benefit, in terms of:

- safety
- effectiveness (including staging performance and the impact of staging on changes in clinical management and changes in clinical outcomes), and
- cost-effectiveness

does EUS provide in the pre-operative staging of patients with oesophageal tumours (but having no evidence of metastases), over and above the current clinical practice of using upper endoscopy, computed tomography (CT) and positron emission tomography (PET) (when available)?

## Clinical pathway

The upstream clinical pathway for the evaluation of patients with suspected oesophageal neoplasia is shown in **Figure 1.** This flowchart presents the proposed pathway for EUS in the staging of oesophageal neoplasms, together with current clinical practice to the point of patient diagnosis. The pathway depicting current practice represents management, which is accepted as appropriate practice for the majority of patients in Australia. Following staging, patient management follows the flowchart depicted in **Figure 18 (Appendix G)**, and is dependent on the diagnosed stage of disease.




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

[1] The use of PET in the clinical pathway is based on the opinion of the clinical experts on the Advisory Panel and does not imply endorsement by MSAC of the technology, which is currently under review.

**Figure 1 Upstream clinical pathway to evaluate patients with suspected oesophageal neoplasia**

## Assessment framework

A systematic review of the medical literature was undertaken to identify relevant studies of the value of EUS in the staging of oesophageal neoplasia. Direct evidence regarding the impact of EUS on health outcomes was sought. In the absence of trials providing direct evidence, evidence regarding the impact of EUS on clinical management and diagnostic accuracy was assessed. This indirect evidence was then combined with the evidence for treatment effectiveness to assess the impact of EUS on health outcomes.

## Review of the literature

The medical literature was searched to identify all relevant studies and reviews published up to 2005. Searches were conducted in the primary databases indicated in **Table 7**.

### Search strategy

#### Primary databases

**Table 7 Electronic databases searched: use of EUS to evaluate oesophageal neoplasms**

| Database | Period covered/date searched |
|---|---|
| Medline | 1966 to February, week 3, 2005 |
| EMBASE | 1980 to 2005, week 9 |
| PreMedline | To 28 February 2005 |
| Cochrane Library | Issue 3, 2005 (4 August 2005) |

The search terms included the following (as determined from the PPICO criteria):

- endosonography, endoscopic ultrasound, echoendoscopy, interventional ultrasound
- oesophageal neoplasms, oesophageal cancer, oesophageal tumour, oesophageal adenocarcinoma, oesophageal carcinoma
- computed tomography, CT, CAT scan, PET, positron emission tomography.

Complete details of the literature searches performed within the Medline and EMBASE databases are presented in **Appendix D**.

#### Secondary databases

Searches of the secondary databases/sites listed on page 27 were also performed.

Additional searches were conducted to source epidemiological and economic information, as required.

## Selection criteria

**Table 8 Selection criteria for included studies—oesophageal neoplasia staging**

**Research question**: What additional benefit, in terms of safety, effectiveness and cost-effectiveness, does EUS ± FNA provide in the pre-operative staging of patients with oesophageal tumours (but no evidence of metastases), over and above the current clinical practice of using upper endoscopy, CT and PET (when available)?

| Selection criteria | Inclusion | Exclusion |
|---|---|---|
| **Study design** | | |
| All studies | Studies with ≥ 10 patients receiving EUS[a] | Non-systematic reviews, letters and opinion pieces, non-human or *in vitro* studies |
| Health outcomes studies | Studies comparing health outcomes with and without the use of EUS | |
| Accuracy studies | Studies investigating combined value of EUS and CT and/or PET, or replacement value with individual patient data | Trials reporting replacement value of CT and EUS without individual patient data |
| Management studies | Pre-test, post-test management studies | |
| **Population** | Patients in whom an oesophageal tumour has been identified by prior diagnostic tests | Patient population of mixed GI indications with inadequate data separation |
| **Prior tests** | Not specified for inclusion or exclusion criteria | |
| **Index test** | Use of EUS ± FNA for staging of oesophageal neoplasia as currently approved by the TGA | Intraductal ultrasound; catheter or mini-probes; intra-operative endosonography |
| **Comparator** | | |
| Health outcomes studies | Clinical practice in the absence of EUS | |
| Accuracy studies | Current clinical practice of using CT and/or PET in the absence of EUS | |
| Management studies | Pre-test management plan | |
| **Reference standard** | | |
| Accuracy studies | Histopathology<br>Surgical staging | Reference standard not available for all patients |
| **Outcomes** | | |
| Health outcomes studies | Effect on health outcomes | Inadequate data reporting |
| Accuracy studies | Diagnostic performance | |
| Management studies | Effect on clinical management | |

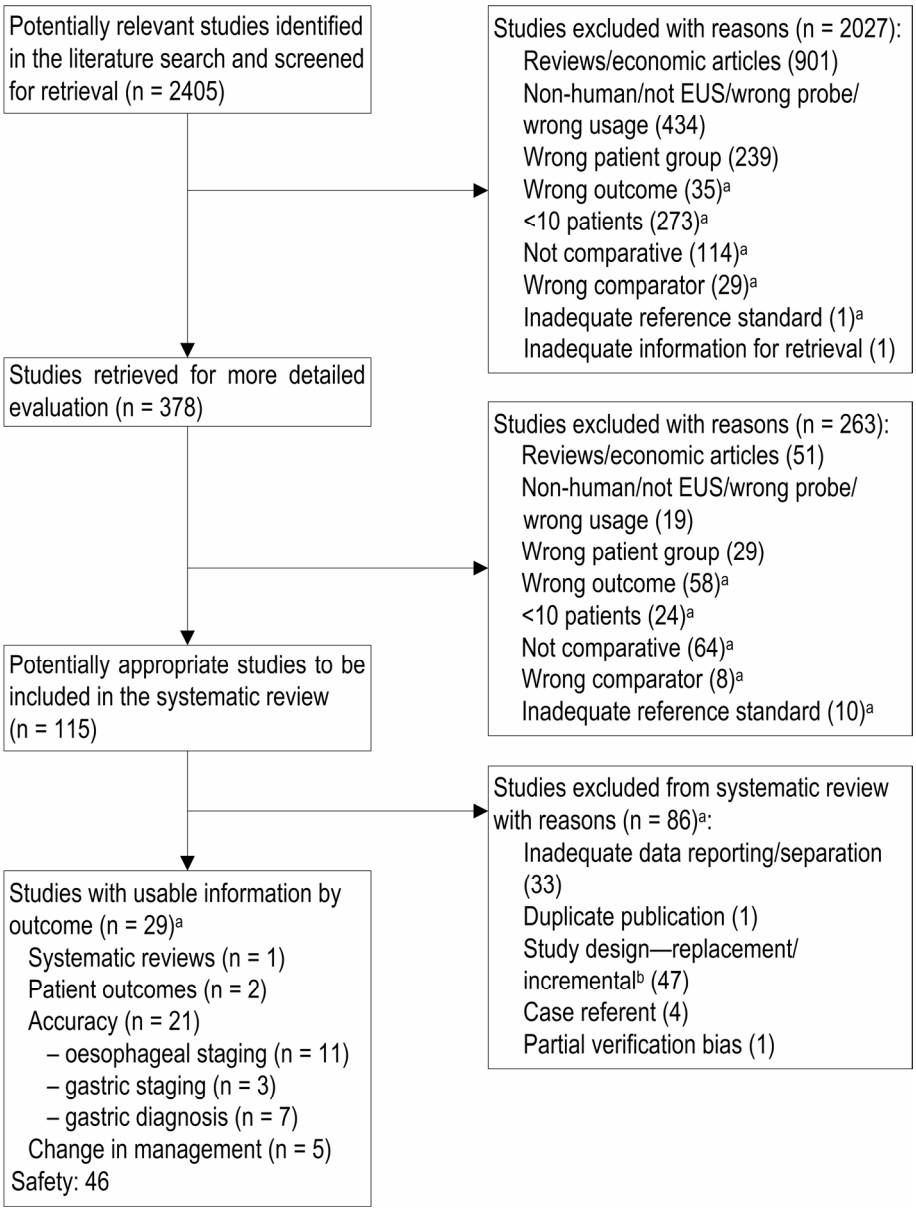
Abbreviations: CT, computerised tomography; EUS, endoscopic ultrasound; FNA, fine needle aspiration; GI, gastrointestinal; PET, positron emission tomography; TGA, Therapeutic Goods Administration

[a] Studies with < 10 patients were included in the assessment of adverse event and safety data

## Search results

The results from the gastric, oesophageal, and management and health outcomes searches were pooled due to a high degree of overlap. There were 21 citations specifically relating to pancreatic or biliary indications identified in the management and health outcomes search that were transferred to the pancreatic and biliary search results. A total of 2,405 non-duplicate citations remained.

The QUOROM flowchart in **Figure 2** summarises the exclusion of studies from the safety and effectiveness review of EUS for oesophageal and gastric neoplasms. A total of 2,405 references were identified by the search, of which 731 were reviewed for safety data, and 29 were included in the effectiveness review.




Abbreviation: EUS, endoscopic ultrasound
Adapted from Moher et al (1999)
[a] Studies reviewed for safety data (219 reviewed in full, 512 reviewed abstracts)
[b] Replacement studies compare the diagnostic accuracy of the comparator test with the index test, while the included incremental studies compare the comparator test alone with the index test combined with the comparator test.

**Figure 2 QUOROM flowchart used to identify and select studies from the literature review of oesophageal and gastric neoplasms**

For safety, and due to the large number of studies identified, studies of fewer than 10 patients and non-comparative studies or studies against inappropriate comparators were reviewed initially in abstract form only. If safety data were reported, the publication was retrieved and reviewed in full. Studies published in a language other than English were not reviewed for safety data.

# Gastric neoplasia

## Research question

The PPICO criteria developed *a priori* for this diagnostic application of EUS are given in **Table 9**.

**Table 9 PPICO criteria for EUS use in gastric neoplasia**

| Population | Prior tests | Index test | Comparator | Outcomes |
|---|---|---|---|---|
| Patients with diagnosed gastric cancer | Gastroscopy plus biopsy<br>Computed tomography<br>Positron emission tomography | EUS for staging | Current clinical practice in the absence of EUS | Change in clinical outcomes<br>Change in clinical management<br>Diagnostic accuracy |
| Patients with gastric submucosal tumour identified by prior imaging or endoscopy | Gastroscopy | Endoscopic ultrasound for diagnosis (± fine needle aspiration) | | |

Abbreviations: PPICO, target population, prior tests, index test, comparator, outcomes; EUS, endoscopic ultrasound

The research questions for this indication, based on these criteria, are as follows.

1. What additional benefit, in terms of:

- safety
- effectiveness (including staging performance and the impact of staging on changes in clinical management and changes in clinical outcomes), and
- cost-effectiveness

does EUS provide in the pre-operative staging of patients with gastric malignant tumours (but no evidence of metastases), over and above the current clinical practice of using upper endoscopy, CT and PET (when available)?

2. To what extent is EUS:

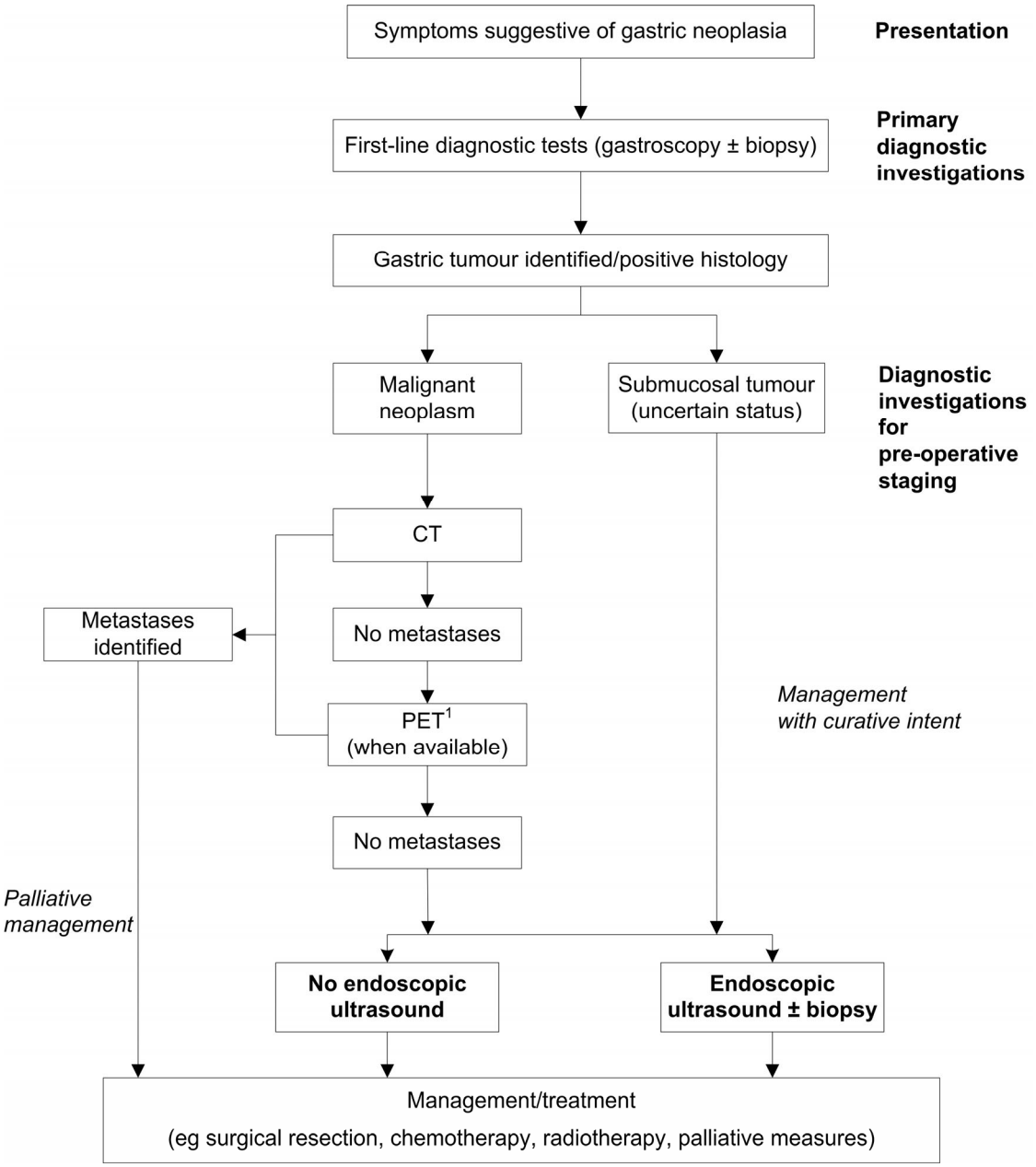
- effective (including diagnostic/staging performance and the impact of diagnosis/staging on changes in clinical management and changes in clinical outcomes)
- safe, and

- cost-effective

in the diagnosis and/or staging of gastric submucosal tumours in patients with symptoms associated with gastric neoplasia, over and above the current clinical practice of using upper endoscopy.

## Clinical pathway

The upstream clinical pathway for the evaluation of patients with suspected gastric neoplasia or gastric submucosal tumour is shown in **Figure 3**. This flowchart indicates the proposed pathway for EUS in the diagnosis and/or staging of gastric neoplasms, together with current clinical practice. The pathway depicting current practice represents management that is accepted as appropriate practice for the majority of patients in Australia. The clinical management pathway is displayed to the point of patient diagnosis and/or staging. Following staging, patient management follows the flowchart depicted in **Figure 19 (Appendix G)**, and is dependent on the diagnosed stage of disease.




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

[1] The use of PET in the clinical pathway is based on the opinion of the clinical experts on the Advisory Panel and does not imply endorsement by MSAC of the technology, which is currently under review.

**Figure 3 Upstream clinical pathway to evaluate patients with suspected gastric neoplasia**

## Assessment framework

A systematic review of the medical literature was undertaken to identify relevant studies and reviews of the value of EUS in the diagnosis and staging of gastric neoplasia. Direct evidence regarding the impact of EUS on health outcomes was sought. In the absence of trials providing direct evidence, evidence regarding the impact of EUS on clinical management and diagnostic accuracy was assessed. This indirect evidence was then combined with the evidence for treatment effectiveness to assess the impact of EUS on health outcomes.

## Review of the literature

The medical literature was searched to identify all relevant studies and reviews published up to 2005. Searches were conducted in the primary databases indicated in **Table 10**.

### Search strategy

#### Primary databases

**Table 10 Electronic databases searched: use of EUS to evaluate gastric neoplasms**

| Database | Period covered/date searched |
|---|---|
| Medline | 1966 to February, week 3, 2005 |
| EMBASE | 1980 to 2005, week 09 |
| PreMedline | To 28 February 2005 |
| Cochrane Library | Issue 3, 2005 (4 August 2005) |

The search terms included the following (as determined from the PPICO criteria):

- endosonography, endoscopic ultrasound, echoendoscopy, interventional ultrasound
- stomach neoplasms, stomach cancer, stomach carcinoma, stomach tumour, gastric cancer, gastric carcinoma, gastric neoplasm, gastric tumour, gastric adenoma, gastric carcinoid, gastric polyp, cardia cancer, cardia carcinoma, cardia neoplasm, cardia tumour, cardio oesophageal cancer, cardio oesophageal neoplasm, cardio oesophageal tumour, gastric cardia.

Complete details of the literature searches performed within the Medline and EMBASE databases are presented in **Appendix D**.

#### Secondary databases

Searches of the secondary databases/sites listed on page 27 were also performed.

Additional searches were conducted to source epidemiological and economic information, as required.

## Selection criteria

**Table 11 Selection criteria for included studies—gastric neoplasia staging**

**Research question**: What additional benefit, in terms of safety, effectiveness and cost-effectiveness, does EUS ± FNA provide in the staging of patients with gastric tumours (but no evidence of metastases), over and above the current clinical practice of using upper endoscopy, CT and PET (when available)?

| Selection criteria | Inclusion | Exclusion |
|---|---|---|
| **Study design** | | |
| All studies | Studies with ≥ 10 patients receiving EUS and comparator[a] | Non-systematic reviews, letters and opinion pieces, non-human or *in vitro* studies |
| Health outcomes studies | Studies comparing health outcomes with and without the use of EUS | |
| Accuracy studies | Studies investigating combined value of EUS and CT and/or PET, or replacement value with individual patient data<br>Level II studies (NHMRC criteria) reporting replacement value of EUS and comparator without individual patient data | Replacement studies of EUS against CT of level III or lower (NHMRC criteria) |
| Management studies | Pre-test, post-test management studies | |
| **Population** | Patients in whom a gastric tumour has been identified by prior diagnostic tests | Patient population of mixed GI indications with inadequate data separation |
| **Prior tests** | Not specified for inclusion or exclusion criteria | |
| **Index test** | Use of EUS ± FNA for staging of gastric neoplasia as currently approved by the TGA | Intraductal ultrasound; catheter or mini-probes; intra-operative endosonography |
| **Comparator** | | |
| Health outcomes studies | Clinical practice in the absence of EUS | |
| Accuracy studies | Current clinical practice of using CT in the absence of EUS | |
| Management studies | Pre-test management plan | |
| **Reference standard** | | |
| Accuracy studies | Histopathology<br>Surgical staging | Reference standard not available for all patients |
| **Outcomes** | | |
| Health outcomes studies | Effect on health outcomes | Inadequate data reporting |
| Accuracy studies | Diagnostic performance | |
| Management studies | Effect on clinical management | |

Abbreviations: CT, computerised tomography; EUS, endoscopic ultrasound; FNA, fine needle aspiration; NHMRC, National Health and Medical Research Council; PET, positron emission tomography; TGA, Therapeutic Goods Administration

[a] Studies with < 10 patients were included in the assessment of adverse event and safety data

**Table 12 Selection criteria for included studies—gastric submucosal tumour diagnosis**

| **Research question**: What benefit, in terms of safety, effectiveness and cost-effectiveness, does EUS ± FNA provide in the diagnosis and/or staging of patients with submucosal tumours, additional to the current clinical practice? | | |
|---|---|---|
| **Selection criteria** | **Inclusion** | **Exclusion** |
| **Study design** | | |
| All studies | Studies with ≥ 10 patients receiving EUS[a] | Non-systematic reviews, letters and opinion pieces, non-human or *in vitro* studies |
| Health outcomes studies | Studies comparing health outcomes with and without the use of EUS | |
| Accuracy studies | Studies investigating incremental value or replacement value with individual patient data | |
| | Single arm studies of EUS ± FNA | |
| Management studies | Pre-test post-test management studies | |
| **Population** | Patients in whom a gastric submucosal tumour has been identified by prior diagnostic tests | Case referent studies |
| | | Patient population of mixed GI indications with inadequate data separation |
| **Prior tests** | Not specified for inclusion or exclusion criteria | |
| **Index test** | Use of EUS ± FNA to diagnose gastric submucosal tumours as currently approved by the TGA | Intraductal ultrasound; catheter or mini-probes; intra-operative endosonography |
| **Comparator** | | |
| Health outcomes studies | Clinical practice in the absence of EUS | |
| | Not applicable for single arm studies | |
| Accuracy | Not specified for inclusion or exclusion criteria | |
| Management studies | Pre-test management plan | |
| **Reference standard** | | |
| Accuracy studies | Histology | Reference standard not available for all patients |
| | Clinical follow up | |
| | | Cytology |
| **Outcomes** | | |
| Health outcomes studies | Effect on health outcomes | Inadequate data reporting |
| Accuracy studies | Diagnostic performance | |
| Management studies | Effect on clinical management | |

Abbreviations: EUS, endoscopic ultrasound; FNA, fine needle aspiration; TGA, Therapeutic Goods Administration
[a] Studies with < 10 patients were included in the assessment of adverse event and safety data

### Search results

Due to a high degree of overlap between the gastric and oesophageal neoplasia searches, the results of the literature searches were pooled. These results are displayed in the QUOROM flowchart in **Figure 2**.

# Pancreatic neoplasia

## Research question

The PPICO criteria developed *a priori* for this application of EUS are given in **Table 13**.

**Table 13 PPICO criteria for use of EUS in pancreatic neoplasia**

| Population | Prior tests | Index test | Comparator | Outcomes |
|---|---|---|---|---|
| Patients in whom a solid pancreatic mass has been identified by prior diagnostic tests | Clinical examination<br>Serological testing<br>Abdominal ultrasound<br>Computed tomography (CT) | EUS for diagnosis (± fine needle aspiration) | CT-guided biopsy<br>Current clinical practice in the absence of EUS[a] | Change in clinical outcomes<br>Change in clinical management<br>Diagnostic accuracy |
| Patients in whom a pancreatic cystic lesion has been identified by prior diagnostic tests | | | Current clinical practice in the absence of EUS | |
| Patients with symptoms and biochemical evidence (CA 19-9) associated with pancreatic neoplasia, but negative prior imaging | | | Current clinical practice in the absence of EUS | |
| Patients with symptoms and biochemical evidence (neuroendocrine abnormalities) associated with pancreatic neoplasia, but negative prior imaging | | | Octreotide nuclear medicine scan | |
| Patients with diagnoses of pancreatic neoplasia | | EUS for staging | Current clinical practice in the absence of EUS | |

Abbreviations: PPICO, target population, prior tests, index test, comparator, outcomes; CA, carbohydrate antigen; CT, computed tomography; EUS, endoscopic ultrasound

[a]This comparator was determined as appropriate by the AP following the commencement of the review

The research questions for this indication, based on these criteria, are as follows.

1. To what extent is EUS with or without fine needle aspiration (following abdominal ultrasound and CT):

- safe
- effective (including diagnostic performance and the impact of diagnosis on changes in clinical management and changes in clinical outcomes), and
- cost-effective

in diagnosis of pancreatic neoplasms in patients in whom a solid pancreatic mass has been identified by prior diagnostic tests (without any evidence of metastases), relative to CT-guided biopsy, or over and above the current clinical practice of using abdominal ultrasound and CT?

2. What additional benefit, in terms of:

- safety
- effectiveness (including diagnostic performance and the impact of diagnosis on changes in clinical management and changes in clinical outcomes), and
- cost-effectiveness

does EUS with or without fine needle aspiration provide in the diagnosis of pancreatic neoplasms in patients in whom a cystic lesion has been identified, over and above the current clinical practice of using abdominal ultrasound and CT (without any evidence of metastases)?

3. To what extent is EUS with or without fine needle aspiration:

- safe
- effective (including diagnostic performance and the impact of diagnosis on changes in clinical management and changes in clinical outcomes), and
- cost-effective

in the diagnosis of pancreatic neoplasms in patients with symptoms and biochemical evidence (CA 19-9 or neuroendocrine abnormalities) associated with pancreatic neoplasia, when abdominal ultrasound and CT have failed to identify an abnormality, relative to octreotide nuclear medicine scanning (somatostatin receptor scintigraphy, for suspected endocrine neoplasia), or relative to current clinical practice in the absence of EUS (for suspected exocrine neoplasia)?

4. What additional benefit, in terms of:

- safety
- effectiveness (including staging performance and the impact of staging on changes in clinical management and changes in clinical outcomes), and
- cost-effectiveness

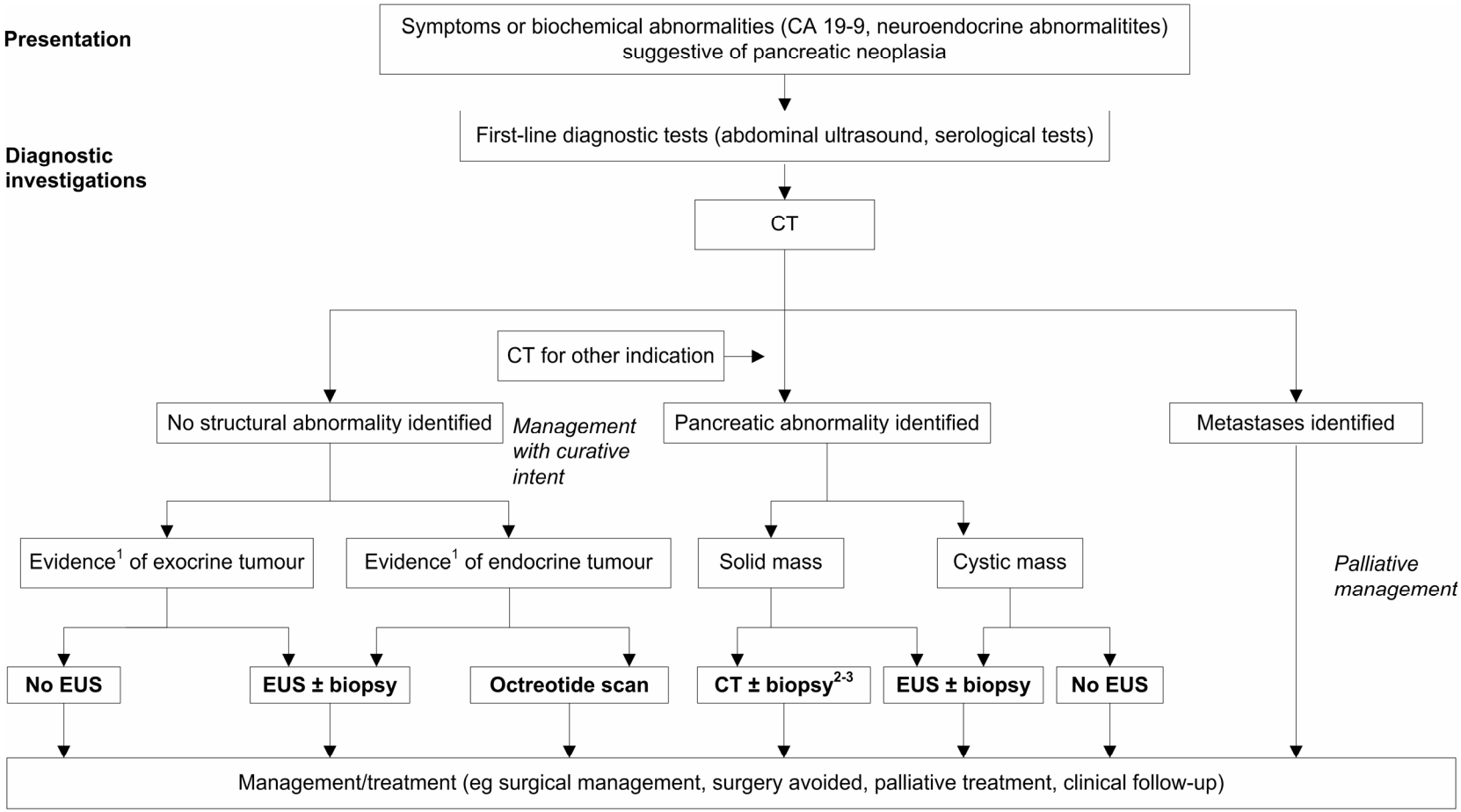
does EUS with or without fine needle aspiration provide in the pre-operative staging of pancreatic neoplasms (in patients with a malignant neoplasm identified by prior testing, but no evidence of metastases), over and above the current clinical practice of using clinical examination, serological testing, abdominal ultrasound and CT?

## Clinical pathway

The upstream clinical pathway for the evaluation of patients with suspected pancreatic neoplasia is shown in **Figure 4**. This displays the clinical management pathway to the point of patient diagnosis. The pathway depicting current practice represents management, which is accepted as appropriate practice for the majority of patients in Australia. Following diagnosis, patient management follows the flowchart depicted in **Figure 20 (Appendix G)**, and is dependent on the diagnosed stage of disease.

### Diagnosis

The flowchart in **Figure 4** indicates the proposed pathway for EUS in the diagnosis and/or staging of pancreatic neoplasms (including ampulla of Vater neoplasms) and pancreatic cysts, together with the pathway for the comparator.

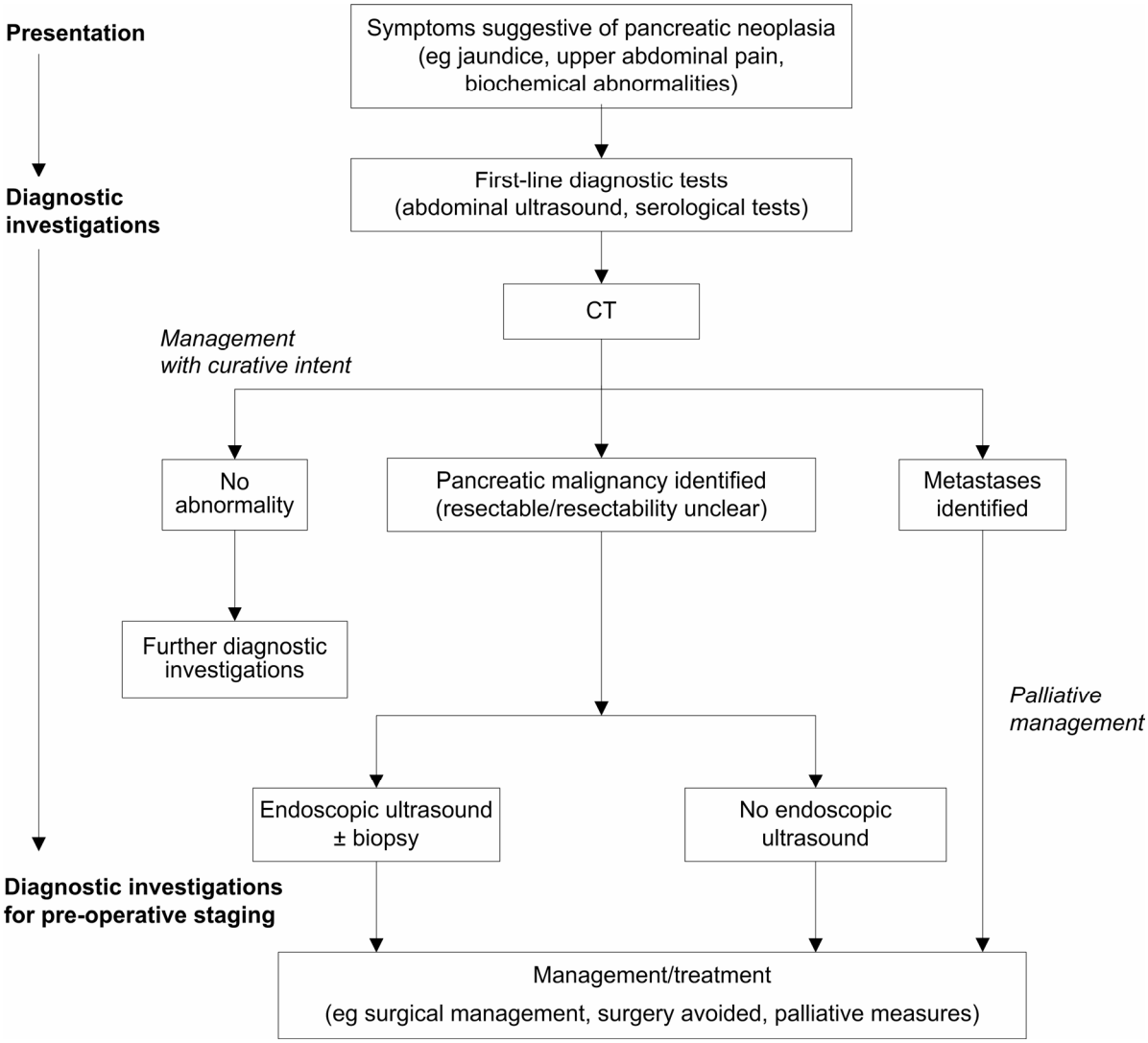



Abbreviations: CT, computed tomography; EUS, endoscopic ultrasound
[1] Symptoms or biochemical evidence
[2] CT-guided biopsy is not advised for small resectable tumours given the potential risk of peritoneal and cutaneous seeding of the cancer along the needle track (Takhar et al 2004)
[3] CT ± biopsy represents two comparators; CT-guided biopsy, or CT alone as initially performed following first-line diagnostic tests

**Figure 4 Upstream clinical pathway to evaluate patients with suspected pancreatic neoplasia**

### Staging

The flowchart in **Figure 5** indicates the proposed pathway for EUS in the staging of pancreatic neoplasms (including ampulla of Vater neoplasms), together with the pathway for the comparator.




Abbreviations: CT, computed tomography; EUS, endoscopic ultrasound

**Figure 5** **Upstream clinical pathway to stage disease progression in patients with pancreatic neoplasia**

## Assessment framework

A systematic review of the medical literature was undertaken to identify relevant studies and reviews of the value of EUS in the diagnosis and staging of pancreatic neoplasia. Direct evidence regarding the impact of EUS on health outcomes was sought. In the absence of trials providing direct evidence, evidence regarding the impact of EUS on clinical management and diagnostic accuracy was assessed. This indirect evidence was then combined with the evidence for treatment effectiveness to assess the impact of EUS on health outcomes.

## Review of the literature

The medical literature was searched to identify all relevant studies and reviews published up to 2005. Searches were conducted in the primary databases indicated in **Table 14**.

### Search strategy

#### Primary databases

**Table 14 Electronic databases searched: EUS evaluation of pancreatic neoplasms**

| Database | Period covered/date searched |
|---|---|
| Medline | 1966 to February, week 3, 2005 |
| | (Single arm EUS search: 1966 to May, week 2, 2005) |
| EMBASE | 1980 to 2005, week 9 |
| | (Single arm EUS search: 1980 to 2005, week 21) |
| PreMedline | To 24 May 2005 |
| Cochrane Library | Issue 3, 2005 (4 August 2005) |

The search terms included the following (as determined from the PPICO criteria):

- endosonography, endoscopic ultrasound, echoendoscopy, interventional ultrasound
- pancreatic neoplasms, pancreatic cyst, Vater's ampulla, insulinoma, pancreatic cancer, pancreatic adenocarcinoma, pancreatic tumour, solid pancreatic mass, pancreatic adenoma, pancreatic insulinoma, pancreatic carcinoma, pancreatic lesion, periampullary carcinoma, periampullary lesion, ampulla of Vater, papilla of Vater, duodenum papilla, cysts, cystadenocarcinoma, cystadenoma, pseudocyst, cystic lesion, cystic mass, cystic tumour, pancreas, antigen 19-9, antigens/tumour associated/carbohydrate, gastrointestinal cancer antigen
- jaundice/obstructive, cholestasis, cholestatic jaundice, mechanical jaundice, obstructive jaundice, retention jaundice, cholestatic icterus, mechanical icterus, obstructive icterus, retention icterus, extrahepatic cholestasis, cholestatic hepatobiliary disease, nonhaemolytic bilirubinemia, nonhaemolytic icterus, nonhaemolytic, jaundice
- tomography, computed tomography, CAT scan, pentetreotide, octreoscan, octreotide, indium radioisotopes/somatostatin, scintigraphy, sciniscanning.

Complete details of the literature searches performed using the Medline and EMBASE databases are presented in **Appendix D**.

### Secondary databases

Searches of the secondary databases/sites listed on page 27 were also performed. Additional searches were conducted to source epidemiological and economic information, as required.

## Selection criteria

**Table 15 Selection criteria for included studies—solid pancreatic mass**

**Research question**: To what extent is EUS ± FNA (following abdominal ultrasound and CT) safe, effective and cost-effective in the diagnosis of pancreatic neoplasms in patients in whom a solid pancreatic mass has been identified by prior diagnostic tests (without any evidence of metastases), relative to CT-FNA/guided biopsy, or over and above the current clinical practice of using abdominal ultrasound and CT?

| Selection criteria | Inclusion | Exclusion |
|---|---|---|
| **Study design** | | |
| All studies | Studies with ≥ 10 patients receiving EUS ± FNA and comparator[a] | Non-systematic reviews, letters and opinion pieces, non-human or *in vitro* studies, retrospective |
| Health outcomes studies | Studies comparing health outcomes with and without the use of EUS | |
| Management studies | Pre-test, post-test management studies | |
| **Population** | Patients with a detected pancreatic mass or lesion | Case referent studies<br>Patients with cystic lesions<br>Patients with mediastinal masses<br>Patient population of mixed GI indications with inadequate data separation |
| **Prior tests** | Not specified for inclusion or exclusion criteria | |
| **Index test** | Use of EUS ± FNA to diagnose pancreatic neoplasia as currently approved by the TGA | Intraductal ultrasound; catheter or mini-probes; TruCut needle biopsy |
| **Comparator** | | |
| Health outcomes studies | Clinical practice in the absence of EUS | |
| Accuracy studies | CT-FNA/guided biopsy<br>Current clinical practice of using CT in the absence of EUS | |
| Management studies | Pre-test management plan | |
| **Reference standard** | | |
| Accuracy studies | Histology<br>Clinical follow up | Reference standard not available for all patients |
| **Outcomes** | | |
| Health outcomes studies | Effect on health outcomes | Inadequate data reporting |
| Accuracy studies | Diagnostic performance | |
| Management studies | Effect on clinical management | |

Abbreviations: CT, computerised tomography; EUS, endoscopic ultrasound; FNA, fine needle aspiration; GI, gastrointestinal; TGA, Therapeutic Goods Administration

[a] Studies with < 10 patients were included in the assessment of adverse event and safety data

There were two comparators considered in the assessment of the value of EUS with or without FNA to diagnose pancreatic solid masses. In most patients, it is considered that EUS would be used as an additional test following CT; it would not replace any other diagnostic test. In this situation, the combined value of EUS and CT was compared with CT by applying an either test positive approach to diagnosis. It was also considered that

the use of EUS in some patients would replace CT-guided biopsy. To assess the value of EUS in this regard, the replacement value of CT-guided biopsy was considered.

Following the initial literature search, no comparative studies indicating the accuracy of EUS (without FNA) versus CT-guided biopsy were identified. Studies suitable to enable an indirect comparison of EUS (without FNA) against CT-guided biopsy were not identified. Therefore, non-comparative studies of the highest level of evidence according to NHMRC criteria for diagnostic accuracy studies for each of these technologies were included for review. The inclusion and exclusion criteria applied to single arm studies of diagnostic accuracy are given in **Table 16** and **Table 17**.

**Table 16 Selection criteria for included single arm studies—solid pancreatic mass (EUS)**

| **Research question**: To what extent is EUS safe, effective and cost-effective in the diagnosis of pancreatic neoplasms in patients in whom a solid pancreatic mass has been identified by prior diagnostic tests? | | |
|---|---|---|
| **Selection criteria** | **Inclusion** | **Exclusion** |
| **Study design** | Studies with ≥ 10 patients receiving EUS[a]<br>Level II or III-1 diagnostic accuracy studies (NHMRC criteria) | Non-systematic reviews, letters and opinion pieces, non-human or *in vitro* studies |
| **Population** | Patients with a detected pancreatic mass or lesion | Case referent studies<br>Patients with cystic lesions<br>Patient population of mixed GI indications with inadequate data separation |
| **Prior tests** | Not specified for inclusion or exclusion criteria | |
| **Index test** | EUS (without FNA) | |
| **Comparator** | Not applicable | |
| **Reference standard** | Histology<br>Clinical follow up | Reference standard not available for all patients |
| **Outcomes** | Diagnostic performance | Inadequate data reporting |

Abbreviations: EUS, endoscopic ultrasound; FNS, fine needle aspiration; GI, gastrointestinal; NHMRC, National Health and Medical Research Council

[a] Studies with < 10 patients were included in the assessment of adverse event and safety data

**Table 17 Selection criteria for included single arm studies—solid pancreatic mass (CT-FNA/ guided biopsy)**

| **Research question:** To what extent is CT-FNA/guided biopsy safe, effective and cost-effective in the diagnosis of pancreatic neoplasms in patients in whom a solid pancreatic mass has been identified by prior diagnostic tests? | | |
|---|---|---|
| **Selection criteria** | **Inclusion** | **Exclusion** |
| **Study design** | Studies with ≥ 10 patients receiving CT-guided biopsy[a]<br>Level II or III-1 diagnostic accuracy studies (NHMRC criteria) | Non-systematic reviews, letters and opinion pieces, non-human or *in vitro* studies |
| **Population** | Patients with a detected pancreatic mass or lesion | Case referent studies<br>Patients with cystic lesions<br>Patient population of mixed GI indications with inadequate data separation |
| **Prior tests** | Not specified for inclusion or exclusion criteria | |
| **Index test** | CT-FNA/guided biopsy | |
| **Comparator** | Not applicable | |
| **Reference standard** | Histology<br>Clinical follow up | Reference standard not available for all patients |
| **Outcomes** | Diagnostic performance | Inadequate data reporting |

Abbreviations: CT, computerised tomography; FNA, fine needle aspiration; GI, gastrointestinal; NHMRC, National Health and Medical Research Council

[a] Studies with < 10 patients were included in the assessment of adverse event and safety data

**Table 18 Selection criteria for included studies—pancreatic cystic lesions**

**Research question**: What additional benefit, in terms of: safety, effectiveness and cost-effectiveness, does EUS ± FNA provide in the diagnosis of pancreatic neoplasms in patients in whom a cystic lesion has been identified, over and above the current clinical practice of using abdominal ultrasound and CT (without any evidence of metastases)?

| Selection criteria | Inclusion | Exclusion |
|---|---|---|
| **Study design** | | |
| All studies | Studies with ≥ 10 patients receiving EUS ± FNA and CT[a] | Non-systematic reviews, letters and opinion pieces, non-human or *in vitro* studies |
| Health outcomes studies | Studies comparing health outcomes with and without the use of EUS | |
| Accuracy studies | Studies investigating combined value of EUS ± FNA and CT, or replacement value with individual patient data | |
| Management studies | Pre-test, post-test management studies | |
| **Population** | Patients in whom a pancreatic cystic lesion has been identified by prior diagnostic tests | Case referent studies<br>Patient population of mixed GI indications with inadequate data separation |
| **Prior tests** | Not specified for inclusion or exclusion criteria | |
| **Index test** | Use of EUS ± FNA to diagnose pancreatic neoplasia as currently approved by the TGA | Intraductal ultrasound; catheter or mini-probes |
| **Comparator** | | |
| Health outcomes studies | Clinical practice in the absence of EUS | |
| Accuracy studies | Current clinical practice of using CT in the absence of EUS | |
| Management studies | Pre-test management plan | |
| **Reference standard** | | |
| Accuracy studies | Histology<br>Clinical follow up | Reference standard not available for all patients |
| **Outcomes** | | |
| Health outcomes studies | Effect on health outcomes | Inadequate data reporting |
| Accuracy studies | Diagnostic performance | |
| Management studies | Effect on clinical management | |

Abbreviations: CT, computerised tomography; EUS, endoscopic ultrasound; FNA, fine needle aspiration; GI, gastrointestinal; TGA, Therapeutic Goods Administration

[a] Studies with < 10 patients were included in the assessment of adverse event and safety data

**Table 19 Selection criteria for included studies—pancreatic no lesion identified on CT**

**Research question**: To what extent is EUS ± FNA safe, effective and cost-effective in the diagnosis of pancreatic neoplasms in patients with symptoms and biochemical evidence (CA 19-9 or neuroendocrine abnormalities) associated with pancreatic neoplasia, when abdominal ultrasound and CT have failed to identify an abnormality, relative to octreotide nuclear medicine scanning (somatostatin receptor scintigraphy, for suspected endocrine neoplasia), or relative to current clinical practice in the absence of EUS (for suspected exocrine neoplasia)?

| Selection criteria | Inclusion | Exclusion |
|---|---|---|
| **Study design** | | |
| All studies | Studies with ≥ 10 patients receiving EUS and comparator[a] | Non-systematic reviews, letters and opinion pieces, non-human or *in vitro* studies |
| Health outcomes studies | Studies comparing health outcomes with and without the use of EUS | |
| Accuracy studies | *Exocrine*: studies investigating combined value of EUS ± FNA[b] and CT or replacement value with individual patient data<br>*Endocrine*: replacement studies | *Exocrine*: studies reporting replacement value of CT and EUS without individual patient data |
| Management studies | Pre-test, post-test management studies | |
| **Population** | *Exocrine*: EUS performed in patients in whom a pancreatic mass has not been identified by CT<br>*Endocrine*: patients with a suspected neuroendocrine tumour | Patients with Zollinger-Ellison syndrome<br>Screening in asymptomatic MEN-1 patients<br>Patient population of mixed GI indications with inadequate data separation<br>Case referent studies |
| **Prior tests** | Not specified for inclusion or exclusion criteria | |
| **Index test** | Use of EUS ± FNA to diagnose pancreatic neoplasia as currently approved by the TGA | Intraductal ultrasound; catheter or mini-probes |
| **Comparator** | | |
| Health outcomes studies | Clinical practice in the absence of EUS | |
| Accuracy studies | *Exocrine*: current clinical practice of using CT in the absence of EUS<br>*Endocrine*: Octreotide nuclear medicine scan | |
| Management studies | Pre-test management plan | |
| **Reference standard** | | |
| Accuracy studies | Histology<br>Clinical follow up | Reference standard not available for all patients |
| **Outcomes** | | |
| Health outcomes studies | Effect on health outcomes | Inadequate data reporting |
| Accuracy studies | Diagnostic performance | |
| Management studies | Effect on clinical management | |

Abbreviations: CA, carbohydrate antigen; CT, computerised tomography; EUS, endoscopic ultrasound; FNA, fine needle aspiration; GI, gastrointestinal; TGA, Therapeutic Goods Administration

[a] Studies with < 10 patients were included in the assessment of adverse event and safety data

[b] EUS performed only in patients without a mass identified on CT

**Table 20 Selection criteria for included studies—pancreatic staging**

**Research question**: What additional benefit, in terms of safety, effectiveness and cost-effectiveness, does EUS ± FNA provide in the pre-operative staging of pancreatic neoplasms (in patients with a malignant neoplasm identified by prior testing, but no evidence of metastases), over and above the current clinical practice of using clinical examination, serological testing, abdominal ultrasound and CT?

| Selection criteria | Inclusion | Exclusion |
|---|---|---|
| **Study design** | | |
| All studies | Studies with ≥ 10 patients receiving EUS and comparator[a] | Non-systematic reviews, letters and opinion pieces, non-human or *in vitro* studies |
| Health outcomes studies | Studies comparing health outcomes with and without the use of EUS | |
| Accuracy studies | Studies investigating incremental value or replacement value with individual patient data | Studies reporting replacement value of CT and EUS without individual patient data |
| Management studies | Pre-test, post-test management studies | |
| **Population** | Patients with diagnosed pancreatic malignancy | |
| **Prior tests** | Not specified for inclusion or exclusion criteria | |
| **Index test** | Use of EUS ± FNA for staging of pancreatic neoplasia as currently approved by the TGA | Intraductal ultrasound; catheter or mini-probes |
| **Comparator** | | |
| Health outcomes studies | Clinical practice in the absence of EUS | |
| Accuracy studies | Current clinical practice of using CT in the absence of EUS | |
| Management studies | Pre-test management plan | |
| **Reference standard** | | |
| Accuracy studies | Histopathology<br>Surgical staging | Reference standard not available for all patients |
| **Outcomes** | | |
| Health outcomes studies | Effect on health outcomes | Inadequate data reporting |
| Accuracy studies | Diagnostic performance | |
| Management studies | Effect on clinical management | |

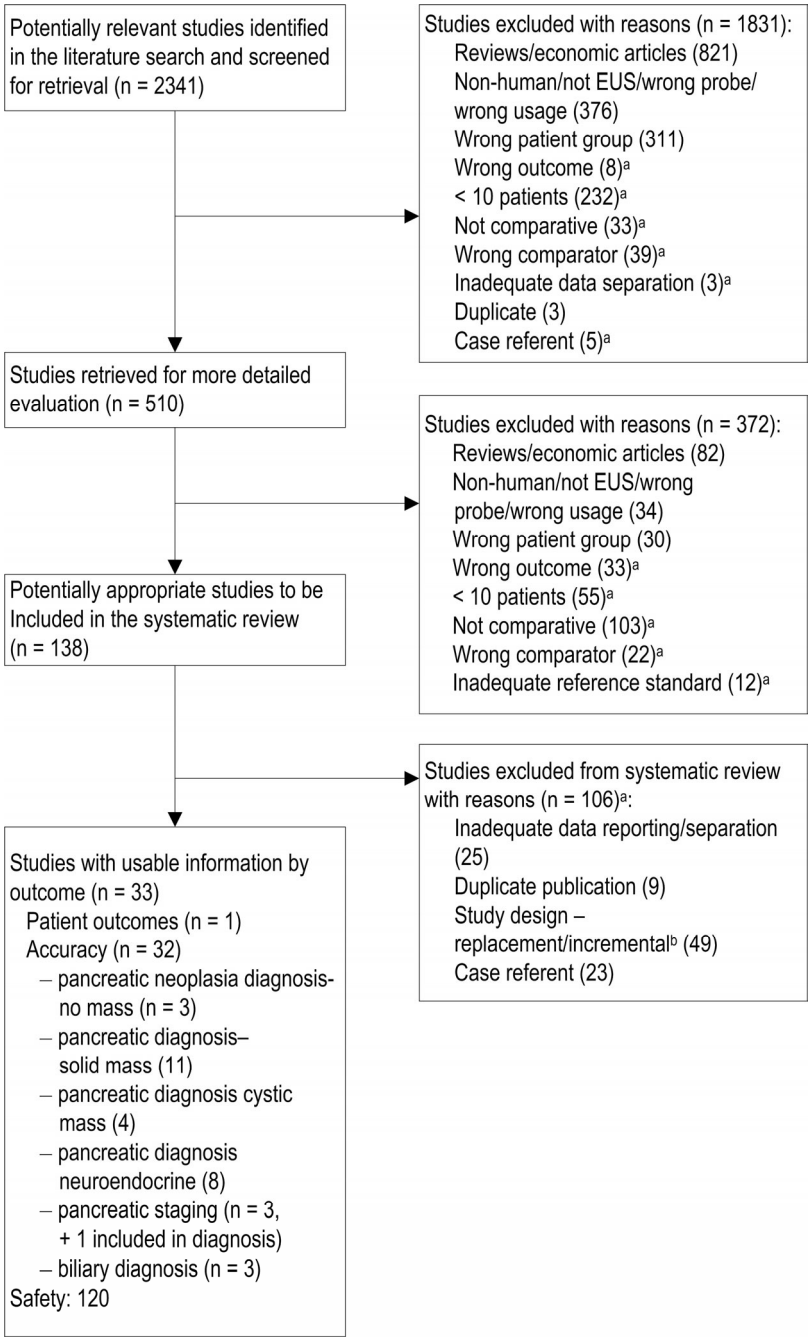
Abbreviations: CT, computerised tomography; EUS, endoscopic ultrasound; FNA, fine needle aspiration; TGA, Therapeutic Goods Administration

[a] Studies with < 10 patients were included in the assessment of adverse event and safety data

## Search results

Results were pooled because there was a high degree of overlap between the yields for biliary tract and pancreatic neoplasia literature searches. There were 21 citations specifically relating to pancreatic or biliary indications, which were identified in the management and health outcomes search, included with these results.

The QUOROM flowchart in **Figure 6** summarises the exclusion of studies from the safety and effectiveness review of EUS for pancreatic and biliary tract neoplasms. A total of 2,341 original citations were identified of which 694 were reviewed for safety data and 33 were included in the effectiveness review.




Abbreviation: EUS, endoscopic ultrasound
Adapted from Moher et al (1999)
[a] Studies reviewed for safety data (265 reviewed in full, 429 reviewed abstracts)
[b] Replacement studies compare the diagnostic accuracy of the comparator test with the index test, while included incremental studies compare the comparator test alone with the index test combined with the comparator test.

**Figure 6 QUOROM flowchart used to identify and select studies for the literature review of biliary tract and pancreatic neoplasms**

Due to the large number of studies identified, studies of fewer than 10 patients, and non-comparative studies or studies against the wrong comparator were reviewed initially in abstract form only. If safety data were reported, the publication was retrieved and reviewed in full. Studies published in languages other than English were not reviewed for safety data.

# Biliary tract neoplasia

## Research question

The PPICO criteria developed *a priori* for this application of EUS are given in **Table 21**.

**Table 21 PPICO criteria for endoscopic ultrasound use in biliary tract neoplasia**

| Population | Prior tests | Index test | Comparator | Outcomes |
|---|---|---|---|---|
| Patients in whom a structural abnormality suggestive of biliary tract neoplasia has been identified by prior diagnostic imaging | Abdominal ultrasound<br>Computed tomography<br>ERCP or MRCP | EUS ± FNA | Current clinical practice in the absence of EUS[a] | Change in clinical outcomes<br>Change in clinical management<br>Diagnostic accuracy |

Abbreviations: PPICO, target population, prior tests, index test, comparator, outcomes; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound, MRCP, magnetic resonance cholangiopancreatography
[a] This comparator was determined as appropriate by the AP following the commencement of the review.

The research question for this indication, based on these criteria, is as follows.

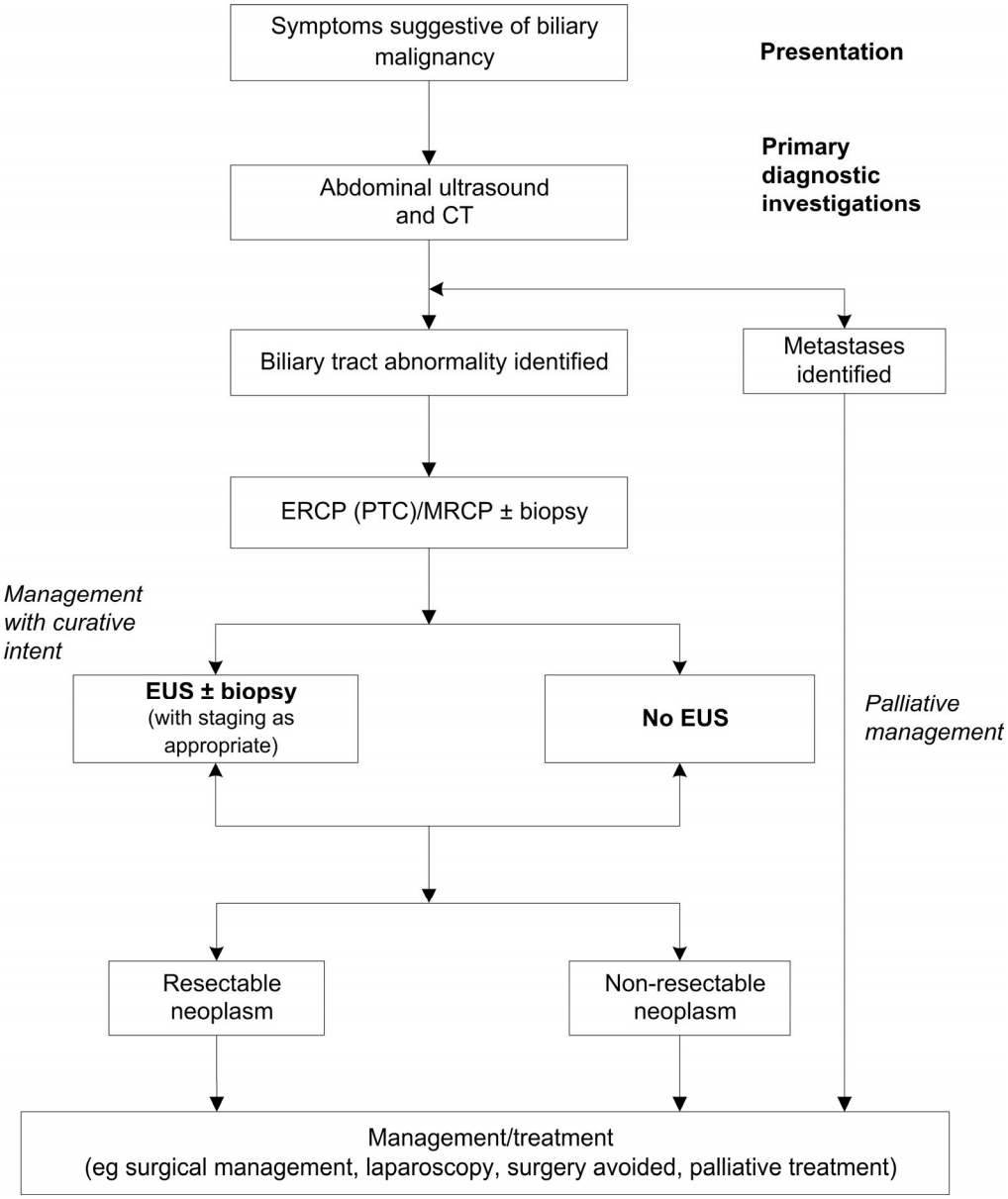
What additional benefit, in terms of:

- safety
- effectiveness (including staging performance and the impact of staging on changes in clinical management and changes in clinical outcomes), and
- cost-effectiveness

does EUS with or without fine needle aspiration provide in the diagnosis and staging of biliary tract neoplasms in patients with a structural abnormality suggestive of biliary tract neoplasia, over and above the current clinical practice of using abdominal ultrasound, CT (with no evidence of metastases), and ERCP or MRCP?

## Clinical pathway

The upstream clinical pathway for the evaluation of patients with suspected biliary tract neoplasia is shown in **Figure 7**. This displays the clinical management pathway to the point of patient diagnosis. The pathway depicting current practice represents management that is accepted as appropriate practice for the majority of patients in Australia. Following diagnosis, patient management occurs according to the flowchart depicted in **Figure 21 (Appendix G)**, and is dependent on the diagnosed stage of disease.




Abbreviations: CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; MRCP, magnetic resonance cholangiopancreatography; PTC, percutaneous transhepatic cholangiopancreatography

**Figure 7 Upstream clinical pathway to evaluate patients with suspected biliary tract neoplasia**

## Assessment framework

A systematic review of the medical literature was undertaken to identify relevant studies and reviews relating to the value of EUS in the diagnosis and staging of biliary tract neoplasia which sought direct evidence regarding the impact of EUS on health outcomes. Evidence concerning the impact of EUS on clinical management and diagnostic accuracy was appraised in the absence of trials providing direct evidence. Indirect and treatment effectiveness evidence were combined to assess the impact of EUS on health outcomes.

## Review of the literature

The medical literature was searched to identify relevant studies published up to 2005. Searches were conducted in the primary databases indicated in **Table 22**.

### Search strategy

#### Primary databases

**Table 22 Electronic databases searched: use of EUS to evaluate biliary tract neoplasms**

| Database | Period covered/date searched |
|---|---|
| Medline | 1966 to February, week 2, 2005 |
| EMBASE | 1980 to 2005, week 8 |
| PreMedline | To 18 February 2005 |
| Cochrane Library | Issue 3, 2005 (4 August 2005) |

The search terms included the following (as determined from the PPICO criteria):

- endosonography, endoscopic ultrasound, echoendoscopy, endoscopy/ultrasonography, endoscopic ultrasonics, interventional ultrasound
- biliary tract neoplasms, biliary tract cancer, biliary tract carcinoma, biliary tract tumour, bile duct obstruction, bile duct stricture, gallbladder cancer, gallbladder neoplasm, gallbladder tumour, gallbladder polyp, gallbladder carcinoma
- cholangiography, ERCP, PTC, MRCP, bile duct radiography, pancreatocholangiography
- Vater's ampulla, papilla of Vater, ampulla of Vater, duodenum papilla.

Complete details of the literature searches performed using the Medline and EMBASE databases are presented in **Appendix D**.

#### Secondary databases

Searches of the secondary databases/sites listed on page 27 were also performed.

Additional searches were conducted to source epidemiological and economic information, as required.

## Selection criteria

The following inclusion and exclusion criteria were applied to the studies identified in the literature search.

**Table 23 Selection criteria for included studies—diagnosis and staging of biliary tract neoplasia**

**Research question:** What additional benefit, in terms of safety, effectiveness and cost-effectiveness, does EUS ± FNA provide in the diagnosis and staging of biliary tract neoplasms in patients with a structural abnormality suggestive of biliary tract neoplasia, over and above the current clinical practice of using abdominal ultrasound, CT (with no evidence of metastases), and ERCP or MRCP?

| Selection criteria | Inclusion | Exclusion |
|---|---|---|
| **Study design** | | |
| All studies | Studies with ≥ 10 patients receiving EUS and comparator[a] | Non-systematic reviews, letters and opinion pieces, non-human or *in vitro* studies |
| Health outcomes studies | Studies comparing health outcomes with and without the use of EUS | |
| Accuracy studies | Studies investigating combined value of EUS and cholangiopancreatography, or replacement value with individual patient data | Studies reporting replacement value of cholangiopancreatography and EUS without individual patient data |
| Management studies | Pre-test, post-test management studies | |
| **Population** | Studies in patients with a structural abnormality suggestive of biliary tract neoplasia identified by prior diagnostic imaging | Anomalous pancreaticobiliary junction patients<br>Portal cavernoma patients<br>Case referent studies |
| **Prior tests** | Not specified for inclusion or exclusion criteria | |
| **Index test** | Use of EUS ± FNA for diagnosis and staging of pancreaticobiliary neoplasia as currently approved by the TGA | Intraductal ultrasound; catheter or mini-probes |
| **Comparator** | | |
| Health outcomes studies | Clinical practice in the absence of EUS | |
| Accuracy studies | Current clinical practice of using cholangiopancreatography in the absence of EUS ± FNA | Replacement studies against ERCP/MRCP of level III or lower (NHMRC criteria) |
| Management studies | Pre-test management plan | |
| **Reference standard** | | |
| Accuracy studies | Histopathology<br>Surgical staging | Reference standard not available for all patients |
| **Outcomes** | | |
| Health outcomes studies | Effect on health outcomes | Inadequate data reporting |
| Accuracy studies | Diagnostic performance | |
| Management studies | Effect on clinical management | |

Abbreviations: CT, computerised tomography; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; FNA, fine needle aspiration; MRCP, magnetic resonance cholangiopancreatography; NHMRC, National Health and Medical Research Council; TGA, Therapeutic Goods Administration

[a] Studies with < 10 patients will be included in the assessment of adverse event and safety data

## Data extraction

A *proforma* addressing the key parameters: trial and study population characteristics, tests used and outcomes reported, and which was based on data collection procedures in the Cochrane Reviewers' Handbook (Alderson et al 2004) was developed to aid data extraction.

## Statistical methods

### Methodological considerations

Data on the incremental, or additional, value of EUS over prior tests were required because practical use of this technology for many of the proposed indications would be supplementary to the current cascade of diagnostic testing. It is likely that EUS would only be performed following negative or uncertain prior testing for diagnostic purposes. The diagnostic approach is equivalent to a positive test for either procedure being counted as a positive result (the either test positive approach).

When incremental data concerning the value of a test are required, comparative studies describing the performance of two tests as replacement alternatives do not provide the required information. These data do not indicate how many additional patients would be diagnosed by the second technology, over and above the first. Where individual patient data are reported, information can be derived from the studies. Should appropriate evidence of the incremental value of EUS be unavailable for the proposed indications, replacement studies may be used to obtain a range in sensitivity and specificity.
The minimum sensitivity of the combined tests should be no less than the higher sensitivity of the two tests, while the maximum specificity will not be greater than the lower specificity of either (Macaskill et al 2002). The maximum combined sensitivity is calculated by adding the number of true positive results from each test and dividing the sum by the number of individuals with the disease in the study group. The sensitivity is 1.00 if the combined number of true positives is greater than the number of people with the disease. The minimum combined specificity is calculated by subtracting the total number of each test's false positives from the number of disease-free individuals, and then dividing this result by the number without disease. The maximum combined sensitivity and minimum combined specificity assume that different individuals are classified as positives by each test.

Case referent studies reporting the performance of two tests in a population where all patients have the target condition are not instructive because they do not provide information about the performance of the test in those without the condition of interest (ie specificity data). There is also evidence that estimates of test sensitivity increase with increasing disease prevalence (Medical Services Advisory Committee [MSAC] 2004). Because the disease prevalence in case referent studies (100%) is unlikely to accurately reflect the rate in the population where the test would be used, they were excluded in favour of studies in more appropriate populations where available.

EUS is likely to be used as an additional test for cancer staging, and the determination of suitability for surgical resection by either EUS or the existing test would yield evidence to base decisions about performing surgeries with curative, opposed to palliative, intent.

The effect of this test cascade would be an either test positive rule of combined tests (positive is defined as unresectability). In this case, sensitivity for suitability for resection may be increased, at the expense of specificity for resection, by comparison with either test alone. The ideal result is exclusion of as many patients who are unsuitable for resection as possible, without losing accuracy, to detect resectability. The desired accuracy estimate is high sensitivity for patients unsuitable for resection, without loss of specificity.

CT results should be interpreted blinded to EUS findings where EUS was used as an additional test. Reading EUS findings with knowledge of CT results is applicable to the current review because this reflects the likely use of EUS in clinical practice.

In many of the studies, the time lag between the performance of the index test and the reference standard is not reported. There is potential for disease progression before verification. It is considered unlikely that in this clinical circumstance there would be a significant delay before surgery was performed; this is unlikely to be a major source of bias.

### Diagnostic performance

Evaluating accuracy of a new diagnostic test requires comparison with its comparators and the best available proxy for the true disease status—the reference standard. The new diagnostic test and its comparators can be independently compared with the reference standard to assess sensitivity, specificity, accuracy, diagnostic odds ratio (DOR) and likelihood ratios.

The sensitivity of a test is defined as the proportion of all patients with the disease who test positive; the specificity is the proportion of all patients without the disease who test negative. The accuracy of a test is the proportion of all patients correctly identified by the test as positive or negative by comparison with the reference standard. Accuracy is dependent on the prevalence of disease in a study. Extremes of prevalence would potentially influence the proportion of patients correctly identified by the test. Caution should be taken when interpreting this measure. The diagnostic odds ratio (DOR) is the odds of a positive test in patients with the disease compared with those who do not have the disease. A DOR of 100 provides convincing evidence of the test's ability to discriminate the presence or absence of the disease.

The likelihood ratio of a positive test is the probability that a positive test result would come from a person with the condition, opposed to obtaining a positive test result from someone who did not have the condition. The likelihood ratio of a negative test is the probability that a negative test result would come from a person with the condition, opposed to obtaining a negative test result from someone who did not have the condition. A positive ratio of $> 10$ and a negative ratio $< 0.1$ provide convincing diagnostic evidence. A positive likelihood ratio of $> 5$ and a negative likelihood ratio of $< 0.2$ provide strong diagnostic evidence (Medical Services Advisory Committee [MSAC] 2004). Bayes' theorem indicates that the post-test odds of disease equals the pre-test odds of disease multiplied by the likelihood ratio. Using this approach, the post-test probability of disease can be determined, for any given pre-test disease probability.

### Impact on management

When a diagnostic test supplements the clinical pathway, evidence of a change in management is a key component of the evidence base. The most appropriate design for investigating whether there is a change in management is a pre-test, post-test case series study. Where a pre-test management plan is not reported, the outcomes of a study cannot truly reflect a change in patient management, and the outcomes are likely to be biased. Therefore, where studies conducted according to the appropriate design were available, other studies claiming to report changes in management were not included for review.

### Safety

Review of the papers identified in the literature search for reported adverse events informed assessment of the safety of EUS and EUS-FNA in relation to gastro-oesophageal and pancreaticobiliary neoplasia. All included and excluded studies were reviewed for safety. Studies involving fewer than 10 patients, excluding non-comparative studies and studies against inappropriate comparators, were reviewed in abstract form only.

Ninety-five per cent confidence intervals for safety data were calculated for the incidence of events per diagnostic test. Due to the low number of events recorded, exact binomial confidence intervals were calculated for event types. Similarly, Fisher's exact test was used to obtain *p* values for the difference between the type of technology used, and these were adjusted using Bonferroni's correction for multiple comparisons, which in this case, is considered to have the value of three for each outcome.

## Appraisal of the evidence

Appraisal of the evidence was conducted in three stages.

- Stage 1: appraisal of the applicability and quality of individual studies included in the review.
- Stage 2: ranking the evidence through appraisal of the precision, size and clinical importance of the primary outcomes used to determine the safety and effectiveness of the test.
- Stage 3: integration of this evidence in order to draw conclusions about the net clinical benefit of the index test in the context of Australian clinical practice.

### Appraisal of the quality and applicability of individual studies

The quality and applicability of the included studies was assessed against pre-specified criteria according to the study design (**Appendix C**).

### Ranking the evidence

Studies evaluating the direct impact of the test or treatment of patient outcomes or management were ranked according to the study design, using the levels of evidence designated by the National Health and Medical Research Council (NHMRC) (**Table 24**).

Studies of diagnostic accuracy were ranked according to the NHMRC levels of evidence for diagnosis shown in **Table 25.**

Studies were also graded according to the pre-specified quality and applicability criteria, as shown in **Table 26**.

**Table 24 NHMRC levels of evidence for effectiveness studies**

| Level of evidence | Study design |
|---|---|
| I | Evidence obtained from a systematic review of level II studies |
| II | Evidence obtained from properly designed randomised controlled trials |
| III-1 | Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method) |
| III-2 | Evidence obtained from comparative studies with concurrent controls: non-randomised experimental trials, cohort studies, case-control studies, or interrupted time series with a control group |
| III-3 | Evidence obtained from comparative studies without concurrent controls: historical control studies, two or more single-arm studies, or interrupted time series without a parallel control group |
| IV | Evidence obtained from case series, either post-test or pre-test/post-test outcomes |

Source: NHMRC (2005)

**Table 25 NHMRC levels of evidence for diagnosis**

| Level of evidence | Study design |
|---|---|
| I | Evidence obtained from a systematic review of level II studies |
| II | Evidence obtained from studies of test accuracy with: an independent blinded comparison with a valid reference standard, among consecutive patients with a defined clinical presentation |
| III-1 | Evidence obtained from studies of test accuracy with: an independent blinded comparison with a valid reference standard, among non-consecutive patients with a defined clinical presentation |
| III-2 | Evidence obtained from studies of test accuracy with: a comparison with reference standard that does not meet the criteria required for level II or III-1 evidence |
| III-3 | Evidence obtained from diagnostic case-control studies |
| IV | Evidence obtained from studies of diagnostic yield (no reference standard) |

Source: NHMRC (2005)

**Table 26 Grading system used to rank included studies**

| Validity criteria | Description | Grading system |
|---|---|---|
| **Appropriate comparison** | Did the study evaluate a direct comparison of the index test strategy versus the comparator test strategy? | C1 direct comparison<br>CX other comparison |
| **Applicable population** | Did the study evaluate the index test in a population that is representative of the subject characteristics (age and sex) and clinical setting (disease prevalence, disease severity, referral filter and sequence of tests) for the clinical indication of interest? | P1 applicable<br>P2 limited<br>P3 different population |
| **Quality of study** | Was the study designed to avoid bias? | |
| | High quality = no potential for bias, based on predefined key quality criteria | Q1 high quality |
| | Medium quality = some potential for bias in areas other than those pre-specified as key criteria | Q2 medium |
| | Poor quality = poor reference standard and/or potential for bias based on key pre-specified criteria | Q3 poor reference standard, poor quality or insufficient information |

The ideal design for a comparative accuracy study of diagnostic tests is one where each test being compared is performed for all individuals. Study was graded as CX (other comparison) when both tests were not performed in most patients in the study.

For the purposes of this review, an applicable patient population was considered to be one that reflected the research question for each indication. To be graded as applicable, studies should have no clear spectrum bias in the patient selection. That is, all consecutive patients with the appropriate clinical presentation should be included in the analysis. Patient populations applicable to the research question but with known spectrum bias were considered to have limited applicability.

Study quality was determined by a number of predefined factors. A high quality study was considered to be one conducted in a consecutive series of patients without any potential for verification bias. Verification bias occurs when some patients included in a study do not have a valid reference standard. There is no potential for verification bias when data from patients with a valid reference standard only are analysed.

Differential verification bias occurs when different reference standards are used to verify positive and negative index test results. Where an index test is used for staging carcinoma it may be impossible to avoid differential verification bias. For patients with advanced disease and/or co-morbidity who are not candidates for surgery, the most likely reference standard would be long-term clinical follow up. This means that it may be impossible to have a high quality study where an index test is used for staging, even when an applicable consecutive patient population is assessed. Although clinical follow up is considered a valid reference standard for patients not considered for surgery, there is still potential for differential verification as a different reference standard is used.

A further factor affecting study quality is selection bias. Studies are subject to selection bias when patient inclusion is based on receiving the index test or reference standard. For example, in a study of the use of EUS for staging, if only surgically resected patients were evaluated, patients with late-stage disease would potentially have been excluded

from such studies. Therefore, the patients included are unlikely to represent a consecutive series of patients receiving EUS, thereby resulting in considerable selection bias. To avoid selection bias, the accuracy of EUS should be reported in a consecutive series of patients who meet the criteria to receive the index test (ie have a defined clinical presentation). These criteria should be based on pre-test characteristics of the patients. The disease status of all patients should be verified by a high quality, valid reference standard.

Lastly, it should be possible to reconstruct a $2 \times 2$ table to verify calculations of diagnostic accuracy outcomes. In this way, the number of true positive, false positive, true negative and false negative results can be extracted for appraisal.

## Interpretation of the evidence

The evidence presented was interpreted using the dimensions of evidence defined by the NHMRC additional levels of evidence and grades for recommendations for developers of guidelines (NHMRC 2005).

These dimensions consider important aspects of the evidence supporting a diagnostic test and include three main domains:

- strength of the evidence based on the effectiveness of study design, quality of evidence and statistical precision of the results of the included studies
- size of the effect
- relevance of the evidence.

Assessment of the size of the effect and relevance of the evidence are determined using expert clinical input.

## Expert advice

An advisory panel with expertise in endoscopic ultrasound, surgery, gastroenterology, radiology, radiotherapy and consumer issues was established to evaluate the evidence and provide advice to MSAC from a clinical perspective. In selecting members for advisory panels, MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations and consumer bodies for nominees. Membership of the advisory panel is listed in **Appendix B**.

# Results of assessment

## Is it safe?

### Oesophageal and gastric neoplasia

The safety of EUS and EUS-FNA in relation to gastric and/or oesophageal lesions was assessed by reviewing the papers identified by the literature search outlined in **Figure 2** for reported adverse events. A total of 731 studies were reviewed for safety, 219 of which were reviewed in full. The remaining 512 studies (made up of those involving fewer than 10 patients, excluded non-comparative studies and studies involving inappropriate comparators) were initially reviewed in abstract form only. Full papers were reviewed if complications were reported in the abstracts of these 512 studies. Of the 731 studies reviewed, only 46 (6%) reported the safety of EUS/EUS-FNA, thus limiting the reliability of the conclusions made from this review concerning the safety of these technologies to diagnose or stage oesophageal and gastric neoplasms. Of the patients reviewed for EUS, 0.56 per cent experienced an adverse event, compared with 2.65 per cent of patients who underwent EUS-FNA.

It is noteworthy that the EUS-FNA sample size was small (565 patients) compared with EUS (2,521 patients), which also limits the reliability of conclusions made about the safety of EUS-FNA for gastro-oesophageal lesions. Of the 2,521 patients, 13 experienced serious complications related to EUS. Perforation occurred in 0.32 per cent of patients (8/2521) and 0.20 per cent of patients experienced bleeding (5/2521) which was managed with endoscopic haemostatic methods. There were 463 failures reported due to non-traversable lesions (463/2521, 18%) in the reviewed studies. It was reported that one patient (0.04%) developed hemiparesis during EUS; this patient recovered apart from some slight residual facial paresis. Of the 565 patients who underwent EUS-FNA, 15 incurred minimal self-limited bleeding as a minor complication (Remer et al 2002). No complications were reported in 99.4 per cent of EUS patients (2507/2521) and 97.35 per cent of EUS-FNA patients (550/565) in relation to staging/diagnosis of gastro-oesophageal lesions.

Use of EUS and EUS FNA to stage and diagnose gastro-oesophageal cancers is considered to be associated with a low risk of adverse events.

**Table 27** **Adverse events reported in association with tests performed to diagnose gastric and oesophageal neoplasia**

| | EUS | | | EUS FNA | | | Total EUS[c] | | |
|---|---|---|---|---|---|---|---|---|---|
| | **n/2521** | **%** | **Exact 95% CI** | **n/565** | **%** | **Exact 95% CI** | **n/3086** | **%** | **Exact 95% CI** |
| Total events | 14 | 0.56 | 0.3, 0.9 | 15 | 2.65 | 1.5, 4.3 | 29 | 0.94 | 0.63, 1.35 |
| ***Serious adverse events*** | | | | | | | | | |
| Perforation | 8 | 0.32 | 0.1, 0.6 | 0 | 0.00 | 0, 0.65† | 8 | 0.26 | 0.11, 0.51 |
| Bleeding | 5 | 0.20 | 0.06, 0.46 | 15[b] | 2.65 | 1.5, 4.3 | 20 | 0.65 | 0.40, 1.00 |
| ***Adverse events*** | | | | | | | | | |
| Pancreatitis | | 0.00 | 0, 0.14† | 0 | 0.00 | 0, 0.65† | 0 | 0.00 | 0.00, 0.12† |
| Fever | 0 | 0.00 | 0, 0.14† | 0 | 0.00 | 0, 0.65† | 0 | 0.00 | 0.00, 0.12† |
| Abdominal pain | 0 | 0.00 | 0, 0.14† | 0 | 0.00 | 0, 0.65† | 0 | 0.00 | 0.00, 0.12† |
| Cholangitis | 0 | 0.00 | 0, 0.14† | 0 | 0.00 | 0, 0.65† | 0 | 0.00 | 0.00, 0.12† |
| Infection | 0 | 0.00 | 0, 0.14† | 0 | 0.00 | 0, 0.65† | 0 | 0.00 | 0.00, 0.12† |
| Cardiorespiratory events | 0 | 0.00 | 0, 0.14† | 0 | 0.00 | 0, 0.65† | 0 | 0.00 | 0.00, 0.12† |
| Over-sedation | 0 | 0.00 | 0, 0.14† | 0 | 0.00 | 0, 0.65† | 0 | 0.00 | 0.00, 0.12† |
| Hypotension | 0 | 0.00 | 0, 0.14† | 0 | 0.00 | 0, 0.65† | 0 | 0.00 | 0.00, 0.12† |
| Haematoma | 0 | 0.00 | 0, 0.14† | 0 | 0.00 | 0, 0.65† | 0 | 0.00 | 0.00, 0.12† |
| Vasovagal events | 0 | 0.00 | 0, 0.14† | 0 | 0.00 | 0, 0.65† | 0 | 0.00 | 0.00, 0.12† |
| Hypoxia | 0 | 0.00 | 0, 0.14† | 0 | 0.00 | 0, 0.65† | 0 | 0.00 | 0.00, 0.12† |
| Other | 1 | 0.04 | 0.01, 0.22 | 0 | 0.00 | 0, 0.65† | 1 | 0.03 | 0.00, 0.18 |
| **No complications** | **2507** | **99.44** | **99.07, 99.7** | **550** | **97.35** | **95.65, 98.50** | **3051** | **0.99** | **0.99, 1.00** |

Abbreviations: CI, confidence interval; EUS, endoscopic ultrasound; FNA, fine needle aspiration

[a] Patient with throat discomfort/disorder

[b] Self-limited bleeding

† One-sided 95% computed CI

## Pancreaticobiliary neoplasia

A total of 694 pancreaticobiliary studies were reviewed for safety. Initial reviews of abstract forms were conducted for 429 of the 694 studies (those involving fewer than 10 patients, non-comparative studies that were excluded and studies against the wrong comparator). Of the 429 studies, 13 reported safety data, and these were retrieved for further review. Most (n = 158, 60%) of the 265 studies initially reviewed in full did not report complications.

A fifth (n = 22, 20%) of the 120 reviewed studies relating to safety reported safety from diverse patient populations with a range of tumour types or mixed pancreaticobiliary diseases, although pancreaticobiliary tumours were predominant. Adverse events associated with these studies of mixed tumour/disease types are reported in **Appendix I.** The adverse events associated with diagnosis or staging of solely pancreaticobiliary tumours are presented in **Table 28.**

No deaths associated with adverse events were reported to have occurred as a result of EUS, EUS-FNA or CT-guided FNA/biopsy in any of the reviewed studies. It was found that one study reported the death of a patient as an adverse event; but the patient was found to have died from pancreatic cancer and was excluded as an adverse event in this review. Of the reviewed studies, there were only 12 (with a total of 830 patients) that reported adverse events associated with CT-guided FNA/biopsy. The small sample size had the effect of limiting the reliability of conclusions drawn about the safety of this technology.

A total of 2,240 patients underwent EUS in the studies reviewed. No cases of perforation were reported in relation to EUS. There was one reported case of intracerebral bleeding in a patient undergoing EUS, but was found to be unrelated to the technology. Over a quarter (n = 17, 28%) of 61 EUS studies reported the use of colour Doppler in conjunction with FNA to identify and limit the risk of bleeding. Of the 3,080 patients in the reviewed studies who underwent EUS-FNA, two patients (0.06%) experienced perforations. The perforation was recognised before completion of the FNA in one patient; and was identified after completion in another. Overall, two of the 5,320 patients (0.04%) experienced perforation due to EUS performed either with or without FNA of pancreaticobiliary lesions. Both patients required laparotomies to repair the perforations.

Fine needle aspiration (FNA) was used in 10 of the 12 CT-FNA/biopsy studies. The remaining two used needle biopsy. Larger (14–20) gauge needles were used for needle biopsy than for FNA (21–23 gauge). The use of finer needles could be expected to reduce the likelihood of adverse events, such as bleeding, occurring in association with aspiration of material, compared with the larger gauge needles commonly used for biopsy. Despite this, more cases of bleeding occurred with EUS-FNA than with CT-guided FNA/biopsy. The difference was not statistically significant (0.49% and 0.24%, respectively; $p > 0.05$[3]). It is difficult to evaluate the effects of needle size accurately from these studies, given the limited size of the CT-guided FNA/biopsy population reporting safety.

[3] Bonferroni's correction for multiple comparisons, which in this case numbered three for each outcome, $p < 0.05$.

Pancreatitis and abdominal pain were the most frequently reported adverse events associated with EUS-FNA and CT-FNA/biopsy. Pancreatitis was not reported in patients undergoing EUS, but occurred in 0.42 per cent of EUS-FNA patients (13/3080) and in 0.72 per cent of CT-guided biopsy patients (6/837). Abdominal pain was reported in only one patient undergoing EUS (0.04%, 1/2240), compared with the higher incidence in patients undergoing EUS-FNA (0.55%, 17/3080) or CT-FNA/biopsy (0.72%, 6/837).

Antibiotics were not routinely administered to patients who underwent EUS-FNA of solid masses in the reviewed studies. The use of prophylactic antibiotics was reported in five of nine studies reporting safety in association with EUS-FNA of cystic masses (ie in 56% of studies; and involving 443 patients). Only one of the reviewed studies of EUS-FNA for solid masses reported the use of antibiotics. Antibiotic use during CT-FNA/biopsy was not reported in any of the reviewed studies possibly because these studies mostly considered solid masses.

Infection and cardiorespiratory events occurred in 0.13 per cent (3/2240) and 0.09 per cent (2/2240) of EUS patients respectively, and one patient was over-sedated (0.04%). Among the EUS-FNA patients, 1.1 per cent (34/3080) experienced minor complications, including mild abdominal pain, distension, nausea, vomiting, diarrhoea or minor bleeding at the biopsy site (there were no systemic symptoms as a result of the bleeding) ($p < 0.05/3$), compared with EUS and CT-FNA/biopsy. Over-sedation was reported in relation to three patients—one (0.03%) was recorded as such, and two (0.06%) were documented as having resultant hypoxia.

Haematoma (0.36%, 3/837) and vasovagal complications (0.48%, 4/837) were reported in patients undergoing CT-guided FNA/biopsy. CT-guided FNA/biopsy was associated with significantly higher numbers of vasovagal complications than EUS-FNA and EUS (all $p < 0.05/3$), which may relate to the types of sedative co-administered after CT-FNA/biopsy. Both of these events were only reported in studies of CT-guided FNA/biopsy.

The conclusions regarding the safety of CT-guided FNA/biopsy are considered limited for several reasons: small sample size, studies of this technology tended to be older (with the possibility of introducing selection bias), and poor and infrequent reporting of safety data in the literature. In general, few EUS-FNA or CT-guided biopsy studies were followed up sufficiently to capture recurrences related to peritoneal seeding. The review of adverse events reported in publications identified from the literature search for pancreaticobiliary EUS studies demonstrated that EUS had a lower complication rate in terms of total adverse events, when compared with EUS-FNA and CT-guided FNA/biopsy ($p < 0.05/3$). There were significantly more cases of pancreatitis and abdominal pain in patients who received EUS-FNA, compared with those undergoing EUS, highlighting the increased risk associated with adding FNA to EUS. There was no difference in the safety of EUS-FNA compared with CT-FNA/biopsy.

**Table 28 Adverse events reported in association with tests performed to evaluate pancreatic and biliary tract neoplasia**

| | EUS | | | EUS-FNA | | | CT-FNA/biopsy | | | Total EUS | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n/2240 | % | Exact 95% CI | n/3080 | % | Exact 95% CI | n/837 | % | Exact 95% CI | n/5320 | % | Exact 95% CI |
| **Total events** | 9 | 0.40 | 0.18, 0.76 | 90 | 2.92 | 2.36, 3.58 | 28 | 3.35 | 2.23, 4.80 | 99 | 1.86 | 1.51, 2.26 |
| ***Serious adverse events*** | | | | | | | | | | | | |
| Perforation | 0 | 0.00 | 0.00, 0.16† | 2 | 0.06 | 0.01, 0.23 | 0 | 0.00 | 0.00, 0.44† | 2 | 0.04 | 0.00, 0.14 |
| Bleeding | 1 | 0.04 | 0.00, 0.25 | 15 | 0.49 | 0.27, 0.80 | 2 | 0.24 | 0.03, 0.86 | 16 | 0.30 | 0.17, 0.49 |
| ***Adverse events*** | | | | | | | | | | | | |
| Pancreatitis | 0 | 0.00* | 0.00, 0.16† | 13 | 0.42 | 0.22, 0.72 | 6 | 0.72 | 0.26, 1.55 | 13 | 0.24 | 0.13, 0.42 |
| Fever | 0 | 0.00 | 0.00, 0.16† | 4 | 0.13 | 0.04, 0.33 | 0 | 0.00 | 0.00, 0.44† | 4 | 0.08 | 0.02, 0.19 |
| Abdominal pain | 1 | 0.04* | 0.00, 0.25 | 17 | 0.55 | 0.32, 0.88 | 6 | 0.72*** | 0.26, 1.55 | 18 | 0.34 | 0.20, 0.53 |
| Cholangitis | 0 | 0.00 | 0.00, 0.16† | 0 | 0.00 | 0.00, 0.12† | 3 | 0.36 | 0.07, 1.04 | 0 | 0.00 | 0.00, 0.07† |
| Infection | 3 | 0.13 | 0.03, 0.39 | 2 | 0.06 | 0.01, 0.23 | 0 | 0.00 | 0.00, 0.44† | 5 | 0.09 | 0.03, 0.22 |
| Cardiorespiratory events | 2 | 0.09 | 0.01, 0.32 | 0 | 0.00 | 0.00, 0.12† | 0 | 0.00 | 0.00, 0.44† | 2 | 0.04 | 0.00, 0.14 |
| Over-sedation | 1 | 0.04 | 0.00, 0.25 | 1 | 0.03 | 0.00, 0.18 | 1 | 0.12 | 0.00, 0.66 | 2 | 0.04 | 0.00, 0.14 |
| Hypotension | 0 | 0.00 | 0.00, 0.16† | 0 | 0.00 | 0.00, 0.12† | 2 | 0.24 | 0.03, 0.86 | 0 | 0.00 | 0.00, 0.07† |
| Haematoma | 0 | 0.00 | 0.00, 0.16† | 0 | 0.00 | 0.00, 0.12† | 3 | 0.36 | 0.07, 1.04 | 0 | 0.00 | 0.00, 0.07† |
| Vasovagal events | 0 | 0.00 | 0.00, 0.16† | 0 | 0.00** | 0.00, 0.12† | 4 | 0.48*** | 0.13, 1.22 | 0 | 0.00 | 0.00, 0.07† |
| Hypoxia | 1 | 0.04 | 0.00, 0.25 | 2 | 0.06 | 0.01, 0.23 | 0 | 0.00 | 0.00, 0.44† | 3 | 0.06 | 0.01, 0.16 |
| Other | 0 | 0.00* | 0.00, 0.16† | 34[a] | 1.10**, *** | 0.77, 1.54 | 1[b] | 0.12 | 0.00, 0.66 | 34 | 0.64 | 0.44, 0.89 |
| **No complications** | **2231** | **99.60** | **99.2, 99.8** | **2990** | **97.08** | **96.4, 97.6** | **809** | **96.65** | **95.2, 97.8** | **5221** | **98.14** | **97.74, 98.49** |

Abbreviations: CI, confidence interval; CT-FNA, computed tomography guided fine needle aspiration; EUS, endoscopic ultrasound; EUS-FNA, endoscopic ultrasound guided fine needle aspiration

[a] Minor complications including mild abdominal pain, distension, nausea, vomiting, diarrhoea or minor bleeding at the biopsy site

[b] One case of pneumothorax and one case of pancreatic duct leakage

* $p < 0.05$, significantly different from EUS-FNA; ** $p < 0.05$, significantly different from CT-FNA/biopsy; *** $p < 0.05$, significantly different from EUS

† One-sided 95% computed CI

# Is it effective?

# Direct evidence

## Does it improve health outcomes?

The studies identified reported only survival, relapse-free survival or tumour recurrence rate as health outcomes. Studies addressing other health outcomes, such as quality of life, were not found. The potential positive impact of EUS on health outcomes when used for staging is not in relation to survival for most patients.

### Oesophageal and gastric neoplasia

There were two studies identified that provided level III-3 evidence (NHMRC 2005) about the impact of EUS on health outcomes when used to stage cancers of the oesophagus and gastro-oesophageal junction (Harewood et al 2004; van Westreenen et al 2005) (**Table 29**). Both were retrospective interrupted time series studies that lacked parallel control groups. This allowed strong potential for bias. An ongoing randomised controlled trial was also identified (UK COGNATE).

Harewood and Kumar (2004) assessed the impact of using EUS for staging on the clinical outcomes of patients with oesophageal cancer. Patients with histopathological confirmation of squamous cell carcinoma or adenocarcinoma of the oesophagus were included if they were found to be free of distant disease based on chest and abdomen CT evidence. A cytotechnologist whose role was to provide assessment during the procedure was present when EUS-guided FNA was performed. The 60 patients in the non-EUS group were from the 1998 study period before EUS was routinely available. The 13 patients in the EUS group were recruited (from late 1998) following the introduction of EUS for routine evaluation. There were 94 patients from the 2000 study period and significantly more patients received pre-operative neoadjuvant therapy in the EUS group than in the control group (32.7% vs 15.0% respectively; $p = 0.01$). This finding is appreciable if it means that more patients in the EUS group received pre-operative therapy due to a change in patient management and/or more accurate staging.

The primary outcomes of the study were overall survival and relapse-free survival. The median follow up was 15 months in the EUS group and 21 months for the non-EUS group. Surviving recurrence-free patients in both groups were followed up for at least 24 months. The mortality rate was 42.1 per cent in the EUS group and 53.3 per cent in the non-EUS group. When adjusted for age, sex, tumour stage and tumour location using Cox proportional hazards, EUS was associated with reduced mortality (adjusted hazard ratio: 0.66; 95% CI: [0.47, 0.90]; $p = 0.008$). The tumour recurrence rate was 43.0 per cent in the EUS group and 60.6 per cent in the non-EUS group. After adjustment using Cox proportional hazards, EUS was associated with a reduced tumour recurrence rate (adjusted hazard ratio: 0.63; 95% CI: [0.43, 0.87]; $p = 0.004$). The shorter follow up in the EUS group may have contributed to the lower death and tumour recurrence rates.

Van Westreenen et al (2005) conducted a study that included 203 patients with biopsy-proven malignancy of the oesophagus or gastro-oesophageal junction who were eligible for potentially curative surgery. Patients were staged pre-operatively with CT

alone between 1992 and 1996 (n = 106), or with CT and EUS in 1997 (n = 36). The study also reported outcomes for the combined use of CT, EUS and PET (n = 61). These data were not included in the current review because outcomes for the combined use of CT and PET were not reported, resulting in an absence of useful information on the incremental value of EUS. Resection was abandoned in 78 patients due to M1 disease (n = 59), locally unresectable tumours (T4, n = 14), or metastatic spread with local unresectability (n = 5). Survival data for the remaining 59 patients receiving CT alone and the 18 patients receiving CT and EUS who underwent oesophagectomy were analysed using the Kaplan-Meier method. The median survival was 28.0 months for patients staged with CT alone and 25.6 months for patients staged with CT and EUS. There was no difference in survival between patients staged using CT only and CT and EUS (hazard ratio = 0.98, 95% CI: [0.48, 2.00]).

The ongoing randomised controlled trial on the effect of EUS on health outcomes (UK COGNATE, Cancer of the oesophagus or gastricus: new assessment of the technology of endosonography trial), sponsored by the NHS Research and Development Health Technology Assessment Program, investigates the role of EUS in the staging and management of patients with gastric and oesophageal cancer. The inclusion criteria for the trial are: patients with T1 tumours localised to the gastric or oesophageal mucosa who may benefit from endoscopic treatment; patients with a range of tumours who may be identified by EUS as either likely to benefit from curative surgery or likely to have residual disease after major surgery with its attendant risks; and patients with T3 or T4 tumours who may be identified by EUS as likely to benefit from multimodal treatment. Patients are randomised to arms that either provide or do not provide EUS following standard staging investigations. The primary outcome is survival. Secondary outcomes have an impact on complete resection rate, quality of life and health resource utilisation. The trial was expected to end in January 2009.

### Pancreatic neoplasia

A single study by Erickson and Garza (2000) was identified that provides level III-3 evidence (NHMRC 2000) concerning impact of EUS on health outcomes when used to diagnose pancreatic cancer (**Table 30**). This retrospective observational study was an interrupted time series with no parallel control group that was conducted in the USA. The study provided comparative data on stage at diagnosis and median survival for patients over different historical time periods during which CT-guided FNA and biopsy, as opposed to EUS-guided FNA, was used. Throughout the study period, all operable patients with presumed resectable tumours underwent surgery. The primary chemotherapy agent used was fluorouracil; and some patients were also administered gemcitabine during the study.

This study reported that during the CT-FNA/Bx period (January 1993–May 1995), 15 per cent, 8 per cent, 10 per cent and 61 per cent of patients had stage I–IV pancreatic cancer at diagnosis, respectively. In contrast, 15 per cent, 17 per cent, 21 per cent and 43 per cent of pancreatic cancer patients in the EUS-FNA period (August 1995–December 1997) had stage I–IV disease at diagnosis, respectively. Significantly fewer patients were diagnosed by surgery during the EUS-FNA period than the CT-FNA/Bx period (7% vs 29% of cases, respectively). EUS successfully detected carcinoma in 13 per cent of patients whose tumours were not detected by CT; a further 21 per cent of patients whose tumours were seen, but not confirmed by CT imaging, were diagnosed with EUS.

The proportion of patients undergoing surgical resection did not differ between the two time periods (13% vs 14% during CT-FNA/Bx and EUS-FNA periods respectively). The median survival of patients with pancreatic cancer without liver metastases was significantly increased during the EUS-FNA period (205 days vs 102 days; $p < 0.02$, log-rank test). This outcome may have been influenced by changes in management; the authors claim that therapeutic options and outcomes had changed little over this time period. There was the addition of gemcitabine to the chemotherapy treatment of some patients in the EUS-FNA period. A strong potential for bias exists with this study design.

**Table 29 Included studies that compare health outcomes resulting from the use of EUS and CT for staging oesophageal cancer**

| Author (year) | Study design | Patients (N) | EUS characteristics | Comparator | Treatment | Level of evidence |
|---|---|---|---|---|---|---|
| Harewood and Kumar (2004) | Retrospective interrupted time series without a parallel control group<br>(1998, 2000) | Histopathologically confirmed oesophageal cancer<br>(167) | Radial echoendoscopes (Olympus GF-UM30, GF-UM20)<br>Operator: 1 of 4 experienced endosonographers | CT: slice thickness (5–7 mm) and scanning time remained unchanged over time<br>(1998) | Presumed resectable: surgery<br>Adjuvant therapy: chemoradiation | III-3<br>High potential for bias, clearly reported |
| Van Westreenen et al (2005) | Retrospective interrupted time series without a parallel control group<br>(1992–2002) | Biopsy-proven malignancy of the oesophagus or gastro-oesophageal junction<br>(142) | Radial scanner (Olympus GF-UM20) for EUS, linear-array scanner (Pentax FGUX-36) for EUS-FNA<br>Operator: 1 experienced endoscopist<br>(1997) | CT<br>(1992–1996) | Patients staged as T1-3 N0 M0: oesophagectomy as curative treatment<br>Resection abandoned if staged as T4, N1 or M1 | III-3<br>High potential for bias, clearly reported |

Abbreviations: CT, computed tomography; EUS, endoscopic ultrasound; FNA, fine needle aspiration

**Table 30 Included study comparing EUS-FNA and CT-FNA/Bx effects on health outcomes to diagnose pancreatic masses**

| Author (year) | Study design | Patients (N) | EUS characteristics | Comparator | Treatment | Level of evidence |
|---|---|---|---|---|---|---|
| Erickson and Garza (2000) | Retrospective interrupted time series without a parallel control group<br>(1993–1997) | Diagnosed with pancreatic carcinoma<br>(136) | EUS-FNA<br>(August 1995–December 1997) | CT-guided FNA or biopsy<br>(January 1993–May 1995) | Operable and staged as resectable: surgery fluorouracil gemcitabine in some from May 1997 | III-3<br>High potential for bias, clearly reported |

Abbreviations: CT, computed tomography; EUS, endoscopic ultrasound; FNA, fine needle aspiration

# Linked evidence

## Is it accurate?

### Oesophageal neoplasia

#### Staging

***Systematic review***

A systematic review by Harris et al (1998) reviewed use of EUS in gastro-oesophageal cancer. This study aimed to review the literature relating to the use of EUS for the pre-operative staging of gastro-oesophageal cancer, especially regarding staging performance and staging impact. This differs from the current review, which specifically focuses on evidence comparing the performance of EUS incrementally over CT alone for the staging of gastro-oesophageal cancer.

The systematic review by Harris et al (1998) was considered high quality according to all criteria for systematic review appraisal (see **Table 108, Appendix C**). Primary databases searched were accessed in 1996 and 1997, and included Medline, Bath Information and Data Services (BIDS)—Institute of Scientific Information (ISI), EMBASE, Cochrane Library and others.

Key findings of the review included:

- EUS is highly effective for the discrimination of stages T1 and T2 from T3 and T4, in both the oesophagus and the stomach. Performance for T staging of the cardia may be less able to discriminate between stages
- the performance of EUS in lymph node staging was found to be less accurate than tumour staging. Staging for metastases using EUS alone was not satisfactory
- non-traversable stenosis reduces the accuracy of staging performance of EUS, but evidence on whether dilatation was justified was not available.

The calculated pooled summary estimates of the Q* statistic for accuracy of diagnosis by EUS alone are summarised in **Table 31**.

**Table 31 Summary accuracy estimates (Q*) for tumour and lymph node staging**

| EUS indication | Pooled accuracy (Q*)[a] |
|---|---|
| ***Tumour staging*** | |
| Oesophageal tumour staging | 0.89 |
| Gastric tumour staging | 0.93 |
| Gastro-oesophageal tumour staging | 0.91 |
| ***Lymph node staging*** | |
| Lymph nodes associated with oesophageal tumours | 0.82 |
| Lymph nodes associated with gastric tumours | 0.76 |
| Lymph nodes associated with gastro-oesophageal tumours | 0.79 |

[a] Determined by equally weighted least squares method

Harris et al (1998) did not identify any direct evidence concerning the impact of EUS on health outcomes when used for diagnosis or staging. The two pre-test, post-test management studies identified by Harris et al (1998) (Jafri et al 1996; Nickl et al 1996) are also discussed in this assessment.

Harris et al (1998) identified eight studies reporting the comparative values of EUS and CT. Of these, five reported the performance of EUS and CT for T staging; seven reported performance for N staging; and two reported M staging. The results for each study were presented separately and were not pooled. Two of the eight studies reported the incremental value of EUS over CT, one concerning oesophageal cancer staging (Botet et al 1991a) (**Table 32**) and the other for gastric cancer staging (Botet et al 1991b) (**Table 33**). Both studies are included in this assessment.

The limited quantity of data available meant that conclusions could not be made about the comparative values of EUS and CT in gastro-oesophageal cancer staging. Harris et al (1998) concluded that the available evidence did not support use of EUS for M staging and that it should not be used without a complementary technique such as CT.

**Table 32 Grouped TNM oesophageal cancer staging from Botet et al (1991a) cited in Harris et al (1998)**

| | EUS + CT | | | CT | | |
|---|---|---|---|---|---|---|
| | TNM I or II | TNM III | TNM IV | TNM I or II | TNM III | TNM IV |
| Sensitivity | 77.8 | 94.1 | 81.3 | 55.6 | 58.8 | 75.0 |
| Specificity | 97.0 | 80.0 | 100.0 | 81.8 | 72.0 | 100.0 |
| PPV | 87.5 | 76.2 | 100.0 | 45.5 | 58.8 | 100.0 |
| NPV | 94.1 | 95.2 | 89.7 | 87.1 | 72.0 | 86.7 |
| Accuracy | 92.9 | 85.7 | 92.9 | 76.2 | 66.7 | 90.5 |
| OR | 112.0 | 64.0 | N/A | 5.6 | 3.7 | N/A |

Abbreviations: CT, computed tomography; EUS, endoscopic ultrasound; N/A, not applicable; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value; TNM, tumour node metastasis

**Table 33 Grouped TNM gastric cancer staging from Botet et al (1991b) cited in Harris et al (1998)**

| | EUS + CT | | | CT | | |
|---|---|---|---|---|---|---|
| | TNM I or II | TNM III | TNM IV | TNM I or II | TNM III | TNM IV |
| Sensitivity | 90.9 | 66.7 | 57.1 | 54.5 | 46.7 | 33.3 |
| Specificity | 77.3 | 77.8 | 100.0 | 77.3 | 64.7 | 81.5 |
| PPV | 66.7 | 71.4 | 100.0 | 54.5 | 53.8 | 28.6 |
| NPV | 94.4 | 73.7 | 89.7 | 77.3 | 57.9 | 84.6 |
| Accuracy | 81.8 | 72.7 | 90.9 | 69.7 | 56.3 | 72.7 |
| OR | 34.0 | 7.0 | N/A | 4.1 | 1.6 | 2.2 |

Abbreviations: CT, computed tomography; EUS, endoscopic ultrasound; N/A, not applicable; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value; TNM, tumour node metastasis

### *Primary studies*

Information on the incremental value of EUS following CT and/or positron emission tomography (PET) in the staging of oesophageal cancer was identified in 11 studies. The characteristics of these studies are presented in **Table 34**. All one but one (Date et al 1990) were reported as prospective designs.

Five of the 11 studies were designed to investigate the combined value of EUS and CT (Botet et al 1991a; Flamen et al 2000; Heeren et al 2004; Luketich et al 2000; Sihvo et al 2004). Botet et al (1991a) determined group staging by counting EUS findings for T and N staging and CT findings for M staging. Sihvo et al (2004) appeared to report combined results by applying a similar method, which is indicated by increases in sensitivity and specificity. The studies by Flamen et al (2000) and Heeren et al (2004) both reported on combined values using an either positive approach. Luketich et al (2000) did not report the method used but appeared to follow a similar technique that was indicated by an increase in sensitivity with a decrease in specificity.

It was also found that six studies were designed to assess the replacement value of EUS and CT, but reported individual patient data that enabled calculation of the incremental value of EUS following CT (Choi et al 2000; Date et al 1990; Hordijk et al 1993a; Hordijk et al 1993b; Lerut et al 2000; Ziegler et al 1991). In accordance with the research question for this review, the EUS results from patients in whom CT (and PET where applicable) identified distant metastases were excluded. EUS was not reported with knowledge of CT results, reducing the applicability to the research question.

A significant issue in considering the applicability of the patients in these studies to those in the population relevant to this assessment is whether all consecutive patients receiving the index test were included or were data from those with an adequate reference standard only analysed. Patients undergoing surgical resection only were evaluated, so it is possible that some people with late stage disease were excluded from such studies. Included patients were unlikely to represent a consecutive series of those receiving EUS. This may bias the accuracy estimate of EUS for detection of non-resectable disease in these studies. The pre-test probability (ie the prevalence) of late stage disease in the study populations is likely to be lower than commonly found in clinical practice.

Only one study (Botet et al 1991a) provided high quality evidence in an applicable patient population for the assessment of EUS in oesophageal cancer staging. This study provided level II evidence for diagnostic accuracy according to the NHMRC levels of evidence (NHMRC 2005). The included population was appropriate because it was made up of consecutive patients with oesophageal cancer who were planned for surgery. Because all patients underwent curative or palliative surgery, this study employed a valid reference standard for all patients receiving the index test. In this and other studies where all patients underwent surgery, the reference standard was high quality and the studies were not subject to differential verification bias.

There were eight studies considered to be medium quality and limited applicability (Choi et al 2000; Date et al 1990; Heeren et al 2004; Hordijk et al 1993a; Hordijk et al 1993b; Lerut et al 2000; Sihvo et al 2004; Ziegler et al 1991). These studies were considered to have significant selection bias because they included only patients undergoing curative surgical resection or excluded patients based on EUS results. All studies used an appropriate reference standard for all patients which limited verification bias. In seven studies, patients undergoing radical or subtotal oesophagectomy only were included. This introduced selection bias and reduced applicability of these studies. Selection bias was also present in the eighth study (Heeren et al 2004) because some patients were potentially excluded based on the results of EUS. These eight studies provided level III-1 evidence according to NHMRC levels of evidence for diagnosis (NHMRC 2005).

There were two other studies that provided level III-2 evidence according to NHMRC levels of evidence for diagnosis (NHMRC 2005). Flamen et al (2000) included a population of consecutive patients who were evaluated for resectability, consequently making this study applicable to the current review. The reference standard consisted of surgery for most patients; some had clinical and radiographic follow up only (duration not reported), resulting in differential verification bias and reducing the quality of the study. Luketich et al (2000) assessed a sample of patients included in the Flamen et al (2000) study based on their having received the reference standard intervention, laparoscopic staging. The authors did not report whether patients were consecutive, which reduced the study quality due to selection bias. The quality of this study was further reduced because of differential verification bias, as a valid reference standard was not used in all patients.

A further limitation to the applicability of the included studies relates to the age of the technologies used (**Table 34**). Only the Olympus GF-UM20 radial scanner was considered to be appropriate; older models and linear scanners were deemed to be superseded.

The study by Botet et al (1991a) was a high quality prospective case series conducted with 50 consecutive patients undergoing surgery for biopsy-proven epidermoid carcinoma or adenocarcinoma of the oesophagus. The EUS and CT technologies described in this study have been superseded (**Table 34**). This aspect limits its applicability. Of the 50 patients, eight were excluded because CT had previously been performed. The remaining 42 patients were included in the analysis.

The study by Flamen et al (2000) was a prospective case series in 74 consecutive patients with biopsy-proven carcinomas of the oesophagus (n = 43) or gastro-oesophageal junction (n = 31) who had been evaluated for resectability. The study reported two outcomes that were included in the current review: the detection of malignant lymph node involvement and the detection of stage IV disease. Only 39 patients were included for the former outcome. Inclusion was made on the basis of receiving the reference standard, which consisted of histological examination of materials obtained from a two- or three-field lymphadenectomy in these 39 patients. This population is considered to be of limited applicability. Lerut et al (2000) report a duplicate study of this patient group where outcomes were expressed per patient rather than per node.

The detection of stage IV disease in the study by Flamen et al (2000) was assessed in the whole patient population, which provided high applicability for this outcome. This study is subject to differential verification bias because patients were assessed using different reference standards.

Luketich et al (2000) prospectively evaluated a series of patients with potentially resectable oesophageal cancer who were undergoing minimally invasive surgical staging. Patients determined to have bulky, unresectable locoregional disease or unequivocal, multiple sites of metastases by CT or EUS were excluded from the study. The remaining 53 patients were included in the analysis. As some patients' tumours were determined to be unresectable by EUS, they were not included. This was not an appropriate patient population and the study was of limited applicability. Not all patients received the same reference standard, thus reducing the quality of the study due to differential verification bias.

The study by Choi et al (2000) was a prospective case series in 61 consecutive patients with biopsy-proven oesophageal cancer who underwent FDG (F-18 fluorodeoxyglucose) PET. Transthoracic oesophagectomy was performed in all patients except 13 who either refused surgery (n = 5) or whose disease was determined to be inoperable (n = 8); the basis for inoperability was unclear in three of these patients. These patients were not included in the data analysis. Patients whose tumours were determined to be unresectable and who were not undergoing palliative surgical therapy were excluded from the patient population. Histological examination in the remaining 48 patients who underwent surgery revealed squamous cell carcinoma in all cases. The results from pre-operative staging with FDG PET, CT and EUS were compared with histological examination in these 48 patients. There is likely to be a referral bias in the population included this study, because these patients probably had more prior tests than is typical in clinical practice.

Date et al (1990) studied 20 patients with squamous cell carcinoma of the oesophagus who underwent subtotal oesophagectomy. The authors did not report whether the study was prospective. The study results are of limited applicability because only patients undergoing surgical resection were included.

Heeren et al (2004) conducted a prospective study in 74 consecutive patients with resectable carcinomas of the oesophagus (n = 40) or gastro-oesophageal junction (n = 34). Two patients had distant organ disease (M1b) and were not surgical candidates. This study reported the detection accuracy of combined CT and EUS for distant nodal disease (M1a) in the remaining 72 patients. EUS was performed in 46 patients using a radial scanner, and in eight patients using a small-calibre probe. EUS was performed inadequately for the remaining 20 patients, and corresponding patient data were excluded from the analysis. The use of a mini-probe in some of the patients limits the applicability of the findings in this study. Surgery for resection or exploration without resection was performed in 68 patients. The remaining four patients received EUS-guided FNA of lymph nodes. Since EUS-guided FNA was used as a reference standard, this study is subject to verification bias because the index test is incorporated into the reference standard for this subset of patients.

There were two prospective studies by Hordijk et al that investigated the use of EUS for T-staging in patients with resectable carcinoma of the oesophagus or gastro-oesophageal junction (Hordijk et al 1993a) and in patients with resectable carcinoma of the oesophagus following induction chemotherapy (Hordijk et al 1993b). It is unclear whether some patients in the latter study (n = 11) are a subset of the patients in the former study (n = 41). In all 11 patients presented in the study by Hordijk et al (1993b), the results of T staging with CT and EUS were obtained following induction chemotherapy. The 41 patients in the other study (Hordijk et al 1993a) did not include those who received non-operative treatment because distant metastases had been detected on external US or CT (total 62). This exclusion criterion is appropriate to this review.

Sihvo et al (2004) carried out a prospective case series in patients with histologically proven adenocarcinoma of the oesophagus or the gastro-oesophageal junction. Patients were excluded if they could not undergo surgery due to medical reasons or if conventional staging showed that the tumour was unresectable, leaving 55 patients included in the analysis. The study outcomes presented included accuracy measures for the detection of locoregional lymph node metastases (N staging) among patients undergoing lymphadenectomy (N = 43) and the detection of distant metastases (M staging) in all 55 patients.

In the prospective study by Ziegler et al (1991), all patients admitted to hospital for investigation of oesophageal tumours were included. Of 52 patients with histologically proven squamous cell carcinoma of the oesophagus, 15 patients did not undergo surgery due to the presence of distant metastases or because of general clinical conditions. It was not reported whether some of these patients were excluded from surgery on the basis of EUS findings. Of the remaining 37 patients included in the analysis, 34 underwent surgery. There were three patients who did not have surgery and died in hospital. Therefore, all received an adequate reference standard.

**Table 34** **Included studies addressing the incremental value of EUS over CT in oesophageal neoplasm staging**

| Author (year) Country | Study design | Patients (N) | Prior tests (%) | EUS characteristics | CT and PET characteristics | Reference standard (%) | Study quality[a] |
|---|---|---|---|---|---|---|---|
| Botet et al (1991a)<br>USA | Prospective, consecutive patients, inclusion based on clinical presentation<br>Incremental data, EUS for TN staging, CT for M staging<br>December 1986–December 1988 | Patients with epidermoid carcinoma or adenocarcinoma of the oesophagus planned for palliative or curative surgery<br>(42) | Endoscopy (100%) | EUS: Olympus GF-UM2, GF-UM3<br>Operator: radiologist | CT: dynamic CT, 1200SX Picker Int or GE9800 GE Medical Systems, 10 mm slices<br>Multiple radiologists of comparable experience<br>Performed after EUS | Surgery (100%) | C1 P2 Q1<br>*Quality*: high<br>*Applicability*: limited<br>Outdated technology, not either positive approach, patient group applicable |
| Choi et al (2000)<br>Korea | Prospective, reference standard-based inclusion<br>Replacement study with individual patient data<br>February 1997–December 1998 | Patients with biopsy-proven oesophageal cancer undergoing oesophagectomy with 2- or 3-field lymph node dissection<br>(48) | Bone scintigraphy (100%), oesophagogastro-duodenoscopy (100%), bronchoscopy (100%), abdominal (100%) and neck sonography (1.6%) within 3 weeks of PET | EUS: Olympus GF-UM20 radial scanner<br>Operator: one gastroenterologist<br>Blinded to other imaging modalities | CT: Helical CT, 5 mm or 7 mm collimation<br>Interpreted before surgery by 1 radiologist<br>PET: advance PET scanner, General Electric Medical Systems, 5 minutes/frame | Surgery (100%) | C1 P2 Q2<br>*Quality*: medium<br>Selection bias<br>*Applicability*: limited<br>Resected patients only |
| Date et al (1990)<br>Japan | Unclear direction, reference standard-based inclusion<br>Replacement study with individual patient data<br>1985–1988 | Patients with squamous cell carcinoma of the oesophagus, undergoing subtotal oesophagectomy<br>(20) | Barium swallow and endoscopic evaluation (100%) | EUS: Olympus GF-UM2 radial system fibrescope, with balloon-filling technique | CT: details not reported | Surgery (100%) | C1 P2 Q2<br>*Quality*: Medium<br>Selection bias<br>*Applicability*: limited<br>Resected patients only, outdated technology |

| Author (year)<br>Country | Study design | Patients (N) | Prior tests (%) | EUS characteristics | CT and PET characteristics | Reference standard (%) | Study quality[a] |
|---|---|---|---|---|---|---|---|
| Flamen et al (2000)<br>Belgium | Prospective, consecutive patients, inclusion based on clinical presentation<br>Incremental data, either positive<br>October 1997–December 1998 | Mixed population of oesophageal and GOJ biopsy-proven cancer patients evaluated for resectability<br>(74) | Laboratory tests, neck US, barium oesophagogram, bronchoscopy 100%) | EUS: Olympus UM-20 radial scanner (% NR), Pentax linear sector scan (% NR)<br>Operator: 1–3 examiners with 4–12 years of experience<br>Blinded to other imaging modalities | CT: spiral CT; 5 mm slices<br>PET: CTI-Siemens 931/08/12 scanner | Surgery (68%), dedicated radiographic techniques (NR), or clinical and radiographic follow up (NR) | C1 P1 Q2<br>*Quality*: medium<br>Differential verification bias<br>*Applicability*: applicable (stage IV)<br>Limited (nodes) |
| Lerut et al (2000)<br>Belgium<br>Substudy of Flamen et al (2000) | Prospective, reference standard-based inclusion<br>Replacement study with individual patient data<br>October 1997–December 1998 | Mixed population of oesophageal and GOJ biopsy-proven cancer patients undergoing primary curative surgery with 2- or 3-field lymphadenectomy<br>(39) | Laboratory tests, neck US, barium oesophagogram, bronchoscopy (100%) | EUS: Olympus UM-20 radial scanner, Pentax linear sector scan<br>Operator: 1–3 examiners with 4–12 years of experience | CT: spiral CT; 5 mm slices<br>PET: CTI-Siemens 931/08/12 scanner | Surgery (100%) | C1 P2 Q2<br>*Quality*: medium<br>Selection bias<br>*Applicability*: limited<br>Resected patients only |
| Heeren et al (2004)<br>Netherlands | Prospective, test-based inclusion<br>Incremental data, either positive<br>January 1996–January 2002 | Mixed population of patients with resectable carcinoma of the thoracic oesophagus and GOJ based on CT, EUS and US<br>(72) | Neck ultrasonography (100%) | EUS: Olympus GF-UM20 radial scanner (n = 46) or Olympus MH-908 small-calibre probe (n = 8); inadequate EUS in 20 patients<br>Blinded to other staging methods | CT: fourth generation units (SR7000 Philips Medical Systems), or spiral Siemens Somatron Plus 4<br>Operator: experienced oncological radiologist<br>PET: Siemens ECAT HR+ positron camera | Surgical resection with curative attempt (56%), explorative laparotomy (39%), FNA biopsy (6%) | C1 P2 Q2<br>*Quality*: medium<br>Selection bias<br>*Applicability*: limited<br>Potentially excluded patients determined unresectable by EUS<br>15% patients mini-probe |
| Hordijk et al (1993a)<br>Netherlands | Prospective study, non-consecutive, inclusion based on clinical presentation | Mixed population of patients with carcinoma of the oesophagus or GOJ proven by endoscopic biopsy | Endoscopy, neck US, guided cytological needle aspiration biopsy (100%) | EUS: Olympus GF-UM3/EUM3 | CT: Somatom Plus | Surgery (100%)<br>Time lag: 2 weeks | C1 P2 Q2<br>*Quality*: medium<br>Selection bias |

| Author (year)<br>Country | Study design | Patients (N) | Prior tests (%) | EUS characteristics | CT and PET characteristics | Reference standard (%) | Study quality[a] |
|---|---|---|---|---|---|---|---|
| | Replacement study with individual patient data<br>January 1990–June 1991 | undergoing transhiatal oesophagectomy<br>(41) | | | | | *Applicability*: limited<br>Outdated technology, patient group applicable |
| Hordijk et al (1993b)<br>Netherlands | Prospective study, non-consecutive, inclusion based on clinical presentation<br>Replacement study with individual patient data<br>January 1990–September1992 | Patients with resectable squamous cell carcinoma of the oesophagus undergoing transhiatal oesophagectomy following induction chemotherapy<br>(11) | Endoscopy, neck US, guided cytological needle aspiration biopsy (100%) | EUS: Olympus GF-UM3 EUM3 | CT: third-generation Somatom plus | Surgery (100%) | C1 P2 Q2<br>*Quality*: medium<br>Selection bias<br>*Applicability*: limited<br>Post-induction chemotherapy resectable patients only, outdated technology |
| Luketich et al (2000)<br>USA | Prospective study, reference standard-based inclusion<br>Incremental data, method not reported<br>May 1995–September 1998 | Patients with potentially resectable oesophageal cancer<br>(53) | No prior tests reported | EUS: details not reported | CT: details not reported | Laparoscopic staging with intraoperative ultrasound (83%) and video-thoracoscopy (79%) | C1 P2 Q2<br>*Quality*: medium<br>Selection bias, differential verification bias<br>*Applicability*: limited<br>Potentially excluded patients determined unresectable by EUS, potentially outdated technology |
| Sihvo et al (2004)<br>Finland | Prospective study, reference standard-based inclusion<br>Incremental data, method not reported<br>December 1998–October 2003 | Mixed population of patients with histologically proved adenocarcinoma of the oesophagus (36%) or GOJ (64%) undergoing radical oesophagectomy and lymphadenectomy<br>(55) | Endoscopy (100%) | EUS: details not reported | CT: details not reported<br>PET: advance PET scanner, General Electric Medical Systems, 5 minutes/frame | Primary surgery with 2-field lymphadenectomy (78%), explorative surgery with palliative treatment (22%) | C1 P2 Q2<br>*Quality*: medium<br>Selection bias<br>*Applicability*: limited<br>Resected patients only |

| Author (year)<br>Country | Study design | Patients (N) | Prior tests (%) | EUS characteristics | CT and PET characteristics | Reference standard (%) | Study quality[a] |
|---|---|---|---|---|---|---|---|
| Ziegler et al (1991)<br>Germany | Prospective study, reference standard-based inclusion<br>Replacement study with individual patient data<br>January 1986–July 1988 | Patients with histologically proven squamous cell carcinoma of the oesophagus undergoing subtotal oesophageal resection<br>(37) | Not reported | EUS: Siemens linear array scanner<br>Operator: fully trained endoscopist | CT: Siemens Somatom DRG or DRH, 8–10 mm section distance | Surgery (92%), necropsy (8%)<br>Time lag: 2 weeks | C1 P2 Q2<br>*Quality*: medium<br>Selection bias<br>*Applicability*: limited<br>Resected patients only, potentially excluded patients determined unresectable by EUS, outdated technology |

Abbreviations: CT, computed tomography; EUS, endoscopic ultrasound; FNA, fine needle aspiration; GOJ, gastro-oesophageal junction; NR, not reported; PET, positron emission tomography; US, ultrasound
[a] Grading system used to rate the study quality is explained in **Table 26**

The use of EUS for staging has the greatest impact on clinical management when detecting late stage disease and avoiding unnecessary surgery. Therefore, data on the sensitivity of EUS for the detection of advanced disease are extracted in preference to data differentiating early stages. Detection of lymph node metastases may also aid in the selection of patients for adjunctive therapies with curative intent.

Based on three medium to high quality studies, the combined use of CT + EUS increases the sensitivity for detection of late stage oesophageal cancer (**Table 35**).

**Table 35 Incremental value of EUS following CT in the AJCC oesophageal cancer staging**

| Author (year) | Prevalence n/N (%) | Non-traversable tumours (%) | Sensitivity (%) (late stage) | | Specificity (%) (early stage) | | Accuracy (%) | | Quality[a] |
|---|---|---|---|---|---|---|---|---|---|
| | | | CT | CT + EUS | CT | CT + EUS | CT | CT + EUS | |
| ***Detection of stage AJCC III or IV*** | | | | | | | | | |
| Botet et al (1991a)[b] | 33/42 (21.4) | 0/42 | 78.8 | 97.0 | 66.7 | 77.8 | 76.2 | 92.9 | C1 P2 Q1 |
| ***Detection of AJCC stage IV*** | | | | | | | | | |
| Botet et al (1991a)[b] | 16/42 (38.1) | 0/42 | 75.0 | 81.3 | 100 | 100 | 90.5 | 92.9 | C1 P2 Q1 |
| Flamen et al (2000)[c] | 34/74 (45.9) | 19/74 (25.7) | 41.2 | 47.1 | 82.5 | 77.5 | 63.5 | 63.5 | C1 P1 Q2 |
| Sihvo et al (2004)[d] | 19/55 (34.5) | 7/55 (12.7) | 31.6 | 42.1 | 97.2 | 100 | 74.5 | 80.0 | C1 P2 Q2 |

Abbreviations: AJCC, American Joint Committee on Cancer; CT, computed tomography; EUS, endoscopic ultrasound
[a] Grading system used to rate the study quality is explained in **Table 26**
[b] EUS results used for T and N staging, and CT for M staging
[c] Either positive for stage IV disease
[e] Author's method for combining data is unclear, but cannot be either positive for stage IV approach

The diagnostic value of the combined use of EUS + CT in Botet et al (1991a) was determined by using EUS results for T and N staging and CT for M staging. This approach resulted in an increase in both the sensitivity and specificity for late stage oesophageal cancer, but does not reflect the likely interpretation of EUS findings in practice. An increase in specificity cannot occur when two tests are used in an either positive approach. Although Sihvo et al (2004) did not report the methods used to combine the EUS and CT results, the same approach appeared to have been used, as there was a similar increase in both the sensitivity and specificity. In contrast, the accuracy of CT + EUS reported by Flamen et al (2000) was determined by an either test positive approach for stage IV disease. Therefore, the small increase in sensitivity was observed with a loss in specificity when EUS findings are combined with those of CT in this manner. A loss of specificity represents over staging in some additional patients with early stage cancer. Since different methods were used to combine EUS and CT results, it is not possible to pool accuracy data on group staging.

Stage IV is differentiated from stage III on the basis of distant metastases (organs or lymph nodes) only. Therefore, interpretation of these data should be considered in conjunction with those of the accuracy of EUS for distant nodes (**Table 36**). These data similarly demonstrate an increase in sensitivity with a trade-off of loss of specificity when EUS is used in addition to CT.

**Table 36 Incremental value of EUS following CT or CT+PET to detect distant lymph node metastasis (M1a) of oesophageal cancer**

| Author (year) | Prevalence n/N (%) | Non-traversable tumours (%) | Sensitivity (%) (M1a) | | Specificity (%) (M0) | | Accuracy (%) | | Quality[a] |
|---|---|---|---|---|---|---|---|---|---|
| | | | CT | CT + EUS | CT | CT + EUS | CT | CT + EUS | |
| ***Detection of M1a—distant nodes*** | | | | | | | | | |
| Lerut et al (2000)[b] | 10/39 (25.6) | 5/39 (12.8) | 20.0 | 60.0 | 82.8 | 72.4 | 66.7 | 69.2 | C1 P2 Q2 |
| Heeren et al (2004)[c] | 24/72 (33.3) | NR | 20.8 | 29.2 | 97.9 | 95.8 | 72.2 | 73.6 | C1 P2 Q2 |

Abbreviations: CT, computed tomography; EUS, endoscopic ultrasound.
[a] Grading system used to rate the study quality is explained in **Table 26**.
[b] Study patients are included in Flamen et al (2000); data are presented per patient.
[c] EUS was not performed adequately in 20 patients.

There were four studies of medium quality and limited applicability identified that reported individual patient data for T staging. Data were extracted for the detection of T4 tumours in three of these studies and an either test positive approach was used. In all three studies, the combination of CT and EUS for T staging led to an increased sensitivity (**Table 37**). In two of the three studies, this occurred with no loss of specificity. In the third study, conducted in a population with a low prevalence (pre-test probability) of stage IV disease (Hordijk 1993a), there was a small decrease in specificity. Where the sensitivity of CT was 100 per cent, the combination of EUS and CT was naturally equivalent.

In two of the included studies (Hordijk et al 1993b; Hordijk et al 1993a), data were extracted for the detection of T3 or T4 tumours. The addition of EUS led to a decrease in specificity in one study and no change in the other study, which was conducted in a small population with low prevalence.

An ROC plot was constructed for the detection of T4 stage as seen in **Figure 22** in **Appendix H**. It is likely that some of the observed heterogeneity is due to the low prevalence seen in Hordijk et al (1993a). The results from these studies were not pooled due to the heterogeneity observed.

**Table 37 Incremental value of EUS following CT in T staging of oesophageal cancer**

| Author (year) | Prevalence n/N (%) | Non-traversable tumours (%) | Sensitivity (%) (late stage) | | Specificity (%) (early stage) | | Accuracy (%) | | Quality[a] |
|---|---|---|---|---|---|---|---|---|---|
| | | | CT | CT + EUS | CT | CT + EUS | CT | CT + EUS | |
| ***Detection of T4*** | | | | | | | | | |
| Date et al (1990)[b] | 11/20 (55.0) | 4/20 (20.0) | 90.9 | 100 | 44.4 | 44.4 | 70.0 | 75.0 | C1 P2 Q2 |
| Hordijk et al (1993a) | 1/41 (2.4) | 15/41 (36.6) | 100 | 100 | 70.0 | 67.5 | 70.7 | 68.3 | C1 P2 Q2 |
| Ziegler et al (1991) | 20/37 (54.1) | 7/37 (18.9) | 55.0 | 95.0 | 76.5 | 76.5 | 64.9 | 86.5 | C1 P2 Q2 |
| ***Detection of T3 or T4*** | | | | | | | | | |
| Hordijk et al (1993a)[c] | 29/41 (70.7) | 15/41 (36.6) | 100 | 100 | 41.7 | 33.3 | 82.9 | 80.5 | C1 P2 Q2 |
| Hordijk et al (1993b)[c] | 3/10[d] (30.0) | 1/11 (9.1) | 100 | 100 | 28.6 | 28.6 | 50.0 | 50.0 | C1 P2 Q2 |

Abbreviations: CT, computed tomography; EUS, endoscopic ultrasound

[a] Grading system used to rate the study quality is explained in **Table 26**

[b] Outcomes were defined as degree of adventitial involvement. A positive finding (A3) indicated the adventitia was interrupted or lost with continuity of low tumour echoes to adjacent organs and was considered equivalent to T4 in terms of TNM staging.

[c] These data were obtained from 12 year old studies using outdated technology and expertise and does not reflect the quality of current EUS practice.

[d] Excludes one patient with unpassable tumour stenosis

Accuracy data on EUS and CT in locoregional lymph node (N) staging were provided by five separate studies classified as medium quality and limited applicability (**Table 38**). The combination of CT and EUS for N staging increased the sensitivity by comparison with CT alone in all five studies, but resulted in a decrease in specificity of staging in all but one study (Sihvo et al 2004). The study by Sihvo et al (2004) showed no change in specificity when EUS was added to CT. The method for combining the results of the two tests was not specified and it is possible that an either test positive approach was not applied. All other data represent an either test positive approach.

**Table 38 Incremental value of EUS following CT or CT + PET in oesophageal cancer N staging**

| Author (year) | Prevalence n/N (%) | Non-traversable tumours (%) | Sensitivity (%) (late stage, N1) | | Specificity (%) (early stage, N0) | | Accuracy (%) | | Quality[a] |
|---|---|---|---|---|---|---|---|---|---|
| | | | CT | CT + EUS | CT | CT + EUS | CT | CT + EUS | |
| **Following CT** | | | | | | | | | |
| ***Outcomes per patient*** | | | | | | | | | |
| *Limited applicability, medium quality studies* | | | | | | | | | |
| Choi et al (2000)[b] | 32/48 (66.7) | 12/45[c] (25.0) | 40.6 | 68.8 | 100 | 75.0 | 60.4 | 70.8 | C1 P2 Q2 |
| Lerut et al (2000)[d] | 21/32 (65.6) | 4/32 (12.5) | 42.9 | 81.0 | 90.9 | 45.5 | 59.4 | 68.8 | C1 P2 Q2 |
| Luketich et al (2000)[e] | 36/53 (67.9) | 13/47[e] (27.7) | 33.3 | 86.1 | 88.2 | 41.2 | 50.9 | 71.7 | C1 P2 Q2 |
| Sihvo et al (2004)[f] | 26/43 (60.5) | 7/43 (16.3) | 42.3 | 84.6 | 82.4 | 82.4 | 58.1 | 83.7 | C1 P2 Q2 |
| Ziegler et al (1991) | 25/37 (67.6) | 7/37 (18.9) | 40.0 | 72.0 | 66.7 | 50.0 | 48.6 | 64.9 | C1 P2 Q2 |
| **Following CT + PET** | | | | | | | | | |
| | | | CT+PET | CT+PET+ EUS | CT+PET | CT+PET+ EUS | CT+PET | CT+PET+ EUS | |
| Choi et al (2000) | 32/48 (66.7) | 12/45 (25.0) | 84.4 | 87.5 | 87.5 | 62.5 | 85.4 | 79.2 | C1 P2 Q2 |
| Lerut et al (2000)[d] | 15/25 (60.0) | 2/25 (8.0) | 53.3 | 86.7 | 80.0 | 40.0 | 64.0 | 68.0 | C1 P2 Q2 |
| Sihvo et al (2004)[f] | 26/43 (60.5) | 7/43 (16.3) | 50.0 | 84.6 | 100 | 100 | 69.8 | 90.7 | C1 P2 Q2 |

Abbreviations: CT, computed tomography; EUS, endoscopic ultrasound; PET, positron emission tomography
[a] Grading system used to rate the study quality is explained in **Table 26**
[b] Includes coeliac nodes
[c] Excludes three patients who were unable to tolerate EUS
[d] Study patients are included in Flamen et al (2000); data are presented per patient
[e] EUS was not performed for six patients
[f] Authors' method for combining data is unclear, but cannot be either test positive for stage IV approach

The accuracy of N staging reflects on the accuracy of selection of patients into stage IIa or IIb (AJCC group staging) and helps to determine whether adjunctive therapies (chemotherapy and/or radiotherapy) are indicated. Hence, more patients who are likely to benefit from this therapy would be selected, with a trade-off of additional patients receiving unnecessary adjunctive therapies.

An ROC plot was constructed for these results, as seen in **Figure 23** in **Appendix H**. There appeared to be a large amount of between-studies variance so these results were not pooled.

It is important to note that two studies (Choi et al 2000; Flamen et al 2000) assessing N staging included coeliac lymph nodes among regional lymph nodes. According to AJCC TNM staging criteria, these should be categorised as M1a stage disease (see **Table 36**). Inclusion of coeliac nodes in N staging may result in an altered accuracy estimate for this outcome. Two studies did not include coeliac lymph nodes for N staging (Lerut et al 2000; Sihvo et al 2004). The classification of regional lymph nodes was unclear in the remaining two studies (Luketich et al 2000; Ziegler et al 1991).

Three studies assessing N staging reported the incremental value of EUS in addition to CT and PET (Choi et al 2000; Lerut et al 2000; Sihvo et al 2004) (**Table 38**). These studies enabled calculation of the incremental value of EUS over CT alone and CT plus PET in the same patient group. The comparison between these two data sets indicates that the incremental value of EUS over prior staging tests is decreased when PET is available. Because the additional value of PET over CT in patients described in the study by Choi et al (2000) is greater than EUS alone, the further benefit of EUS is diminished when PET is performed. The incremental value of EUS over CT and PET in Choi et al (2000) appears to be less than the values observed in Lerut et al (2000) and Sihvo et al (2004). This may be accounted for by the inclusion of coeliac lymph nodes when assessing N staging in Choi et al (2000), as described above. In practice, EUS will not be performed if distant (M1a) lymph node metastases are identified on PET (see **Figure 1**). The presented data by Lerut et al (2000) do not include patients with distant metastases identified by PET. Therefore, the accuracy data for N staging from this study most closely reflect how EUS will be used in clinical practice.

### Gastric neoplasia

#### Staging

A study was identified that provided evidence on the incremental value of EUS over CT alone in staging patients with gastric cancer (Botet et al 1991b) (**Table 39**). This study did not determine group staging by CT and EUS using an either test positive approach, as was the case with an earlier study by the same authors (Botet et al 1991a). There were 50 consecutive patients with biopsy-proven gastric adenocarcinoma enrolled in the study with curative or palliative surgery planned for all. Of these, 17 patients received CT at other institutions and were excluded. The remaining 33 patients were included in the analysis. This was considered an appropriate population; it consisted of consecutive patients who were included on the basis of receiving the index test. Hence, there was no selection bias. Because all patients underwent surgery, a valid reference standard was used and there was no verification bias. The time lag between receiving CT and EUS and undergoing surgery was not reported; it is unlikely that there would be a significant delay in this clinical circumstance and is unlikely to be a major source of bias. The EUS technology used in this study was outdated and applicability is thereby reduced.

**Table 39 Studies included in the assessment of the incremental value of EUS over CT in gastric neoplasia staging**

| Author (year)<br>Country | Study design | Patients (N) | Prior tests (%) | EUS characteristics | CT characteristics | Reference standard (%) | Study quality[a] |
|---|---|---|---|---|---|---|---|
| Botet et al (1991b)<br>USA | Unclear direction, consecutive patients, inclusion based on clinical presentation<br>December 1986–December 1988 | Histologically proven gastric adenocarcinoma planned for palliative or curative surgery (33) | Biopsy (100%) | EUS: Olympus GFUM2, GFUM3; stomach water-filled electively<br>Blinded to CT | CT: dynamic CT, 1200SX Picker Int or GE9800 GE Medical Systems; 10 mm slices<br>Multiple radiologists<br>Performed after EUS | Pathological examination of resected tumours and perigastric lymph nodes (100%) | C1 P2 Q1<br>*Quality*: high<br>*Applicability*: limited<br>Outdated technology, patient group applicable |

Abbreviations: CT, computed tomography; EUS, endoscopic ultrasound
[a] Grading system used to rate the study quality is provided in **Table 26**

**Table 40 Incremental value of EUS following CT in the AJCC group staging of gastric cancer**

| Author (year) | Prevalence n/N (%) | Sensitivity (%) (late stage) | | Specificity (%) (early stage) | | Accuracy (%) | | Quality[a] |
|---|---|---|---|---|---|---|---|---|
| | | CT | CT + EUS | CT | CT + EUS | CT | CT + EUS | |
| ***Detection of AJCC stage IV*** | | | | | | | | |
| Botet et al (1991b)[b] | 11/33[c] (33.3) | 72.7 | 90.9 | 72.7 | 77.3 | 72.7 | 81.8 | C1 P2 Q1 |

Abbreviations: AJCC, American Joint Committee on Cancer; CT, computed tomography; EUS, endoscopic ultrasound; PET, positron emission tomography

[a] Grading system used to rate the study quality is provided in **Table 26**

[b] Not an either positive approach. Likely to be EUS for TN and CT for M based on Botet et al (1991a)

[c] Number of tumours

The single incremental study identified for gastric staging (Botet et al 1991b) was of high quality and medium applicability. Combining the results for AJCC group staging from EUS and CT resulted in both a greater sensitivity and specificity for late stage gastric cancer relative to CT alone. This increase in both values indicated that the authors had not used an either positive approach when determining group stage from the tests. An increase in specificity will not occur in practice where an either test positive approach for the combination of the two tests is used. The study used an inappropriate method for combining the findings of EUS and CT. The technology used was outdated, which reduced applicability.

Due to the limited evidence available for this research question, high quality studies (NHMRC level II studies for diagnosis [NHMRC 2005]) providing evidence for the replacement value of EUS and CT were also included for review.

There were two studies identified that were considered to provide level II evidence of diagnostic accuracy (Habermann et al 2004; Perng et al 1996). These studies of the replacement value of CT and EUS were of high quality and limited applicability. Both were prospective studies in a series of consecutive patients with gastric cancer who all underwent subsequent tumour resection. The EUS equipment used in each study was outdated, which reduced the applicability of the studies. The EUS sonograms in Habermann et al (2004) were assessed by an endoscopist who was blinded to the results of CT, further reducing the applicability of this study. In both studies, a valid reference standard—tumour resection with lymphadenectomy and histopathological examination of resected specimens—was used.

**Table 41 Studies included in the assessment of EUS replacement value compared with CT in gastric neoplasia staging**

| Author (year)<br>Country | Study design | Patients (N) | Prior tests (%) | EUS characteristics | CT characteristics | Reference standard (%) | Study quality[a] |
|---|---|---|---|---|---|---|---|
| Habermann et al (2004)<br>Germany | Prospective, consecutive patients, inclusion based on clinical presentation<br>February 1998–March 2000 | Patients with gastric cancer | Endoscopic biopsy (100%) | EUS: Olympus GF-UM2, GF-UM3 radial sector scan<br>Operator: single endoscopist with 8 years of experience<br>Blinded to CT<br>Performed within 3 days of CT | CT: Siemens single-detector row CT scanner, Somatom Plus 4<br>Operator: two radiologists, both with 7 years of experience<br>Performed within 3 days of EUS | Partial or complete gastrectomy with D1 or D2 lymphadenectomy (100%) | C1 P2 Q1<br>*Quality*: high<br>*Applicability*: limited<br>Outdated technology, patient group applicable |
| Perng et al (1996)<br>Taiwan | Prospective, consecutive patients, inclusion based on clinical presentation<br>November 1989–December 1993 | Patients with gastric adenocarcinoma | Not reported | EUS: Olympus EU-M3 radial mechanical sector scan | CT: Siemens Somatom DRH, 8 mm section intervals | Surgery (100%)<br>Time lag: 12 days from CT | C1 P2 Q1<br>*Quality*: high<br>*Applicability*: limited<br>Outdated technology, patient group applicable |

Abbreviations: CT, computed tomography; EUS, endoscopic ultrasound
Note: D1 lymphadenectomy denotes that all N1 nodes are removed en bloc with the stomach; D2 lymphadenectomy denotes that all N1 and N2 nodes are removed en bloc with the stomach
[a] Grading system used to rate the study quality is provided in **Table 26**

**Table 42 Diagnostic accuracy of EUS and CT in T staging gastric neoplasms**

| Author (year) | Prevalence n/N (%) | Sensitivity (%) | | Specificity (%) | | Accuracy (%) | | Quality[a] |
|---|---|---|---|---|---|---|---|---|
| | | CT | EUS | CT | EUS | CT | EUS | |
| ***Detection of T4*** | | | | | | | | |
| Habermann et al (2004) | 3/51 (5.9) | 100 | 100 | 95.8 | 100 | 96.1 | 100 | C1 P2 Q1 |
| Perng et al (1996)[b] | 23/69 (33.3) | 52.2 | 82.6 | 91.3 | 95.7 | 78.3 | 91.3 | C1 P2 Q1 |
| ***Detection of T3 or T4*** | | | | | | | | |
| Habermann et al (2004) | 22/51 (43.1) | 77.3 | 81.8 | 82.8 | 89.7 | 80.4 | 86.3 | C1 P2 Q1 |

Abbreviations: CT, computed tomography; EUS, endoscopic ultrasound

[a] Grading system used to rate the study quality is provided in **Table 26**

[b] Results were poorly reported in this study and accuracy measures were confirmed by cross-checking figures reported in the tables with those in the text of the paper.

In both replacement studies, EUS was more accurate than CT for distinguishing T4 from early stage tumours, with an equal or higher sensitivity and specificity (**Table 42**). The findings from Habermann et al (2004) also demonstrated a higher sensitivity and specificity for EUS over CT for the detection of T3 or T4 tumours.

An ROC plot was constructed for these results (**Figure 24** in **Appendix H**). These results were not pooled because there appeared to be a large amount of between-studies variance.

This head-to-head comparison of the replacement value of the two tests does not indicate the sensitivity and specificity for T staging when the two tests are used in combination. A range of possible values that would be observed if the two tests had been used in combination in the study population can be determined (see page 57): if both tests in the study by Habermann et al (2004) were used in combination in an either test positive approach, the sensitivity for the detection of T4 tumours would have been 100 per cent, with a specificity for early stage tumours of 95.8 per cent. In the study by Perng et al (1996), the combined EUS and CT sensitivity for detection of T4 would have been between 82.6 and 100 per cent, with a specificity of between 87.0 and 91.3 per cent.

**Table 43 Comparison of EUS and CT in lymph node (N) staging of gastric neoplasms**

| Author (year) | Prevalence n/N (%) | Sensitivity (%) | | Specificity (%) | | Accuracy (%) | | Quality[a] |
|---|---|---|---|---|---|---|---|---|
| | | CT | EUS | CT | EUS | CT | EUS | |
| ***Detection of N1 or N2*** | | | | | | | | |
| Habermann et al (2004) | 31/50 (62.0) | 74.2 | 96.8 | 84.2 | 100 | 78.0 | 98.0 | C1 P2 Q1 |
| Perng et al (1996)[b] | 37/69 (53.6) | 27.0 | 67.6 | 81.3 | 75.0 | 52.2 | 71.0 | C1 P2 Q1 |
| ***Detection of N2*** | | | | | | | | |
| Habermann et al (2004) | 19/50 (38.0) | 73.7 | 84.2 | 77.4 | 93.5 | 76.0 | 90.0 | C1 P2 Q1 |
| Perng et al (1996)[b] | 20/69 (29.0) | 30.0 | 60.0 | 91.8 | 91.8 | 73.9 | 82.6 | C1 P2 Q1 |

Abbreviations: CT, computed tomography; EUS, endoscopic ultrasound

[a] Grading system used to rate the study quality is provided in **Table 26**

[b] Results were poorly reported in this study and accuracy measures were confirmed by cross-checking figures reported in the tables with those in the text of the paper.

Both high quality replacement studies demonstrated that EUS had a higher sensitivity than CT for the detection of lymph nodes (**Table 43**). Habermann et al (2004) demonstrated that EUS had a greater specificity, while in Perng et al (1996) the specificity of EUS was lower than in CT.

An ROC plot was constructed for these results (**Figure 25** and **Figure 26** in **Appendix H**). These results were not pooled because there appeared to be a large amount of between-studies variance.

In the study by Habermann et al (2004), had EUS been used as an incremental test with an either positive approach, the sensitivity of EUS + CT for the detection of N1 or N2 staging would have been between 96.8 and 100 per cent, with a specificity of 84.2 per cent. For the detection of N2 staging, the combined tests would give a sensitivity of between 84.2 and 100 per cent, with a specificity of between 71.0 and 77.4 per cent. In the study by Perng et al (1996), if the tests had been used in combination for the detection of N1 or N2, the sensitivity would have been between 67.6 and 94.6 per cent, with a specificity of between 56.3 and 75.0 per cent. For the detection of N2 staging the combined tests would give a sensitivity of between 60.0 and 90.0 per cent, with a specificity of between 83.7 and 91.8 per cent.

### Submucosal tumours diagnosis

There were seven studies concerning EUS accuracy to diagnose suspected gastric submucosal tumours included for review. Details of these studies are summarised in **Table 44**.

A prospective study by Caletti et al (1989) reported the value of EUS in the differentiation of gastrointestinal submucosal tumours (SMT) from extramural compression. This study was considered to be of medium quality and had limited applicability due to the use of outdated technology. The study included a consecutive group of patients presenting with gastric tumours suspected on endoscopy (Caletti et al 1989). The data were subject to differential verification bias because a high quality reference standard was not used for all patients for this outcome. The time period for

clinical follow up was not reported. According to NHMRC levels of evidence for diagnosis (NHMRC 2005), this study provided level III-2 evidence for this outcome.

A total of five studies provided information on the use of EUS (without FNA) to differentiate malignant from benign gastric submucosal tumours (Ando et al 2002; Caletti et al 1991; Kwon et al 2005; Matsui et al 1998; Tsai et al 2001). Of these, two studies also reported the use of EUS-FNA for this outcome (Ando et al 2002; Matsui et al 1998). Another study reported on the use of EUS-FNA to differentiate low-grade from high-grade malignant gastric gastrointestinal stromal tumours (GIST) (Okubo et al 2004).

All six studies were of medium quality and limited applicability. According to NHMRC levels of evidence criteria for diagnosis, four studies provided level III-1 evidence (Ando et al 2002; Matsui et al 1998; Okubo et al 2004; Tsai et al 2001) and two studies provided level III-2 evidence (Caletti et al 1991; Kwon et al 2005) for this outcome.

The study by (Ando et al 2002) was prospective; another was retrospective (Kwon et al 2005) and four studies were unclear in direction (Caletti et al 1991; Matsui et al 1998; Okubo et al 2004; Tsai et al 2001).

In five studies, the tumours were classified histologically in a manner that is no longer considered valid (Ando et al 2002; Caletti et al 1991; Matsui et al 1998; Okubo et al 2004; Tsai et al 2001) (see background page 13). The true disease status of patients in these studies is unknown according to current criteria. This severely limits the applicability of these studies with respect to current clinical practice. The study by Kwon et al (2005) used current classification for histological diagnosis of submucosal tumours. This study also used current EUS technology.

In two studies (Ando et al 2002; Tsai et al 2001), patients were included if they had undergone surgical resection for SMTs. In the study by Kwon et al (2005), patients were included on the basis of SMT confirmed by histological or cytological diagnosis. These formed a subset of the total population undergoing EUS for investigation of SMTs. The applicability of these three studies is limited because the patient populations were not representative of all patients undergoing EUS following endoscopy for suspected SMT. In the study by Okubo et al (2004), the applicability was limited because patient inclusion was based on obtaining sufficient samples for analysis by EUS-FNA.

In the studies by Caletti et al (1991) and Matsui et al (1998), patients were included on the basis of SMT identified by EUS. This is considered an appropriate patient population. The population considered was not a consecutive series of patients; there is the potential for selection bias in these studies.

There was no verification bias in the studies by Ando et al (2002), Caletti et al (1991), Okubo et al (2004) and Tsai et al (2001)—all included patients received a high quality reference standard. In the study by Matsui et al (1998), some patients received clinical follow up and repeated imaging as a reference standard. This was considered a valid reference standard within the context of this disease. The study by Kwon et al (2005) was subject to differential verification bias because FNA cytology was used as a reference standard in some patients.

The level of experience of the endosonographers was not reported in any of the included studies. In all studies, it was possible to construct $2 \times 2$ tables to confirm sensitivity and specificity values.

**Table 44 Studies included in the assessment of the value of EUS to diagnose gastric submucosal tumours (non-comparative studies)**

| Author (year)<br>Country | Study design | Patients (N) | Prior tests (%) | EUS characteristics | Reference standard (%) | Study quality[a] |
|---|---|---|---|---|---|---|
| Ando et al (2002)<br>Japan | Prospective, reference standard-based inclusion<br>October 1993– March 2000 | Patients who underwent resection of SMTs diagnosed by EUS (22 gastric, 1 duodenal)<br>(23) | NR | EUS: Olympus GF-UM20, radial<br>EUS-FNA: Convex Array, Pentax FG-32UA or FG36UX. Needle 22 G, average passes 2.83 (range 1–5) | Surgery (100%) | P2 Q2<br>*Quality*: medium<br>Selection bias<br>*Applicability:* limited<br>Resected patients only |
| Caletti et al (1989)<br>Italy | Prospective, consecutive patients<br>January 1986–April 1988 | Patients from a group of twenty five with endoscopically proven gastric SMTs[b]<br>(24) | Abdominal ultrasound (100%)<br>Multiple forceps biopsy (63%)<br>Endoscopy (100%) | EUS: Olympus GF-UM2/EUM2 with rotating transducer of 7.5 or 10 MHz. | Surgery (58%); abdominal ultrasound (42%); follow up (13%), time period not reported[c] | P2 Q2<br>*Quality*: medium<br>Differential verification bias<br>*Applicability*: limited<br>Outdated technology |
| Caletti et al (1991)<br>Italy | Unclear direction, test-based inclusion<br>January 1989–October 1990 | Patients with gastric SMTs with solid intramural growth detected by EUS<br>(21) | NR | EUS: Olympus GF-UM3/EUM3 | Surgery (76%); follow up (6-month intervals) by EUS and guillotine needle biopsy (24%) | P2 Q2<br>*Quality*: medium<br>Potential selection bias<br>*Applicability:* limited<br>Outdated histological classification |
| Kwon et al (2005)<br>Korea | Retrospective, reference-standard-based inclusion<br>August 2001–September 2003 | Patients with gastric SMTs confirmed by histology or cytology<br>(34) | NR | EUS: Olympus GF-UM240, UM-2R/3R, EU-M30 (7.5, 12/20 MHz), radial | Histological diagnosis by endoscopic resection; surgery; or core needle biopsy; FNA cytology[e] | P2 Q2<br>*Quality*: medium<br>Differential verification bias<br>Potential selection bias<br>*Applicability*: limited<br>SMT confirmed by reference standard |

| Author (year)<br>Country | Study design | Patients (N) | Prior tests (%) | EUS characteristics | Reference standard (%) | Study quality[a] |
|---|---|---|---|---|---|---|
| Matsui et al (1998)<br>Japan | Unclear direction, test-based inclusion<br>October 1993–May 1997 | Patients from group of 174 presenting with upper gastrointestinal SMTs diagnosed by EUS[d]<br>(20) | NR | EUS: Olympus GF-UM20, radial<br>EUS-FNA: Convex array, Pentax FG-32UA or FG-36UX. Pentax needle 22 G, average passes 4.3 | Surgical resection (65%); clinical follow up (35%) by repeated endoscopy and EUS at 6-month intervals, mean 14-month period (range 9–28 months) | P2 Q2<br>*Quality*: medium<br>Potential selection bias<br>*Applicability*: limited<br>Outdated histological classification |
| Okubo et al (2004)<br>Japan | Unclear direction, test-based inclusion<br>January 1997–March 2002 | Patients with resected GIST confirmed by IHC<br>(14) | EUS: Olympus GF-UM200, radial (100%), prior to EUS-FNA | EUS-FNA: Olympus GF-UCT 240, 22 G needle, 1–4 passes (average of 2.4 passes), NA-10J-KB or NA-11J-KB (Olympus)<br>Cytologist present | Surgery (100%) | P2 Q2<br>*Quality*: medium<br>Potential selection bias<br>*Applicability*: limited<br>Resected patients only |
| Tsai et al (2001)<br>Taiwan | Unclear direction, reference standard-based inclusion<br>October 1994–March 2000 | Patients with histologically proven gastric GIST undergoing resection or biopsy<br>(52) | Endoscopy (100%) | EUS: Olympus EU-M3, radial scanner | Surgery (98%); biopsy (2%) | P2 Q2<br>*Quality*: medium<br>Selection bias<br>*Applicability:* limited<br>Resected patients only |

Abbreviations: EUS, endoscopic ultrasound; FNA, fine needle aspiration; GIST, gastrointestinal stromal tumour; IHC, immunohistochemistry; NR, not reported; SMT, submucosal tumours

[a] Grading system used to rate the study quality is provided in **Table 26**

[b] EUS failed in one patient with a small SMT (0.5 cm) located in the prepyloric antral region

[c] Some patients had more than one reference standard

[d] The number of patients receiving each reference standard was not reported.

[e] Data from two duodenal patients were excluded. The reason for exclusion of the remaining 152 patients was not reported.

The study by (Caletti et al 1989) was medium quality and limited applicability. It reported the performance of EUS in the differentiation of gastric SMTs from extramural compression (**Table 45**). This study was subject to differential verification bias because some patients diagnosed with extramural compression received a reference standard of clinical follow up for an unknown time period. This study indicated that EUS was highly accurate in the differentiation of gastric SMTs from extramural compression.

**Table 45 EUS diagnostic accuracy to differentiate gastric SMTs from extramural compression**

| Author (year) Country | Prevalence n/N (%) | Patients | Sensitivity (%) | Specificity (%) | Accuracy (%) | Quality[a] |
|---|---|---|---|---|---|---|
| Caletti et al (1989) Italy | 13/24[b] (54) | Endoscopically proven gastric SMT | 100 | 100 | 100 | P2 Q2 |

Abbreviation: SMT, submucosal tumour
[a] Grading system used to rate the study quality is provided in **Table 26**
[b] One case of retroperitoneal haematoma was counted as an extrinsic compression

There were five studies of medium quality that employed outdated criteria for the histological classification of tumours (Ando et al 2002; Caletti et al 1991; Matsui et al 1998; Okubo et al 2004; Tsai et al 2001) (**Table 46**). Of these, three studies used two different thresholds of tumour size as the definition of a malignant tumour (Ando et al 2002; Matsui et al 1998; Tsai et al 2001) (**Table 46**). In the study by Okubo et al (2004), one mitotic figure per five fields was used to define high-grade malignancy. Caletti et al (1991) did not report a definition of malignancy. The use of outdated classification severely limits the applicability of these five studies. The diagnostic accuracy of EUS as determined in these studies and reported in **Table 46** should be interpreted with caution.

**Table 46 EUS accuracy to diagnose malignant gastric submucosal tumours in studies using outdated classification**

| Author (year) Country | Prevalence n/N (%) | Patient group | Definition of EUS outcome | Sensitivity (%) | Specificity (%) | Accuracy (%) | Quality[a] |
|---|---|---|---|---|---|---|---|
| **EUS** | | | | | | | |
| Ando et al (2002) Japan | 6/23 (26.1) | Gastric SMT identified by EUS and resected | Tumour > 5 cm, irregular border, cystic spaces | 83.3 | 76.5 | 78.3 | P2 Q2 |
| Caletti et al (1991) Italy | 2/21 (9.5) | Gastric SMT with solid intramural growth detected by EUS | Not reported | 0 | 94.7 | 85.7 | P2 Q2 |
| Matsui et al (1998) Japan | 3/20 (15) | Gastric SMT identified by EUS | Tumour > 3 cm, echoinhomogenicity, irregular borders | 66.7 | 82.4 | 80.0 | P2 Q2 |
| Tsai et al (2001) Taiwan | 11/52 (21.2) | Gastric SMT | Tumour > 5 cm, sonolucence, irregular margin | 72.7 | 90.2 | 86.5 | P2 Q2 |
| **EUS-FNA** | | | | | | | |
| Ando et al (2002) Japan | 6/23 (26.1) | Gastric SMT identified by EUS and resected | High number of mitotic figures; high cellularity; severe nuclear atypia | 66.7 | 100 | 91.3 | P2 Q2 |
| Matsui et al (1998) Japan | 3/20 (15) | Gastric SMT identified by EUS[b] | Mitotic figures; high cellularity; nuclear atypia | 100 | 100 | 100 | P2 Q2 |
| Okubo et al (2004) Japan | 5/14 (36) | GIST confirmed by immunohistochemical staining of resection specimen | High-grade malignancy: 1/5 HPF mitotic figure; high cellularity; severe nuclear atypia | 40 | 100 | 78.6 | P2 Q2 |

Abbreviations: EUS, endoscopic ultrasound; FNA, fine needle aspiration; GIST, gastrointestinal stromal tumour; HPF, high-power field; SMT, submucosal tumour

[a] Grading system used to rate the study quality is provided in **Table 26**

[b] Specimens for cytological diagnosis were inadequate in three cases. These specimens were counted as true negatives as there was no change in tumour size and echo characteristics during follow up.

There were three studies found that demonstrated moderate performance of EUS in terms of diagnostic accuracy for determining malignancy (Ando et al 2002; Matsui et al 1998; Tsai et al 2001). In the study by Caletti et al (1991), there was a low prevalence of malignancy. EUS demonstrated no sensitivity for detection of malignant tumours, but was highly specific for the diagnosis of benign tumours. All four studies were moderately accurate for the diagnosis of both malignant and benign tumours. All these study findings are of severely limited applicability.

The studies by Ando et al (2002) and Matsui et al (1998) also reported the performance of EUS-FNA in the differentiation of malignant versus benign SMTs identified by EUS. The sensitivity of EUS-FNA for the diagnosis of malignancy varied widely between the two studies. Both studies were highly specific for the diagnosis of benign tumours. In the study by Matsui et al (1998), EUS was highly accurate in the diagnosis of both malignant and benign tumours. This measure of accuracy should be interpreted with caution, because it is prevalence dependent. The study by Okubo et al (2004) reported on the performance of EUS-FNA to differentiate between low- and high-grade malignant gastrointestinal stromal tumours (GISTs). EUS sensitivity for the diagnosis of high-grade malignancy was poor, but specificity for the diagnosis of low-grade malignant tumours was again high. These studies were of medium quality and the use of outdated tumour classification severely limits their applicability.

The study by Ando et al (2002) also reported immunohistochemical analysis of GISTs. There were no statistically significant differences between benign and malignant tumours with respect to immunohistochemical activity (c-kit, CD34, muscle actin, and S-100) in this study. This finding should be considered with caution in light of the outdated histological classification system used in this study.

There was one medium quality and limited applicability study that provided evidence of the performance of EUS for the diagnosis of malignant gastric SMTs using current classification criteria (Kwon et al 2005) (**Table 47**). A diagnosis of leiomyoma or benign GIST made using EUS was considered a negative finding. A diagnosis of leiomyosarcoma or malignant GIST made using EUS was considered a positive finding. For classification of true disease status, GISTs considered as middle- and high-risk according to current histological classification (Fletcher et al 2002) were regarded as malignant by Kwon et al (2005). This study was potentially subject to differential verification bias as a result of the use of cytology as a reference standard in some patients. This study had limited applicability because it included only patients with histological or cytological confirmation of gastric SMTs.

The accuracy of EUS for the diagnosis of malignant SMTs as determined in this study is shown in **Table 47**. EUS was moderately sensitive in the diagnosis of malignant tumours and highly specific in the diagnosis of benign tumours. EUS was highly accurate for the diagnosis of both malignant and benign tumours. This measure of accuracy should be interpreted with caution because it is prevalence dependent. The diagnostic odds ratio and likelihood ratios provide strong evidence for the performance of EUS in the differentiation of malignant from benign gastric SMTs.

**Table 47 EUS accuracy to diagnose malignant and benign gastric submucosal tumours**

| Author (year) Country | Prevalence n/N (%) | Patient group | Definition of EUS Outcome | Sensitivity (%) | Specificity (%) | Accuracy (%) | Diagnostic odds ratio | LR+ | LR– | Quality[a] |
|---|---|---|---|---|---|---|---|---|---|---|
| Kwon et al (2005) Korea | 8/34 (23.5) | Gastric SMT confirmed by histological diagnosis | Tumour ≥ 3 cm, echoinhomogenicity, irregular borders, stippled high echo, cystic structure[b] | 75.0 | 96.2 | 91.2 | 75.0 | 19.5 | 0.26 | P2 Q2 |

Abbreviations: EUS, endoscopic ultrasound; LR+, positive likelihood ratio; LR–, negative likelihood ratio; SMT, submucosal tumour

[a] Grading system used to rate the study quality is provided in **Table 26**

[b] All criteria for the definition of EUS outcome may not apply to two tumours diagnosed as carcinoid tumours by EUS.

The search identified four studies that provided information on the performance of EUS in the diagnosis of malignant SMTs using an outdated classification system. Data from these studies were not considered informative.

There were two studies reporting the accuracy of EUS-FNA for the diagnosis of malignant SMTs identified. Another study was identified that reported the accuracy of EUS-FNA for the diagnosis of high-grade malignancy GIST. All three studies used an outdated classification system. There was insufficient evidence to determine whether FNA together with EUS aids diagnosis of gastric SMTs.

A small study of limited applicability and medium quality indicated that EUS was highly accurate in differentiating gastrointestinal SMTs from extramural compression. Another small study of limited applicability and medium quality provided strong evidence of the value of EUS in the diagnosis of malignant SMTs.

### Pancreatic neoplasia

#### Pancreatic neoplasia diagnosis

##### *Pancreatic solid mass identified*

There were two comparators considered when assessing the diagnostic value of EUS with or without FNA in the diagnosis of pancreatic solid masses. It was considered that EUS would be used as an additional test following CT in most patients; it would not replace the use of any other diagnostic test. In this situation, the combined value of EUS and CT would be compared with CT alone, with an either test positive approach to diagnosis. It was considered that the use of EUS for some patients would replace CT-guided biopsy. The replacement value of CT-guided biopsy is considered in this review to assess the value of EUS in this way.

*EUS/EUS-FNA versus no EUS (following CT)*

There were two replacement studies of EUS and CT in the diagnosis of pancreatic solid masses identified that reported individual patient data allowing calculation of the additional value of EUS. The characteristics of these studies are listed in **Table 48**.

A study of medium quality, conducted in an applicable patient population, investigated the diagnostic accuracy of EUS in a non-consecutive subgroup of patients with a pancreatic solid mass lesion (Okai et al 1999). Because this subgroup was non-consecutive based on clinical presentation, a potential for selection bias was present in this analysis. This study did not report excluding patients with metastatic disease. Patients with malignant diagnoses based on EUS had confirmation of their disease status by surgery, cytology, autopsy or follow up with a clinical course compatible with malignancy. A patient with a malignant diagnosis received cytology to confirm disease status. This is not a valid reference standard for the purpose of this review; it is unlikely that this would have affected the results to any major degree. Patients diagnosed with a benign mass using EUS had either surgery or both clinical and imaging follow up for longer than 12 months. Therefore, as a valid reference standard was not used for all patients, this study is considered to provide level III-2 evidence according to NHMRC criteria for diagnostic accuracy (NHMRC 2005).

The other study identified was poor quality and had limited applicability (Harrison et al 1999). This study was a retrospective analysis investigating the performance of EUS and CT for the diagnosis and staging of pancreatic malignancy. The patient group were those undergoing pre-operative EUS and CT to evaluate a possible pancreatic mass.
All patients' disease status was established during surgery. This was regarded as a poor quality study because the basis for inclusion of patient records is unclear. It is likely that inclusion was based on whether patients underwent exploratory laparotomy. Therefore, it is possible that the study included only those with a EUS or CT finding that indicated surgical necessity. This study reported individual patient data that allowed the incremental sensitivity and specificity of EUS and CT over CT alone to be calculated in a subgroup of patients with a mass detected by CT. Because this subgroup was non-consecutive based on clinical presentation, a potential for selection bias was present in this analysis. These patients were part of a surgical series so the applicability of this study is diminished. Finally, an unspecified number of patients received non-spiral CT which lowered applicability because of the difference in index test approach in the remainder of patients. This study is considered to provide level III-1 evidence according to NHMRC criteria for diagnostic accuracy (NHMRC 2005).

The accuracy of EUS over CT alone for both identified studies is shown in **Table 49**.

**Table 48 Incremental value of EUS over CT alone to diagnose pancreatic solid mass: included studies**

| Author (year) | Study design | Patients (N) | Prior tests (%) | EUS characteristics | CT characteristics | Reference standard (%) | Study quality[a] |
|---|---|---|---|---|---|---|---|
| Okai et al (1999)<br>Japan | Prospective, test-based inclusion<br>Replacement study with individual patient data | Evaluated for pancreatic disease with a pancreatic solid mass lesion detected by US, CT or EUS (36) | Biochemical tests, US | EUS: Olympus GF-UM3, GF-UM20 or JF-UM200 radial scanner | CT: CT/T 9800 System with intravenous contrast agent with 5 mm sections at 5 mm intervals | Surgery (39), Autopsy (8), cytology (3), Clinical follow up with imaging (50) | C1 P1 Q2<br>*Quality*: Medium Selection bias, Inadequate reference standard<br>*Applicability*: Applicable |
| Harrison et al (1999)<br>USA | Retrospective, test-based inclusion<br>Replacement study with individual patient data | Obstructive jaundice (11), abdominal pain and weight loss (6), incidental CT finding (2).<br>Undergoing exploratory surgery (19)<br>No mass on CT (6) | Not reported | EUS: Olympus GF-UM20 radial scanner | CT: Spiral and non-spiral CT | Surgery (100) | C1 P2 Q3<br>*Quality:* poor insufficient information on inclusion, possibly test referent<br>*Applicability:* Limited Different CT technology Surgical exploration series |

Abbreviations: CT, computed tomography; EUS, endoscopic ultrasound; US, ultrasound

[a] Grading system used to rate the study quality is provided in **Table 26**

**Table 49 Accuracy of the incremental value of CT and EUS over CT alone to diagnose malignant pancreatic solid mass**

| Author (year) | Prevalence n/N (%) | Sensitivity (%) | | Specificity (%) | | Accuracy (%) | | Quality[a] |
|---|---|---|---|---|---|---|---|---|
| | | CT | CT+EUS | CT | CT+EUS | CT | CT+EUS | |
| Okai et al (1999) | 19/36 (52.8) | 78.9 | 100.0 | 88.2 | 76.5 | 83.3 | 88.9 | C1 P1 Q2 |
| Harrison et al (1999) | 9/12 (75.0) | 88.9 | 88.9 | 33.3 | 0 | 75.0 | 66.7 | C1 P2 Q3 |

Abbreviations: CT, computed tomography; EUS, endoscopic ultrasound; NR, not reported
[a] Grading system used to rate the study quality is provided in **Table 26**

In the study by Harrison (1999), EUS provided no additional value over CT in pancreatic mass diagnosis. These findings must be considered in light of the small patient numbers and the high prevalence of malignancy (surgical series) in this population. Due to the low quality and limited applicability of this study, this finding should be cautiously considered.

The study by Okai et al (1999) indicated that the diagnostic accuracy of EUS and CT was greater than that of CT alone. Using the either test positive approach to individual patient data, sensitivity increased from 78.9 per cent to 100 per cent; there was a small decrease in specificity—from 88.2 per cent to 76.5 per cent. While according to NHMRC levels of evidence for diagnosis this study is of a lower level, it involved a more relevant patient group. The findings of this study are more relevant to the purpose of this review.

On the basis of one applicable study, the available data suggest that EUS offers a small increase in sensitivity by comparison with using CT alone in the diagnosis of malignant solid mass pancreatic tumours. This occurred with a small loss of specificity.

*EUS-FNA versus CT-biopsy*

There were two comparative studies identified that reported on the accuracy of EUS-guided FNA and CT-guided biopsy in the diagnosis of pancreatic solid masses. The characteristics of these studies are shown in **Table 50**.

Of these, one study was medium quality and conducted in an applicable patient population (Harewood and Wiersema 2002). This study investigated the diagnostic accuracy of EUS-FNA in a consecutive group of patients recruited on the basis of a known or suspected solid pancreatic mass. Patients with biopsies with metastatic disease were excluded from the study. A subgroup of these patients had also received CT-guided biopsy. The comparative sensitivity and specificity of EUS-FNA and CT-guided biopsy could be calculated based on data provided for this subgroup. A selection bias was present in this analysis because this subgroup was non-consecutive based on clinical presentation. This study compared all findings with a valid reference standard. Patients with malignant diagnoses based on EUS-FNA had their disease status confirmed during surgery or cytologically with a clinical course compatible with malignancy. Patients diagnosed with benign masses using EUS-FNA had either surgery or both clinical and imaging follow up for longer than 12 months. Therefore, this study is considered to provide level III-1 evidence according to NHMRC criteria for diagnostic accuracy (NHMRC 2005).

The other two comparative studies identified were poor quality and applicability was unknown (Qian et al 2003). This study was a retrospective analysis investigating the comparative performance of EUS-FNA versus CT-FNA for the diagnosis of pancreatic malignancy. The patient group was made up of people undergoing pancreatic FNA, with clinical or histological follow up (80% of all patients undergoing biopsy). Details of the indication for which FNA was performed were not provided, but the group included patients with solid and cystic pancreatic lesions. Similarly, prior tests were not described. Thus, there was potential for referral bias.

The study reported parallel data—tests were performed in different patient groups, not a sequence of the same patients. The possibility that the disease prevalence and spectrum differed between the patient groups created a significant potential for bias in estimating test performance. The authors stated that EUS was used on more difficult lesions; in particular, a higher proportion of small (< 3 cm) lesions were examined by EUS, compared with lesions examined by CT-FNA (67% vs 36% of the different patient groups, respectively). This was associated with a higher rate of unsatisfactory specimen collection for EUS (25% for EUS vs 12% for CT). The reference standards for positive cases were surgery, nodal/omental metastatic biopsy, and death from metastatic carcinoma or radiological and clinical follow up. Negative cases were confirmed by surgical biopsy/excision in 45 per cent of cases or clinical and CT follow up for at least two years (55% of cases). The study was therefore subject to differential verification bias.

The accuracy of EUS-FNA versus CT-FNA/guided biopsy reported in the two identified studies is shown in **Table 51**.

**Table 50 EUS-FNA versus CT-FNA/guided biopsy to diagnose pancreatic malignancy in patients with identified pancreatic mass: included studies**

| Author (year) | Study design | Patients (N) | Prior tests (%) | EUS characteristics | Comparator | Reference standard (%) | Study quality[a] |
|---|---|---|---|---|---|---|---|
| Harewood and Wiersema (2002) | Prospective, test-based inclusion<br>Incremental value study, replacement value calculable | Known or suspected solid pancreatic mass, with previous CT-guided biopsy, excluding diagnosed metastatic<br>(61)[b] | CT scan (100%) | EUS: Olympus GF-UM20 or GF-UM30 radial scanner<br>EUS-FNA: Olympus GF-UC30P or Pentax FG-32UA linear array, 22 G Wilson Cook needle Median of five passes | CT-guided biopsy: 18–20 G guiding needle with 22 G aspiration needle Median of three passes, range 2–5<br>Cytopathologist present (84%) | Surgery, > 12 month clinical and imaging follow up, cytology and compatible clinical course | C1 P1 Q2<br>*Quality*: medium Selection bias<br>*Applicability*: applicable |
| Qian and Hecht (2003) | Retrospective, test-based inclusion<br>Parallel test application<br>January1995–June 2001 | Patient population characteristics not reported (includes solid and cystic lesions)<br>(137) | Not reported | EUS: NR<br>EUS-FNA: uncontrolled with respect to needle size, number of passes or presence of cytologist. Generally, 2–3 passes, 22 G needle | CT-FNA<br>Details not reported | Surgery, clinical/radiographic (CT) data, > 2 years follow up | CX P2 Q3<br>*Quality*: poor Selection bias, detection bias (tests not in same patients), poor reporting<br>*Applicability*: limited Prior tests unclear, includes cystic lesions |

Abbreviations: CT, computed tomography; EUS, endoscopic ultrasound; FNA, fine needle aspiration; NR, not reported

[a] Grading system used to rate the study quality is provided in **Table 26**

[b] The patients reported in this comparison are a subgroup of the entire study population.

**Table 51 Accuracy of EUS-FNA versus CT-FNA/guided biopsy to diagnose pancreatic malignancy in patients with identified pancreatic mass**

| Author (year) | Prevalence n/N (%) | Sensitivity (%) | | Specificity (%) | | Accuracy (%) | | Quality[a] |
|---|---|---|---|---|---|---|---|---|
| | | CT-Bx/FNA | EUS-FNA | CT-Bx/FNA | EUS-FNA | CT-Bx/FNA | EUS-FNA | |
| Harewood and Wiersema (2002) | 53/61 (87) | 6[c] | 91[b] | 100[c] | 100[b] | 18 | 92 | C1 P1 Q2 |
| Qian and Hecht (2003)[d] | EUS-FNA: 38/63 (67)<br>CT-FNA: 35/47 (74) | 69 | 34 | 100 | 100 | 77 | 60 | CX P2 Q3 |

Abbreviations: Bx, biopsy; CT, computed tomography; EUS, endoscopic ultrasound; FNA, fine needle aspiration

[a] Grading system used to rate the stud y quality is provided in **Table 26**

[b] Inadequate specimen and atypical results were counted as negative findings

[c] Inadequate samples unclear – either excluded or counted as negative findings

[d] There is a strong potential for bias in the findings of this study due to the poor study quality, particularly the parallel test study design.

Qian and Hecht (2003) commented that EUS-FNA might be less sensitive and more specific than CT-FNA in diagnosing pancreatic malignancies in different groups of patients with identified pancreatic masses. This finding is associated with EUS-FNA being performed in a patient group with a higher proportion of lesions smaller than 3 cm (which probably accounts for the higher rate of unsatisfactory specimen collection reported in the EUS-FNA group). The spectrum bias in this study is high. Due to the poor quality and unknown applicability of this study, the uncertainty surrounding this finding is high.

The study by Harewood and Wiersema (2002) provided a valid comparison of both tests performed in all patients. In this study, the diagnostic accuracy of EUS-FNA was greater than the reported level of CT-guided biopsy. The specificity estimate is limited in certainty due to the high prevalence of malignancy in the study population. In the publication, atypical and inadequate results were regarded as errors and counted as false positive if a mass was benign; or false negative if a mass was malignant. This potentially underestimated both the sensitivity and specificity of EUS-FNA. In this study, 13 per cent of EUS-FNA patients had inadequate sampling, giving a sensitivity of 91 per cent and a specificity of 50 per cent using this approach. To retain consistency with the accuracy determined for CT-guided biopsy, the data in **Table 51** were determined by counting all such samples as negative EUS results. It is unclear whether the patient group included people whose CT-guided biopsy tissue sample was inadequate. No false positive results for CT-guided biopsy were recorded. It appears that inadequate CT-guided biopsies must have been either excluded or treated as negative findings.

Based on one study of medium quality, the available data suggest that EUS-FNA is more accurate than CT-guided biopsy in the diagnosis of solid mass pancreatic tumours.

*EUS*

No comparative studies were identified that reported both the diagnostic accuracy of EUS and CT-guided biopsy for the diagnosis of pancreatic masses. Neither were there any comparative studies identified that were suitable for indirect comparison against CT-guided biopsy. Therefore, non-comparative studies of the highest quality available, according to NHMRC levels of evidence for diagnostic accuracy studies, were included for review.

A single study was identified that provided level II evidence for the accuracy of EUS in the diagnosis of pancreatic masses (Becker et al 2001). This study considered an echo-enhancing contrast agent and had limited applicability. Only one study providing III-1 evidence was identified and included for review (Brand et al 2000). The characteristics of these studies are shown in **Table 52.**

The high quality, level II study by Becker et al (2001) used consecutive enrolment of patients with solid pancreatic masses. The applicability of this study was diminished by its use of an echo-enhancing contrast agent. This study compared EUS with a valid reference standard of either surgery or histology with or without six months follow up.

The medium quality, level III-1 study by Brand et al (2000) reported on the diagnostic accuracy of EUS in patients with a focal pancreatic mass excluding those with uncomplicated cystic mass or inadequate histology. This study had potential for participant selection bias: enrolment was non-consecutive and based on clinical presentation. This study compared EUS results with a valid reference standard.

**Table 52 Included non-comparative studies of EUS to diagnose pancreatic solid mass**

| NHMRC level of evidence | Author (year) Country | Study design | Patients (N) | Prior tests (%) | EUS | Reference standard (%) | Study quality[a] |
|---|---|---|---|---|---|---|---|
| II | Becker et al (2001) Germany | Direction unclear, consecutive | Patients with solid pancreatic masses; excluding cystic and solid/cystic masses (23) | US (78), CT (22) | EUS: Pentax FG32-UA<br>IV contrast agent (1 mL FS069, Optison) | Surgery, histology, 6 months clinical follow up | P2 Q1<br>*Quality*: high<br>*Applicability*: limited<br>EUS used with a contrast agent |
| III-1 | Brand et al (2000) Germany | Prospective, test-based inclusion | Focal pancreatic mass; excluding uncomplicated cystic mass and patients with inadequate histology (115) | US (NR), CT (NR), ERCP (NR) | EUS: Olympus GF-UM3, GF-UM 20, GF-UM200 | Histopathology (100%) | P2 Q2<br>*Quality*: medium<br>Selection bias<br>*Applicability*: limited<br>Includes solid/cystic lesions |

Abbreviations: CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; IV, intravenous; NHMRC, National Health and Medical Research Council; NR, not reported; US, ultrasound

[a] Grading system used to rate the study quality is provided in **Table 26**

The diagnostic accuracy of EUS, as determined in the included studies, is shown in **Table 53**. The diagnostic accuracy of EUS used in combination with an intravenous contrast agent in the study by Becker et al (2001) was high. The medium quality non-comparative study by Brand et al (2000) in a patient population with focal pancreatic masses demonstrated high sensitivity and low specificity.

**Table 53 Value of EUS to diagnose pancreatic solid mass**

| Author (year) Country | Prevalence n/N (%) | Patient population | Uninterpretable results (%) | Sn (%) | Sp (%) | Accuracy (%) | Quality[a] |
|---|---|---|---|---|---|---|---|
| **EUS with contrast agent (level II)** | | | | | | | |
| Becker et al (2001) Germany | 16/23 (69.6) | Solid pancreatic mass | Not reported | 93.8 | 100.0 | 95.7 | P2 Q1 |
| **EUS with no contrast agent (level III-1)** | | | | | | | |
| Brand et al (2000) Germany | 81/115 (70.4) | Focal pancreatic mass | Not reported | 95.1 | 52.9 | 82.6 | P2 Q2 |

Abbreviations: EUS, endoscopic ultrasound; Sn, sensitivity; Sp, specificity
[a] Grading system used to rate the study quality is provided in **Table 26**

*CT-FNA/guided biopsy*

No studies were identified that provided level II evidence for the accuracy of CT-FNA/guided biopsy in the diagnosis of pancreatic masses. There were seven publications that provided level III-1 evidence which were included for review. Details of these studies are shown in **Table 54**. Of these, two publications appeared to be duplicate studies (Luning et al 1984; Luning et al 1985). Luning et al (1984) was excluded from further review.

All studies compared CT-FNA/guided biopsy with either histology or adequate clinical follow up; these were considered valid reference standards for this disease. The studies all had non-consecutive (based on clinical presentation) patient enrolment, which allows potential for selection bias.

The study by Sperti et al (1994) reported on the accuracy of CT-guided biopsy in the diagnosis of solid pancreatic masses. The patients included in the study by Rodriguez et al (1992) also had identified pancreatic masses. These studies were considered to be highly applicable. Two studies reported that some patients had pancreatic masses that were previously detected using other imaging techniques (Luning et al 1985; Mitchell et al 1988). Mitchell et al (1988) did not clearly describe inclusion criteria. The remaining two studies report that patient recruitment was based on suspected or known neoplasms and may include patients without identified solid masses (Geng et al 1987; Robins et al 1995).

Geng et al (1987) reported that all patients underwent surgery. Surgery is the optimal reference standard, and patient selection was not subject to verification bias. Four studies reported using clinical and imaging follow up for at least five months as a reference standard (Luning et al 1985; Robins et al 1995; Rodriguez et al 1992; Sperti et al 1994). Another study reported using clinical and imaging follow up but did not indicate for what time period (Mitchell et al 1988).

Patients in five of the six studies had biopsies using 22 G needles; Rodriguez et al (1992) used 16.5 G needles. None of the publications clearly stated if a cytopathologist was

present during sampling. Only Rodriguez et al (1992) identified the CT equipment that was used. Considering the age of the studies, it is likely that the technology used would now be considered obsolete. There were reports in three studies of patients undergoing abdominal ultrasound or CT scan previously, which is appropriate to the clinical pathway for this review.

**Table 54 Included level III-1 studies of CT-FNA/guided biopsy to diagnose pancreatic malignancy in patients with identified pancreatic mass**

| Author (year) Country | Study design | Patients (N) | Prior tests (%) | CT-FNA characteristics | Reference standard (%) | Study quality[a] |
|---|---|---|---|---|---|---|
| Geng et al (1987)<br>China | Unclear direction, test-based inclusion | Patients with known pancreatic neoplasms undergoing surgery[c]; excluding patients with other biliopancreatic lesions<br>(20) | Not reported | CT-FNA: unknown device using a 22 G Franseen needle | Surgery (100%) | P2 Q2<br>*Quality:* medium<br>Potential selection bias<br>*Applicability:* limited<br>Unknown whether a mass identified previously |
| Luning et al (1984)<br>Germany | Unclear direction, test-based inclusion<br>Duplicate of Luning et al 1985 | Pancreatic mass or to confirm suspected carcinoma<br>(141) | Not reported | CT-FNA: unknown device using a 22 G needle | Surgery, clinical and imaging follow up, five months of follow up | P2 Q2<br>*Quality*: medium<br>Potential selection bias<br>*Applicability*: limited<br>Data are presented for samples not patients |
| Luning et al (1985)<br>Germany | Unclear direction, test-based inclusion | Pancreatic mass or to confirm suspected carcinoma, excluding pseudocysts<br>(124) | CT (not reported) | CT-FNA: unknown device using a 22 G needle, 1–6 passes were used to obtain the sample | Surgery (36), clinical and imaging follow up (64) | P2 Q2<br>*Quality*: medium<br>Potential selection bias<br>*Applicability*: limited<br>Data are presented for samples, not patients |
| Mitchell et al (1988)<br>USA | Retrospective, test-based inclusion | Precise criteria unknown; most patients had abdominal pain and radiographic evidence of a pancreatic mass; patients excluded for inadequate follow up<br>(41) | Not reported | CT-FNA: unknown device using a 22 G needle | Surgery, clinical and imaging follow up | P2 Q2<br>*Quality*: medium<br>Potential selection bias<br>*Applicability*: limited<br>Inclusion criteria were not limited to previously detected mass |
| Robins et al (1995)<br>USA | Retrospective, test-based inclusion | Pancreatic lesions, excluding inadequate reference standard<br>(90) | Not reported | CT-FNA: unknown device using a 22 G needle | Surgery and autopsy (68), 18 months of clinical and imaging follow up (32) | P2 Q2<br>*Quality*: medium<br>Potential selection bias<br>*Applicability*: limited<br>Inclusion criteria were not limited to previously detected mass |

| Author (year) Country | Study design | Patients (N) | Prior tests (%) | CT-FNA characteristics | Reference standard (%) | Study quality[a] |
|---|---|---|---|---|---|---|
| Rodriguez et al (1992)<br>USA | Retrospective, test-based inclusion | Recently diagnosed pancreatic mass with adequate follow up<br>(41) | CT (88) or ultrasound (12) | CT-biopsy: Siemens Somatom DRH scanner using a 16.5 G Lee needle, with one or two passes to obtain the sample | Surgery, autopsy, six months of clinical and imaging follow up | P1 Q2<br>*Quality*: medium<br>Potential selection bias<br>*Applicability*: applicable |
| Sperti et al (1994)<br>Italy | Retrospective, test-based inclusion | Recently diagnosed solid pancreatic mass<br>(53) | Ultrasound (100) | CT-FNA: unknown device using a 22 G needle | Surgery, autopsy, 12 months of clinical follow up | P1 Q2<br>*Quality*: medium<br>Potential selection bias<br>*Applicability*: applicable |

Abbreviations: CT, computed tomography; FNA, fine needle aspiration
[a] Grading system used to rate the study quality is provided in **Table 26**

The diagnostic accuracy of CT-guided biopsy for the detection of malignancy in pancreatic masses is shown in **Table 55**. Where possible, atypical/uninterpretable samples were included as negative test results, and samples reported as suspicious were counted as positive test results.

There was a modest variation in the prevalence of malignant tumours within the studies, ranging from 70 per cent to 93 per cent. None of the studies reported exclusion of patients with known metastatic disease. The study by Luning et al (1985), which reported results per biopsy, had a prevalence of 36 per cent. Therefore, the severity of disease in the patients in these studies may be greater than encountered in practice.

All studies presenting results on a per patient basis reported 100 per cent specificity for CT-guided biopsy in the determination of malignancy. The study providing results on a per biopsy basis reported an imperfect specificity of 84 per cent. Reporting results on this basis is less applicable to use of this technology in practice. It should also be noted that Luning et al (1985) treated all inadequate samples as incorrect findings and counted them as either false negative or false positive results. This contributed to a conservative estimate of both the sensitivity and specificity.

A study of high applicability and medium quality used a 16.5 G biopsy needle, and reported CT-guided biopsy sensitivity at 45 per cent and 100 per cent specificity (Rodriguez et al 1992). Another study of high applicability and medium quality used a 22 G needle, and reported 98 per cent sensitivity and 100 per cent specificity (Sperti et al 1994). The sensitivities to detect malignancy in studies rated to be limited applicability and medium quality were in the range 74 to 100 per cent. These studies all used 22 G needles.

In summary, the available data are insufficient in terms of quality and quantity to determine whether EUS (without FNA) is more accurate than CT-guided biopsy in the diagnosis of pancreatic solid masses.

**Table 55 Accuracy of CT-FNA/guided biopsy to diagnose pancreatic malignancy in patients with identified pancreatic mass**

| Author (year)<br>Country | Prevalence<br>n/N (%) | Patient population | Uninterpretable result<br>(%) | Sn<br>(%) | Sp<br>(%) | Acc<br>(%) | Quality[a] |
|---|---|---|---|---|---|---|---|
| **Applicable patient group** | | | | | | | |
| Rodriguez et al (1992)[b]<br>USA | 29/41<br>(70.7) | Recently diagnosed pancreatic mass with adequate follow up | 8/41<br>(19.5) | 44.8 | 100.0 | 61.0 | P1 Q2 |
| Sperti et al (1994)<br>Italy | 54/58<br>(93.0) | Recently diagnosed solid pancreatic mass | 0/54<br>(0.0) | 98.1 | 100.0 | 98.3 | P1 Q2 |
| **Limited applicability patient group** | | | | | | | |
| Geng et al (1987)<br>China | 18/20<br>(90.0) | Patients with known pancreatic neoplasms undergoing surgery[c]; excluding patients with other biliopancreatic lesions<br>Positive results were also obtained in 20 tumours with a diameter < 30 mm | Not reported | 100.0 | 100.0 | 100.0 | P2 Q2 |
| Mitchell et al (1988)<br>USA | 38/41<br>(92.7) | Precise criteria unknown; most patients had abdominal pain and radiographic evidence of a pancreatic mass; patients excluded for inadequate follow up | Not reported | 73.7 | 100.0 | 75.6 | P2 Q2 |
| Robins et al (1995)[d,e]<br>USA | 63/90<br>(70.0) | Suspected pancreatic neoplasm, excluded if inadequate reference standard<br>Lesions ranged in size from 15 mm to 150 mm | Not reported | 85.7 | 100.0 | 88.9 | P2 Q2 |
| **Per biopsy** | | | | | | | |
| Luning et al (1985)[f]<br>Germany | 41/124<br>(36.3) | Pancreatic mass or to confirm suspected carcinoma, excluding pseudocysts | 15/124<br>(12.1) | 71.1 | 83.5 | 79.0 | P2 Q2 |

Abbreviations: Acc, accuracy; Sn, sensitivity; Sp, specificity
[a] Grading system used to rate the study quality is provided in **Table 26**
[b] When non-diagnostic results are excluded, sensitivity = 52%; specificity = 100%
[c] Ampullary lesions grouped with pancreatic
[d] Inconclusive lesions treated as suspicious
[e] Islet cell tumours treated as positives
[f] Equivocal and uninterpretable finding counted towards the false negative and false positive rates

*Diagnosis of pancreatic solid mass tumours: summary*

To assess the diagnostic value of EUS with or without FNA following CT in the detection of pancreatic solid masses two comparators were considered—
CT alone with no further tests and CT-guided biopsy.

On the basis of one medium quality applicable study, the available data suggest that EUS offers a small incremental benefit over using CT alone in the diagnosis of solid mass pancreatic tumours.

Similarly, EUS-FNA was considered more accurate than CT-guided biopsy in the diagnosis of solid mass pancreatic tumours on the basis of one applicable study of medium quality. It could not be determined whether EUS (without FNA) is more accurate than CT-guided biopsy in the diagnosis of pancreatic solid masses, because the quality and quantity of available data were insufficient.

### *Pancreatic cystic lesion*

No studies were identified that reported the incremental value of EUS over CT in the diagnosis of pancreatic cystic lesions. Studies reporting the replacement value of CT and EUS in the diagnosis of pancreatic cystic lesions (cystic masses, intraductal papillary or mucinous tumours) were included for review.

The literature review yielded four studies of medium quality (Baba et al 2004; Cellier et al 1998; Levy et al 1995; Yamao et al 2001). Of these, one was an appropriate direct comparison in which both CT and EUS were performed in all patients (Yamao et al 2001). In the other three studies, the comparison between EUS and CT was lower quality because both tests were not carried out for all patients (Baba et al 2004; Cellier et al 1998; Levy et al 1995). This has the potential to result in an inaccurate performance comparison.

Of the four studies, three were for patients with intraductal papillary-mucinous tumours (IPMT) (Baba et al 2004; Cellier et al 1998; Yamao et al 2001) and one was for patients with cystic pancreatic tumours (Levy et al 1995).

The characteristics of the four included studies are summarised in **Table 56**.

The patient population in the study by Levy et al (1995) was a consecutive series of patients with cystic pancreatic tumours. Use of superseded technology in this study limited its applicability. This study was subject to differential verification bias because some patients received surgery and others received an unspecified combination of clinical follow up, radiology or cytology for verification of true disease status (Levy et al 1995).

The applicability of the remaining three studies was limited. All of these studies included only patients receiving the reference standard. Only patients undergoing surgery were included in two studies (Cellier et al 1998; Yamao et al 2001).
Only patients with histologically proven IPMT were included in the remaining study (Baba et al 2004). Verification bias was absent in three studies (Baba et al 2004; Cellier et al 1998; Yamao et al 2001) because all patients received a
high quality reference standard.

It was possible to construct 2 × 2 tables to confirm the sensitivity and specificity values for CT and EUS for three of the studies (Cellier et al 1998; Levy et al 1995; Yamao et al 2001). The accuracy data reported by Baba et al (2004) are given here.

According to NHMRC levels of evidence (NHMRC 2005), three studies were rated as providing level III-1 evidence for diagnostic accuracy (Baba et al 2004; Cellier et al 1998; Yamao et al 2001). The study by Levy et al (1995) is rated level III-2.

**Table 56 Included studies of EUS and CT (without biopsy) to diagnose pancreatic cystic lesions**

| Author (year) Country | Study design | Patients (N) | Prior tests | EUS characteristics | CT characteristics | Reference standard (%) | Study quality[a] |
|---|---|---|---|---|---|---|---|
| Baba et al (2004) Japan | Retrospective, reference standard-based inclusion June 1988–February 2002 | Patients with IPMT diagnosed by histopathology (121) | Unclear: Possibly ERCP | EUS: radial scan type (brand not reported) (N = 49) | CT: details not reported (N = 121) | Histopathology (100%) | CX P2 Q2 *Quality:* medium; potential selection bias, detection bias *Applicability:* limited; histologically proven IPMT |
| Cellier et al (1998) Belgium France | Retrospective, reference standard-based inclusion 1980–1995 | Patients who had surgical resection for pathologically diagnosed IPMT (36) | Unclear: Possibly ERP | EUS: Olympus GF-UM3 (n = 11); GF-UM20 (n = 10) (performed between 1990 and 1995) (N = 21) | CT: various generations of conventional imagers used; spiral CT not used (N = 25) 10 patients only also received EUS | Surgery (100%) | CX P2 Q2 *Quality*: medium; selection bias, detection bias *Applicability:* limited; resected patients only |
| Levy et al (1995) France | Retrospective, consecutive patients 1988–1993 | Patients with cystic pancreatic tumours; excluded patients with cystic papillary and cystic endocrine tumours and non-tumoral cystic lesions (35) | NR | EUS: Olympus GF-UM3/EU-M3 and GF-UM20/EU-M20 (N = 31) | CT: details not reported (N = 35) | Surgery (83%); other tests (clinical follow up, radiological or cytological: 17%) | CX P2 Q2 *Quality*: medium; differential verification bias, detection bias *Applicability:* limited; outdated technology |
| Yamao et al (2001) Japan | Unclear direction, reference standard-based inclusion September 1991–October 1999 | Patients who had resection of IPMT (49) | Unclear: Possibly US and IDUS | EUS: JF-UM20 (7.5 MHz) and GF-UM240 (7.5 and 12 MHz) with ultrasound processors EU-M20 and M240 (N = 49) | CT: Yokogawa CT 9200 and General Electronics Hi-speed advantage (Helical CT) (N = 49) | Surgery (100%) | C1 P2 Q2 *Quality*: medium; selection bias *Applicability*: limited; resected patients only |

Abbreviations: CT, computed tomography; EUS, endoscopic ultrasound; ERP, endoscopic retrograde pancreatography; ERCP, endoscopic retrograde cholangiopancreatography; IDUS, intraductal ultrasonography; IPMT, intraductal papillary-mucinous tumour; NR, not reported; US, ultrasonography

[a] Grading system used to rate the study quality is provided in **Table 26**

**Table 57 Accuracy of EUS and CT (without biopsy) to diagnose malignant pancreatic cystic lesions**

| Author (year) | Prevalence n/N (%) | Patients | Definition of outcome | Sensitivity (%) | | Specificity (%) | | Accuracy (%) | | Quality[a] |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | CT | EUS | CT | EUS | CT | EUS | |
| **Direct comparison** | | | | | | | | | | |
| Yamao et al (2001) | 42/49 (86) | Patients who had resection of IPMT | Neoplasia[b,d] | 36 | 88 | 100 | 71 | 45 | 86 | C1 P2 Q2 |
| | 12/49 (25) | | Invasive carcinoma[c,d] | 33 | 50 | 100 | 97 | 84 | 86 | |
| **Both tests not performed in all patients** | | | | | | | | | | |
| Baba et al (2004)[e] | 74/121[f] (61) | Patients with IPMT diagnosed by histopathology | Cyst diameter[g] | 46 | 54.1 | 76.9 | 85.8 | 60.4 | 68.2 | CX P2 Q2 |
| | | | Main pancreatic duct diameter[h] | 50.5 | 40.4 | 81 | 74.9 | 61.6 | 53 | |
| | | | Height of protruding lesion[i] | 52.7 | 67.7 | 95.7 | 87.9 | 69.4 | 76.4 | |
| Cellier et al (1998) | EUS 9/21 (43)<br>CT 13/25 (52) | Patients who had surgical resection for IPMTs | Rupture and spread/invasion | 69.2 | 77.8 | 83.3 | 75.0 | 76.0 | 76.2 | CX P2 Q2 |
| Levy et al (1995) | EUS 6/31 (19)<br>CT 7/35 (20) | Patients with cystic pancreatic tumours | Adenocarcinoma: presence of vegetations, spread, dilated ducts | 100 | 100 | 100 | 96 | 100 | 96.8 | CX P2 Q2 |
| | EUS 14/31 (45)<br>CT 16/35 (46) | | Adenocarcinoma & adenoma: usually anechoic, wall thickening, intracystic partitions[j] | 75 | 86 | 95 | 59 | 86 | 71 | |

Abbreviations: CT, computed tomography; EUS, endoscopic ultrasound; IPMT, intraductal papillary-mucinous tumour

[a] Grading system used to rate the study quality is provided in **Table 26**

[b] Thickening and protrusion

[c] Heterogeneous pattern or interruption of duct wall

[d] Tumour not delineated in one case each for CT and EUS. For CT, the final diagnosis of this tumour was hyperplasia, so counted here as a true negative. For EUS, final diagnosis was invasive adenocarcinoma, so counted here as a false negative

[e] Receiver operating characteristic (ROC) curves were used to establish optimal cut-off values (sizes in mm) to distinguish benign from malignant tumours; cyst diameter: CT = 33.7, EUS = 33.9; main pancreatic duct diameter: CT = 8.2, EUS = 11.4; height of protruding lesion: CT = 2.9, EUS = 5.4

[f] For total 121 patients

[g] CT in 77 patients, EUS in 38 patients; unclear how many received both tests

[h] CT in 44 patients, EUS in 21 patients; unclear how many received both tests

[i] CT was performed in all (121) patients, EUS in 49 patients

[j] Differentiation of cystic from serous neoplasms

Three studies provided a low quality comparison of EUS and CT in the diagnosis of pancreatic cystic lesions. Different criteria were used in two studies to define malignant IPMTs (Baba et al 2004; Cellier et al 1998) (**Table 57**). In these studies, the accuracy of EUS relative to CT varied. The sensitivity and the specificity of the tests were generally similar. In a further study conducted in patients with cystic tumours (Levy et al 1995), the CT diagnostic accuracy was high in relation to adenocarcinoma. Therefore, EUS provided no additional value for this outcome. The specificity of CT was greater than EUS to differentiate cystic from serous neoplasms. This occurred with a moderate increase in sensitivity for diagnosis of cystic neoplasms by EUS. The possibility that the disease prevalence and spectrum differs between the patient groups assessed by CT and EUS in these studies provides a significant potential for bias in the comparison.

A direct comparison of CT and EUS in all patients was provided in one study (Yamao et al 2001) (**Table 57**). This study reported test accuracy for diagnosis of malignant IPMTs. The study was medium quality and had limited applicability. EUS was more sensitive and less specific than CT to differentiate neoplastic from non-neoplastic, or invasive from non-invasive IPMT. Based on this study, the addition of EUS to CT to diagnose IPMT is likely to increase the sensitivity for detection of malignancy.

In the study by Yamao et al (2001), the head-to-head comparison of the replacement value of the two tests does not indicate the sensitivity and specificity when they are used in combination. As described previously (see page 57), a range of possible values that would be observed if the two tests were used in combination in the study population can be determined. If both tests were used in combination in this study, in an either test positive approach, the sensitivity for the detection of neoplasia would have been between 88 and 100 per cent, with specificity for non-neoplastic lesions of 71.4 per cent. The sensitivity for the detection of invasive lesion would have been between 50 and 83 per cent with specificity for non-invasive lesion of 97 per cent.

### *No pancreatic mass identified on CT*

EUS would be used as an additional test in the diagnosis of exocrine pancreatic neoplasia in patients presenting with symptoms or biochemical abnormalities of pancreatic neoplasia, but in whom no pancreatic abnormality had previously been identified on US or CT. Thus, the effect of this test cascade would be that EUS is performed only in those patients with no mass identified on CT. In this case, sensitivity for diagnosis is expected to increase, but this may be at the expense of specificity, by comparison with use of CT alone.

There were three studies reporting on the diagnostic accuracy of EUS and CT in the diagnosis of pancreatic neoplasia identified and included for review. Of these, one study reported the value of EUS in addition to CT and ERCP in diagnostically problematic patients (Snady et al 1992). Another study reported the performance of EUS in a total patient population in addition to the subgroup with no definite mass identified on CT (Agarwal et al 2004). The third study reported individual patient data enabling determination of the incremental value of EUS in patients with no mass seen on CT. Study characteristics and details of the tests investigated appear in **Table 58**.

**Table 58 Assessment of the incremental value of EUS over CT to diagnose pancreatic neoplasia: included studies**

| Author (year) Country | Study design | Patients (N) | Prior tests | EUS characteristics | CT characteristics | Reference standard (n) | Study quality[a] |
|---|---|---|---|---|---|---|---|
| Agarwal et al (2004) USA | Retrospective, test-based inclusion<br>Replacement study, reported subgroup EUS in those negative on CT<br>November 2000–November 2001 | Obstructive jaundice + biliary stricture on ERCP (47), suspected pancreatic mass on CT (19), > 2 episodes pancreatitis in 6 months (15)<br>Subgroup with no identifiable mass on spiral CT (25/81) | ERCP (47), CT (19) of total group | EUS: Radial (Olympus EUM-30) + linear (Pentax FG-32A) when mass lesion identified<br>FNA: Echo-tip FNA (1–7 passes) | Incremental value in addition to: multidetector spiral CT scanner (Lightspeed CT, GE Medical System) with multiphasic pancreas protocol | Pathology, cytology, or follow up > 1 year (100%) | C1 P2 Q2<br>*Quality:* medium potential selection bias, differential verification bias<br>*Applicability:* limited many patients had prior ERCP with stricture identified (referral bias); EUS in some suspected mass on CT (indirect signs) |
| Harrison et al (1999) USA | Retrospective, likely reference-standard based inclusion (possibly test referent)<br>Replacement study but reported individual patient data | Obstructive jaundice (11), abdominal pain and weight loss (6), incidental CT finding (2)<br>Undergoing exploratory surgery<br>No mass on CT (6) | Not reported | EUS: Olympus UM20, 7.5 MHz<br>Single endoscopist | CT<br>Details not reported | Surgery (100%) | C1 P2 Q3<br>*Quality:* poor insufficient information on inclusion, possibly test referent<br>*Applicability:* limited; surgical exploration series, prior tests NR |
| Snady et al (1992) | Design unclear, non-consecutive<br>Replacement value, EUS interpreted with CT+ERCP knowledge<br>May 1998–February 1990 | Diagnostically problematic (60), most abnormality on US, obstructive jaundice (11); pancreatic mass < 5 cm on CT + pain, jaundice or abnormal duct (43); pain + abnormal pancreatogram (6),<br>No evidence metastases | US + CT and/or ERCP | Olympus GF-UM2, 7.5 MHz<br>Unblinded | CT: described elsewhere<br>7 patients received repeat CT<br>ERCP: Olympus JF10 or JFV10 | Surgery (53%), biopsy (17%), clinical follow up > 6 months (30%) | C1 P2 Q3<br>*Quality:* poor<br>Selection bias, no 2 × 2, poor reporting<br>*Applicability:* limited<br>CT results pooled with ERCP, outdated technology, some patients' lesions < 5 cm on CT, 12% received repeat CT |

Abbreviations: EUS, endoscopic ultrasound; CT, computed tomography; ERCP, Endoscopic retrograde cholangiopancreatography; FNA, fine needle aspiration; NR, not reported; US, ultrasound

[a] Grading system used to rate the study quality is provided in **Table 26**

There were two studies identified that provided information on the incremental value of EUS in the diagnosis of pancreatic cancer, following a negative CT.

Both additional EUS value studies were retrospective case series in which patient selection was made on the basis of tests received. The retrospective nature of the studies provides some potential for selection bias.

Both studies reported data concerning patients with clinical suspicion of pancreatic cancer, with a prevalence of 88 and 79 per cent. The larger study reported data from a consecutive series of patients, reducing the potential for selection bias (Agarwal et al 2004). In this study, all findings were confirmed by a reference standard of pathology, cytology or clinical follow up for a minimum of one year. Cytology is considered an imperfect reference standard; therefore, this study may be subject to differential verification bias. This study reported data on the accuracy of EUS and EUS-FNA to diagnose pancreatic neoplasia compared with CT (Agarwal et al 2004). Subgroup data on the accuracy of EUS and EUS-FNA were reported in patients without a definite mass identified on prior CT, enabling determination of the incremental value of EUS. All focal masses identified on spiral CT or EUS (without FNA) were considered malignant. EUS-FNA was considered positive only if there was a definitive cytological diagnosis of malignancy. A patient diagnosed with lymphoma was excluded from the data. A large proportion of the included patients had obstructive jaundice with a biliary stricture seen on ERCP. This may falsely elevate the prevalence of malignancy in the series and bias the accuracy results.

The smaller study compared the performance of EUS and CT in a series of 19 patients. The study reported individual patient data so the incremental value of EUS following CT in those with no mass identified could be extracted (Harrison et al 1999). The patient population were patients undergoing EUS pre-operative staging in advance of exploratory laparotomy. The basis for inclusion of patient records is unclear; it is likely that inclusion was based on whether patients received exploratory laparotomy. It is possible that the study included only those with EUS or CT findings that indicated surgical necessity. The study is rated as poor quality. There is a strong possibility of spectrum bias; the reported 79 per cent prevalence rate of pancreatic cancer was possibly higher than in the applied population.

The patient data extracted from these two studies reflect a population in whom CT was performed. Patients with negative or uncertain CT findings had follow up EUS investigation. On this basis, the populations of these studies are highly applicable to the clinical question in focus. It is unclear whether the included patients had raised CA19-9 levels. Diagnoses of malignancies were based on identification of a focal mass in one study only. The populations also included patients who had undergone ERCP or were part of a surgical series. These factors limit the applicability of the findings.

Data indicating the additional value of EUS and EUS-FNA following negative CT to diagnose pancreatic cancer are shown in **Table 59**. A plot of these studies in receiver-operating characteristics (ROC) space indicated that the heterogeneity in the data for EUS was not due to a threshold effect (**Figure 27** in **Appendix H**). These data were not pooled.

**Table 59 Incremental value of EUS following CT in pancreatic cancer diagnoses—EUS diagnoses in patients with no pancreatic mass identified only**

| Author (year) | Prevalence n/N (%) | Negative/ uncertain CT (%) | Sensitivity (%) | | Specificity (%) | | Accuracy (%) | | Quality[a] |
|---|---|---|---|---|---|---|---|---|---|
| | | | CT | CT + EUS | CT | CT + EUS | CT | CT + EUS | |
| **EUS** | | | | | | | | | |
| Agarwal et al (2004) | 71/81 (88) | 18/81 (22) | 75[b] | 100 | 70 | 50 | 74 | 94 | C1 P2 Q2 |
| Harrison et al (1999) | 15[c]/18 (79) | 8/18 (42) | 53[d] | 100 | 33 | 0 | 50 | 83 | C1 P2 Q3 |
| **EUS-FNA** | | | | | | | | | |
| Agarwal et al (2004) | 71/81 (88) | 18/81 (22) | 75[b] | 97 | 70 | 70 | 74 | 94 | C1 P2 Q2 |

Abbreviations: EUS, endoscopic ultrasound; CT, computed tomography; EUS-FNA, endoscopic ultrasound guided fine needle aspiration
[a] Grading system used to rate the study quality is provided in **Table 26**
[b] Counting probable masses as negative
[c] Including one ampullary carcinoma
[d] Counting suspicious findings as positive

A study by Snady et al (1992) compared the accuracy of EUS with CT plus ERCP. It is unclear whether the study was retrospective or prospective. EUS was performed in all patients and interpreted with knowledge of the CT and ERCP results. The reported comparison provides low quality information on the incremental benefit of EUS (**Table 60**). The study was poorly reported, with high potential for bias.

The applicability of this study was limited. The study patient group was different from patients who will have the technology in current clinical practice. The study included many patients who had a pancreatic mass of < 5 cm identified on CT (43/60, 72%). EUS was performed for all patients, not only those who tested negative on CT. The reported outcome was the differentiation of benign from malignant pancreaticobiliary lesions. Data were not available to reconstruct a 2 × 2 table for this study. Data were reported on the accuracy for detection of any abnormality (dilated or strictured ducts, or mass) and for predicting any specific diagnosis. These data are not included in this review because they do not differentiate between neoplastic disease and other causes.

**Table 60 Additional value of EUS interpreted with CT and ERCP knowledge to differentiate between benign and malignant pancreaticobiliary lesions**

| Author (year) | Prevalence n/N (%) | Sensitivity (%) | | Specificity (%) | | Accuracy (%) | | Quality[a] |
|---|---|---|---|---|---|---|---|---|
| | | CT+ ERCP | CT + ERCP + EUS | CT+ ERCP | CT + ERCP + EUS | CT+ ERCP | CT + ERCP + EUS | |
| Snady et al (1992)[b] | 40/60 (66) | 75 | 85 | 65 | 80 | 72 | 83 | C1 P2 Q3 |

Abbreviations: CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound
[a] Grading system used to rate the study quality is provided in **Table 26**
[b] EUS performed in all patients including some patients with a mass identified on CT
Note: there is a strong potential for bias in the findings of this study due to the poor study quality. The techniques used are also likely to be outdated

On the basis of two studies of limited applicability and medium quality, the additional use of EUS for patients with clinical suspicion of pancreatic cancer, but no definite CT-identified mass, increases pancreatic cancer diagnosis sensitivity. Increased sensitivity occurs at the cost of a trade-off in specificity. The implications of this trade-off are investigated in the economic section of this report.

On the basis of one limited applicability and medium quality study, it appears that EUS-FNA is associated with a similar increase in sensitivity to EUS alone in the diagnosis of pancreatic cancer in patients with negative or equivocal CT results. In contrast to the increase in sensitivity gained through the additional use of EUS, the use of EUS-FNA increased sensitivity with no loss of specificity.

***Neuroendocrine tumours***

Studies reporting the use of EUS to diagnose pancreatic neuroendocrine tumours provided data on correct localisation, rather than sensitivity or specificity for diagnosis. Detected tumours were followed up with surgical or biopsy reference standard, but the true disease status of all patients undergoing testing was not known. Data on those testing negative were generally not provided nor correlated with any reference standard.

There were eight publications reporting correct localisation of EUS and somatostatin receptor scintigraphy (SRS) to diagnose pancreatic neuroendocrine tumours identified (**Table 61**). Of these, four publications (Proye et al 1998; Zimmer et al 1994; Zimmer et al 1995; Zimmer et al 1996) were excluded from analysis because they reported patient series included in later studies (Mirallie et al 2002; Zimmer et al 1995; Zimmer et al 1996; Zimmer et al 2000). The remaining four publications had usable outcomes and were included in the review (De Angelis et al 1999; Fendrich et al 2004; Mirallie et al 2002; Zimmer et al 2000). These studies did not indicate whether masses were identified on CT in these patients. All of these studies reported the comparative accuracy of EUS and SRS for tumour localisation in a series of patients with neuroendocrine tumours who were undergoing surgical resection following a positive imaging finding. Hence, the included patients do not represent a consecutive series of patients eligible for EUS on the basis of presenting symptoms, and there may be spectrum bias in the included population.

Data were presented on a per tumour basis, rather than per patient in three of the studies (De Angelis et al 1999; Fendrich et al 2004; Zimmer et al 2000). This may bias the comparative accuracy by including findings for multiple tumours from the same patients.

Performance data of both tests in all patients (Mirallie et al 2002; Zimmer et al 2000) were provided in two studies. Of these, one study reported individual patient data; data were extracted only for patients in whom both tests were performed. This study also reported results on a per patient basis, rather than a per tumour basis. SRS and EUS were not both performed in all patients in any of the other studies. The quality of the comparison may not accurately reflect the relative performance of the tests.

There was detection bias in two studies because they were not performed in all patients (De Angelis et al 1999; Fendrich et al 2004). Two studies were retrospective (Fendrich et al 2004; Mirallie et al 2002) and the design was unclear in another two (De Angelis et al 1999; Zimmer et al 2000). A major limitation regarding the applicability of most of the included studies was lack of indication about whether CT was performed before EUS and SRS.

**Table 61 Trial characteristics of comparative studies of EUS and SRS in patients with pancreatic neuroendocrine tumours**

| Author (year) | Study design | Patients (N) | Prior tests | EUS characteristics | SRS characteristics | Reference standard | Study quality[a] |
|---|---|---|---|---|---|---|---|
| De Angelis et al (1998)<br>1991–1998 | Study subset (unclear direction), reference standard-based inclusion | Suspected PETs undergoing resection (25/39); 42 tumours: 23 pancreatic, 8 duodenal, 11 lymph nodes<br>MEN-1 or Werner's syndrome (3) | Biochemistry. Comparison with CT, US and angiography | Olympus GF-UM2/GF-UM3 7.5 or 12 MHz<br>Single investigator<br>(N = 19) | 111-In-octreotide, 4- and 24-hour SPECT images<br>(N = 9)<br>Both tests in 47% | Surgery (100%) | CX P2 Q2<br>*Quality:* medium<br>Selection bias, detection bias, insufficient information on negative tests<br>*Applicability:* limited<br>Surgical series, no prior CT or US, outdated technology, not all pancreatic, results per tumour |
| Fendrich et al (2004)<br>1987–2003 | Retrospective, reference standard-based inclusion | Sporadic insulinomas, undergoing surgery (36) | Biochemistry, fasting test<br>Comparison with CT, US, MRI and angiography | Details NR<br>(N = 23) | Details NR<br>(N = 14)<br>Both tests in 61% | Surgery (100%) | CX P2 Q2<br>*Quality:* medium<br>Selection bias, detection bias, insufficient information on negative tests<br>*Applicability:* limited.<br>Surgical series, results per tumour, no prior CT or US |
| Mirallie et al (2002)<br>1991–2000 | Retrospective, reference standard-based inclusion<br>Individual patient data presented | PETs, insulinomas (16), gastrinomas (18)<br>MEN-1 (7) | Biochemistry | Olympus, 7.5 or 12 MHz<br>Experienced operator | 111-In-pentreotide, Octreoscan, 111-185 MBq, 4- and 24-hour (all); 48-hour (n = 2) images<br>Both tests in 100% (data extracted) | Surgery (100%) | C1 P2 Q2<br>*Quality:* medium<br>Selection bias, insufficient information on negative tests<br>*Applicability:* limited.<br>Spectrum bias, prior US and CT not reported, EUS model NR |
| Proye et al (1998)<br>Duplicate series to Mirallie et al (2002) | Retrospective, reference standard-based inclusion | Insulinomas (20), gastrinomas (21)<br>MEN-1 (6) | Biochemistry | Olympus, 7.5 or 12 MHz<br>One of four experienced operators | 111-In-pentreotide, Octreoscan, 111-185 MBq, 4- and 24-hour images<br>Both tests in 100% (data extracted) | Surgery (100%) | C1 P2 Q2<br>*Quality:* medium<br>selection bias, insufficient information<br>*Applicability:* limited<br>Surgical series, prior CT not reported |
| Zimmer et al (2000)<br>1990–1997 | Unclear direction, reference standard-based inclusion | Pancreatic insulinomas, gastrinomas and non-functional gastropancreatic | Comparison with CT, US and MRI | Olympus GF-UM 3/20, 7.5 or 12 MHz<br>Tests within 4 weeks<br>One or two | 100–200 MBq 111-In-labelled pentetreotide, Octreoscan 111, 4-, 24- and 48-hour planar images; 24-hour SPECT | Surgery (100%) | C1 P2 Q2<br>*Quality:* medium<br>Selection bias<br>*Applicability:* limited<br>Surgical series, no prior CT or US, not all |

| Author (year) | Study design | Patients (N) | Prior tests | EUS characteristics | SRS characteristics | Reference standard | Study quality[a] |
|---|---|---|---|---|---|---|---|
| | | NETs (40)<br>MEN-1 (1) | | experienced operators | images<br>Tests within 4 weeks<br>One or two experienced operators | | pancreatic, results per tumour |
| Zimmer et al (1994)<br>1991–1993<br>Duplicate series to Zimmer et al (2000) | Prospective, consecutive patients | Confirmed or suspected NETs of stomach (1), duodenum (6), pancreas (17), liver (1); in 18 consecutive patients<br>Insulinomas (4), gastrinomas (4) | Comparison with CT, US and MRI | Olympus GF-UM3 | 100–200 MBq 111-In-labelled pentetreotide; Siemens Orbiter 7500 gamma camera; 2-, 24- and some 48-hour images; 24-hour SPECT images (61%) | Surgery (78%), US-guided biopsy (11%), or endoscopic biopsy (11%) | C1 P2 Q1<br>*Quality:* high<br>Consecutive patients, valid reference standard<br>*Applicability:* limited.<br>No prior CT or US, outdated technology |
| Zimmer et al (1995)<br>1991–1994<br>Duplicate series to Zimmer et al (2000) | Prospective, non-consecutive | Insulinomas (6), gastrinomas (7)<br>MEN-1 (1) | Comparison with CT, US and MRI | Olympus GF-UM 3/20, 7.5 or 12 MHz | 100–200 MBq 111-In-labelled pentetreotide; Siemens Orbiter 7500 gamma camera; 2-, 24- and some 48-hour images; SPECT images (38%)<br>Tests within 4 weeks<br>One or two experienced operators | Surgery (85%), US-guided or CT-guided biopsy (15%) | C1 P2<br>*Quality:* Not assessed, foreign language<br>Potential selection bias<br>*Applicability:* limited<br>No prior CT or US, some outdated technology |
| Zimmer et al (1996)<br>1991–1993<br>Duplicate series to Zimmer et al (2000) | Prospective, non-consecutive | Insulinomas (10), gastrinomas (10)<br>MEN-1 (1) | Serum calcium, PTH, PLH<br>Comparison with CT, US and MRI | Olympus GF-UM 3/20, 7.5 or 12 MHz | 100–200 MBq 111-In-labelled pentetreotide; Siemens Orbiter 7500 gamma camera; 2-, 24- and some 48-hour images; 24-hour SPECT images<br>Tests within 4 weeks<br>One or two experienced operators | Surgery, (90%) US-guided or CT-guided biopsy (10%) | C1 P2 Q2<br>*Quality:* medium<br>Potential selection bias<br>*Applicability:* limited<br>No prior CT or US, some outdated technology |

Abbreviations: CT, computed tomography; EUS, endoscopic ultrasound; In, indium; MEN-1, multiple endocrine neoplasia type-1; MRI, magnetic resonance imaging; NET, neuroendocrine tumour; NR, nor reported; PET, pancreatic endocrine tumour; PLH, prolactin hormone; PTH, parathyroid hormone; SPECT, single-photon emission computed tomography; SRS, somatostatin receptor scintigraphy; US, ultrasound

[a] Grading system used to rate the study quality is provided in **Table 26**

**Table 62** presents data on correct localisation from one study reporting findings on a per patient basis (Mirallie et al 2002). In this study, the reported results do not differentiate between detection of primary tumour or lymph node metastases. This study included a series of patients undergoing surgery and individual patient data were reported. Therefore, data represent only those patients in whom both tests were conducted. Patients in whom node metastases but no primary tumours were found were excluded. This study indicates that EUS appears to have a higher rate of correct localisation for insulinomas than SRS, but a similar accuracy for gastrinomas.

**Table 62 Localisation of neuroendocrine tumours by EUS and SRS (outcomes per patient)**

| Author (year) | MEN-1 n/N | Prevalence n/N (%) | Correct localisation (%) | | Quality[a] |
|---|---|---|---|---|---|
| | | | EUS | SRS | |
| ***Insulinomas—pancreatic tumours*** | | | | | |
| Mirallie et al (2002) | 6/16 | 14/16 (88) | 79 | 50 | C1 P2 Q2 |
| ***Gastrinomas—pancreatic or duodenal tumours*** | | | | | |
| Mirallie et al (2002) | 2/18 | 16/18 (89) | 56 | 56 | C1 P2 Q2 |

Abbreviations: EUS, endoscopic ultrasound; MEN-1, multiple endocrine neoplasia type-1; SRS, somatostatin receptor scintigraphy
[a] Grading system used to rate the study quality is provided in **Table 26**
Note: Data on the correct localisation of neuroendocrine tumours as reported on a per tumour basis are presented in **Table 63**. Reporting findings in this manner may bias the comparison.

**Table 63** presents the rates of correct localisation of neuroendocrine tumours by EUS and SRS on a per tumour basis. In the study by De Angelis et al (1999), EUS correctly excluded lesions in the pancreas for two patients with benign histopathology (one normal, one diffuse islet cell hyperplasia). SRS test results were not clearly reported for these patients. EUS was more accurate overall in correctly localising pancreatic insulinomas. The advantage of EUS over SRS appears to be greater in these included studies than in the study by Mirallie et al (2002); this effect is likely to be due to the bias introduced by presenting data on a per tumour basis. The comparative performance of EUS and SRS varied greatly between the two included studies. The study by (Zimmer et al 2000) provides a more reliable comparison; this study indicates that the performance of the tests is similar.

**Table 63 Localisation of pancreatic neuroendocrine tumours by EUS and SRS (outcomes per tumour)**

| Author (year) | Tumour type | Prevalence n (tumours)/ N (patients) | Correct localisation (%) | | Quality[a] |
|---|---|---|---|---|---|
| | | | EUS | SRS | |
| ***Pancreatic insulinoma and gastrinoma combined*** | | | | | |
| De Angelis et al (1998) | PETs, 11 insulinomas | 23/19 (EUS)<br>13/9 (SRS) | 87 | 15 | CX P2 Q2 |
| ***Insulinomas*** | | | | | |
| Fendrich et al (2004) | Insulinomas | 23 (EUS)<br>14 (SRS) | 65 | 0 | CX P2 Q2 |
| Zimmer et al (2000) | Pancreatic insulinomas | 17/11 | 94 | 12 | C1 P2 Q2 |
| ***Gastrinomas*** | | | | | |
| De Angelis et al (1998) | Duodenal gastrinomas | 8/4 | 38 | 0 | CX P2 Q2 |
| Zimmer et al (2000) | Pancreatic, duodenal, lymph nodes and hepatic tumours | 15/11 | 80 | 87 | C1 P2 Q2 |

Abbreviations: EUS, endoscopic ultrasound; PET, pancreatic endocrine tumour; SRS, somatostatin receptor scintigraphy
[a] Grading system used to rate the study quality is provided in **Table 26**
Note: Presenting data on a per tumour basis is likely to bias the apparent comparative performance of the tests.

In summary, the evidence of the comparative performance of EUS and SRS in the diagnosis of pancreatic neuroendocrine tumours is of limited applicability to a patient group who have tested negative by CT. The available evidence indicates that EUS has greater accuracy in the correct localisation of pancreatic insulinomas than does SRS.

Clinical expert opinion indicates that correct localisation will frequently lead to less radical surgery in this patient group.

### Staging of pancreatic neoplasia

There were four studies included for review that provided incremental value data of EUS in addition to CT in pancreatic carcinoma staging. Each of these studies were considered to have limited applicability: two medium quality studies reported complete data on the accuracy of determination of resectability (Awad et al 1997; Mertz et al 2000); another medium quality study reported accuracy data for CT and EUS to determine T-staging and lymph node metastases (Harrison et al 1999). The fourth study, deemed to be poor quality, provided incomplete pancreatic cancer staging diagnostic accuracy information (Tomazic et al 2000). This study should be interpreted cautiously because of the absence of specificity data.

Awad et al (1997) reported a consecutive series of 30 patients who received CT and 16 EUS patients. The basis for EUS patient selection was not reported. This study is not considered to be a high quality comparison. EUS was performed for some patients with liver metastases identifiable on CT. This indicates limited applicability of this study population. The study reported accuracy of combined CT and EUS, but inadequate data reporting meant that reconstruction of a $2 \times 2$ table to confirm outcomes was not possible. There was no verification bias in the study because all patients' findings were confirmed by exploratory laparotomy.

Mertz et al (2000) executed a prospective study investigating agreement between EUS and CT, as well as the replacement value, to assess vascular invasion. This enabled calculation of the additional value of EUS. This study was subject to selection bias because patient inclusion was based on surgical confirmation of vascular staging. There was no verification bias in this study.

Harrison et al (1999) conducted a retrospective study reporting individual data for TNM staging by CT and EUS. This enabled calculation of the additional value of EUS following CT. The patient population was composed of patients undergoing pre-operative staging using EUS in advance of exploratory laparotomy. The basis for inclusion of patient records is unclear, but it is likely that inclusion was based on whether patients received exploratory laparotomy. Therefore, it is possible that some patients who were determined unresectable by EUS or CT were excluded from this study, which accounts for the low prevalence of stage III or IV disease. The potential for bias in this study is considered to be high.

Tomazic and Pegan (2000) reported on a series of patients undergoing surgical resection for periampullary carcinoma. It is likely that patients whose disease was determined unresectable by EUS were excluded from this study, introducing strong selection bias. It is also unclear how data were combined to give the value of EUS plus CT. Tests sensitivity data were extracted from the figures and could not be confirmed by constructing a $2 \times 2$ table. Specificity data could not be determined. This study is considered poor quality and limited in applicability. The study was not subject to verification bias.

**Table 64 Assessment of the incremental value of EUS over CT in pancreatic neoplasia staging: included studies**

| Author (year)<br>Country | Study design | Patients (N) | Prior tests | EUS characteristics | CT characteristics | Reference standard | Study quality[a] |
|---|---|---|---|---|---|---|---|
| Awad et al (1997)<br>USA | Direction unclear, consecutive patients received CT<br>Incremental value<br>(1992–1996) | Histologically proven pancreatic (25) or ampullary (5) adenocarcinoma<br>Basis for EUS unclear | Not reported | EUS: Olympus EM-20, 7.5 MHz<br>N = 16 (53%)<br>EUS not in all patients | CT: 150 mL Omnipaque contrast<br>N = 30 | Exploratory laparotomy (100%) | C1 P2 Q2<br>*Quality:* medium<br>No 2 x 2 data, basis for receiving EUS unclear<br>*Applicability:* limited<br>EUS performed in some patients with liver metastases on CT, EUS selection unclear |
| Harrison et al (1999)<br>USA | Retrospective, reference-standard-based inclusion<br>Replacement study with individual patient data | Suspected pancreatic carcinoma undergoing pre-operative assessment (18)<br>Pancreatic (17), ampullary (1) | Not reported | EUS: Olympus UM20, 7.5 MHz<br>Single endoscopist | CT<br>Details not reported | Exploratory laparotomy (100%) within 30 days | C1 P2 Q2<br>*Quality:* medium<br>Potential for selection bias; poor reporting<br>*Applicability:* limited;<br>Insufficient information on patient selection, all operative patients |
| Mertz et al (2000)<br>USA | Unclear direction, reference-standard-based inclusion<br>Replacement study with test agreement<br>(August 1996–January 1999) | Resectable pancreatic adenocarcinoma (abnormal prior imaging), confirmed diagnosis. Subset with surgical confirmation of vascular invasion (16/35) | CT and/or US, ERCP | EUS: Pentax FG 32UA (Precision Instrument Corp)<br>FNA: 22 G GIP needle (Mediglobe), > 3 passes, cytopathologist present<br>Single examiner, prior experience 257 cases | Helical CT: Somatom Plus, (Siemens Medical Systems) or Tomoscan AV scanner (Phillips Medical Systems), 5 mm collination<br>One of three senior CT radiologists<br>Blinding: not reported | Subset data: surgery (100%) | C1 P2 Q2<br>*Quality:* medium<br>Selection bias<br>*Applicability:* limited<br>Surgical series; ERCP in some, outdated technology |
| Tomazic and Pegan (2000)<br>Slovenia | Unclear, likely reference-standard-based inclusion<br>Incremental value | Undergoing surgical resection for pancreatic (13), ampullary (3), CBD (2) and duodenal (1) carcinoma | Not reported | EUS: not reported | CT: not reported | Surgical resection (100%) | C1 P2 Q3<br>*Quality:* poor<br>Poor reporting; selection bias; no 2 x 2 verification<br>*Applicability:* limited<br>Referral pattern unclear, surgical resection series |

Abbreviations: CBD, common bile duct; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; FNA, fine needle aspiration; US, ultrasound

[a] Grading system used to rate the study quality is provided in **Table 26**

**Table 65 Incremental value of EUS following CT in pancreatic cancer staging accuracy**

| Author (year) | Unresectability definition | Prevalence (late stage) n/N | Sensitivity[b] (late stage) (%) | | Specificity (early stage) (%) | | Accuracy (%) | | Quality[a] |
|---|---|---|---|---|---|---|---|---|---|
| | | | CT | CT + EUS | CT | CT + EUS | CT | CT + EUS | |
| **Unresectability** | | | | | | | | | |
| ***Medium quality*** | | | | | | | | | |
| Awad et al (1997)[d] | Liver metastases; occlusion or encasement of coeliac artery and major branches, SMA, SMV, portal vein | 15/30 (50%) | 13 | 63 | 100 | 63 | 57 | 63 | C1 P2 Q2 |
| Mertz et al (2000) | Invasion of major vessel | 6/16 (38%) | 50 | 100 | 100 | 100 | 81 | 100 | C1 P2 Q2 |
| ***Poor quality*** | | | | | | | | | |
| Tomazic and Pegan (2000) | Liver or peritoneal metastases; invasion of SMA, SMV, portal vein | 24/43 (56%) | 46[c] | 75[c] | – | – | 70 | – | C1 P2 Q3 |
| **AJCC staging** | | | | | | | | | |
| Harrison et al (1999) | Stage III or IV | 3/18 (16%) | 0 | 0 | 100 | 100 | 83 | 83 | C1 P2 Q2 |
| **N-staging** | | | | | | | | | |
| Harrison et al (1999) | N-staging | 6/16 (38) | 0 | 100 | 100 | 60 | 63 | 75 | C1 P2 Q3 |

Abbreviations: CI, confidence interval; CT, computed tomography; EUS, endoscopic ultrasound; SMA, superior mesenteric artery; SMV, superior mesenteric vein

[a] Grading system used to rate the study quality is provided in **Table 26**

[b] Unresectability counted as a positive outcome

[c] Data estimated from **Figures 2** and **3**

[d] In the total population of 30, EUS performed in only 16. Basis for selection of patients for EUS is unclear

In summary, the four reviewed studies indicated that combining EUS and CT is likely to increase the sensitivity determining unresectability of pancreatic cancer. There may be a trade-off in terms of reduced specificity for resectability. The results of the reviewed studies were inconsistent for this outcome.

### Biliary tract neoplasia

#### Diagnosis

This assessment included two studies that report the value of EUS (without FNA) as an additional test following cholangiopancreatography (Rosch et al 2002a; Wierzbicka-Paczos et al 1999a). Wierzbicka-Paczos and Butkiewicz (1999b) was a poor quality study that was designed to investigate the incremental value of EUS over ERCP, but did not clearly report accuracy outcomes. This study was included in the absence of others reporting high quality data on the additional value of EUS performed in all patients. (Rosch et al 2002b) designed a replacement study of EUS, MRCP, ERCP and CT, and also reported data on the accuracy of combined tests. The accuracy of findings resulting from combined tests was reported where both tests were in agreement. It appears that findings where combined test results disagreed were excluded from reported results. This is likely to have the effect of overestimating the accuracy of combined tests.

An additional study reporting the supplementary value of EUS-FNA following cholangiopancreatography was identified and included for review (Rosch et al 2004).

All three included studies investigating incremental value of EUS (with or without FNA) were prospective and reported EUS performance in populations that included subjects with pancreatic and biliary tract malignancies. Applicability to extrahepatic biliary tract malignancies alone may be limited. This population is considered appropriate because the presenting symptoms of these disorders are similar.

**Table 66 Assessment of EUS accuracy versus ERCP/MRCP to diagnose biliary tract neoplasia: included studies**

| Author (year) Country | Study design | Patients (N) | Detected tumours by locations | Prior tests | EUS characteristics | ERCP/MRCP characteristics | Reference standard | Study quality[a] |
|---|---|---|---|---|---|---|---|---|
| Rosch et al (2002b)<br>Germany<br>1995–1997 | Prospective; non-consecutive; retrospective blinded image review; replacement value (additional value reported) | Suspected biliary strictures, presenting with jaundice or cholestasis, no pain<br>(50) | Peripancreatic (21), hilar (3) and biliary recurrence (2) of malignancy | Serological testing, US | EUS: sector scanners Olympus UM20 and GF-UM30 | MRI: 1.5T Glyroscan ACSII, Philips Medical Systems, standard body coil<br>MRCP: 3D multichunk, TR 5500, TE300, slice 1.2 mm | Surgery (26%), or biopsy/cytology (16%), clinical follow up (> 12 months, 58%) | C1 P2 Q2[a]<br>*Quality:* medium differential verification bias, cannot re-construct 2 x 2[b]<br>*Applicability:* limited<br>No prior CT. Many had surgically altered anatomy. Accuracy for tests in agreement |
| Rosch et al (2004)<br>Germany<br>1998–2000 | Prospective in consecutive patients, replacement value | Indeterminate biliary stricture or pancreatic head mass<br>(50) | CBD (8), hilar (4), pancreatic head (16); clearly resectable and ampullary excluded | US, CT | EUS: (47)<br>EUS ± FNA: (28) radial scanner, Olympus GF-UM20 and GF-UM30<br>Three highly experienced operators (> 1000 procedures)<br>No cytopathologist present | ERCP + cytology by over-the-guidewire brush, spiral brush and intrabiliary forceps (50)<br>Three highly experienced operators (> 1000 procedures) | Surgery, biopsy, clinical follow up (for minimum of 12 months) | C1 P2 Q1<br>*Quality:* High<br>*Applicability:* limited ERCP result for three combined tissue sampling methods |
| Wierzbicka-Paczos and Butkiewicz (1999b)<br>Poland<br>1994–1997 | Prospective, non-consecutive incremental value | Extrahepatic cholestasis unexplained by US, ERCP and CT<br>(50) | Pancreatic cancer (1), pancreatic tumour (6), pancreatic pseudotumour (1), ampullary (9), biliary tract (2), gallbladder (1) | Clinical examination and biochemistry, US (100%), CT (6%), ERCP (68%) | EUS: linear scanner, Pentax FG-32UA/ Hitachi 405 EUB, 7.5 MHz | ERCP | Surgery | C1 P2 Q3<br>*Quality:* Poor<br>Accuracy outcomes not clearly reported<br>*Applicability:* Limited. Some patients had no structural abnormality identified, most no prior CT, many patients had pancreatic cancers |

Abbreviations: CBD, common bile duct; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; FNA, fine needle aspiration; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; US, ultrasound

[a] Grading system used to rate the study quality is provided in **Table 26**

[b] For data on combined value of MRCP and EUS

### *EUS*

The review considered two studies concerning the diagnostic value of EUS in addition to cholangiopancreatography in the diagnosis of malignant versus benign causes of biliary obstruction.

A medium quality study by Rosch et al (2002b) was designed to determine the replacement value of several diagnostic tests. This study also reported the combined value of EUS and MRCP. A $2 \times 2$ table could not be constructed for this outcome and EUS was not interpreted by applying available MRCP results. This study was considered medium quality in relation to the additional value of EUS. The reported results are for the sensitivity and specificity as determined by results for which the tests were in agreement. This may not represent clinical practice, where an either test positive approach is likely to be adopted. This reduces the applicability of the findings. The data also appear to exclude findings where two combined tests were in disagreement. This approach is likely to overestimate the combined accuracy of the tests.

Rosch et al (2002) reported intention-to-diagnose (ITD) data for the value of ERCP/MRCP and EUS in the full series of 50 patients. Presentation of the results according to ITD captures the failure/contraindication rate of the tests. EUS was not performed for six patients (12%) with surgically altered anatomy in the included population. MRCP was not performed for two patients because of their claustrophobia. The high proportion of patients with surgically altered anatomy suggests referral bias and may underestimate the additional benefit of EUS. The study involved retrospective blinded re-interpretation of test results; clinical information may have prompted recall of the final outcome for the patients. Diagnosis was confirmed by surgery, biopsy or cytology in 42 per cent of patients. The reference standard was more than 12 months follow up in the remaining 58 per cent of patients with benign diagnoses, which is appropriate in this clinical circumstance. The possible differential verification bias in this study is unlikely to have had a significant impact on the validity of the results; cytology is not considered a high quality reference standard.

The criterion for diagnosis of malignancy by EUS in this study was the presence of a mass lesion with a malignant appearance or eccentric thickening of the bile duct wall, especially in conjunction with secondary signs of malignancy (eg vascular infiltration, evidence of metastases). Criteria to discern benign disease were absence of characteristics seen on the previous image and/or signs of pancreatitis. MRCP diagnostic criteria for malignancy were irregular and/or biliary duct strictures concomitantly associated with pancreatic duct stricture. This study is considered to provide level III-1 evidence for diagnostic accuracy according to NHMRC criteria and is rated as C1, P2, Q2 evidence for this research question.

**Table 67 Additional value of EUS over ERCP to diagnose pancreaticobiliary malignancy**

| Author (year) | Cancer site | Prevalence n/N (%) | Sensitivity (%) | | Specificity (%) | | Quality[a] |
|---|---|---|---|---|---|---|---|
| | | | MRCP | MRCP + EUS[b] | MRCP | MRCP + EUS[b] | |
| Rosch et al (2002b) | Peripancreatic (21), hilar (3) and biliary recurrence (2) | 26/50 (52) | 85 | 85 | 71 | 88 | C1 P2 Q2 |

Abbreviations: EUS, endoscopic ultrasound; MRCP, magnetic resonance cholangiopancreatography

[a] Grading system used to rate the study quality is provided in **Table 26**

[b] Result for both tests in agreement

The results of this medium quality and limited applicability study indicate that the additional use of EUS following MRCP may increase the diagnostic specificity of pancreaticobiliary malignancy. Results are presented for findings where both tests are in agreement, which may not reflect how the test results are interpreted in practice.

Wierzbicka-Paczos and Butkiewicz (1999b) reported the accuracy of EUS in a series of 50 patients in whom extrahepatic cholestasis had not been accounted for by prior US, CT or ERCP. Ultrasound was performed for all patients; ERCP was conducted for 68 per cent; 40 per cent of patients underwent surgeries and 32 per cent had endoscopic sphincterectomies. Poor reporting of study results made it difficult to determine a clear correlation between the diagnostic test results and the reference standard findings. The possibility of partial verification bias exists. This study was considered to be poor quality and to have limited applicability (C1, P2, Q3). Malignancy prevalence in this study was 26 per cent (13/50). Malignancies were pancreatic (one), ampullary (nine), biliary (two) and gallbladder (one). EUS diagnosed cancer of the pancreas in one case, of the ampulla of Vater in three cases, and of the bile duct in two cases. In one case of ampullary cancer, ERCP had indicated suspicion of pancreatic cancer. In total, EUS diagnosed seven cases of pancreatic lesions (including one case of cancer) and 19 tumours overall. In three of these, tumours were previously indicated as suspicious by US, and in one case, tumour was suspected on ERCP. This study provides some supportive poor quality evidence that EUS may offer additional value over and above that of ERCP in the diagnosis of pancreaticobiliary neoplasia.

Evidence was insufficient to determine if EUS (without FNA) has value when used in addition to cholangiopancreatography to diagnose biliary tract malignancy.

### *EUS-FNA*

A high quality study by Rosch et al (2004) reported EUS with FNA accuracy compared with ERCP, plus three tissue sampling methods, to diagnose malignant, as opposed to benign causes, of biliary obstruction in 50 patients. This study reported that 28 of 47 patients examined by EUS had lesions aspirated using FNA. The study was designed to assess the replacement value of EUS-FNA and ERCP-cytology/biopsy; endoscopists were blinded to tissue diagnosis results from alternative techniques. Results of the combined value of EUS and ERCP with three tissue sampling methods were reported. The accuracy of ERCP tissue sampling results is likely to overestimate accuracy because they were derived from a combination of three tissue sampling methods.
The apparent additional value of EUS may be reduced. Although it is unclear how results were combined, it is most likely that an either test positive approach was taken. Both EUS and ERCP were performed by one of three highly experienced endoscopists (> 1000 procedures), thus the accuracy of both techniques may be greater than may be observed in clinical practice. ERCP and EUS investigations were conducted within two days of each other.

The patient population was a consecutive group of patients with obstructive jaundice in whom a tissue diagnosis was required. Requirement for tissue diagnosis was defined by a definite mass where resection was not planned, or when there was uncertainty regarding the presence of a mass lesion. Patients included in the study had an indeterminate biliary stricture or pancreatic head mass (including hilar masses) and were excluded if the mass was accessible for endoscopic biopsy or if US or CT demonstrated that the mass was clearly resectable.

Disease status was confirmed by surgery, other biopsy, positive index test result plus follow up or further evidence of malignancy, or follow up in the absence of a positive diagnosis (mean 20 months, minimum follow up for benign patients 12 months) or death. Final diagnoses were pancreatic tumours (32%), biliary (common bile duct or hilar) tumours (24 %), chronic pancreatitis (12%) and common bile duct benign strictures (32%). This study is considered to provide level II evidence for diagnostic accuracy by NHMRC criteria and is rated as C1, P2, and Q1 evidence for this research question.

**Table 68 Incremental value of tissue sampling guided by EUS over ERCP to diagnose malignant pancreaticobiliary tumours**

| Author (year) | Prevalence n/N (%) | Sensitivity (%) | | Specificity (%) | | Accuracy (%) | | Quality[a] |
|---|---|---|---|---|---|---|---|---|
| | | ERCP-cytology[b] | ERCPc + EUS-FNA | ERCP-cytology[b] | ERCPc+ EUS-FNA | ERCP-cytology[b] | ERCP+ EUS-FNA | |
| Rosch et al (2004) | EUS: 26/47 (55)<br>ERCP: 28/50 (56) | 54 | 71 | 100 | 100 | 74 | 86 | C1 P2 Q1 |

Abbreviations: ERCP, endoscopic retrograde cholangiopancreatography; ERCPc, endoscopic retrograde cholangiopancreatography cytology; EUS, endoscopic ultrasound; FNA, fine needle aspiration

[a] Grading system used to rate the study quality is provided in **Table 26**

[b] ERCP results from a combination of three tissue sampling methods incorporating cytology and biopsy: over-the-guidewire brush, spiral brush and intrabiliary forceps

In this high quality study, EUS-FNA was found to be of value in increasing the sensitivity and diagnostic accuracy for the detection of pancreaticobiliary malignancy when used in addition to ERCP-tissue sampling by three methods.

## Does it change patient management?

There were five studies identified that reported the effects of EUS on patient management as determined by the use of a pre-test management plan (**Table 69**). An Australian study reporting the effects of EUS on patient management was excluded because its design was retrospective and pre-test management plan use was not reported (Kaffes et al 2002).

Care was taken when determining applicability of studies: it is important to note who completed the management plans, because referring clinicians' management plans are most likely to affect patient management in practice. In all but one study, referring clinicians completed the management plans. The remaining study (Nickl et al 1996) required endosonographers to complete management plans, thereby reducing the applicability of this study.

A recent prospective study by Chong et al (2005) aimed to determine the impact of EUS upon a series of patients with mixed indications (R. Chen, personal communication). The impact of EUS was defined as any alteration in diagnosis, subsequent patient management or requirement of additional investigations following EUS. The study included 330 consecutive patients undergoing EUS and/or EUS-FNA of whom 231 had completed pre- and post-test questionnaires that provided data suitable for analysis. These included patients being investigated for suspected diagnosis or staging of pancreatic masses or bile duct strictures (41%), diagnosis of oesophageal thickening or staging of oesophageal cancer (19%), diagnosis or staging of gastric masses (15%), and diagnosis and/or staging of lung cancer or mediastinal lymph nodes (3.7%). The results

of this study are presented in **Table 70**. Management was changed for all indications in 68.1 per cent of patients undergoing EUS and in 39.5 per cent of patients undergoing EUS-FNA. Surgery was avoided in 17 per cent of all patients and additional investigations were avoided in 50 per cent. Referring doctors reported EUS to be very useful in guiding further management in 52.8 per cent of cases, moderately useful in 38.1 per cent, minimally useful in 4.8 per cent and not useful in 4.3 per cent.

Jafri et al (1996) conducted a prospective study specifically designed to assess the effect of EUS on patient management. As well as changes in management, physicians were asked to rate their certainty of diagnosis pre- and post-test and the perceived usefulness of the technology. The patient group in this study was not separated by indication and the EUS technology was outdated, which reduced the applicability of the population. The study assessed 63 patients; these patients were not consecutive so there is a possibility of patient selection bias. The main study outcomes are reported in **Table 70**. EUS informed change in patient management in 46 per cent of patients, surgery was avoided in 12.7 per cent and further investigations were avoided in 25.4 per cent. Change in management was also reported to result in less invasive courses of therapy in 66 per cent of patients. Physicians rated endoscopic ultrasound as highly useful and had significant value in increasing the level of certainty of diagnosis.

A third prospective, pre-test post-test EUS management study was a 10-centre American Endosonography Club Study (Nickl et al 1996). Of 428 consecutive patients undergoing EUS, 35 procedures were performed for research purposes; the remaining 393 patients were included in the analysis. Management plans were completed by endosonographers, as opposed to clinicians providing potential for bias in this study. The endosonographers involved in this study were experienced and no centre contributed more than 20 per cent of the dataset. The results of the study were not reported according to specific indications. Staging of oesophageal cancers and evaluation of upper gastrointestinal submucosal lesions each accounted for 10 per cent of examinations. Pancreatic studies comprised 41 per cent of evaluations, of which 19 per cent were for a known pancreatic mass. Biliary tract studies comprised 4 per cent of evaluations. Of all enrolled subjects, 7.2 per cent (31/428) had incomplete examinations and 1.6 per cent (7/428) failed. Almost half (47 %) of the failed or incomplete examinations were due to inability to cross a malignant oesophageal stricture. EUS informed change to management plans in 74 per cent (95% CI: [69.4, 78.6]) of 393 evaluable patients (**Table 70**). These were rated as being of major importance in 31 per cent of changes, and were related to avoidance of surgery in 34 per cent, change from other invasive management to non-invasive management in 15 per cent, and change from management to discharge from follow up for 18 per cent. Of those whose management changed, the cost, risk and invasiveness of the altered management regime were regarded as being less, more or equal to the pre-EUS plan in 55 per cent, 37 per cent and 8 per cent of patients, respectively. The proportion of patients for who no further diagnostic testing was recommended increased from 27 per cent to 50 per cent for post-EUS.

Shah et al (2004) carried out a high quality prospective study involving 90 patients. Patients were from a consecutive series of 489 patients. Exclusions from the study were based on EUS referral by Shah et al (2004), pre-test communication between endosonographers and referring clinicians regarding management strategy, or based on inability to contact referring clinicians before EUS. Overall, management plans were altered for 51 per cent (46/90) of patients after EUS procedures. The investigators reported no significant difference in the frequency of post-EUS management changes in relation to the EUS examination site. The number of patients in some categories was low

and the study was unlikely to be powered to detect this effect. The group undergoing oesophageal EUS included patients being evaluated for mediastinal masses and submucosal lesions (n = 5), and cancer staging (n = 12). This reduces the applicability of the patient population. Similarly, the data for gastric EUS related to a mixture of staging (n = 5) and submucosal mass evaluation (n = 10). Pancreatic EUS indications were for solid masses (n = 19), cystic lesions (n = 6) and suspected masses (n = 18). EUS-FNA altered management in 45 per cent of patients; in this small population that included a mix of oesophageal, gastric, pancreatic and rectal EUS (n = 20 in total, **Table 70**). EUS resulted in performing procedures which were associated with a lower risk of adverse events or were less complex in 32 per cent, 47 per cent and 35 per cent of oesophageal, gastric and pancreatic patients, respectively. Surgery was avoided in 16 per cent of all patients undergoing EUS.

Preston et al (2003) conducted a study investigating the impact of EUS for staging in the management of 100 consecutive patients with oesophageal or oesophagogastric junction carcinomas. The patients were identified retrospectively and their history and staging data were summarised. The patient summaries were distributed to three oesophagogastric surgeons in a random, coded and blinded fashion. Initially, the patient summaries were distributed without EUS data. The surgeons independently determined a management plan for each patient. A month later, the patient summaries were re-coded, re-randomised and re-distributed to the same surgeons, this time including EUS data. The surgeons then determined a second management plan. Another month later the initial summaries without EUS data were again re-randomised, re-coded and re-distributed and the process repeated. The surgeons were blinded to the patient outcomes. Information was also collected on the value of the EUS data for each patient. EUS was rated as useful by the three surgeons in 87 per cent, 65 per cent and 63 per cent of patients, with median scores for usefulness (on a scale of –5 to 5) of 3, 2 and 2, respectively. The level of agreement between the surgeons was low; the mean level of agreement of 56 per cent (between two assessments) without EUS data, and 62 per cent with EUS data.

The investigators attempted to reduce bias in the study by analysing data on concordant management plans. When only concordant management plans were analysed, the number of patients in whom radical surgery, non-surgical curative therapy, or neoadjuvant therapy with surgery was planned did not change. There was an increase in the number of patients for whom there was agreement for non-surgical palliative therapy (from 18.5% to 24%).

Interpretation of this study to give an estimated proportion of patients in whom surgery could be avoided is difficult. The reported results represent an increase in concordance, not an average of the number of patients in whom a change of management was recorded for each surgeon. The study highlights how the effect of EUS on change in management would vary between physicians using the data.

In general, where studies included more than 10 patients in each outcome, EUS changed management in 24–74 per cent of patients among all indications, while for EUS-FNA, management changed in 31–43 per cent. Use of EUS resulted in surgery being avoided in 10–18 per cent of patients, and further imaging or therapy was avoided in 14–57 per cent of patients.

**Table 69 Assessment of the effect of EUS on patient management: included studies**

| Author (year) Country | Study design | Patients (N) | EUS accuracy | EUS/comparator characteristics | Physicians determining management | Quality[a] |
|---|---|---|---|---|---|---|
| Chong et al (2005) Australia | Prospective pre-test, post-test case series in consecutive patients (August 2002–June 2004) | Mixed indications, including oesophageal (32.5%), gastric (15.2%), pancreaticobiliary (31.1%), lung/mediastinal disease (19.5%) and duodenal (1.7%) (231) | In 68 patients (30%) undergoing final surgery or histology *Accuracy* = 84% | Olympus GF-UM20, GF-UM160 or GF-UC140P radial scanner Performed by single experienced gastroenterologist | Referring doctors: physicians (62%), surgeons (38%) | Q1 P1 C1 *Quality:* high *Applicability:* applicable |
| Jafri et al (1996) USA | Prospective pre-test, post-test case series | Mixed indications including oesophageal, gastric and pancreatic (63) | Not reported | Olympus GF-UM3 | Referring physicians | Q2 P2 C1 *Quality:* medium Selection bias *Applicability:* limited Mixed indications |
| Nickl et al (1996) USA | Prospective pre-test, post-test case series in consecutive patients (April 1992–February 1995) | Mixed indications, including oesophageal (19%), gastric (15%), pancreatic (41%) and biliary (3.7%) (393) | Not reported | 15 sonographers, seniors at 10 centres experienced in an average of 628 examinations each (range 100–2000), for 5.2 (1–14) years | Endosonographer Completed < 6 hours following EUS | Q1 P2 C1 *Quality:* high *Applicability:* limited Plans completed by endosonographers |
| Preston et al (2003) UK | Blinded re-assessment of consecutive patients with pre-test post-test plan (June 1996–June 1999) | Patients with oesophageal or oesophagogastric junction carcinoma (100) | In patients undergoing primary resection (29) *T staging:* Se: 76.4% Sp: 75.0% Ac: 75.9% *N staging:* Se: 83.3% Sp: 87.5% Ac: 85.7% | Olympus GF-UM20 radial scanner, no dilatation | Consultant oesophagogastric surgeons (3) Blinded to outcomes | Q1 P2 C1 *Quality:* high *Applicability:* limited Outcomes reported in different manner to other studies |
| Shah et al (2004) USA | Prospective pre-test, post-test case series (March 2002–August 2002) | Oesophageal (22), gastric (15), pancreatic (43), rectal (10) (90) | Not reported | Operator blinded to pre-test management plan | Surgeons (33%), non-EUS gastroenterologists (58%), oncologists (3%), internists (4%), pulmonologist (1%) | Q1 P2 C1 *Quality:* high *Applicability:* limited Mixed indications |

Abbreviations: Ac, accuracy; EUS, endoscopic ultrasound; FNA, fine needle aspiration; Se, sensitivity; Sp, specificity

[a] Grading system used to rate the study quality is provided in **Table 26**

**Table 70 Effect of EUS on patient management change**

| Author (year) | Anatomical indication | EUS change in management n/N (%) | EUS-FNA change in management n/N (%) | Surgery avoided n/N (%) | Imaging/therapy to clinical follow up n/N (%) |
|---|---|---|---|---|---|
| ***Oesophageal*** | | | | | |
| Chong et al (2005) | Oesophageal cancer, high grade Barrett's or thickening, nodules or SM lumps—staging and/or diagnosis | 23/72 (31.9) | 1/3 (33.3) | – | 25/75 (33.3) |
| | Oesophageal cancer—staging | 15/48 (31.3) | | – | – |
| Nickl et al (1996) | Oesophageal cancer—staging | 10/43 (24) | – | – | – |
| Shah et al (2004) | Oesophageal cancer or mediastinal masses—staging and/or diagnosis | 12/22 (56) | 4/4 (100) | 4/22 (18.2) | 3/22 (13.6) |
| ***Gastric*** | | | | | |
| Chong et al (2005) | Gastric masses | 19/34 (55.9) | – | – | 16/35 (47.1) |
| | Gastric masses—diagnosis | 16/29 (55.2) | | – | – |
| | Gastric tumours—staging | 3/6 (50) | | – | – |
| Nickl et al (1996) | Gastric cancer—staging | 31% | – | – | – |
| | Gastric submucosal tumour—diagnosis | 67% | – | – | – |
| Shah et al (2004) | Gastric cancer or SM masses—staging and/or diagnosis | 9/15 (60) | 0/1 (0) | 2/15 (13.3) | 6/15 (40.0) |
| ***Pancreaticobiliary*** | | | | | |
| Chong et al (2005) | Pancreaticobiliary | 11/21 (52.4)[a] | 22/51 (43.1)[a] | – | 41/72 (56.9) |
| | Pancreatic masses or bile duct strictures—diagnosis | 29/68 (42.6) | | – | – |
| | Periampullary carcinomas—staging | 2/3 (66.7) | | – | – |
| Nickl et al (1996) | Pancreatic mass—diagnosis | 9/34 (26) | – | – | – |

| Author (year) | Anatomical indication | EUS change in management n/N (%) | EUS-FNA change in management n/N (%) | Surgery avoided n/N (%) | Imaging/therapy to clinical follow up n/N (%) |
|---|---|---|---|---|---|
| Shah et al (2004) | Pancreatic masses (solid or cystic) – diagnosis | 21/43 (49) | 4/13 (31) | 7/43 (16.3) | 6/43 (14.0) |
| ***All indications combined*** | | | | | |
| Chong et al (2005) | Mixed, including oesophageal, gastric, pancreaticobiliary and mediastinal/lung indications | 47/69 (68.1) | 64/162 (39.5) | 39/231 (17) | 115/231 (50) |
| Jafri et al (1996) | Mixed, including oesophageal, gastric, pancreatic | 29/63 (46) | – | 8/63 (12.7) | 16/63 (25.4) |
| Nickl et al (1996) | Mixed indications | 291/393 (74) | – | 41/393 (10) | 87/386 (22.5) |

Abbreviations: EUS, endoscopic ultrasound; FNA, fine needle aspiration; SM, submucosal

[a] The 33 patients with altered management included one patient receiving therapeutic drainage of a pseudocyst; another patient was unaccounted.

## Does treatment change health outcomes?

Treatment effectiveness is an important component of diagnostic test linked evidence. In this review, evidence of EUS accuracy in the diagnosis of gastric, pancreatic and biliary tract neoplasia is presented. Assessment of studies providing evidence of treatment efficacy for these conditions was required. Where it is used for cancer staging, the primary purpose of EUS is to change patient management. This usage does not require treatment effectiveness evidence.

The ideal study design to investigate treatment effectiveness is a randomised controlled trial comparing the current treatment with the absence of treatment. The primary curative treatment for many carcinomas is surgical resection with or without adjunctive therapies. Conducting a randomised controlled trial that compares the effectiveness of active treatment to no treatment is clearly unethical.

Evidence will be extracted from observational patient survival studies of people diagnosed at earlier stages of disease who receive curative treatments, compared with patients with later disease stage diagnoses when cure is rarely possible. The primary component of treatment for those diagnosed early will be surgical resection. By contrast, people with late stage diagnoses, and who are receiving palliative therapy, will not have had surgical resections. A comparison of long-term survival by stage at diagnosis can indicate the curative success of cancer treatments.

### Gastric neoplasia

The NSW Central Cancer Registry has published data on the five-year relative survival of patients with gastric cancer during the period 1980–1995 (Supramaniam et al 1998). These data show that the risk of death at five years for patients with gastric cancer who had metastatic spread at the time of diagnosis was more than five times that of people with localised disease, after adjusting for age, sex and period of diagnosis (that is, 1980–1984 vs 1985–1989 vs 1990–1995). The five-year relative survival of patients with localised, regional and distant disease at diagnosis was 49.5 per cent, 22.7 per cent and 1.8 per cent, respectively.

Curative resection procedures are confined to patients with localised disease (no extensive nodal involvement) at the time of surgical exploration (National Cancer Institute 2004b). By contrast, patients with distant disease at diagnosis are not candidates for curative treatments. Palliative chemotherapy does not generally prolong life for patients with stage IV disease who have haematogenous or peritoneal metastases. Palliative surgical resection is performed for patients with continued bleeding or obstruction.

These observational survival data indicate that curative treatments available for people diagnosed with gastric carcinoma increase long-term survival.

### Pancreatic neoplasia

Complete surgical resection can result in five-year survival rates of 18–24 per cent in patients with small, localised pancreatic cancers, where there is no evidence of lymph node metastases or extension of pancreatic carcinoma beyond the pancreatic capsule

(National Cancer Institute 2004d)[4]. This contrasts with an overall five-year survival rate of less than 1 per cent for patients with advanced cancer.

The NSW Central Cancer Registry has also published data on the five-year relative survival of patients with pancreatic cancer for the period 1980–1995 (Supramaniam et al 1998). These data show that the risk of death at five years for pancreatic cancer patients whose disease had metastasised was more than double patients with localised disease, after adjusting for sex, age and period of diagnosis (that is, 1980–1984 vs 1985–1989 vs 1990–1995). The five-year relative survival of patients with localised, regional and distant disease at diagnosis was 12.8, 5.3 and 0.6 per cent, respectively.

Surgical resection is considered to be the only curative treatment for pancreatic carcinoma. Resection is reserved to patients whose disease is localised. These findings suggest that curative treatments available for pancreatic carcinoma increase long-term survival.

### Biliary tract neoplasia

The NSW Central Cancer Registry has published further data on the five-year relative survival of patients with gallbladder cancer during the period 1980–1995 (Supramaniam et al 1998). These data show that the risk of death at five years for gallbladder cancer patients whose disease had metastasised was triple people with localised disease, after adjusting for age, sex and period of diagnosis (that is, 1980–1984 vs 1985–1989 vs 1990–1995). The five-year relative survival of patients with localised, regional and distant disease at diagnosis was 30, 11, and 0.7 per cent, respectively.

Data from the US Surveillance Epidemiology and End Results (SEER) Program of the National Cancer Institute indicate survival rates for patients with extrahepatic bile duct cancer over the 10-year period of 1977–1986, by stage at diagnosis (Henson et al 1992). These survival data are based on 1251 patients with known stage assessment and include carcinomas of the ampulla of Vater. Survival was greater in people diagnosed at earlier disease stage who were more likely to have received curative treatments.

**Table 71 Survival by stage at diagnosis among patients with extrahepatic bile duct carcinoma (SEER program data, 1977–1986)**

| Stage at diagnosis | Definition of stage | Number of patients | Two-year survival |
|---|---|---|---|
| I | Tumour confined to extrahepatic bile ducts | 353 | 0.27 |
| II | Involvement of bile ducts and regional lymph nodes | 70 | 0.12 |
| III | Direct extension to adjacent organs | 453 | 0.17 |
| IV | Distant metastases | 375 | 0.04 |

Source: Henson et al (1992)

[4] Based on evidence from population-based consecutive series studies of patients that include overall survival data.

Complete resection remains the only means of cure for biliary tract cancer. Complete resection is possible only for a minority of patients with localised extrahepatic bile duct cancer (National Cancer Institute 2004c). These data suggest that curative treatments available for biliary tract carcinoma increase long-term survival.

## What are the economic considerations?

The cost-effectiveness and financial impact of EUS and EUS-FNA was evaluated for indications where there was clinical evidence that the procedure was more accurate than the comparator. An economic analysis was not performed for indications with a relatively small eligible population (ie endocrine pancreatic tumours and biliary tract neoplasia) (see pages 19 and 24.) An economic evaluation was not performed where there was insufficient evidence to provide information on the effect of EUS or EUS-FNA on the management of the condition (ie gastric submucosal tumours) (see page 151).

The current capacity to perform EUS and EUS-FNA in Australia is limited by the availability of EUS equipment and the number of technically trained experts able to perform the procedure. There are currently approximately 11 centres in Australia that have EUS equipment. According to expert opinion, approximately 1,320 EUS procedures can be performed in Australia each year. This assumes that each centre is equipped to perform 200 procedures annually, but because of the expertise and technical training required, at present each centre's capacity is limited on average to approximately 120 procedures per year. Hence, the annual cost for the first three years, should EUS and EUS-FNA be listed on the Medicare Benefits Schedule (MBS), is estimated to be $1,098,600 for EUS and $2,279,010 for EUS-FNA. This calculation assumes that each centre's entire yearly capacity is used for either EUS or EUS-FNA. Therefore these annual costs represent the lower and upper limits of potential annual costs for all 11 centres performing 120 procedures per year.

### Oesophageal cancer staging

The economic evaluation presented in this section applies to oesophageal cancer staging.

A decision analytic model assessing value for money of introduction of EUS relative to CT to stage oesophageal cancer reveals an incremental cost of $206.62 per patient receiving EUS following CT. Economic evaluation results should be interpreted in the context of the key underlying assumptions. Certainty around several key assumptions would improve the reliability of the results of this analysis:

- will the sensitivity of EUS and CT observed in clinical studies and reported in the literature be observed in clinical practice?
- will positive results of EUS prevent all further diagnostic procedures, including unnecessary surgery, in practice?

The estimated number of patients eligible to receive EUS for oesophageal cancer staging is less than the estimated current capacity to provide the service in Australia. It is estimated that approximately 814 patients would be eligible to receive EUS procedures in the first year should it be listed on the MBS. This number would increase to approximately 828 patients by the end of the third year of use. The aggregate expenditure

through the MBS is estimated to be $677,285 in the first year, rising to $689,438 in the third year following listing.

## Assessment of value for money of EUS

### Why an economic analysis is required

A cost-minimisation analysis allows comparison of the net costs of programs that achieve the same outcome. This evaluation technique is determined to be appropriate to appraise the economic impact of EUS use to stage oesophageal cancer. The use of EUS to determine TNM staging for oesophageal cancers is not expected to change survival outcomes. Detection of advanced disease (stage IV) signifies unresectability and obviates the need for surgery. The incremental cost of EUS can be determined by assigning a decision analytic model.

A review of the literature did not identify any economic evaluations that examined the diagnostic and clinical management pathways considered in this assessment report. To date, there have been no economic evaluations that capture the impact of EUS on the MBS and the Australian healthcare system for this indication. A cost-minimisation analysis using a decision analytic model to estimate the total healthcare cost implications to the MBS of introducing EUS for oesophageal cancer staging is presented.

### Key assumptions

- The economic evaluation compares the use of EUS with CT for oesophageal cancer staging.
- The economic evaluation assigns a cost-minimisation analysis. Only direct healthcare costs are calculated in the base analysis and final health outcomes are assumed to be equivalent among treatment groups.
- The prevalence of late-stage oesophageal cancer was derived from the literature.
- The analysis is confined to patients who present with symptoms suggestive of oesophageal neoplasia with positive findings identified using a first-line diagnostic test (eg upper endoscopy, barium studies) and no indication of metastases on CT or PET (when available).
- EUS and CT performance characteristics were derived from the literature and are presented as clinical evidence throughout this assessment report.
- Morbidity and the cost of CT are not incorporated into the model because it is assumed that all patients undergo CT diagnostic investigation. It is assumed that such variables would be the same in both arms of the model.
- Morbidity associated with palliative measures, such as radiation and chemotherapy, are not included in the analysis because they are assumed to be similar in both arms of the model.

- The cost of EUS used in the analysis is based on the calculated cost of consumable items, professional time, and depreciation of capital equipment associated with the procedure (see **Appendix J**).

- A discount rate per annum is not applied to costs because it was assumed that costs occur within the first year after initial diagnosis.

### Patient population used in the economic model

The proposed indication for EUS is for the staging of disease in patients presenting with symptoms suggestive of oesophageal neoplasia who have positive findings identified using a first-line diagnostic test (eg upper endoscopy, barium studies) and no indication of metastases on CT or PET (when available). The population in the economic analysis is based on the population examined in the clinical evidence presented in this assessment report. The population is representative of those likely to receive EUS in an MBS setting.

### Economic model structure

A decision analytic model was developed to estimate the downstream healthcare resource utilisation associated with oesophageal cancer staging. The model uses data from the literature to evaluate the performance characteristics of EUS and estimates the cost implications associated with reducing unnecessary surgical procedures.

Patients in the model receive either EUS following CT or CT alone. Given that the detection of late-stage disease is a contraindication to surgical resection, it was assumed that identification of stage IV oesophageal cancer would result in a decision not to operate. It was further assumed that patients were not subjected to unnecessary surgical investigation.

The sensitivities of EUS plus CT and of CT alone were used to determine the proportion of patients with advanced stage disease. These patients would not be subject to surgical procedures; they would receive palliative care instead. The false-negative rates (1–sensitivity of test) of both EUS in addition to CT and CT alone are used to determine the proportion of patients in whom unresectable disease was found at surgery.

Improvements in the sensitivity of a diagnostic test may correspond with a decrease in specificity and an increase in the number of false-positive results (1–specificity of test). The specificities of EUS plus CT and of CT alone are not included in this analysis. In the context of staging, a false-positive would mean that the results of the diagnostic test indicate that the individual has late stage cancer, and therefore, is not eligible for resection, when in fact the patient has early stage cancer and would be eligible for resection. From a cost perspective, a decrease in specificity and increase in the false-positive rate decreases cost (ie patients in whom resection is appropriate would not be resected because the diagnostic test indicates that they have late stage cancer). Accounting for this would be inappropriate because it would overestimate the value of the diagnostic test from an economic perspective (ie cost savings from avoiding a procedure where the procedure should have been performed.) A more conservative cost estimate is provided by not incorporating specificity into the analysis.

## Variables used in the economic model

### Resource utilisation and costs

**Table 72** lists the cost variables used in this analysis. The cost of EUS is based on the calculated cost of consumable items; professional time and depreciation of capital equipment associated with the diagnostic test (see **Appendix J** for calculations). The cost of CT is assumed to be the same in both arms of the model and is excluded from the analysis. The Australian Refined Diagnostic Related Group (AR-DRG) classification code for stomach, oesophageal and duodenal procedures with malignancy was used to estimate the cost of surgical resection procedures when unresectablity is determined at the time of surgery.

**Table 72 Cost of diagnostic and surgical procedures for oesophageal cancer staging**

| Diagnostic or surgical procedure | Resource utilised | Unit cost | Reference |
|---|---|---|---|
| EUS | Capital equipment cost per patient | $547.52 | Appendix J |
| | Direct medical cost[a] | $284.75 | |
| | **Total cost per service** | **$832.27** | |
| Surgical procedure | AR-DRG G03A | $23,080 | National Hospital Cost Data Collection Cost Report Round 7 (2002–2003)[b] |

Abbreviations: EUS, endoscopic ultrasound; AR-DRG, Australian Refined Diagnosis Related Group
[a] Includes proposed professional fee and cost of associated medical services
[b] Public sector version (AR-DRG G03A – stomach, oesophageal and duodenal procedures with malignancy)

## Other clinical variables

All clinical variables, including prevalence of unresectable oesophageal cancer and sensitivity of EUS plus CT and of CT alone were derived from the literature and are listed in **Table 73**.

**Table 73 Other clinical variables for oesophageal cancer staging**

| Variable | Value | Reference |
|---|---|---|
| Prevalence of unresectable oesophageal cancer (n/N) | 0.459 (34/74) | Flamen (2000) (**Table 35**) |
| Unresectable cancer determined by CT | 0.412 | Sensitivity of CT, Flamen (2000) (**Table 35**) |
| Unresectable cancer determined by EUS following CT | 0.471 | Sensitivity of EUS + CT, Flamen (2000) (**Table 35**) |
| Determined unresectable at time of surgery after CT | 0.588 | False-negative = 1 – sensitivity of CT |
| Determined unresectable at time of surgery after CT + EUS | 0.529 | False-negative = 1 – sensitivity of EUS + CT |

Abbreviations: EUS, endoscopic ultrasound; CT, computed tomography

## Results of the economic evaluation

The results were calculated based on a cost-minimisation analysis using Microsoft Excel®. This method estimates the incremental cost of performing EUS following CT for oesophageal cancer staging, relative to the use of CT alone. The evaluation captures both the cost of EUS and surgical resection, as well as the cost-offsets associated with the avoidance of unnecessary surgery. On average, detection of advanced disease is achieved at a lower cost with the use of CT alone than with EUS following CT to determine oesophageal cancer staging (**Table 74**). The incremental cost of performing EUS, and hence avoiding unnecessary surgical procedures, is $206.62 per patient.

**Table 74 Total healthcare costs estimated in the economic analysis for oesophageal cancer staging**

| Summary result | EUS following CT | CT alone | Incremental |
|---|---|---|---|
| Mean cost per patient | $6,441.96 | $6,235.34 | $206.62 |

## Sensitivity analysis

A sensitivity analysis was conducted using prevalence and sensitivity values from two additional studies (Sihvo 2004; Botet et al 1991a) identified and included in the assessment of the diagnostic accuracy of EUS following CT over CT alone for oesophageal cancer staging. The incremental cost per patient receiving EUS following CT increased to $313.52 and $361.86 when the prevalence of unresectable oesophageal cancer (AJCC stage IV) was varied to reflect the values from the two additional studies. Applying the diagnostic sensitivity values presented in the study by Sihvo et al (2004) resulted in a cost saving of $281.18 per patient receiving EUS following CT. The upper range sensitivity variables were taken from Botet et al (1991a). This produced an incremental cost of $164.20 per patient receiving EUS following CT.

**Table 75 Sensitivity analysis variables for oesophageal cancer staging**

| Variable | Value | Reference |
|---|---|---|
| Prevalence of unresectable oesophageal cancer (lower, upper) | 0.35–0.38 | Sihvo (2004), Botet (1999) (**Table 35**) |
| Incremental gain in diagnostic sensitivity<br>Sensitivity of CT (75.0)<br>Sensitivity of CT + EUS (81.3) | 6.3 | Botet (1999) (**Table 35)** |
| Incremental gain in diagnostic sensitivity<br>Sensitivity of CT (31.6)<br>Sensitivity of CT + EUS (42.1) | 10.5 | Sihvo (2004) (**Table 35**) |
| Determined unresectable at time of surgery after CT | 0.25–0.68 | False-negative = 1 – sensitivity of CT |
| Determined unresectable at time of surgery after CT + EUS | 0.19–0.58 | False-negative = 1 – sensitivity of EUS + CT |

**Table 76 Sensitivity analysis results for oesophageal cancer staging**

| Variable changed | Cost per patient receiving EUS following CT | Cost per patient receiving CT alone | Incremental cost per patient receiving EUS following CT |
|---|---|---|---|
| Prevalence of unresectable oesophageal cancer | | | |
| based on lower range value[c] | $5,050.04 | $4,688.18 | $361.86 |
| based on upper range value[c] | $5,483.44 | $5,169.92 | $313.52 |
| Sensitivity of diagnostic tests[a] | | | |
| Sihvo (2004) | $6,972.18 | $7,253.36 | –$281.18[b] |
| Botet (1999) | $2,815.28 | $2,651.08 | $164.20 |

[a] Varying the sensitivity of EUS plus CT and CT alone changes four variables simultaneously: (1) unresectable cancer determined by CT; (2) unresectable cancer determined by EUS plus CT; (3) proportion of cancer determined unresectable at time of surgery after CT; and (4) proportion of cancer determined unresectable at time of surgery after EUS following CT

[b] This represents a cost saving.

[c] Lower and upper range refers to variable range presented in **Table 75**

## Gastric cancer staging

The economic evaluation presented in this section applies to gastric cancer staging.

A decision analytic model was used to assess the value for money of the introduction of EUS relative to CT for the staging of gastric cancer. The model revealed that there are lower total healthcare costs overall, with an estimated saving between $1506.50 and $2845.14 per patient receiving EUS following CT. Results from the economic evaluation should be interpreted in the context of the key underlying assumptions. Certainty around several key assumptions would improve the reliability of the results of this analysis:

- will the sensitivity of EUS observed in clinical studies and reported in the literature be observed in clinical practice?
- will positive results of EUS prevent all further diagnostic procedures, including unnecessary surgery, in practice?

It is estimated that approximately 1,719 patients would be eligible to receive EUS procedures in the first year should it be listed on the MBS, increasing to approximately 1,750 patients by the end of the third year of use. Not accounting for limitations in capacity and expertise needed to perform EUS in Australia, the aggregate expenditure through the MBS is estimated to be $1,430,796 in the first year, rising to $1,456,471 in the third year following listing.

## Assessment of value for money of EUS

### Why an economic analysis is required

A cost-minimisation analysis allows the net costs of programs that achieve the same outcome to be compared. This evaluation technique is determined to be appropriate for appraising the economic impact of using EUS for staging gastric cancer. Optimal pre-operative staging would restrict surgery for resection to those patients, in whom there is a reasonable likelihood of resectability, thus eliminating unnecessary operations for patients who are unlikely benefit from them. The incremental cost of EUS can be determined by employing a decision analytic model.

A review of the literature did not identify any economic evaluations that examined the diagnostic and clinical management pathways considered in this assessment report. To date, there have been no economic evaluations that capture the impact of EUS on the MBS and the Australian healthcare system for this indication. Therefore, a cost-minimisation analysis is presented using a decision analytic model to estimate the total healthcare costs implications to the MBS of introducing EUS for gastric cancer staging.

### Key assumptions

- The economic evaluation compares the use of EUS following CT with CT alone for gastric cancer staging.
- The economic evaluation employs a cost-minimisation analysis. Direct healthcare costs only were calculated in the base analysis and final health outcomes are assumed to be equivalent among treatment groups.

- The prevalence of late-stage gastric cancer was derived from the literature.
- The analysis is confined to patients presenting with symptoms suggestive of gastric neoplasia who have positive findings using a first-line diagnostic test (eg gastroscopy with or without biopsy) and either a submucosal tumour is identified or there is no identification of metastases on CT or PET (when available).
- EUS and CT performance characteristics were derived from the literature and are presented as clinical evidence throughout this assessment report. Data for the detection of late stage disease by AJCC group staging were not identified. Therefore, data on the sensitivity for T4 staging were used to represent unresectable disease. This does not take into account the contribution of nodal staging to determine resectability.
- Morbidity and the cost of CT are not incorporated into the model because it was assumed that all patients undergo CT diagnostic investigation. For this reason, it was assumed that such variables would be the same in both arms of the model.
- Morbidity associated with palliative measures, such as radiation and chemotherapy, were not included in the analysis because they were assumed to be similar in both arms of the model.
- The cost of EUS used in the analysis was based on the calculated cost of consumable items, professional time, and depreciation of capital equipment associated with the procedure (see **Appendix J**).
- An annual discount rate was not applied to costs because it was assumed that costs occur within the first year after initial diagnosis.

### Patient population used in the economic model

The proposed indication for EUS relevant to this section is for disease staging in patients presenting with symptoms suggestive of gastric neoplasia. These patients would also have positive findings made using first-line diagnostic tests, such as gastroscopy with or without biopsy, and either a submucosal tumour or no detection of metastases on CT or PET (when available). The population in the economic analysis was based on the population examined in the clinical evidence presented in this assessment report. The population is representative of the patient population likely to receive EUS in an MBS setting.

### Structure of the economic model

A decision analytic model was employed to estimate the downstream healthcare resource utilisation associated with gastric cancer staging. The model uses data from the literature to evaluate the performance characteristics of EUS and estimate the cost implications associated with reducing unnecessary surgical procedures.

In the model, patients receive either EUS following CT or CT alone. Given that detection of late-stage disease is a contraindication to surgical resection, it is assumed that identification of T4 gastric cancer would result in a decision not to operate. It also is assumed that patients are not subjected to unnecessary surgical exploration.

The minimum and maximum combined sensitivities of EUS plus CT and of CT alone are used to determine the proportion of patients with advanced disease. These patients would not be subject to surgical procedures but would receive palliative care.
The false-negative rates (1–sensitivity of test) of EUS in addition to CT and CT alone were used to determine the proportion of patients in whom unresectable disease would be found at surgery.

Improvements in the sensitivity of a diagnostic test may correspond with a decrease in specificity and an increase in the number of false-positive results (1–specificity of test). The specificities of EUS plus CT and of CT alone are not included in this analysis.
In the context of staging, a false-positive would mean that the results of the diagnostic test indicates that the patient had late stage cancer, and was ineligible for resection, when the patient actually had early stage cancer and was eligible for resection. From a cost perspective, a decrease in specificity and increase in the false-positive rate decreases cost (ie patients in whom resection is appropriate would not be resected because the diagnostic test indicates that they have late stage cancer). Accounting for this would be inappropriate because it would overestimate the value of the diagnostic test from an economic perspective (ie cost savings from avoiding a procedure where the procedure should have been performed). A more conservative cost estimate is provided by not incorporating specificity into the analysis.

### Variables used in the economic model

#### Resource utilisation and costs

**Table 77** lists the cost variables used in this analysis. The cost of EUS is based on the calculated cost of consumable items; professional time and depreciation of capital equipment associated with the diagnostic test (see **Appendix J** for calculations). The cost of CT is assumed to be the same in both arms of the model and was excluded from the analysis. The Australian Refined Diagnostic Related Group (AR-DRG) classification code for stomach, oesophageal and duodenal procedures with malignancy was used to estimate the cost of a surgical resection procedure when unresectablity is determined at the time of surgery.

**Table 77 Cost of diagnostic and surgical procedures for gastric cancer staging**

| Diagnostic or surgical procedure | Resource utilised | Unit cost | Reference |
|---|---|---|---|
| EUS | Capital equipment cost per patient | $547.52 | **Appendix J** |
| | Direct medical cost[a] | $284.75 | |
| | **Total cost per service** | **$832.27** | |
| Surgical procedure | AR-DRG G03A | $23,080 | National Hospital Cost Data Collection Cost Report Round 7 (2002–2003)[b] |

Abbreviations: EUS, endoscopic ultrasound; AR-DRG, Australian Refined Diagnosis Related Group
[a] Includes proposed professional fee and cost of associated medical services
[b] Public sector version (AR-DRG G03A–stomach, oesophageal and duodenal procedures with malignancy)

### Other clinical variables

All clinical variables, including prevalence of unresectable gastric cancer and sensitivity of EUS plus CT and of CT alone have been derived from the literature and are listed in **Table 78**.

**Table 78 Other clinical variables for gastric cancer staging**

| Variable | Value | Reference |
|---|---|---|
| Prevalence of unresectable gastric cancer (n/N) | 0.34 (23/69) | Perng (1996) (**Table 42**) |
| Unresectable gastric determined by CT | 0.52 | Sensitivity of CT, Perng (1996) (**Table 42**) |
| Unresectable cancer determined by EUS following CT (minimum combined sensitivity)[a,b] | 0.826 | Minimum combined sensitivity of EUS plus CT, Perng (1996) (**Table 42**) |
| Unresectable cancer determined by EUS following CT (maximum combined sensitivity)[a,b] | 1.0 | Maximum combined sensitivity of EUS plus CT, Perng (1996) (**Table 42**) |
| Determined unresectable at time of surgery after CT | 0.174 | False-negative = 1 – sensitivity of CT |
| Determined unresectable at time of surgery after CT + EUS (1 – minimum combined sensitivity)[a] | 0.478 | False-negative = 1 – minimum combined sensitivity of EUS + CT |
| Determined unresectable at time of surgery after CT + EUS (1 – maximum combined sensitivity)[a] | 0 | False-negative = 1 – maximum combined sensitivity of EUS + CT |

Abbreviations: EUS, endoscopic ultrasound; CT, computed tomography
[a] Minimum and maximum combined sensitivities and specificities were calculated from studies of the replacement value of the tests, as described in Statistical methods (**page 57**)
[b] Data for the detection of late stage disease (according to AJCC group staging) were not identified. Therefore, data on the sensitivity for T4 staging was used to represent unresectable disease. This does not take into account the contribution of nodal staging to determine resectability.

## Results of the economic evaluation

The results were calculated based on a cost-minimisation analysis using Microsoft Excel®. This method estimates the incremental cost of performing EUS following CT for the staging of gastric cancer, relative to CT alone. The evaluation captures both the cost of EUS and surgical resection, as well as the cost-offsets associated with avoiding unnecessary surgery. On average, detection of advanced disease was achieved at a lower cost with the use of EUS following CT than with CT alone to determine gastric cancer staging (**Table 79**). Performing EUS and consequently avoiding unnecessary surgical procedures results in a cost saving of between $1,506.50 and $2,845.14 per patient.

**Table 79 Total healthcare costs estimated in the economic analysis for gastric cancer staging**

| Summary result | EUS following CT | CT alone | Incremental |
|---|---|---|---|
| Mean cost per patient (using minimum combined sensitivity) | $2,170.91 | $3,677.41 | –$1,506.50[a] |
| Mean cost per patient (using maximum combined sensitivity) | $832.27 | $3,677.41 | –$2,845.14[a] |

Abbreviations: EUS, endoscopic ultrasound; CT, computed tomography
[a] This represents a cost saving.

## Sensitivity analysis

A sensitivity analysis was conducted using prevalence and sensitivity values from the additional study (Habermann et al 2004) identified and included in the clinical assessment of the diagnostic accuracy of EUS over CT for the staging of gastric cancer. The incremental cost per patient receiving EUS following CT increased to $411.29 and $170.34 when the prevalence of unresectable gastric neoplasia (detection of T4) was varied to reflect the value from the additional study. Applying the diagnostic sensitivity values presented in the study by Habermann et al (2004) resulted in an incremental cost of $832.27 per patient receiving EUS following CT. The cost of surgical resection may vary due to co-morbidities and complications. For this reason, the cost of surgical resection was varied between the lower and upper range values. The lower range value

resulted in a cost saving per patient of $110.03 and $649.37. The upper range value resulted in a cost saving of $1702.18 and $3152.81 per patient.

**Table 80 Sensitivity analysis variables for gastric cancer staging**

| Variable | Value | Reference |
|---|---|---|
| Prevalence of unresectable gastric neoplasia | 0.06 | Habermann et al (2004) |
| Unresectable gastric cancer determined by CT | 1 | Sensitivity of CT, Habermann et al (2004)[a] (**Table 42**) |
| Unresectable gastric cancer determined by EUS following CT | 1 | Sensitivity of EUS + CT, Habermann et al (2004)[a] (**Table 42**) |
| Determined unresectable at time of surgery after CT | 0 | False-negative = 1–sensitivity of CT |
| Determined unresectable at time of surgery after CT + EUS | 0 | False-negative = 1–minimum combined sensitivity of EUS + CT |
| Cost of surgical procedure | $9299–$25,011 | AR-DRG H01C, AR-DRG H01A[b] |

Abbreviations: EUS, endoscopic ultrasound; CT, computed tomography; AR-DRG, Australian Refined Diagnosis Related Group.
[a] Minimum and maximum sensitivity of EUS followed by CT were the same.
[b] National Hospital Cost Data Collection Cost Report Round 7 (2002–2003) public sector version (AR-DRG H01C–Pancreas, liver & shunt procedure without complications; AR-DRG H01A–Pancreas, liver & shunt procedure with catastrophic complications).

**Table 81 Sensitivity analysis results for gastric cancer staging**

| Variable changed | Cost of EUS following CT | Cost of CT alone | Incremental cost per patient receiving EUS following CT |
|---|---|---|---|
| Prevalence of unresectable gastric cancer | $1,073.23[a] | $661.93 | $411.29 |
| | $832.27[b] | | $170.34 |
| Sensitivity of diagnostic tests Habermann et al (2004)[c,d] | $832.27 | $0 | $832.27 |
| Cost of surgical procedure–upper range | | | |
| (Minimum combined sensitivity) | $2,282.91 | $3,985.09 | –$1,702.18[e] |
| (Maximum combined sensitivity) | $832.27 | | –$3,152.81[e] |
| Cost of surgical procedure–lower range | | | |
| (Minimum combined sensitivity) | $1,371.61 | $1481.64 | –$110.03 |
| (Maximum combined sensitivity) | $832.27 | | –$649.37 |

[a] Based on minimum combined sensitivity
[b] Based on maximum combined sensitivity
[c] Varying the sensitivity of EUS plus CT and CT alone changes four variables simultaneously: (1) unresectable cancer determined by CT; (2) unresectable cancer determined by EUS following CT; (3) proportion of cancer determined resectable at time of surgery after CT; and (4) proportion of cancer determined resectable at time of surgery after EUS following CT.
[d] Minimum and maximum combined sensitivity of EUS plus CT were the same
[e] This represents cost savings.

## Diagnosis of gastric submucosal tumours

### Why an economic analysis is not required

Although clinical evidence that examined the sensitivity and specificity of EUS in the diagnosis of malignant and benign gastric submucosal tumours (Kwon et al 2005) was identified, it was insufficient to provide information on the effect of EUS on the management of submucosal tumours. Only one study was identified that provided information on the effect of EUS on the management of gastric submucosal tumours (Nickl et al 1996). It was reported that 67 per cent of EUS studies performed for the

evaluation of gastric submucosal tumours resulted in a change in management. Yet, details of the management change were not provided and the study was considered to have considerable potential for bias. As a result, due to the lack of informative data about how EUS would change management in this particular patient subgroup, and the small quantity of data on the diagnostic accuracy of EUS, a detailed economic analysis was not performed.

## Pancreatic cancer staging

The economic evaluation presented in this section applies to staging pancreatic cancer.

A decision analytic model was used to assess the value for money of introducing EUS relative to CT to facilitate staging pancreatic cancer. The model reveals that there are lower total overall healthcare costs, with an estimated cost saving of $2,149.95 per patient receiving EUS following CT. Nevertheless, results from the economic evaluation should be interpreted in the context of the key underlying assumptions. Certainty around several key assumptions would improve the reliability of the results of this analysis. These key assumptions are:

- will the sensitivity of EUS observed in clinical studies and reported in the literature be observed in clinical practice?
- will positive results of EUS prevent all further diagnostic procedures, including unnecessary surgery, in practice?

It was estimated that approximately 1,326 patients would be eligible to receive EUS procedures in the first year should it be listed on the MBS; the estimated number would increase to approximately 1,350 patients by the end of the third year of use. Not accounting for limitations in capacity and expertise needed to perform EUS in Australia, the aggregate expenditure through the MBS is estimated to be $1,103,400 in the first year, rising to $1,123,200 in the third year following listing.

## Assessment of value for money of EUS

### Why an economic analysis is required

A cost-minimisation analysis allowed the net costs of programs that achieve the same outcome to be compared. This evaluation technique was determined to be appropriate to appraise the economic impact of using EUS to stage pancreatic cancer. Using EUS to determine pancreatic cancer staging is not expected to change health outcomes; the detection of late-stage disease signifies unresectability and obviates the need for surgery because detection of metastases is a contraindication to surgical resection. By employing a decision analytic model, the incremental cost of EUS can be determined.

A review of the literature did not identify any economic evaluations that examined the diagnostic and clinical management pathways considered in this assessment report. One prospective study (Soriano et al 2004) compared efficacy of endoscopic ultrasonography, helical computed tomography, magnetic resonance imaging, and angiography in pre-operative staging of pancreatic cancer. The decision analysis demonstrated that the best strategy to assess tumour resectability was based on CT or EUS as the initial test, followed by the alternative technique in potentially resectable cases. Cost minimisation

analysis favoured the sequential strategy in which EUS was used as a confirmatory technique for patients in whom helical CT suggested resectability of the tumour.

To date, there have been no economic evaluations that capture the impact of EUS on the MBS and the Australian healthcare system for this indication. Therefore, a cost-minimisation analysis is presented using a decision analytic model to estimate the total healthcare costs implications to the MBS of introducing EUS for the staging of pancreatic cancer.

### Key assumptions

- The economic evaluation compares use of EUS with CT for staging pancreatic cancer.
- The economic evaluation employs a cost-minimisation analysis. Only direct healthcare costs are calculated in the base analysis and final health outcomes are assumed to be equivalent between treatment groups.
- The prevalence of late-stage pancreatic cancer was derived from the literature.
- The analysis is confined to patients presenting with symptoms suggestive of pancreatic neoplasia (eg jaundice, upper abdominal pain, biochemical abnormalities) who have a positive finding using a first-line diagnostic test (eg abdominal ultrasound, serological tests) followed by identification of pancreatic malignancy on CT, where CT results alone are inconclusive as to whether resection is possible.
- EUS and CT performance characteristics were derived from the literature and presented as clinical evidence throughout this assessment report.
- Morbidity and the cost of CT are not incorporated into the model because it was assumed that all patients undergo CT diagnostic investigation. It was further assumed that such variables would be the same in both arms of the model.
- Morbidity associated with palliative measures, such as radiation and chemotherapy, are not included in the analysis because they are assumed to be similar in both arms of the model.
- The rate of complications associated with Whipple's procedure was taken from the literature.
- The cost of EUS used in the analysis was based on the calculated cost of consumable items; professional time and depreciation of capital equipment associated with the procedure (see **Appendix J**).
- A discount rate per annum was not applied to costs because it was assumed that costs occur within the first year after initial diagnosis.

### Patient population used in the economic model

The proposed indication for EUS relevant to this section is for disease staging in patients presenting with symptoms suggestive of pancreatic neoplasia—such as jaundice, upper abdominal pain, or biochemical abnormalities—who have positive findings using first-line diagnostic tests—including abdominal ultrasound and serological tests—followed by identification of pancreatic malignancy on CT, where CT results alone are inconclusive about whether resection is possible. The population in the economic analysis is based on the population examined in the clinical evidence presented in this assessment report. The population is representative of patients likely to receive EUS in an MBS setting.

### Structure of the economic model

A decision analytic model was employed to estimate the downstream healthcare resource utilisation associated with staging pancreatic cancer. The model uses data from the literature to evaluate the performance characteristics of EUS and estimate the cost implications associated with reducing unnecessary surgical procedures.

In the model, patients receive either EUS following CT or CT alone. Given that detection of late-stage disease is a contraindication to surgical resection, it was assumed that identification of advanced pancreatic cancer would result in a decision not to operate. For this reason it was also assumed that patients would not be subjected to unnecessary surgical exploration.

The sensitivities of EUS plus CT, and of CT alone, were used to determine the proportion of patients with advanced disease. These patients would not be subject to surgical procedures, but would receive palliative care. The false-negative rates (1–sensitivity of test) of EUS in addition to CT, and CT alone, were used to determine the proportion of patients in whom unresectable disease would be found at surgery.

Improvements in diagnostic test sensitivity may correspond with a decrease in specificity and an increase in the number of false-positive results (1–specificity of test). The specificities of EUS plus CT, and of CT alone, were not included in this analysis. In the context of staging, a false-positive would mean that the results of the diagnostic test indicate that the patient has late stage cancer, and therefore, was not eligible for resection, when the patient actually had early stage cancer and would be eligible for resection. From a cost perspective, a decrease in specificity and increase in the false-positive rate decreases cost (ie patients for whom resection is appropriate would not be resected because the diagnostic test indicates that they have late stage cancer). Accounting for this would be inappropriate because it would overestimate the value of the diagnostic test from an economic perspective (ie cost savings from avoiding a procedure where the procedure should have been performed.) A more conservative cost estimate is provided by not incorporating specificity into the analysis.

### Variables used in the economic model

#### Resource utilisation and costs

**Table 82** lists the cost variables used in this analysis. The cost of EUS was based on the calculated cost of consumable items; professional time and depreciation of capital equipment associated with the diagnostic test (see **Appendix J** for calculations). The cost of CT was assumed to be the same in both arms of the model and is excluded from the analysis. The AR-DRG for pancreas, liver and shunt procedures with and without

complications was used to estimate the cost of a surgical resection procedure when unresectability is determined at the time of surgery.

**Table 82 Cost of diagnostic and surgical procedures for pancreatic cancer staging**

| Diagnostic or surgical procedure | Resource utilised | Unit cost | Reference |
|---|---|---|---|
| EUS | Capital equipment cost per patient | $547.52 | **Appendix J** |
| | Direct medical cost[a] | $284.75 | |
| | **Total cost per service** | **$832.27** | |
| Surgical procedure without complications | AR-DRG H01C | $9,299 | National Hospital Cost Data Collection Cost Report Round 7 (2002–2003)[b] |
| Surgical procedure with complications | AR-DRG H01B | $12,393 | National Hospital Cost Data Collection Cost Report Round 7 (2002–2003)[b] |

Abbreviations: EUS, endoscopic ultrasound; AR-DRG, Australian Refined Diagnosis Related Group
[a] Includes proposed professional fee and cost of associated medical services
[b] Public sector version (AR-DRG H01C–Pancreas, liver & shunt procedure without complications; AR-DRG H01B–Pancreas, liver & shunt procedure with severe or moderate complications)

### Other clinical variables

All clinical variables, including prevalence of unresectable pancreatic cancer and sensitivity of EUS plus CT and of CT alone, were derived from the literature and are listed in **Table 83**.

**Table 83 Other clinical variables for pancreatic cancer staging**

| Variable | Value | Reference |
|---|---|---|
| Prevalence of unresectable pancreatic neoplasia (n/N) | 0.5 (15/30) | Awad et al (1997) (**Table 65**) |
| Unresectable neoplasia determined by CT | 0.13 | Sensitivity of CT (Awad et al 1997) (**Table 65**) |
| Unresectable neoplasia determined by EUS following CT | 0.63 | Sensitivity of EUS plus CT (Awad et al 1997) (**Table 65**) |
| Determined unresectable at time of surgery after CT | 0.87 | False-negative = 1 – sensitivity of CT |
| Determined unresectable at time of surgery after CT + EUS | 0.37 | False-negative = 1 – sensitivity of EUS + CT |
| Complication rate associated with surgical procedure[a] | 0.15 | Harewood and Wiersema (2001) |

Abbreviations: EUS, endoscopic ultrasound; CT, computed tomography
[a] Complication rate for procedures where unresectability is determined at the time of surgery is assumed to be the same as the pancreaticoduodenal resection complication rate

### Results of the economic evaluation

The results were calculated based on a cost-minimisation analysis using Microsoft Excel®. This method estimates the incremental cost of performing EUS following CT for the staging of pancreatic cancer, relative to CT alone. The evaluation captures both the cost of EUS and surgical resection as well as the cost-offsets associated with avoiding unnecessary surgeries. On average, detection of advanced disease is achieved at a lower cost with the use of EUS following CT than with CT alone to determine staging of pancreatic cancer (**Table 84**). Performing EUS, and hence avoiding unnecessary surgical procedures, results in a cost savings of $2,149.95 per patient.

**Table 84 Total healthcare costs estimated in the economic analysis**

| Summary result | EUS following CT | CT alone | Incremental |
|---|---|---|---|
| Mean cost per patient | $3,039.12 | $5,189.07 | –$2,149.95[a] |

[a] This represents a cost saving.

## Sensitivity analysis

A sensitivity analysis was conducted using prevalence and sensitivity values from the additional study (Mertz et al 2000) identified and included in the assessment of the diagnostic accuracy of EUS over CT for pancreatic cancer staging. Varying the prevalence of unresectable pancreatic neoplasia to reflect the value presented by Mertz et al (2002) resulted in a cost saving of $1,404.40 per patient. Changing the sensitivity of EUS plus CT, and CT alone, produced a cost saving of $2,149.95 per patient. The cost of surgical resection may vary due to the severity of complications. Consequently, the cost of surgical resection with complications was varied to represent the cost of surgical resection with catastrophic rather than severe complications. This resulted in a cost saving of $4,831.28 per patient. The rate of complication associated with surgical resection was also varied based on a range of values identified in the literature. The lower range value resulted in a cost saving of $2,188.63 per patient. The upper range value resulted in a cost saving of $2,033.93 per patient.

**Table 85 Sensitivity analysis variables for pancreatic cancer staging**

| Variable | Value | Reference |
|---|---|---|
| Prevalence of unresectable pancreatic neoplasia | 0.38 | Mertz et al (2000) (**Table 65**) |
| Unresectable neoplasia determined by CT | 0.5 | Sensitivity of CT (Mertz et al 2000) (**Table 65**) |
| Unresectable neoplasia determined by EUS following CT | 1.0 | Sensitivity of EUS plus CT (Mertz et al 2000) (**Table 65**) |
| Determined unresectable at time of surgery after CT | 0.5 | False-negative = 1 – sensitivity of CT |
| Determined unresectable at time of surgery after CT + EUS | 0 | False-negative = 1 – sensitivity of EUS + CT |
| Cost of surgical procedure with complication | $25,011 | AR-DRG H01A[a] |
| Rate of complication associated with surgical procedure[b] | 0.1–0.3 | Harewood and Wiersema (2001) |

Abbreviations: EUS, endoscopic ultrasound; CT, computed tomography; AR-DRG, Australian Refined Diagnosis Related Group
[a] National Hospital Cost Data Collection Cost Report Round 7 (2002–03) public sector version (AR-DRG H01A–Pancreas, liver & shunt procedure with catastrophic complications)
[b] Complication rate for procedures where unresectability is determined at the time of surgery is assumed to be the same as the pancreaticoduodenal resection complication rate.

**Table 86 Sensitivity analysis results for pancreatic cancer staging**

| Variable changed | Cost of EUS following CT | Cost of CT alone | Incremental cost per patient receiving EUS following CT |
|---|---|---|---|
| Prevalence of unresectable pancreatic neoplasia | $2,487.41 | $3,891.80 | –$1,404.40[b] |
| Sensitivity of diagnostic tests[a] | $832.27 | $2,982.23 | –$2,149.95[b] |
| Cost of surgical procedure with complication | $5,023.30 | $9,854.58 | –$4831.28[b] |
| Rate of complication associated with surgical procedure (lower range) | $3,067.74 | $5,256.37 | –$2,188.63[b] |
| Rate of complication associated with surgical procedure (upper range) | $2,953.26 | $4,987.19 | –$2,033.93[b] |

[a] Varying the sensitivity of EUS plus CT and CT alone changes four variables simultaneously: (1) unresectable cancer determined by CT; (2) unresectable cancer determined by EUS following CT; (3) proportion of cancer determined unresectable at time of surgery after CT; and (4) proportion of cancer determined unresectable at time of surgery after EUS following CT

[b] This represents a cost saving.

## Diagnosis of pancreatic neoplasia

The presented economic evaluation applies to diagnosis of pancreatic neoplasia in patients who present with symptoms of biochemical abnormalities (eg CA 19-9) suggestive of pancreatic neoplasia.

The economic considerations appropriate to this application are twofold:

- assessment of value for money associated with the introduction of endoscopic ultrasound (EUS) and endoscopic ultrasound with fine needle aspiration biopsy (EUS-FNA)
- estimation of the aggregate financial implications to the Medicare Benefits Schedule (MBS) of the introduction of EUS and EUS-FNA.

A separate modelled economic evaluation of EUS following CT and EUS-FNA following CT was conducted for each of the following distinct upstream diagnostic pathways:

- evidence of exocrine tumours following CT
- identification of solid mass on CT
- identification of cystic lesion on CT.

An economic evaluation comparing EUS following CT, versus CT alone, for diagnosis of pancreatic exocrine tumours produced an incremental cost of $23,347 per life year gained. EUS-FNA following CT, versus CT alone, produced an incremental cost of $35,766 per life year gained.

An economic evaluation comparing EUS following CT to CT alone for diagnosis of pancreatic solid masses produced an incremental cost of $29,089 per life year gained.

The value of performing EUS following CT, versus CT alone, for diagnosis of intraductal papillary-mucinous tumours (IPMTs) of the pancreas, a type of cystic lesion,

was assessed using a cost-minimisation approach. The economic evaluation produced an incremental cost between $520 and $705 per patient receiving EUS following CT.

Results from these economic evaluations should be interpreted in the context of key assumptions made in the economic models. Certainty around several key assumptions would improve the reliability of the results of the economic models:

- will the sensitivity and specificity of EUS and EUS-FNA observed in clinical studies and reported in the literature be observed in clinical practice?
- will positive results of EUS and EUS-FNA prevent all further diagnostic procedures in practice?

It was estimated that approximately 3,062 patients would be eligible for EUS or EUS-FNA in the first year should either procedure be listed on the MBS, increasing to approximately 3,117 patients by the end of the third year of use. Not accounting for limitations in capacity and expertise needed to perform EUS and EUS-FNA in Australia, the aggregate expenditure on EUS through the MBS is estimated to be $2,548,774 in the first year, rising to $2,594,510 in the third year following listing. The aggregate expenditure on EUS-FNA through the MBS is estimated to be $5,287,348 in the first year, rising to $5,382,227 in the third year following listing.

## Assessment of value for money of EUS and EUS-FNA

### Why an economic model is required

An economic model allows long-term costs and outcomes to be estimated when a technology is newly available and insufficient time has elapsed to collect long-term data.

A review of the literature did not identify any economic evaluations that modelled the diagnostic and clinical management pathways examined in this assessment report. To date, there have been no economic evaluations that capture the impact of EUS or EUS-FNA on the MBS and the Australian healthcare system. Two economic models were developed to estimate the longer-term costs and benefits associated with MBS listing of EUS and EUS-FNA for diagnosis of pancreatic exocrine tumours and solid masses. A third model assessed the cost of EUS for diagnosis of pancreatic IPMTs in terms of potential MBS listing.

Each economic model follows a sample of hypothetical patients with symptoms or biochemical abnormalities as they move through the diagnostic pathway and incur downstream health resource costs over and above the cost of the initial diagnostic procedure. The models allow a comparison of the total healthcare cost implications and health outcomes associated with EUS and EUS-FNA.

## Model I—Evidence of pancreatic exocrine tumour

### Key assumptions

- The economic model compares use of EUS and EUS-FNA following CT with CT alone for diagnosing pancreatic neoplasia where no structural abnormality has been identified on CT but where there is suspicion of an exocrine pancreatic tumour.

- Only direct healthcare costs and benefits have been calculated.
- Patients referred for EUS, EUS-FNA, or CT were assumed to have the same comorbidities. All other diagnostic and additional clinical decision-making is assumed to be similar.
- The prevalence of exocrine pancreatic tumours and the proportion of patients in each stage of pancreatic cancer, based on TNM classification, were derived from the literature.
- Morbidity and the cost of CT are not incorporated into the model because it is assumed that all patients undergo CT diagnostic investigation. It was assumed that such variables would be the same in all arms of the model.
- Morbidity associated with palliative measures such as radiation or chemotherapy was not included in the analysis, but was assumed to be similar in all arms of the model.
- Patients remain in the model until death or until the confirmation of a true negative diagnostic result is obtained.
- It was assumed that all incidence of mortality related to the safety of palliative and curative management procedures or treatments were captured by the median survival rate.
- The specificity and sensitivity of EUS and EUS-FNA following CT and CT alone were derived from evidence presented in the clinical section of this assessment report.
- It was assumed that the median survival of patients with exocrine pancreatic tumour(s) is determined by the curative or palliative treatment received rather than the stage of pancreatic cancer.
- Complications associated with EUS and EUS-FNA were excluded from the analysis since their cost and effect were assumed to be negligible.
- It was assumed that MBS fees used in the economic analysis incorporate the cost of consumable items, professional time, and depreciation of capital equipment associated with the procedure.
- Economic model costs included diagnostic procedure used and curative or palliative management from time of diagnosis until death.
- An annual discount rate was not applied to costs because it was assumed that all costs occur within the first year after diagnosis due to the short median survival rate of patients with pancreatic cancer. An annual discount rate of 5 per cent was applied to benefits accrued beyond the first year.

### Patient population used in the economic model

The proposed indication for EUS and EUS-FNA is for diagnosis of pancreatic neoplasms in patients with symptoms and biochemical evidence (CA 19-9) associated with pancreatic neoplasia, for whom CT has failed to identify an abnormality, but symptoms persist, and there is biochemical evidence that suggests malignancy is present. The population in the economic model was based on the population described in the clinical section of this assessment report. The population is representative of patients likely to receive EUS or EUS-FNA in an MBS setting.

### Structure of the economic model

A decision analytic model was developed to estimate the downstream healthcare resource utilisation associated with the diagnosis of pancreatic neoplasia. The model uses data available in the literature to evaluate the possible outcomes associated with diagnosis of exocrine pancreatic tumours and to identify the most desirable healthcare strategy among the different diagnostic alternatives.

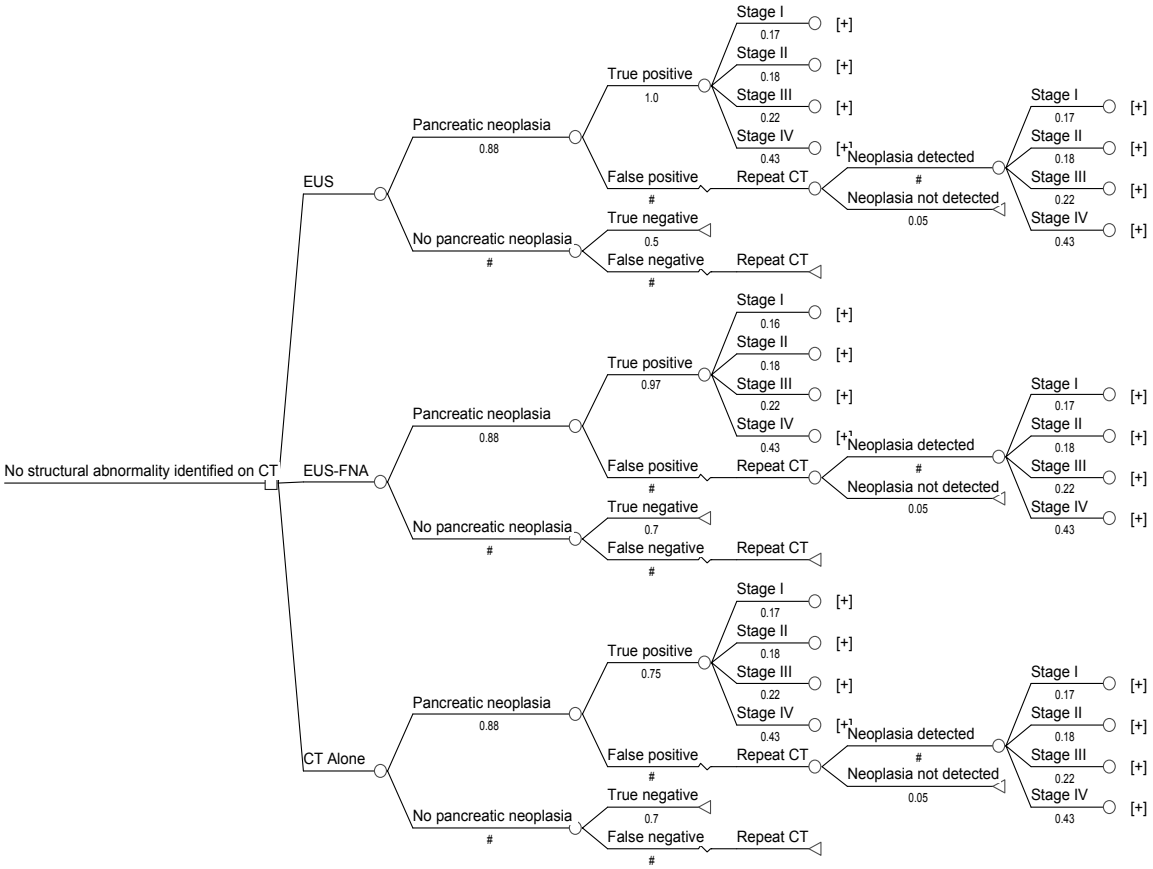



**Figure 8 Modelled diagnostic pathways**

In the model, patients receive either CT followed by EUS, CT followed by EUS-FNA, or CT alone. Patients remain in the model until death or they receive a true negative diagnostic result.

Complications associated with the diagnostic procedure were not included in the model. This is supported by the safety analysis, presented in this assessment report, which found complications associated with EUS and EUS-FNA to be negligible.

Patients who receive a true positive diagnostic test result proceed to the management pathway that is appropriate for their stage of pancreatic cancer. Patients who receive a false positive result were assumed to receive a second CT. Patients in whom pancreatic neoplasia is accurately diagnosed proceed to the appropriate management pathway (**Figure 9**; **Figure 10**; **Figure 11**; **Figure 12**). It was also assumed that pancreatic neoplasia remains undetected in 5 per cent of patients and that these patients do not receive treatment. If a true negative result is achieved, the patient exits the model. No further costs are associated with this patient group. If the diagnostic test produces a false negative result, it was assumed that the patient goes directly to surgery at which time the correct diagnosis would be made.

The median survival rate of patients is based on the curative procedure or palliative treatment received. The clinical benefit of using EUS to diagnose pancreatic exocrine tumours was derived from the diagnostic test's increased sensitivity and consequently the reduction in the proportion of patients with neoplasia who are not detected. As such, the difference in survival, on which the incremental cost-effectiveness ratio (ICER) was based, is driven by the proportion of patients with neoplasia who remain undiagnosed. In the model, these patients do not receive therapy and their survival is equivalent to no treatment.

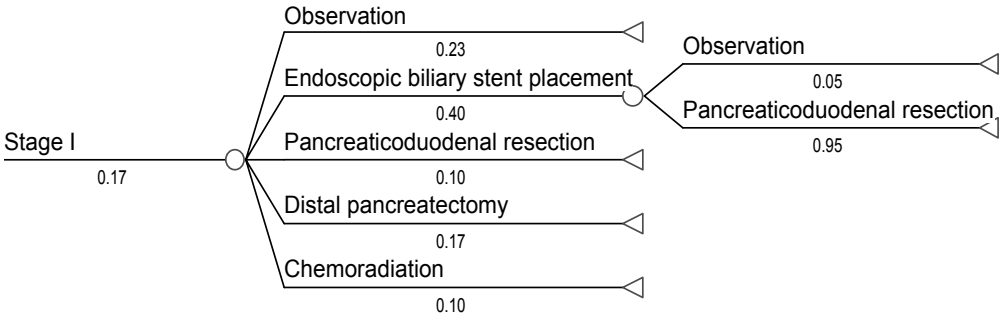



**Figure 9 Modelled management pathway stage I pancreatic neoplasia**

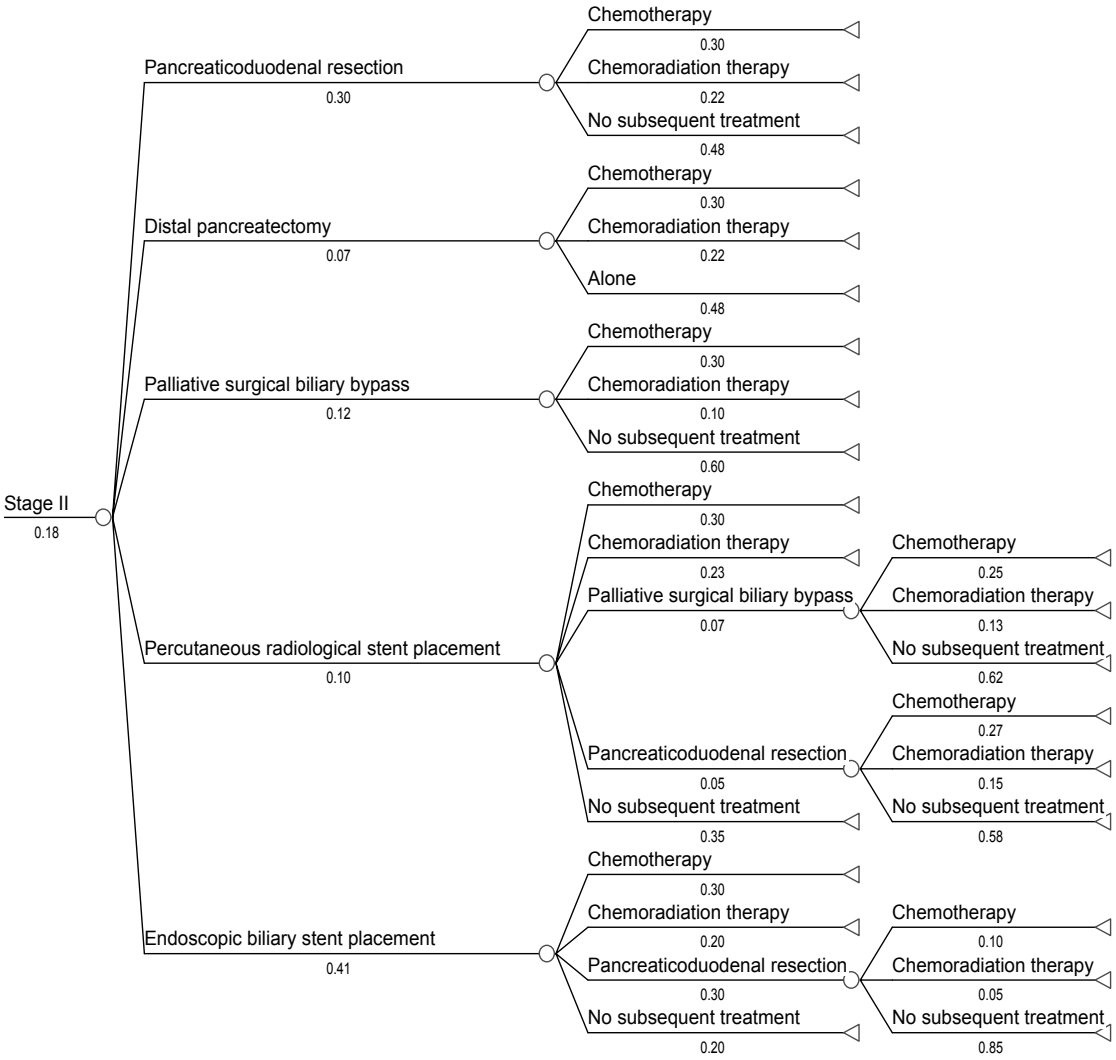



**Figure 10 Modelled management pathway stage II pancreatic neoplasia**

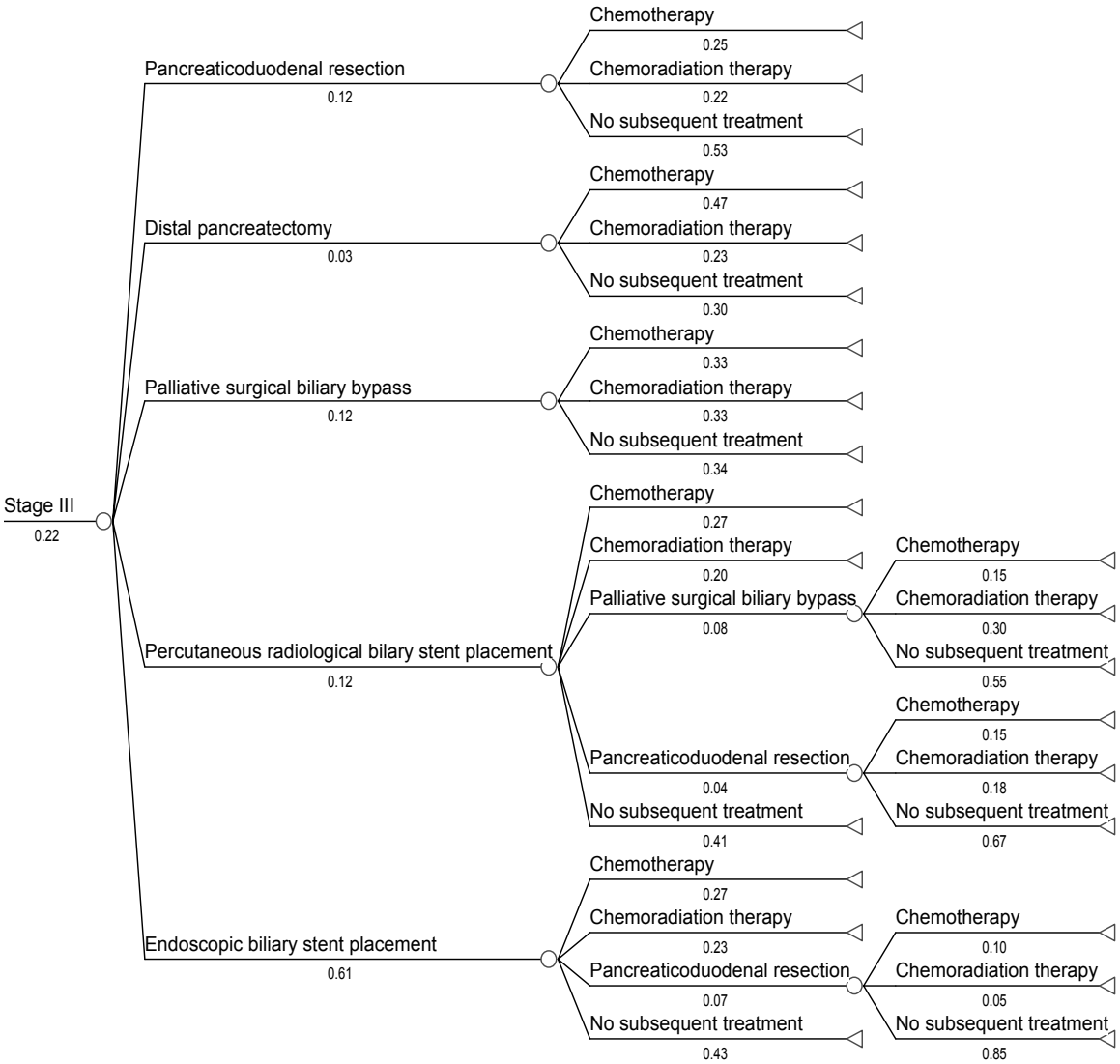



**Figure 11 Modelled management pathway stage III pancreatic neoplasia**

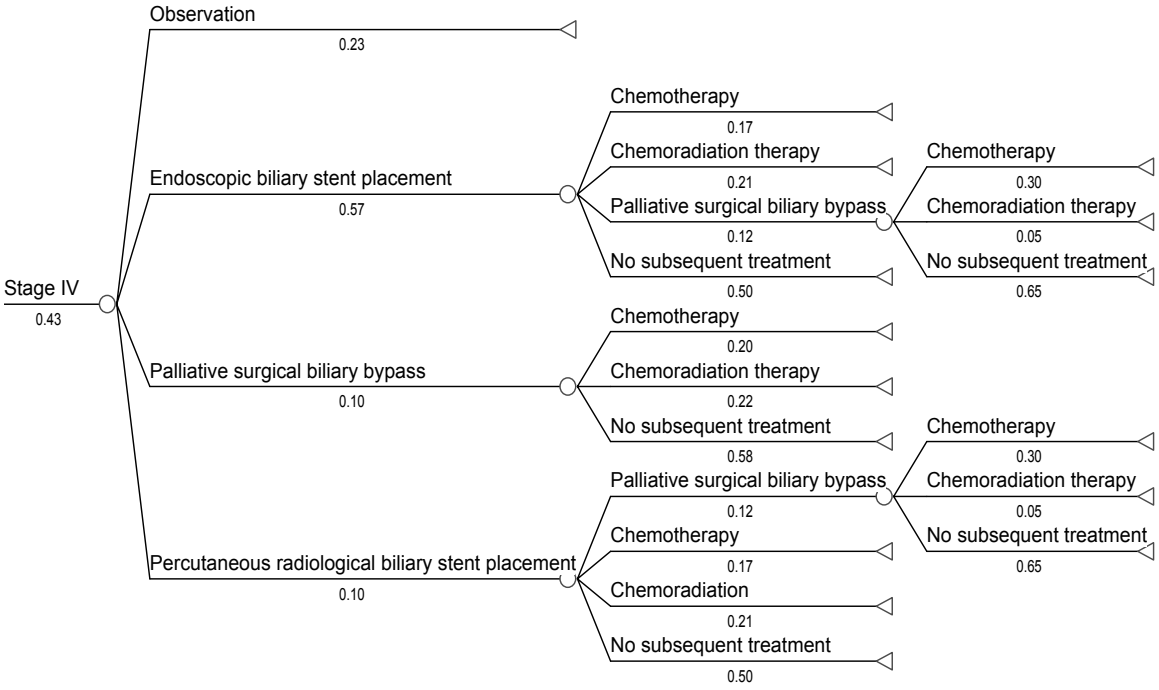



**Figure 12 Modelled management pathway stage IV pancreatic neoplasia**

## Variables used in the economic model

### Diagnostic procedures

**Table 87** presents the costs for each of the diagnostic procedures. These costs include all healthcare resources associated with performing the procedure. Note that the cost of EUS and EUS-FNA includes the professional fee, the cost of consumable items and the depreciation of capital equipment associated with the procedure. A derivation of the component costs supporting this proposed fee is presented in **Appendix J**.

**Table 87 Cost of diagnostic procedures for pancreatic exocrine neoplasia**

| Diagnostic Procedure | Resource utilised | Unit cost | Reference |
|---|---|---|---|
| EUS | Total cost per procedure | $832.27 | See **Appendix J** |
| EUS-FNA | Total cost per procedure | $1,726.52 | See **Appendix J** |
| Repeat CT scan | Total cost per procedure | $360.00 | MBS Item 56407 |
| Laparotomy | Procedure | $410.05 | MBS Item 30373 |
| | Anaesthesia | | |
| | *Pre-anaesthesia consultation* | $36.40 | MBS Item 17603 |
| | *Initiation of management* | $101.10 | MBS Item 20705 |
| | *Time (1 hour 30 minutes)*[a] | $101.10 | MBS Item 23063 |
| | Additional resources[b] | $3,365.00 | AR-DRG H01C |
| | **Total cost per procedure** | **$4,013.65** | |

Abbreviations: EUS, endoscopic ultrasound; EUS-FNA, endoscopic ultrasound with fine needle aspiration biopsy; AR-DRG, Australian Refined Diagnosis Related Group

[a] Estimated time based on expert opinion

[b] Public Sector version of the AR-DRG (National Hospital Cost Data Collection Cost Report Round 7 [2002–03]) operating room, supplies, pharmacy and hotel costs. AR-DRG H01C–Pancreas, liver and shunt procedure without complications

## Management procedures and treatment

**Table 88 Cost of management procedures following pancreatic exocrine neoplasia diagnostic tests**

| Management procedure/ treatment | Resource utilised | Unit cost | Reference |
|---|---|---|---|
| Pancreaticoduo-denal resection | Procedure | $1,495.75 | MBS Item 30584 |
| | Anaesthetic[a] | | |
| | *Pre-anaesthesia consultation* | $36.40 | MBS Item 17603 |
| | *Initiation of management* | $168.50 | MBS Item 20798 |
| | *Time–6 hours 50 minutes* | $556.05 | MBS Item 23330 |
| | | | Quirk et al (1997) |
| | Additional resources[b] | $3,365.00 | AR-DRG H01C |
| | **Total cost per procedure** | **$5,621.70** | |
| Distal pancreatectomy | Procedure | $1,013.35 | MBS Item 30583 |
| | Anaesthetic[c] | | |
| | *Pre-anaesthesia consultation* | $36.40 | MBS Item 17603 |
| | *Initiation of management* | $202.20 | MBS Item 20794 |
| | *Time–3 hours 15 minutes* | $219.05 | MBS Item 23130 |
| | | | Quirk et al (1997) |
| | Additional resources[b] | $3,365.00 | AR-DRG H01C |
| | **Total cost per procedure** | **$4,836.00** | |
| Palliative surgical biliary bypass | Procedure[d] | $1,063.49 | MBS Item 30460 |
| | | | MBS Item 30375 |
| | Anaesthetic[e] | | Khan et al (2005) |
| | *Pre-anaesthesia consultation* | $36.40 | MBS Item 17603 |
| | *Initiation of management* | $117.95 | MBS Item 20706 |
| | *Time–2 hours 44 minutes* | $185.35 | MBS Item 23110 |
| | Additional resources[b] | $3,365.00 | AR-DRG H01C |
| | **Total cost per procedure** | **$4,768.19** | |
| Percutaneous radiological biliary stent placement | Procedure | $470.00 | MBS Item 57341 |
| | Additional resources[b] | $3,365.00 | AR-DRG H01C |
| | **Total cost per procedure** | **$3,835.00** | |
| Endoscopic biliary stent placement | Procedure[f] | $790.95 | MBS Item 30484 |
| | | | MBS Item 30491 |
| | | | MBS Item 30485 |
| | Anaesthetic | | |
| | *Pre-anaesthesia consultation* | $36.40 | MBS Item 17603 |
| | *Initiation of management* | $84.25 | MBS Item 20740 |
| | *Time–1 hour 15 minutes* | $84.25 | MBS Item 23053 |
| | | | Expert opinion |
| | Additional resources[b] | $3,365.00 | AR-DRG H01C |
| | **Total cost per procedure** | **$4,360.85** | |

| Management procedure/ treatment | Resource utilised | Unit cost | Reference |
|---|---|---|---|
| Chemotherapy | 5-fluorouracil | $181.27 | PBS Item 2528C |
| | (600 mg/m$^2$ once weekly for 3 months) | | Burris et al (1997) |
| | | | Expert opinion |
| | | | MBS Item110 |
| | | | MBS Item 116 |
| | Cost of administering treatment | $1,495.55 | MBS Item 13915 |
| | **Total cost of treatment** | **$1,676.82** | |
| Chemoradiation | Radiation | $464.00 | MBS Item 15211 |
| | (40 Gy, 2 courses of 5 days each) | | GTSG (1987) |
| | 5-fluourouracil | $859.88 | PBS Item 2528C |
| | Cost of administering treatment | $8,684.05 | MBS Item 110 |
| | | | MBS Item 116 |
| | | | MBS Item 13915 |
| | **Total cost of treatment** | **$10,007.93** | |

Abbreviations: AR-DRG, Australian Refined Diagnosis Related Group; GTST, Gastrointestinal Tumor Study Group; MBS, Medicare Benefits Schedule; PBS, Pharmaceutical Benefits Schedule

[a] Based on estimated operating time of 410 minutes

[b] Public Sector version of the AR-DRG (National Hospital Cost Data Collection Cost Report Round 7 [2002-03]) operating room, supplies, pharmacy and hotel costs. AR-DRG H01C–Pancreas, liver and shunt procedure without complications

[c] Based on estimated operating time of 195 minutes

[d] Based on multiple operation rule. Procedure ($1063.49) = laparotomy/procedure ($731.80) + laparotomy ($442.25 x 50% = $221.13) + laparotomy ($442.25 x 25% = $110.56)

[e] Based on estimated operating time of 164 minutes

[f] Calculation based on multiple operation rule = Sphincterotomy ($477.95) + Endoscopic stenting of bile duct ($471.20 x 50% = $235.60) + ERCP ($309.60 x 25% = $77.40)

## Other clinical variables

**Table 89 Other clinical variables for pancreatic exocrine neoplasia**

| Variable | Value | Reference |
|---|---|---|
| Prevalence of pancreatic neoplasia | 0.88 | Agarwal et al (2004) (**Table 59**) |
| (n/N) | (71/81) | |
| **Sensitivity** | | |
| EUS+CT | 1.0 | Agarwal et al (2004) (**Table 59**) |
| EUS-FNA+CT | 0.97 | Agarwal et al (2004) (**Table 59**) |
| CT | 0.75 | Agarwal et al (2004) (**Table 59**) |
| **Specificity** | | |
| EUS+CT | 0.50 | Agarwal et al (2004) (**Table 59**) |
| EUS-FNA+CT | 0.70 | Agarwal et al (2004) (**Table 59**) |
| CT | 0.70 | Agarwal et al (2004) (**Table 59**) |
| **Stage of pancreatic cancer** | | |
| Stage I | 0.16 | Erickson & Garza (2000) |
| Stage II | 0.18 | Erickson & Garza (2000) |
| Stage III | 0.22 | Erickson & Garza (2000) |
| Stage IV | 0.43 | Erickson & Garza (2000) |
| **Proportion of patients who receive second diagnostic test if initial test produces false-positive result** | | |
| Repeat CT | 1.0 | Expert opinion |
| **Median survival** | | |
| Pancreaticoduodenal resection | 18 months | Yeo et al (1997) |
| Distal pancreatetomy | 18 months | Yeo et al (1997) |
| Palliative surgical biliary bypass | 6.2 months | Wakeman et al (2004) |
| Percutaneous radiological biliary stent placement | 3.1 months | Wakeman et al (2004) |
| Endoscopic biliary stent placement | 3.1 months | Wakeman et al (2004) |
| Chemotherapy | 4.4 months | Burris et al (1997) |
| Chemoradiation | 9.1 months | Gastrointestinal Tumor Study Group (1987) |
| Radiation | 10.5 months | Debelbower et al (1991) |
| No intervention | 1.6 months | Wakeman et al (2004) |

*4% were unable to be staged. Accordingly, these 4% were evenly distributed among all stages
Abbreviations: CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound

**Table 90 Management variables by stage of pancreatic cancer for pancreatic exocrine neoplasia**

| First treatment | Variable | Second treatment | Variable | Third treatment | Variable |
|---|---|---|---|---|---|
| ***Stage I*** | | | | | |
| Pancreaticoduodenal resection | 0.10 | N/a | | N/a | |
| Distal pancreatectomy | 0.17 | | | | |
| Chemoradiation | 0.10 | | | | |
| Endoscopic biliary stent placement | 0.40 | Pancreaticoduodenal resection | 0.95 | N/a | |
| | | No subsequent treatment | 0.05 | | |
| Observation | 0.23 | N/a | | N/a | |
| ***Stage II*** | | | | | |
| Pancreaticoduodenal resection | 0.30 | Chemotherapy | 0.30 | N/a | |
| | | Chemoradiation | 0.22 | | |
| | | No subsequent treatment | 0.48 | | |
| Distal pancreatectomy | 0.07 | Chemotherapy | 0.30 | N/a | |
| | | Chemoradiation | 0.22 | | |
| | | No subsequent treatment | 0.48 | | |
| Palliative surgical biliary bypass | 0.12 | Chemotherapy | 0.30 | N/a | |
| | | Chemoradiation | 0.10 | | |
| | | No subsequent treatment | 0.60 | | |
| Percuataneous radiological biliary stent placement | 0.10 | Chemotherapy | 0.30 | N/a | |
| | | Chemoradiation | 0.23 | | |
| | | Palliative surgical biliary bypass | 0.07 | Chemotherapy | 0.25 |
| | | | | Chemoradiation | 0.13 |
| | | | | No subsequent treatment | 0.62 |
| | | Pancreaticoduodenal resection | 0.05 | Chemotherapy | 0.27 |
| | | | | Chemoradiation | 0.15 |
| | | | | No subsequent treatment | 0.58 |
| | | No subsequent treatment | 0.35 | N/a | |
| Endoscopic biliary stent placement | 0.41 | Chemotherapy | 0.30 | N/a | |
| | | Chemoradiation | 0.20 | | |
| | | Pancreaticoduodenal resection | 0.30 | Chemotherapy | 0.10 |
| | | | | Chemoradiation | 0.05 |
| | | | | No subsequent treatment | 0.85 |
| | | No subsequent treatment | 0.20 | N/a | |

| First treatment | Variable | Second treatment | Variable | Third treatment | Variable |
|---|---|---|---|---|---|
| ***Stage II*** | | | | | |
| Pancreaticoduodenal resection | 0.12 | Chemotherapy | 0.25 | N/a | |
| | | Chemoradiation | 0.22 | | |
| | | No subsequent therapy | 0.53 | | |
| Distal pancreatectomy | 0.03 | Chemotherapy | 0.47 | N/a | |
| | | Chemoradiation | 0.23 | | |
| | | No subsequent treatment | 0.30 | | |
| Palliative surgical biliary bypass | 0.12 | Chemotherapy | 0.33 | N/a | |
| | | Chemoradiation | 0.33 | | |
| | | No subsequent treatment | 0.34 | | |
| Percutaneous radiological biliary stent placement | 0.12 | Chemotherapy | 0.27 | N/a | |
| | | Chemoradiation | 0.20 | | |
| | | Palliative surgical biliary bypass | 0.08 | | |
| | | | | Chemotherapy | 0.15 |
| | | | | Chemoradiation | 0.30 |
| | | | | No subsequent treatment | 0.55 |
| | | Pancreaticoduodenal resection | 0.04 | Chemotherapy | 0.15 |
| | | | | Chemoradiation | 0.18 |
| | | | | No subsequent treatment | 0.67 |
| | | No subsequent treatment | 0.41 | N/a | |
| Endoscopic biliary stent placement | 0.61 | Chemotherapy | 0.27 | N/a | |
| | | Chemoradiation | 0.23 | | |
| | | Pancreaticoduodenal resection | 0.07 | Chemotherapy | 0.10 |
| | | | | Chemoradiation | 0.05 |
| | | | | No subsequent treatment | 0.85 |
| | | No subsequent treatment | 0.43 | N/a | |

| First treatment | Variable | Second treatment | Variable | Third treatment | Variable |
|---|---|---|---|---|---|
| ***Stage IV*** | | | | | |
| Palliative surgical biliary bypass | 0.10 | Chemotherapy | 0.20 | N/a | |
| | | Chemoradiation | 0.22 | | |
| | | No subsequent treatment | 0.58 | | |
| Percutaneous radiological biliary stent placement | 0.10 | Palliative surgical biliary bypass | 0.12 | Chemotherapy | 0.30 |
| | | | | Chemoradiation | 0.05 |
| | | | | No subsequent treatment | 0.65 |
| | | Chemotherapy | 0.17 | N/a | |
| | | Chemoradiation | 0.21 | | |
| | | No subsequent treatment | 0.50 | | |
| Endoscopically biliary stent placement | 0.57 | Palliative surgical biliary bypass | 0.12 | Chemotherapy | 0.30 |
| | | | | Chemoradiation | 0.05 |
| | | | | No subsequent treatment | 0.65 |
| | | Chemotherapy | 0.17 | N/a | |
| | | Chemoradiation | 0.21 | | |
| | | No subsequent treatment | 0.50 | | |
| Observation | 0.23 | N/a | | N/a | |

### Results of the economic model

The results were calculated based on a cost-effectiveness analysis using DATA 2005 and Microsoft Excel®. This method estimates the incremental cost per life year saved of performing EUS, and EUS-FNA following CT, to diagnose pancreatic neoplasia, relative to CT alone. The evaluation captures the cost of EUS and EUS-FNA, the cost of disease treatment and management, and the clinical benefit of treatment (ie life years gained). On average, diagnosis of pancreatic exocrine neoplasia using EUS following CT is achieved at an incremental cost-effectiveness ratio of $23,347 per life year gained, when compared with CT alone (**Table 91**). Comparing EUS-FNA following CT with CT alone resulted in an incremental cost-effectiveness ratio of $35,766 per life year gained (**Table 92**).

**Table 91 Incremental cost-effectiveness ratio for EUS following CT versus CT alone to diagnose pancreatic exocrine neoplasia**

| Summary result | EUS following CT | CT alone | Incremental |
|---|---|---|---|
| Cost per patient | $6,529 | $5,532 | $997 |
| Life years gained | 5.015 | 4.973 | 0.042 |
| Incremental cost per life year gained | | | **$23,347** |

**Table 92 Incremental cost-effectiveness ratio for EUS-FNA following CT versus CT alone to diagnose pancreatic exocrine neoplasia**

| Summary result | EUS-FNA following CT | CT alone | Incremental |
|---|---|---|---|
| Cost per patient | $7,350 | $5,531 | $1819 |
| Life years gained | 5.024 | 4.973 | 0.051 |
| Incremental cost per life year gained | | | **$35,766** |

### Sensitivity analysis

Sensitivity analyses were conducted to assess the robustness of the model relating to changes in key assumption values.

A sensitivity analysis was conducted using prevalence, sensitivity and specificity values from the additional study (Harrison et al 1999) identified and included in the assessment of the diagnostic accuracy of EUS over CT for diagnosis of pancreatic exocrine neoplasia. Varying the prevalence of pancreatic exocrine neoplasia to reflect the value presented by Harrison et al (1999) resulted in an incremental cost of $25,654 per life year gained for EUS over CT, and $33,627 per life year gained for EUS-FNA over CT. Varying the sensitivity and specificity of EUS plus CT and CT alone produced an incremental cost of $28,988 per life year gained.

**Table 93 Sensitivity analysis variables for pancreatic exocrine neoplasia diagnosis**

| Variable | Value | Reference |
|---|---|---|
| Prevalence of pancreatic exocrine neoplasia | 0.83 | Harrison et al (1999) (**Table 59**) |
| Sensitivity of CT | 0.53 | Harrison et al (1999) (**Table 59**) |
| Sensitivity of EUS plus CT | 1.0 | Harrison et al (1999) (**Table 59**) |
| Specificity of CT | 0.33 | Harrison et al (1999) (**Table 59**) |
| Specificity of EUS plus CT | 0.0 | Harrison et al (1999) (**Table 59**) |

**Table 94 Sensitivity analysis results for EUS following CT versus CT alone for pancreatic exocrine neoplasia diagnosis**

| Summary result | EUS following CT | CT alone | Incremental |
|---|---|---|---|
| **Prevalence of unresectable pancreatic neoplasia** | | | |
| Cost per patient | $6,319 | $5,286 | $1,033 |
| Life years gained | 4.834 | 4.794 | 0.040 |
| Incremental cost per life year gained | | **$25,654** | |
| **Sensitivity and specificity of diagnostic tests** | | | |
| Cost per patient | $6,770 | $5,532 | $1,238 |
| Life years gained | 5.016 | 4.973 | 0.043 |
| Incremental cost per life year gained | | **$28,988** | |

**Table 95 Sensitivity analysis results for EUS-FNA following CT versus CT alone for pancreatic exocrine neoplasia diagnosis**

| Summary result | EUS-FNA following CT | CT alone | Incremental |
|---|---|---|---|
| **Prevalence of unresectable pancreatic neoplasia** | | | |
| Cost per patient | $7,110 | $5,286 | $1,824 |
| Life years gained | 4.848 | 4.794 | 0.054 |
| Incremental cost per life year gained | | **$33,627** | |

## Model II—Evidence of pancreatic solid mass

### Key assumptions

- The economic model compared use of EUS following CT with CT alone to diagnose pancreatic neoplasia where a pancreatic abnormality had been identified on CT.
- Only direct healthcare costs and benefits were calculated.
- Patients referred for either EUS or CT were assumed to have the same comorbidities. All other diagnostic and additional clinical decision-making was assumed to be similar.
- The prevalence of malignant solid masses and the proportion of patients in each stage of pancreatic cancer, based on TNM classification, were derived from the literature.
- Morbidity and the cost of CT were not incorporated into the model because it was assumed that all patients undergo CT diagnostic investigation. For this reason, it was assumed that such variables would be the same in both arms of the model.
- Morbidity associated with palliative measures, such as radiation or chemotherapy, was not included in the analysis, but was assumed to be similar in both arms of the model.

- Patients remain in the model until death or until the confirmation of a true negative diagnostic result is obtained.

- It was assumed that all incidence of mortality related to the safety of palliative and curative management procedures or treatment were captured by the median survival rate.

- The specificity and sensitivity of EUS plus CT, and CT alone, were derived from evidence presented in the clinical section of this assessment report.

- It was assumed that median survival of patients with malignant solid mass was determined by the curative or palliative treatment received rather than the stage of pancreatic cancer.

- Complications associated with EUS were excluded from the analysis because their cost and effect were assumed to be negligible.

- It was assumed that MBS fees used in the economic analysis incorporated the cost of consumable items, professional time, and depreciation of capital equipment associated with the procedure.

- Economic model costs included the diagnostic procedure used and curative or palliative management from time of diagnosis until death.

- An annual discount rate was not applied to costs because it was assumed that all costs occur within the first year after diagnosis was due to the short median survival rate of patients with pancreatic cancer. An annual discount rate of 5 per cent was applied to benefits accrued beyond the first year.

### Patient population used in the economic model

The proposed indication for EUS is for diagnosis of pancreatic neoplasms in patients with symptoms and biochemical evidence (CA 19-9) associated with pancreatic neoplasia, when CT has identified a pancreatic abnormality. The population in the economic model was based on the population described in the clinical section of this assessment report. The population is representative of the patients likely to receive EUS in an MBS setting.

### Structure of the economic model

A decision analytic model was developed to estimate the downstream healthcare resource utilisation associated with diagnosing pancreatic neoplasia. The model uses data available in the literature to evaluate the possible outcomes associated with diagnosis of malignant solid masses in the pancreas and to identify the most desirable healthcare strategy among the different diagnostic alternatives.

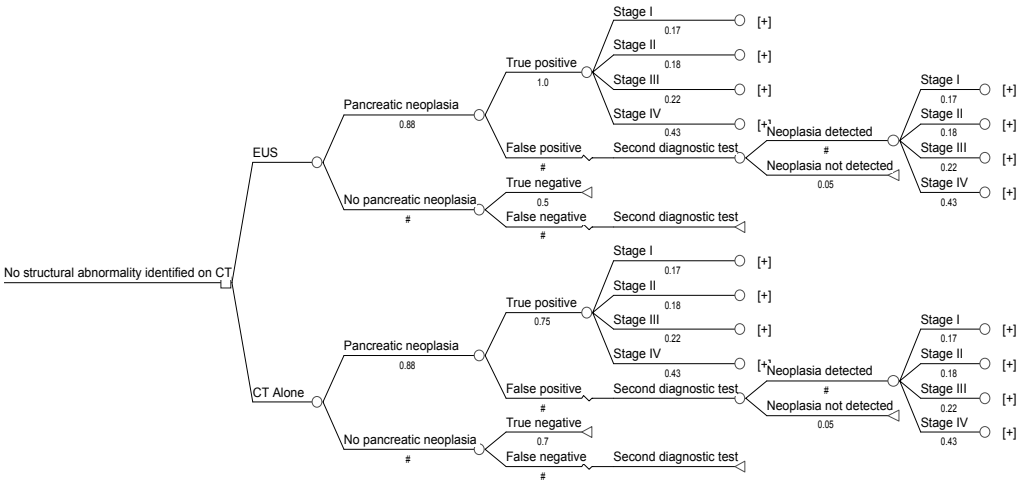



**Figure 13 Modelled diagnostic pathways**

In the model, patients receive either CT followed by EUS or CT alone. Patients remain in the model until they die or until they receive a true negative diagnostic result.

Complications associated with the diagnostic procedure were not included in the model. This is supported by the safety analysis presented in this assessment report, which found complications associated with EUS to be negligible.

Patients who receive a true positive diagnostic test result proceed to the management pathway that is appropriate for their stage of pancreatic cancer. Patients who receive a false positive result are assumed to receive a second diagnostic procedure (ERCP, laparoscopy or laparotomy). Patients in whom pancreatic neoplasia is accurately diagnosed proceed to the appropriate management pathway (**Figure 14**; **Figure 15**; **Figure 16**; **Figure 17**). It was assumed that pancreatic neoplasia remains undetected in 5 per cent of patients and that these patients do not receive treatment. If a true negative result is achieved, the patient exits the model. No further costs are associated with this patient group. If the diagnostic test produces a false negative result, it was assumed that the patient goes directly to surgery at which time the correct diagnosis is made.

The median survival rate of patients was based on the curative procedure or palliative treatment received. The clinical benefit of using EUS to diagnose pancreatic solid masses was derived from the diagnostic test's increased sensitivity and consequent reduction in the proportion of patients with neoplasia who are not detected. As such, the difference in survival, on which the ICER is based, is driven by the proportion of patients with neoplasia who remain undiagnosed. In the model, these patients do not receive therapy and survival is equivalent to receiving no treatment.

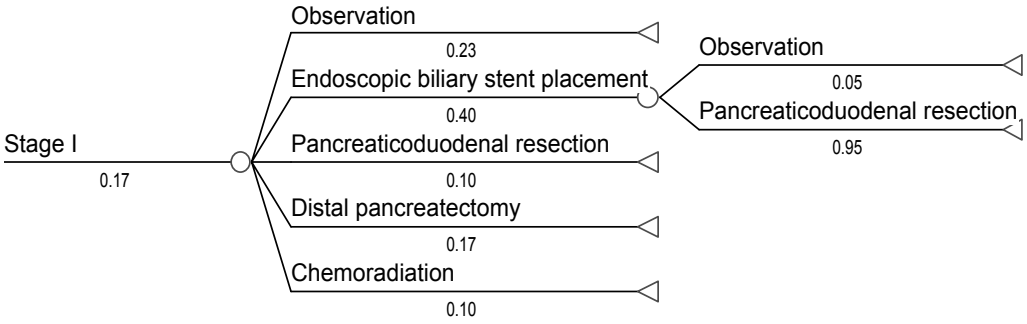



**Figure 14 Modelled management pathway stage I pancreatic neoplasia**

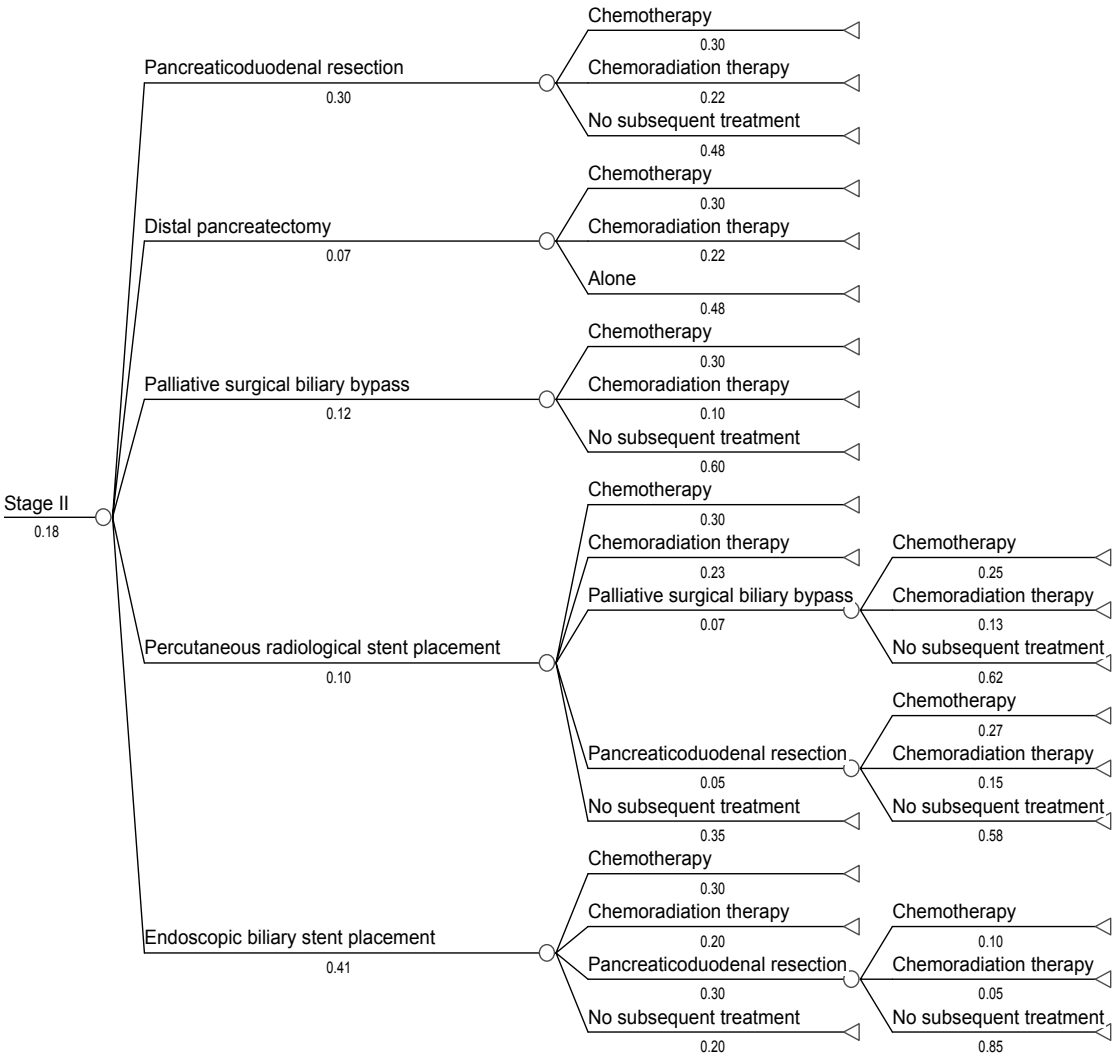



**Figure 15 Modelled management pathway stage II pancreatic neoplasia**

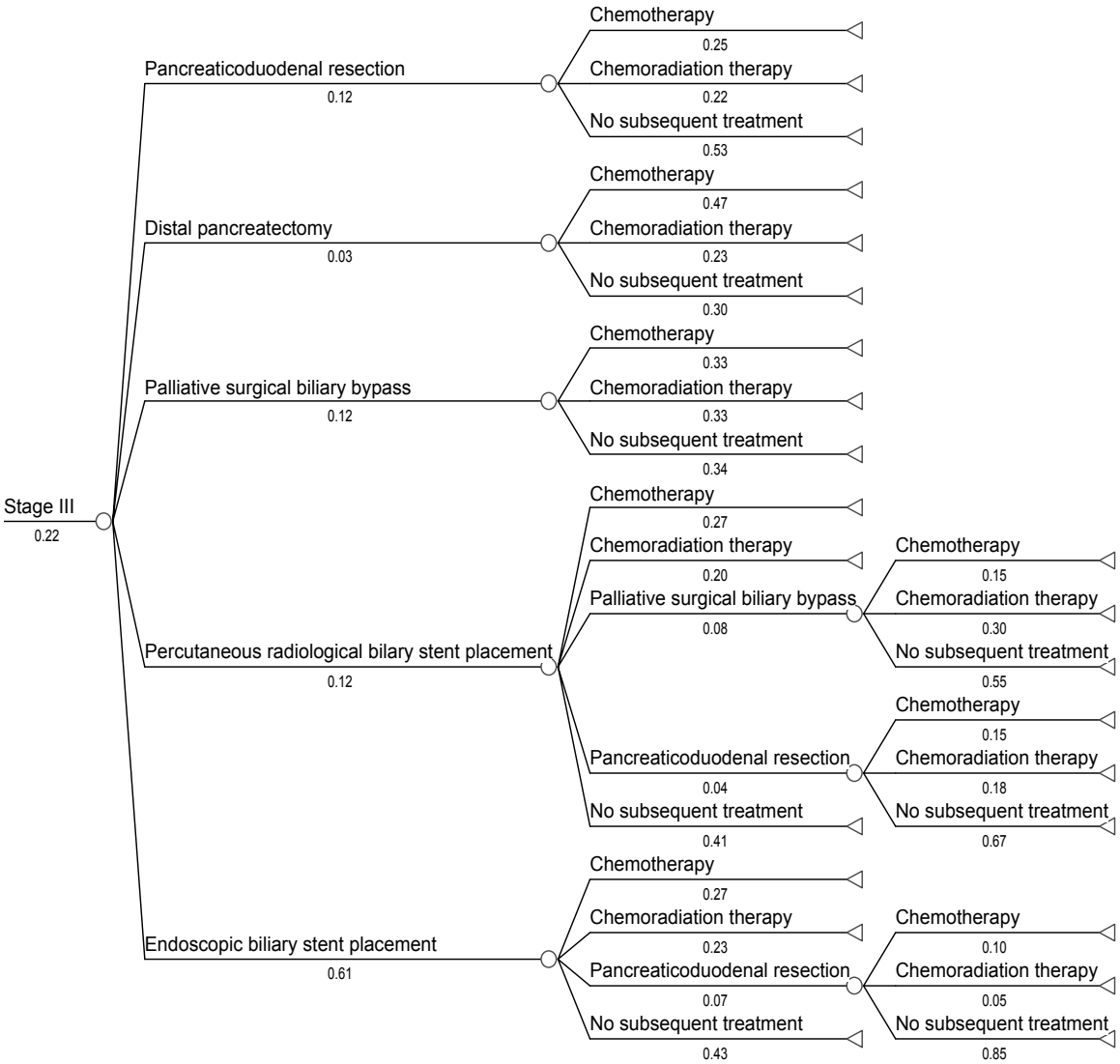



**Figure 16 Modelled management pathway stage III pancreatic neoplasia**

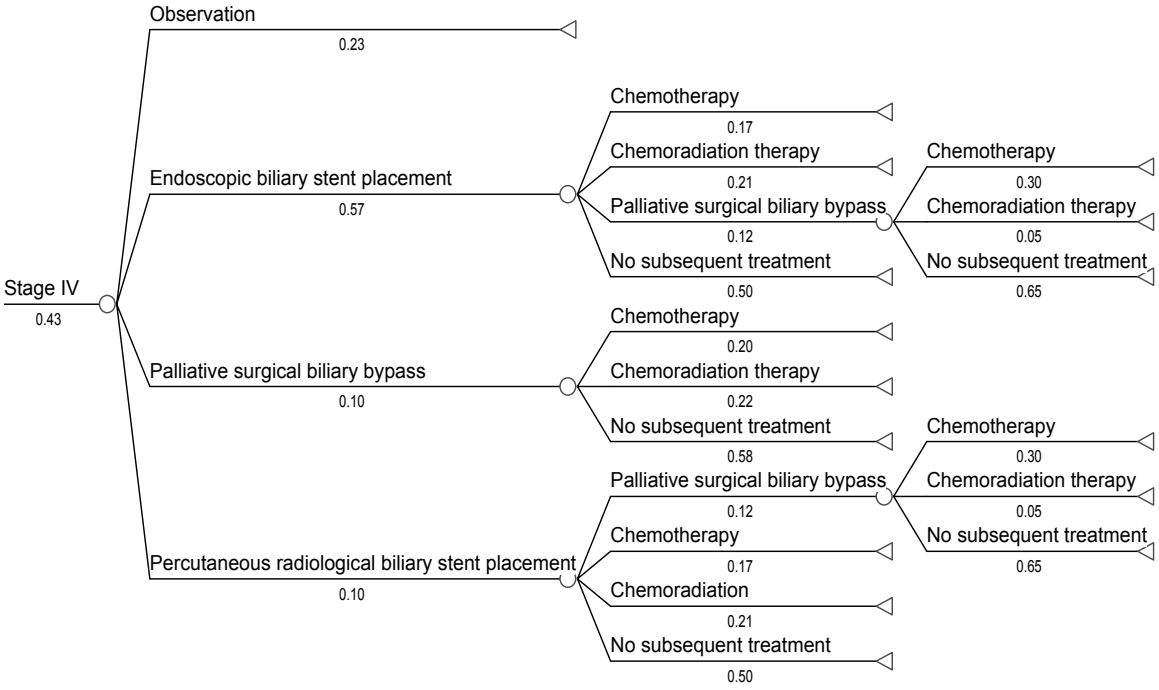



**Figure 17 Modelled management pathway stage IV pancreatic neoplasia**

## Variables used in the economic model

### Diagnostic procedures

**Table 96** presents the costs for each of the diagnostic procedures. These costs include all healthcare resources associated with performing the procedure. Note that the cost of EUS includes the professional fee, the cost of consumable items and the depreciation of capital equipment associated with the procedure. A derivation of the component costs supporting this proposed fee is presented in **Appendix J**.

**Table 96 Cost of diagnostic procedures for malignant pancreatic solid masses**

| Diagnostic Procedure | Resource utilised | Unit cost | Reference |
|---|---|---|---|
| EUS | **Total cost per procedure** | **$832.27** | See **Appendix J** |
| ERCP | Procedure[a] | $632.75 | MBS Item 30485; MBS Item 30484 |
| | Anaesthesia | | |
| | *Pre-anaesthesia consultation* | $36.40 | MBS Item 17603 |
| | *Initiation of management* | $84.25 | MBS Item 20740 |
| | *Time (1 hour 15 minutes)*[b] | $84.25 | MBS Item 23053 |
| | Additional resources[c] | $3,365.00 | AR-DR H01B |
| | **Total cost per procedure** | **$4,202.65** | |
| Laparotomy | Procedure | $410.05 | MBS Item 30373 |
| | Anaesthesia | | |
| | *Pre-anaesthesia consultation* | $36.40 | MBS Item 17603 |
| | *Initiation of management* | $101.10 | MBS Item 20705 |
| | *Time (1 hour 30 minutes)*[b] | $101.10 | MBS Item 23063 |
| | Additional resources[c] | $3,365.00 | AR-DR H01B |
| | **Total cost per procedure** | **$4,013.65** | |
| Laparoscopy | Procedure | $186.60 | MBS Item 30390 |
| | Anaesthesia | | |
| | *Pre-anaesthesia consultation* | $36.40 | MBS Item 17603 |
| | *Initiation of management* | $101.10 | MBS Item 20705 |
| | *Time (1 hour 30 minutes)*[b] | $50.55 | MBS Item 23033 |
| | Additional resources[c] | $3,365.00 | AR-DRG H01B |
| | **Total cost per procedure** | **$3,739.65** | |

Abbreviations: AR-DRG, Australian Refined Diagnosis Related Group; EUS, endoscopic ultrasound; EUS-FNA, endoscopic ultrasound with fine needle aspiration biopsy; ERCP, endoscopic retrograde cholangiopancreatography; MBS, Medicare Benefits Schedule

[a] Calculation based on multiple operation rule = Sphincterotomy ($477.95) + ERCP ($309.60 x 50% = $154.80) = $632.75

[b] Expert opinion

[c] Public Sector version of the AR-DRG (National Hospital Cost Data Collection Cost Report Round 7 [2002–2003]) operating room, supplies, pharmacy and hotel costs. AR-DRG H01C–Pancreas, liver and shunt procedure without complications

## Management procedures and treatment

**Table 97 Cost of management procedures following malignant pancreatic solid mass diagnostic testing**

| Management procedure/ treatment | Resource utilised | Unit cost | Reference |
|---|---|---|---|
| Pancreaticoduo-denal resection | Procedure | $1,495.75 | MBS Item 30584 |
| | Anaesthetic[a] | | |
| | *Pre-anaesthesia consultation* | $36.40 | MBS Item 17603 |
| | *Initiation of management* | $168.50 | MBS Item 20798 |
| | *Time–6 hours 50 minutes* | $556.05 | MBS Item 23330 |
| | | | Quirk et al (1997) |
| | Additional resources[b] | $3,365.00 | AR-DRG H01C |
| | **Total cost per procedure** | **$5,621.70** | |
| Distal pancreatetomy | Procedure | $1,013.35 | MBS Item 30583 |
| | Anaesthetic[c] | | |
| | *Pre-anaesthesia consultation* | $36.40 | MBS Item 17603 |
| | *Initiation of management* | $202.20 | MBS Item 20794 |
| | *Time–3 hours 15 minutes* | $219.05 | MBS Item 23130 |
| | | | Quirk et al (1997) |
| | Additional resources[b] | $3,365.00 | AR-DRG H01C |
| | **Total cost per procedure** | **$4,836.00** | |
| Palliative surgical biliary bypass | Procedure[d] | $1,063.49 | MBS Item 30460 |
| | | | MBS Item 30375 |
| | Anaesthetic[e] | | Khan et al (2005) |
| | *Pre-anaesthesia consultation* | $36.40 | MBS Item 17603 |
| | *Initiation of management* | $117.95 | MBS Item 20706 |
| | *Time–2 hours 44 minutes* | $185.35 | MBS Item 23110 |
| | Additional resources[b] | $3,365.00 | AR-DRG H01C |
| | **Total cost per procedure** | **$4,768.19** | |
| Percutaneous radiological biliary stent placement | Procedure | $470.00 | MBS Item 57341 |
| | Additional resources[b] | $3,365.00 | AR-DRG H01C |
| | **Total cost per procedure** | **$3,835.00** | |
| Endoscopic biliary stent placement | Procedure[f] | $790.95 | MBS Item 30484 |
| | | | MBS Item 30491 |
| | | | MBS Item 30485 |
| | Anesthetic | | |
| | *Pre-anaesthesia consultation* | $36.40 | MBS Item 17603 |
| | *Initiation of management* | $84.25 | MBS Item 20740 |
| | *Time–1 hour 15 minutes* | $84.25 | MBS Item 23053 |
| | | | Expert opinion |
| | Additional resources[b] | $3,365.00 | AR-DRG H01C |
| | **Total cost per procedure** | **$4,360.85** | |

| Management procedure/ treatment | Resource utilised | Unit cost | Reference |
|---|---|---|---|
| Chemotherapy | 5-fluorouracil | $1,81.27 | PBS Items 2528C |
| | (600 mg/m$^2$ once weekly for 3 months) | | Burris et al (1997) |
| | | | Expert opinion |
| | Cost of administering treatment | $1,495.55 | MBS Item110 |
| | | | MBS Item 116 |
| | | | MBS Item 13915 |
| | **Total cost of treatment** | **$1,676.82** | |
| Chemoradiation | Radiation | $464.00 | MBS Item 15211 |
| | (40 Gy, 2 courses of 5 days each) | | GTSG (1987) |
| | 5-fluourouracil | $859.88 | PBS Item 2528C |
| | Cost of administering treatment | $8,684.05 | MBS Item 110 |
| | | | MBS Item 116 |
| | | | MBS Item 13915 |
| | **Total cost of treatment** | **$10,007.93** | |

Abbreviations: AR-DRG, Australian Refined Diagnosis Related Group; GTST, Gastrointestinal Tumor Study Group; MBS, Medicare Benefits Schedule; PBS, Pharmaceutical Benefits Schedule

[a] Based on estimated operating time of 410 minutes

[b] Public Sector version of the AR-DRG (National Hospital Cost Data Collection Cost Report Round 7 [2002-03]) operating room, supplies, pharmacy and hotel costs. AR-DRG H01C – Pancreas, liver and shunt procedure without complications

[c] Based on estimated operating time of 195 minutes

[d] Based on multiple operation rule. Procedure ($1063.49) = laparotomy/procedure ($731.80) + laparotomy ($442.25 x 50% = $221.13) + laparotomy ($442.25 x 25% = $110.56)

[e] Based on estimated operating time of 164 minutes

[f] Calculation based on multiple operation rule = Sphincterotomy ($477.95) + Endoscopic stenting of bile duct ($471.20 x 50% = $235.60) + ERCP ($309.60 x 25% = $77.40)

## Other clinical variables

**Table 98 Other clinical variables for diagnosis of malignant pancreatic solid masses**

| Variable | Value | Reference |
|---|---|---|
| Prevalence of pancreatic neoplasia (n/N) | 0.53 (19/36) | Okai et al (1999) (**Table 49**) |
| **Sensitivity** | | |
| EUS + CT | 1.00 | Okai et al (1999) (**Table 49**) |
| CT | 0.789 | Okai et al (1999) (**Table 49**) |
| **Specificity** | | |
| EUS + CT | 0.765 | Okai et al (1999) (**Table 49**) |
| CT | 0.882 | Okai et al (1999) (**Table 49**) |
| **Stage of pancreatic cancer** | | |
| Stage I | 0.17 | Erickson & Garza (2000) |
| Stage II | 0.18 | Erickson & Garza (2000) |
| Stage III | 0.22 | Erickson & Garza (2000) |
| Stage IV | 0.43 | Erickson & Garza (2000) |
| **Proportion of patients who receive second diagnostic test if initial test produces false-positive result** | | |
| ERCP | 0.5 | Expert opinion |
| Laparoscopy | 0.1 | Expert opinion |
| Laparotomy | 0.4 | Expert opinion |
| **Median survival** | | |
| Pancreaticoduodenal resection | 18 months | Yeo et al (1997) |
| Distal pancreatetomy | 18 months | Yeo et al (1997) |
| Palliative surgical biliary bypass | 6.2 months | Wakeman et al (2004) |
| Percutaneous radiological biliary stent placement | 3.1 months | Wakeman et al (2004) |
| Endoscopic biliary stent placement | 3.1 months | Wakeman et al (2004) |
| Chemotherapy | 4.4 months | Burris et al (1997) |
| Chemoradiation | 9.1 months | Gastrointestinal Tumor Study Group (1987) |
| Radiation | 10.5 months | Debelbower et al (1991) |
| No intervention | 1.6 months | Wakeman et al (2004) |

Abbreviations: CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound

**Table 99 Management variables by pancreatic cancer stage**

| First treatment | Variable | Second treatment | Variable | Third treatment | Variable |
|---|---|---|---|---|---|
| ***Stage I*** | | | | | |
| Pancreaticoduodenal resection | 0.10 | N/a | | N/a | |
| Distal pancreatectomy | 0.17 | | | | |
| Chemoradiation | 0.10 | | | | |
| Endoscopic biliary stent placement | 0.40 | Pancreaticoduodenal resection | 0.95 | N/a | |
| | | No subsequent treatment | 0.05 | | |
| Observation | 0.23 | N/a | | N/a | |
| ***Stage II*** | | | | | |
| Pancreaticoduodenal resection | 0.30 | Chemotherapy | 0.30 | N/a | |
| | | Chemoradiation | 0.22 | | |
| | | No subsequent treatment | 0.48 | | |
| Distal pancreatectomy | 0.07 | Chemotherapy | 0.30 | N/a | |
| | | Chemoradiation | 0.22 | | |
| | | No subsequent treatment | 0.48 | | |
| Palliative surgical biliary bypass | 0.12 | Chemotherapy | 0.30 | N/a | |
| | | Chemoradiation | 0.10 | | |
| | | No subsequent treatment | 0.60 | | |
| Percuataneous radiological biliary stent placement | 0.10 | Chemotherapy | 0.30 | N/a | |
| | | Chemoradiation | 0.23 | | |
| | | Palliative surgical biliary bypass | 0.07 | Chemotherapy | 0.25 |
| | | | | Chemoradiation | 0.13 |
| | | | | No subsequent treatment | 0.62 |
| | | Pancreaticoduodenal resection | 0.05 | Chemotherapy | 0.27 |
| | | | | Chemoradiation | 0.15 |
| | | | | No subsequent treatment | 0.58 |
| | | No subsequent treatment | 0.35 | N/a | |
| Endoscopic biliary stent placement | 0.41 | Chemotherapy | 0.30 | N/a | |
| | | Chemoradiation | 0.20 | | |
| | | Pancreaticoduodenal resection | 0.30 | Chemotherapy | 0.10 |
| | | | | Chemoradiation | 0.05 |
| | | | | No subsequent treatment | 0.85 |
| | | No subsequent treatment | 0.20 | N/a | |

| First treatment | Variable | Second treatment | Variable | Third treatment | Variable |
|---|---|---|---|---|---|
| ***Stage II*** | | | | | |
| Pancreaticoduodenal resection | 0.12 | Chemotherapy | 0.25 | N/a | |
| | | Chemoradiation | 0.22 | | |
| | | No subsequent therapy | 0.53 | | |
| Distal pancreatectomy | 0.03 | Chemotherapy | 0.47 | N/a | |
| | | Chemoradiation | 0.23 | | |
| | | No subsequent treatment | 0.30 | | |
| Palliative surgical biliary bypass | 0.12 | Chemotherapy | 0.33 | N/a | |
| | | Chemoradiation | 0.33 | | |
| | | No subsequent treatment | 0.34 | | |
| Percutaneous radiological biliary stent placement | 0.12 | Chemotherapy | 0.27 | N/a | |
| | | Chemoradiation | 0.20 | | |
| | | Palliative surgical biliary bypass | 0.08 | | |
| | | | | Chemotherapy | 0.15 |
| | | | | Chemoradiation | 0.30 |
| | | | | No subsequent treatment | 0.55 |
| | | Pancreaticoduodenal resection | 0.04 | Chemotherapy | 0.15 |
| | | | | Chemoradiation | 0.18 |
| | | | | No subsequent treatment | 0.67 |
| | | No subsequent treatment | 0.41 | N/a | |
| Endoscopic biliary stent placement | 0.61 | Chemotherapy | 0.27 | N/a | |
| | | Chemoradiation | 0.23 | | |
| | | Pancreaticoduodenal resection | 0.07 | Chemotherapy | 0.10 |
| | | | | Chemoradiation | 0.05 |
| | | | | No subsequent treatment | 0.85 |
| | | No subsequent treatment | 0.43 | N/a | |

| First treatment | Variable | Second treatment | Variable | Third treatment | Variable |
|---|---|---|---|---|---|
| ***Stage IV*** | | | | | |
| Palliative surgical biliary bypass | 0.10 | Chemotherapy | 0.20 | N/a | |
| | | Chemoradiation | 0.22 | | |
| | | No subsequent treatment | 0.58 | | |
| Percutaneous radiological biliary stent placement | 0.10 | Palliative surgical biliary bypass | 0.12 | Chemotherapy | 0.30 |
| | | | | Chemoradiation | 0.05 |
| | | | | No subsequent treatment | 0.65 |
| | | Chemotherapy | 0.17 | N/a | |
| | | Chemoradiation | 0.21 | | |
| | | No subsequent treatment | 0.50 | | |
| Endoscopically biliary stent placement | 0.57 | Palliative surgical biliary bypass | 0.12 | Chemotherapy | 0.30 |
| | | | | Chemoradiation | 0.05 |
| | | | | No subsequent treatment | 0.65 |
| | | Chemotherapy | 0.17 | N/a | |
| | | Chemoradiation | 0.21 | | |
| | | No subsequent treatment | 0.50 | | |
| Observation | 0.23 | N/a | | N/a | |

## Results of the economic model

The results were calculated based on a cost-effectiveness analysis using DATA 2005 and Microsoft Excel®. This method estimates the incremental cost per life year gained of performing EUS following CT for diagnosis of pancreatic neoplasia, relative to CT alone. The evaluation captures the cost of EUS, the cost of disease treatment and management, and the clinical benefit of treatment (ie life years gained.) The incremental cost of EUS following CT over CT alone was $29,089 per life year gained (**Table 100**).

**Table 100 Incremental cost-effectiveness ratio EUS versus CT**

| Summary result | EUS following CT | CT alone | Incremental |
|---|---|---|---|
| Cost per patient | $4,561 | $3,930 | $631 |
| Life years saved | 3.649 | 3.627 | 0.0216 |
| Incremental cost per life year saved | | | **$29,089** |

### Sensitivity analysis

Sensitivity analyses were conducted to assess the robustness of the model to changes in key assumption values.

A sensitivity analysis was conducted using prevalence, sensitivity and specificity values from the additional study (Harrison et al 1999) identified and included in the assessment of the diagnostic accuracy of EUS over CT for diagnosing pancreatic solid masses. Varying the prevalence of malignant pancreatic solid masses to reflect the value presented by Harrison et al (1999) resulted in an incremental cost of $11,493 per life year gained for EUS over CT. CT dominated EUS when the sensitivity and specificity of EUS following CT and CT alone were altered to reflect the values presented in this additional study.

**Table 101 Sensitivity analysis variables for diagnosing pancreatic solid masses**

| Variable | Value | Reference |
|---|---|---|
| Prevalence of malignant pancreatic solid masses | 0.75 | Harrison et al (1999) (**Table 49**) |
| Sensitivity of CT | 0.889 | Harrison et al (1999) (**Table 49**) |
| Sensitivity of EUS plus CT | 0.889 | Harrison et al (1999) (**Table 49**) |
| Specificity of CT | 0.333 | Harrison et al (1999) (**Table 49**) |
| Specificity of EUS plus CT | 0.0 | Harrison et al (1999) (**Table 49**) |

**Table 102 Sensitivity analysis results for EUS following CT versus CT alone for diagnosing pancreatic solid masses**

| Summary result | EUS following CT | CT alone | Incremental |
|---|---|---|---|
| **Prevalence of unresectable pancreatic neoplasia** | | | |
| Cost per patient | $5,718 | $5,365 | $353 |
| Life years gained | 4.511 | 4.480 | 0.031 |
| Incremental cost per life year gained | | **$11,493** | |
| **Sensitivity and specificity of diagnostic tests** | | | |
| Cost per patient | $5,871 | $4,766 | $1,105 |
| Life years gained | 3.637 | 3.637 | 0.0 |
| Incremental cost per life year gained | | Dominated | |

## Model III—Evidence of intraductal papillary-mucinous tumours of the pancreas

### Key assumptions

- The economic model compared the use of EUS following CT with CT alone for diagnosis of intraductal papillary-mucinous tumours (IPMTs) of the pancreas where a pancreatic abnormality has been identified on CT.
- Only direct healthcare costs and benefits are calculated.
- Patients referred for EUS or CT were assumed to have the same comorbidities. All other diagnostic and additional clinical decision-making is assumed to be similar.
- The prevalence of IPMTs was derived from the literature.
- Morbidity and the cost of CT were not incorporated into the model because it was assumed that all patients undergo CT diagnostic investigation. Consequently, it was assumed that such variables would be the same in both arms of the model.
- The specificity and sensitivity of EUS plus CT, and CT alone, were derived from the evidence presented in the clinical section of this assessment report.
- Complications associated with EUS were excluded from the analysis because their cost and effect were assumed to be negligible.
- It was assumed that the AR-DRG used in the analysis incorporates all costs associated with pancreatic surgical resection procedures.
- A discount rate per annum was not applied to costs because it was assumed that costs occur within one year.

### Patient population used in the economic model

The proposed indication for EUS is diagnosis of pancreatic neoplasms in patients with symptoms and biochemical evidence (CA 19-9) associated with pancreatic neoplasia, when CT has identified a pancreatic abnormality. The population in the economic model was based on the population described in the clinical section of this assessment report. The population is representative of patients likely to receive EUS in an MBS setting.

The clinical section of this assessment report did not identify studies from the literature that examined EUS use to diagnose all types of cystic lesions. Consequently, this analysis was limited to evaluating EUS use to diagnose IPMT, which is a subgroup of pancreatic cystic lesions.

### Structure of the economic model

A decision analytic model was developed to estimate the downstream healthcare resource utilisation associated with the diagnosis of pancreatic intraductal papillary-mucinous tumours (IPMTs). The model uses data from the literature to evaluate possible outcomes associated with diagnosis of pancreatic IPMTs and to identify the most desirable healthcare strategy among the different diagnostic alternatives.

The value of performing EUS following CT versus CT alone for diagnosis of pancreatic IPMTs was assessed using a cost-minimisation approach. This approach was selected because there was insufficient published literature that adequately canvases clinical experience. This evaluation technique was determined to be appropriate to appraise the economic impact of using EUS for diagnosis of pancreatic cystic lesions given that evidence from the literature suggest that a majority of IPMTs are resected regardless of whether they are benign, premalignant or malignant (Le Borgne et al 1999; Spinelli et al 2004).

In the model, patients receive either CT followed by EUS, or CT only.

Complications associated with the diagnostic procedure are not included in the model. This is supported by the safety analysis presented in this assessment report, which found that complications associated with EUS were negligible.

The diagnostic test is used to identify neoplasia. Most patients proceed to surgery if neoplasia is detected. It was assumed that 10 per cent of patients with neoplasms do not undergo surgical procedures; but would be subject to observation. If the diagnostic test produces a false positive result for neoplasia (ie neoplasms are not detected), patients would receive a second diagnostic test (EUS-FNA). If neoplasia is detected, the patient is observed or proceeds to surgery. It was also assumed that IPMTs remain undetected in 5 per cent of patients. If EUS produces a false negative result, the patient would receive a second diagnostic test (EUS-FNA) before exiting the model.

### Variables used in the economic model

#### Diagnostic procedures

**Table 96** presents the costs for each of the diagnostic procedures. These costs include all healthcare resources associated with performing the procedure. Note that the cost of EUS and EUS-FNA include the professional fee, the cost of consumable items and the depreciation of capital equipment associated with the procedure. A derivation of the component costs supporting this proposed fee is presented in **Appendix J.**

**Table 103 Cost of diagnostic and surgical procedures for intraductal papillary-mucinous tumours of the pancreas**

| Diagnostic Procedure | Resource utilized | Unit cost | Reference |
|---|---|---|---|
| EUS | **Total cost per procedure** | **$832.27** | See **Appendix J** |
| EUS-FNA | **Total cost per procedure** | **$1726.52** | See **Appendix J** |
| Pancreatic resection without complications | AR-DRG H01C | $9299 | National Hospital Cost Data Collection Cost Report Round 7 (2002–2003)[a] |

[a] Public sector version (AR-DRG H01C—Pancreas, liver & shunt procedure without complications)

### Other clinical variables

**Table 104 Other clinical variables for diagnosis of intraductal papillary-mucinous tumours of the pancreas**

| Variable | Value | Reference |
|---|---|---|
| Prevalence of pancreatic neoplasia (n/N) | 0.86 (42/49) | Yamao et al (2001) (**Table 57**) |
| **Sensitivity (outcome neoplasia)** | | |
| EUS+CT (minimum combined)[a] | 0.88 | Yamao et al (2001) (**Table 57**) |
| EUS+CT (maximum combined)[a] | 1.0 | |
| CT | 0.36 | |
| **Specificity (outcome neoplasia)** | | |
| EUS+CT (minimum combined)[a] | 0.714 | Yamao et al (2001) (**Table 57**) |
| EUS+CT (maximum combined)[a] | 0.714 | |
| CT | 1.0 | |
| Patients with neoplasia who are subject to observation | 0.15 | Advisory panel |
| Neoplasia remains undetected after second diagnostic test | 0.05 | |

Abbreviations: CT, computed tomography; EUS, endoscopic ultrasound
[a] Minimum and maximum combined sensitivities and specificities were calculated as described in Statistical methods

### Results of the economic model

The results were calculated based on a cost-minimisation analysis using Microsoft Excel®. This method estimates the incremental cost per patient of performing EUS following CT relative to CT alone for diagnosis of IPMTs. The evaluation captures the costs of EUS and of disease treatment and management. The incremental cost per patient receiving EUS following CT over CT alone was: $696 for the minimum combined analysis and $509 for the maximum combined analysis. (**Table 100**).

**Table 105 Incremental costs of EUS versus CT for diagnosing intraductal papillary-mucinous tumours of the pancreas**

| Summary result | EUS following CT | CT alone | Incremental |
|---|---|---|---|
| Cost per patient (minimum combined) | $7,172 | $6,476 | $696 |
| Cost per patient (maximum combined) | $6,985 | $6,476 | $509 |

### Sensitivity analysis

Sensitivity analyses were conducted to assess the robustness of the model to changes in the value of key assumptions.

A sensitivity analysis was conducted using prevalence values from an additional identified study (Cellier et al 1998) included in the assessment of the diagnostic accuracy of EUS over CT for diagnosis of pancreatic IPMTs. The study represents the lower range value identified in the clinical section of this assessment report. The upper range value was included in the base case (Yamao et al 2001). Hence, an upper range value was not included in this sensitivity analysis. Varying the prevalence of pancreatic IPMTs to reflect

the value presented by Cellier et al (1998) resulted in an incremental cost per patient of $1,300 and $1,347.

The proportion of patients with neoplasms who were subject to observation was also varied in a sensitivity analysis. The range of values (0.1–0.2) was derived from expert opinion. The sensitivity analysis produced an incremental cost per patient that ranged between $498 and $705.

**Table 106 Sensitivity analysis variables for diagnosis of intraductal papillary-mucinous tumours of the pancreas**

| Variable | Value | Reference |
|---|---|---|
| Prevalence of IPMTs of the pancreas | 0.43 | Cellier et al (1998) (**Table 47**) |
| Patients with neoplasia who are subject to observation | 0.1–0.2 | Expert opinion |

**Table 107 Sensitivity analysis results for EUS following CT versus CT alone for the diagnosis of pancreatic solid masses**

| Summary result | EUS following CT | CT alone | Incremental |
|---|---|---|---|
| **Prevalence of unresectable pancreatic neoplasia (minimum combined)** | | | |
| Cost per patient | $2,966 | $1,619 | $1,347 |
| **Prevalence of unresectable pancreatic neoplasia (maximum combined)** | | | |
| Cost per patient | $2,919 | $1,619 | $1,300 |
| **Patients with neoplasia who are subject to observation (minimum combined)** | | | |
| Cost per patient | $6,831–$7,514 | $6,143–$6,809 | $687–$705 |
| **Patients with neoplasia who are subject to observation (maximum combined)** | | | |
| Cost per patient | $6,641–$7,329 | $6,143–$6,809 | $498–$520 |

# Conclusions

## Safety

Safety data relating to the use of endoscopic ultrasound (EUS) in diagnosing and staging of gastro-oesophageal neoplasia were drawn from reports relating to a total of 2,521 patients receiving EUS and 565 patients receiving EUS-fine-needle aspiration (FNA). Perforation was a rare but serious adverse event that was reported in relation to eight patients receiving either EUS or EUS-FNA (8/3086, 0.26% of patients). A small proportion of patients (0.20%, 5/2521) undergoing EUS experienced bleeding which was managed using endoscopic haemostatic methods. Of the 565 patients who underwent EUS-FNA, 15 (2.7%) experienced minimal self-limited bleeding.

Safety data relating to EUS use in diagnosis and staging of pancreaticobiliary neoplasia came from reports relating to a total of 2,240 patients who underwent EUS and 3,080 patients who experienced EUS-FNA. Occurrence of perforation was reported in two patients who received either EUS or EUS-FNA (0.04%).

In a comparison of the safety of EUS-FNA with computer tomography (CT)-guided biopsy in patients with pancreaticobiliary lesions the frequency of bleeding or pancreatitis did not differ (bleeding: 0.49% [95% CI: 0.27, 0.80] and 0.24% [95% CI: 0.03, 0.86]; pancreatitis: 0.42% [95% CI: 0.22, 0.72] and 0.72% [95% CI: 0.26, 1.55] respectively). The available studies generally did not incorporate follow up that adequately captured possible events related to peritoneal seeding.

The conclusions made about the safety of EUS in diagnosing and staging gastro-intestinal neoplasia are limited by the poor and infrequent reporting of safety data in the identified studies, and limited follow up. Based on the available data, the use of EUS in diagnosing and staging gastrointestinal neoplasia is associated with a very low risk of perforation and is generally a safe procedure. In the diagnosis of pancreatic neoplasia, EUS-FNA is considered generally safe and equally as safe as CT-FNA/biopsy.

## Effectiveness

### Impact on health outcomes

An ongoing randomised controlled trial investigating the role of EUS in staging and management of patients with gastric and oesophageal cancer was identified (UK COGNATE). This trial is expected to conclude in January 2009.

The identified studies reported survival as a health outcome. No studies of other health outcomes, such as quality of life, were identified. There were three studies that provided level III-3 evidence regarding the impact of EUS on patient survival. Of these, two studies related to EUS use in staging oesophageal cancer and one to pancreatic cancer diagnosis. The poor quality and inconsistent findings of the identified studies indicated that these studies were considered inadequate to provide direct evidence of benefit associated with EUS use on patient survival at this time.

It was noted that a major use of EUS is in staging gastro-intestinal malignancies. The potential value of EUS in most cases is not increased survival, but fewer inappropriate surgeries performed. Thus, the potential value of EUS on health outcomes for this indication is likely to be measured in quality of life.

## Is it accurate?

### Systematic review

Harris et al (1998) conducted a systematic review of EUS use in gastro-oesophageal cancer based on data to 1997. This review concluded that EUS is highly effective in discriminating stages T1 and T2 from T3 and T4 in oesophageal and gastric sites. EUS with lymph node staging was found to be less accurate than tumour staging. Staging metastases using EUS alone was unsatisfactory. No conclusions were made about the comparative value of EUS versus CT for gastro-oesophageal cancer staging because of data insufficiencies.

### Oesophageal neoplasia staging

There were 11 studies identified that provided information on the incremental value of EUS following CT and/or positron emission tomography (PET) in group staging of oesophageal cancer. In three studies classified as medium to high quality, the combined use of CT + EUS increased the sensitivity for detection of late stage oesophageal cancer (stage IV or III and IV, AJCC staging). Of the initial 11 studies, two provided data on detection of distant node metastases that similarly demonstrated sensitivity increase with a trade-off of specificity loss when EUS was used in addition to CT.

Evidence supporting the additional value of EUS over CT in T-staging was provided by four studies classified as medium quality and limited applicability. In two of these studies, adding EUS to CT to detect T3 or T4 tumours contributed to a decrease in specificity in one study and no change in the other study conducted in a small population with low prevalence. In three studies, CT with EUS conducted to detect T4 tumours led to increased sensitivity. There was no loss of specificity in two of these three studies. In the third study, conducted in a population with a low prevalence of stage IV disease, there was a small decrease in specificity.

Data concerning EUS accuracy in locoregional lymph node (N) staging specific to the research question was reported in five studies determined to be medium quality and limited applicability. The combination of CT and EUS for N staging increased the sensitivity by comparison with CT alone in all five studies. This occurred with a decrease in staging specificity in all but one study. Three studies assessing N staging reported the incremental value of EUS in addition to both CT and PET. These studies indicated that the incremental value of EUS over prior staging tests may be slightly decreased when PET is available.

Overall, the available evidence indicates that EUS in addition to CT, or CT plus PET, increases detection sensitivity for late stage disease. Increased sensitivity is likely to occur with a small trade-off in specificity.

A satisfactory body of evidence exists to support the additional value of EUS over and above CT, or CT plus PET, in oesophageal cancer staging.

### Gastric neoplasia staging

A high quality study provided evidence of the incremental value of EUS over CT alone to stage disease status in patients with gastric cancer. This study did not determine group staging by CT and EUS using an either test positive approach which is likely to be used in practice (positive test for either procedure being counted as a positive result). Hence, applicability was limited. Combining the results for AJCC group staging from EUS and CT in this study resulted in greater sensitivity and specificity for late stage gastric cancer relative to CT alone. An increase in specificity would not occur in practice where an either test positive approach for the combined use of the tests. Another two studies included for review provided high quality evidence concerning the replacement value of CT and EUS in gastric cancer staging. These studies had limited applicability. In both replacement studies, EUS was more accurate than CT in distinguishing late from early stage tumours (T staging) and lymph node metastases.

The high quality studies that were reviewed provide supportive evidence that the combination of EUS and CT are likely to increase the sensitivity for late stage disease with a possible small trade-off in specificity.

### Diagnosis of gastric submucosal tumours

There were seven studies concerning EUS accuracy in diagnosis of suspected gastric submucosal tumours (SMTs) included for review. Of these, one small study rated as medium quality and limited applicability indicated that EUS (without FNA) was highly accurate in differentiating gastric SMTs from extramural compression. Of the remaining six studies, five provided information on EUS performance in diagnosis of malignant SMTs using an outdated classification system. Data from these studies were considered uninformative. The seventh was a study of medium quality and limited applicability that provided EUS performance evidence for diagnosis of malignant gastric SMTs using current classification criteria. In this study, EUS was moderately sensitive for diagnosis of malignant tumours and highly specific for diagnosis of benign tumours. The diagnostic odds ratio (DOR) and likelihood ratios (LR) provided strong evidence in support of performing EUS to differentiate malignant from benign gastric SMTs. There is currently insufficient evidence to determine whether providing FNA with EUS would add further value to diagnosing SMTs.

Based on two small studies, EUS is highly accurate in differentiating gastric SMTs from extramural compression, and is highly specific for diagnosing benign SMTs using current classification criteria.

### Diagnosis of pancreatic neoplasia

#### Pancreatic solid mass identified

Comparators considered to assess the value of EUS with or without FNA following CT to diagnose pancreatic solid masses were: CT alone with no further tests, and CT-guided biopsy.

#### *EUS versus no EUS (following CT)*

There were two replacement studies of EUS and CT in diagnosis of pancreatic solid masses identified. These studies reported individual patient data that allowed the additional value of EUS to be calculated.

Of these, one medium quality study conducted in an applicable patient population investigated the diagnostic accuracy of EUS in a non-consecutive subgroup of patients with pancreatic solid mass lesions. This study did not report exclusion of patients with metastatic disease. The diagnostic accuracy of EUS and CT was greater than CT alone, with an increase in sensitivity and small decrease in specificity.

In another study that was determined to be poor quality and limited applicability, EUS provided no additional value to CT in diagnosis of pancreatic masses. This finding is not robust when interpreted in light of the study's poor quality and limited applicability.

On the basis of one applicable study, the available data suggest that EUS offers a small incremental benefit over using CT alone in diagnosing solid mass pancreatic tumours.

***EUS/EUS-FNA versus CT-guided biopsy***

No studies comparing EUS (without FNA) with CT-guided biopsy in diagnosing malignant pancreatic solid masses were identified. Non-comparative studies providing the highest level of evidence of diagnostic accuracy for these tests were also included for review. A single level II non-comparative study of EUS using an echo-enhancing contrast agent demonstrated 94 per cent sensitivity and 100 per cent specificity. A second level III-1 study that considered the use of EUS without a contrast agent reported sensitivity of 95 per cent and specificity of 53 per cent. Six level III-1 non-comparative studies of CT-FNA/guided biopsy indicated high specificity and variable sensitivity in diagnosis of malignant pancreatic masses. The available data were insufficient in terms of quality and quantity to determine whether EUS (without FNA) was more accurate in diagnosing malignant pancreatic solid masses than CT-guided biopsy.

Two comparative studies that reported the accuracy of EUS-guided FNA and CT-guided biopsy in diagnosing malignant pancreatic solid masses were identified. Of these, one study designated as poor quality and unknown applicability, reported that the tests were performed in different patient groups, rather than as a sequence in the same patients. The results are considered uninformative. An additional medium quality study that was conducted in a highly applicable patient population excluded patients diagnosed with metastatic disease. This study reported that the sensitivity of EUS-FNA was much greater than CT-guided biopsy (91% vs 6% respectively); both technologies demonstrated perfect specificity.

On the basis of the limited available evidence, EUS-FNA has a greater sensitivity than CT-guided biopsy in diagnosing malignant pancreatic solid masses.

Two comparators were considered in the assessment of the value of EUS with or without FNA following CT in diagnosing malignant pancreatic solid masses: CT alone with no further tests, and CT-guided biopsy. Based on one applicable study classified as medium quality, the available data suggest that EUS offers a small increase in sensitivity when compared with the use of only CT to diagnose malignant solid mass pancreatic tumours. This occurred with a small loss in specificity. This comparator pathway is considered to be the most applicable to current practice in Australia.

If EUS is considered as a replacement test for CT-guided biopsy, EUS-FNA was much more sensitive in diagnosis of malignant solid mass pancreatic tumours on the basis of one applicable, medium quality study. Both tissue sampling techniques had 100 per cent specificity in this study. It could not be determined whether EUS (without FNA) is more

accurate than CT-guided biopsy in diagnosing malignant pancreatic solid masses, because the available data are insufficient in terms of quality and quantity.

**Pancreatic cystic lesion**

No studies were identified that reported the incremental value of EUS over CT (without biopsy) in diagnosing pancreatic cystic lesions. Four medium quality studies reporting the replacement value of CT and EUS in diagnosis of pancreatic cystic lesions (cystic masses, intraductal papillary or mucinous tumours) were reviewed. Three studies provided low quality comparisons of EUS and CT where both tests were not both performed in all patients. These studies contain significant potential for bias in making comparisons and their findings were inconsistent. In one study that provided a direct comparison of CT and EUS in all patients, EUS was more sensitive and less specific than CT.

Based on this single study, the supportive evidence indicates that the addition of EUS to CT (without biopsy) in diagnosing IPMT is likely to increase sensitivity for detection of malignancy with a trade-off loss in specificity.

**No pancreatic mass identified on CT**

Three studies were identified that provided evidence on the value of EUS in addition to CT for diagnosis of exocrine pancreatic neoplasia in patients with no mass identified on CT. Two studies—one medium and one poor quality—were reviewed that determined the incremental value of EUS performed for patients with no mass identified by CT. The applicability of the patients in the studies was considered limited. These studies provided evidence that the use of EUS (without FNA) in addition to CT may increase sensitivity for diagnosis, with a loss of specificity.

An additional poor quality study reported the value of EUS-FNA in addition to CT and endoscopic retrograde cholangiopancreatography (ERCP) in diagnostically problematic patients with a negative or equivocal CT. On the basis of this study, it appears that EUS-FNA is associated with a similar increase in sensitivity to that of EUS alone. In contrast to the increase in sensitivity gained by the additional use of EUS, the use of EUS-FNA increased sensitivity with no loss of specificity.

Three studies of limited applicability indicated that the use of EUS, with or without FNA, for patients with no mass identified on CT increases diagnostic sensitivity of pancreatic cancer. The addition of FNA to EUS may result in no loss of specificity when both tests are used in combination.

**Neuroendocrine tumours**

Four studies provided medium quality and limited applicability evidence concerning the comparative value of EUS and SRS in correct localisation of pancreatic neuroendocrine tumours to a patient group who have tested negative by CT. The available evidence indicated that EUS was more accurate than SRS in the correct localisation of pancreatic insulinomas.

Expert clinical opinion indicates that correct localisation frequently leads to less radical surgeries in this patient group.

### Staging of pancreatic neoplasia

There were four studies of limited applicability included for review that provided specific data on the incremental value of EUS in addition to CT for staging pancreatic carcinoma.

Overall, the diagnostic accuracy of the combined use of CT and EUS in staging pancreatic cancer in the included studies was greater than CT alone. This review found that the diagnostic accuracy of the test would be dependent upon the prevalence of resectable disease in the study population. The reviewed studies reported that the EUS combined with CT increased sensitivity for determining unresectability compared with CT use alone. There may be a trade-off in terms of reduced specificity for resectability. The results of the reviewed studies were inconsistent for this outcome.

#### Diagnosis of biliary tract neoplasia

There were two studies identified that provided evidence of the value of EUS, without FNA, as an additional test following cholangiopancreatography. Of these, one study was classified as poor quality—it did not clearly report accuracy outcomes. This study was included in the absence of others reporting high quality data on the additional value of EUS performed for all patients. The other study was designed as a replacement study of EUS, MRCP, ERCP and CT, but also reported test accuracy data where both tests were in agreement. It appears that findings where both tests disagreed were not included in the results. It was considered that evidence was insufficient to determine whether EUS (without FNA) is of value when used in addition to cholangiopancreatography in diagnosing biliary tract malignancies.

A high quality study reported the accuracy of EUS with FNA in addition to ERCP plus three tissue sampling methods for diagnosis of malignant versus benign causes of biliary obstruction. This study is likely to underestimate the additional value of EUS-FNA. In this high quality study, EUS-FNA was found to have value in increasing the sensitivity and diagnostic accuracy for the detection of pancreaticobiliary malignancy when used in addition to ERCP-guided tissue sampling.

### Does it change patient management?

There were five studies identified that reported the effects of EUS on patient management as determined by the use of pre-test and post-test management plans. This is the appropriate study design for this outcome. In all but one study, the referring clinicians completed management plans as applicable to clinical practice. One high quality study was performed in an Australian setting. In general, EUS findings contributed to avoidance of surgery and other investigations, reducing the number of complex procedures performed. EUS changed management in 24–74 per cent of patients among all indications, while for EUS-FNA, management changed in 31–43 per cent. Use of EUS resulted in avoidance of surgery for 10–18 per cent of patients, and further imaging or therapy was avoided for 14–57 per cent. These studies provide a good body of evidence that the use of EUS in diagnosing and staging gastrointestinal neoplasms reduces invasive patient management.

### Summary of evidence for effectiveness

The available evidence concerning the effectiveness of EUS as likely to be used in clinical practice in Australia was reviewed. When used as an additional test, EUS is expected to result in increased sensitivity with a trade-off loss in specificity.

There was good or satisfactory evidence to support that EUS, when used in addition to current Australian practice:

- alters patient management, including reducing the number of surgical and invasive procedures performed
- increases the accuracy of staging oesophageal carcinoma.

There was supportive or limited evidence that EUS, when used in addition to current Australian practice:

- increases the sensitivity in detection of late stage disease in gastric carcinoma
- is highly accurate in differentiating gastric submucosal tumours from extramural compression
- increases diagnostic sensitivity of pancreatic cancer in patients with no masses identified on CT. The use of FNA in this setting may increase diagnostic sensitivity with a smaller loss of specificity
- provides a small increase in the diagnostic sensitivity of malignant pancreatic solid masses, by comparison with use of CT alone
- with FNA, has greater sensitivity than CT-guided biopsy in diagnosis of malignant pancreatic solid masses
- increases diagnostic sensitivity of malignant pancreatic intraductal papillary-mucinous tumours (IPMT)
- has greater accuracy in correct localisation of pancreatic insulinomas than somatostatin receptor scintigraphy
- increases the sensitivity for determining resectability of pancreatic carcinoma
- with FNA, increases diagnostic accuracy in detecting pancreaticobiliary malignancy, when used in addition to ERCP-guided tissue sampling.

## Cost-effectiveness

Evidence presented in this assessment report demonstrates the economic value and financial impact of using EUS and EUS-FNA. For several staging indications, performing EUS results in a cost savings per patient (from $1,506 for the staging of gastric cancer to $2,149 for the staging of pancreatic cancer). On average, the detection of advanced disease is achieved at a lower cost with the use of EUS following CT than with CT alone. This is due to cost offsets. The detection of advanced disease signifies unresectability and obviates the need for more costly surgical procedures.

Two cost-effectiveness analyses were conducted to assess the value for money of the introduction of EUS and EUS-FNA relative to CT for the diagnosis of pancreatic neoplasia (exocrine tumours and solid masses). The incremental cost-effectiveness ratios

estimated the cost per life year gained for performing the procedure. The two analyses produced a range of reasonable ratio values ($23,347 per life year gained for the diagnosis of pancreatic exocrine tumours using EUS following CT vs CT alone; $29,089 per life year gained for the diagnosis of solid pancreatic masses using EUS following CT vs CT alone; $35,766 per life year gained for the diagnosis of pancreatic exocrine tumours using EUS-FNA following CT vs CT alone).

The results from the economic evaluation should be interpreted in the context of the key underlying assumptions. Certainty around several key assumptions would improve the reliability of the results of this analysis.

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

The membership[5] 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 | Expertise or affiliation |
|---|---|
| Dr Stephen Blamey (Chair) | general surgery |
| Associate Professor John Atherton | cardiology |
| Professor Syd Bell | pathology |
| Associate Professor Michael Cleary | emergency medicine |
| Dr Paul Craft | clinical epidemiology and oncology |
| Dr Kwun Fong | thoracic medicine |
| Dr David Gillespie | gastroenterology |
| Dr Debra Graves | medical administrator |
| Professor Jane Hall | health economics |
| Professor John Horvath | Chief Medical Officer, Department of Health and Ageing |
| Dr Terri Jackson | health economics |
| Professor Brendon Kearney | health administration and planning |
| Professor Frederick Khafagi | nuclear medicine |
| Dr Ray Kirk | health research |
| Associate Professor Donald Perry-Keene | endocrinology |
| Dr Ewa Piejko | general practice |
| Ms Sheila Rimmer | consumer health issues |
| Ms Catherine Farrell | Department of Health and Ageing representative |
| Professor Ken Thomson | radiology |
| Dr Douglas Travis | urology |
| Dr Mary Turner | Australian Health Ministers' Advisory Council representative |
| Dr David Wood | orthopaedic surgery |

[5] This list of MSAC members presented here represents the membership at the time this assessment was considered by MSAC.

# Appendix B Advisory panel

## Advisory panel for MSAC application 1072 Endoscopic ultrasound

| | |
|---|---|
| **Dr Stephen Blamey** (Chair)<br>MBBS, BSc, FACS, FRACS<br>Waverley Endoscopy<br>Mt Waverley, VIC | Member of MSAC |
| **Dr Robert Chen**<br>MBBS, FRACP, MD<br>Department of Gastroenterology<br>St Vincent's Hospital<br>Fitzroy, VIC | Co-opted Member |
| **Dr Gerry FitzGerald**<br>MBBS, MD, BHA, FACEM, FRACMA, FCHSE<br>Chief Health Officer<br>Office of the Chief Health Officer<br>Queensland Health<br>Brisbane, QLD | Member of MSAC |
| **Dr Kwun Fong**<br>MBBS, FRACP, PhD<br>The Prince Charles Hospital<br>Chermside, QLD | Member of MSAC |
| **Dr Trevor Leong**<br>MBBS, MD, FRANZCR<br>Peter MacCallum Cancer Institute<br>Melbourne, VIC | Nominated by the Royal Australian and New Zealand College of Radiologists |
| **Ms Barbara Joss**<br>Public Relations Adv Cert<br>Independent Consumer Representative<br>Riverview, NSW | Nominated by the Consumers' Health Forum |
| **Dr Ian Norton**<br>MBBS, FRACP, PhD<br>Department of Gastroenterology<br>Concord Hospital<br>Concord, NSW | Nominated by the Gastroenterological Society of Australia |
| **Associate Professor Mark Smithers**<br>MBBS, FRACS, FRCS (Eng)<br>Mater Medical Centre<br>South Brisbane, QLD | Co-opted Member |

## Evaluators for MSAC application 1072

| | |
|---|---|
| **Dr Suzanne Dyer**<br>BSc(Hons) PhD GradCertPH | M-TAG Pty Ltd,<br>A unit of IMS Health |
| **Dr John Gillespie**<br>BSc(Hons) PhD | M-TAG Pty Ltd,<br>A unit of IMS Health |
| **Ms Meaghan Lynch**<br>BSc MSc | M-TAG Pty Ltd,<br>A unit of IMS Health |
| **Mr Marc Bevan**<br>BSc(Hons) | M-TAG Pty Ltd,<br>A unit of IMS Health |
| **Dr Amanda Ruth**<br>BSc(Hons) PhD | M-TAG Pty Ltd,<br>A unit of IMS Health |
| **Mr Dane Levison**<br>BSc(Hons) | M-TAG Pty Ltd,<br>A unit of IMS Health |
| **Ms Jolie Hutchinson**<br>BSc(Hons) | M-TAG Pty Ltd,<br>A unit of IMS Health |

# Appendix C Quality criteria

| Study design | Quality checklist |
|---|---|
| **Systematic review** | Was the research question specified? |
| | Was the search strategy documented and adequate? |
| | Were the inclusion and exclusion criteria specified, appropriate and applied in an unbiased way? |
| | Was a quality assessment of included studies undertaken? |
| | Were the methods of the study appraisal reproducible? |
| | Were the characteristics and results of the individual studies summarised? |
| | Were the methods for pooling the data appropriate? |
| | Were sources of heterogeneity explored? |
| | Was a summary of the main results and precision estimates reported? |
| **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? |
| **Cohort study** | Were subjects selected prospectively or retrospectively? |
| | Was the intervention reliably ascertained? |
| | Was there sufficient description about how the subjects were selected for the new intervention and comparison groups? |
| | Was there sufficient description about the distribution of prognostic factors for the new intervention and comparison groups? Were the groups comparable for these factors? |
| | Did the study adequately control for potential confounding factors in the design or analysis? |
| | Was the measurement of outcomes unbiased (ie blinded to treatment group and comparable across groups)? |
| | Was follow up long enough for outcomes to occur? |
| | What proportion of the cohort was followed up and were there exclusions from the analysis? |
| | Were drop-out rates and reasons for drop-out similar across intervention and unexposed groups? |
| **Case-control study** | Was there sufficient description about how subjects were defined and selected for the case and control groups? |
| | Was the disease state of the cases reliably assessed and validated? |
| | Were the controls randomly selected from the source of population of the cases? |
| | Was there sufficient description about the distribution of prognostic factors for the case and control groups? Were the groups comparable for these factors? |
| | Did the study adequately control for potential confounding factors in the design or analysis? |

| | |
|---|---|
| **Case-control study,** ***continued*** | Was the new intervention and other exposures assessed in the same way for cases and controls and kept blinded to case/control status? |
| | How was the response rate defined? |
| | Were the non-response rates and reasons for non-response the same in both groups? |
| | Was an appropriate statistical analysis used? |
| | If matching was used, is it possible that cases and controls were matched on factors related to the intervention that would compromise the analysis due to over-matching? |
| **Case series** | Was the study based on a representative sample selected from a relevant population? |
| | Were the criteria for inclusion and exclusion explicit? |
| | Did all subjects enter the survey at a similar point in their disease progression? |
| | Was follow up long enough for important events to occur? |
| | Were the techniques used adequately described? |
| | Were outcomes assessed using objective criteria or was blinding used? |
| | If comparisons of sub-series were made, were there sufficient description of the series and the distribution of prognostic factors? |
| **Study of diagnostic accuracy** | Was the spectrum of patients representative of the patients who will receive the test in practice? |
| | Were selection criteria clearly described? |
| | Is the reference standard likely to correctly classify the target condition? |
| | Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests? |
| | Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis? |
| | Did patients receive the same reference standard regardless of the index test result? |
| | Was the reference standard independent of the index test (ie the index test did not form part of the reference standard)? |
| | Was the execution of the index test described in sufficient detail to permit replication of the test? |
| | Was the execution of the reference standard described in sufficient detail to permit its replication? |
| | Were the index test results interpreted without knowledge of the results of the reference standard? |
| | Were the reference standard results interpreted without knowledge of the results of the index test? |
| | Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? |
| | Were uninterpretable/ intermediate test results reported? |
| | Were withdrawals from the study explained? |

**Table 108 Quality criteria assessment for Harris et al (1999) systematic review**

| | |
|---|---|
| Was the research question specified? | Yes |
| Was the search strategy documented and adequate? | Yes |
| Were the inclusion and exclusion criteria specified, appropriate and applied in an unbiased way? | Yes |
| Was a quality assessment of included studies undertaken? | Yes |
| Were the methods of the study appraisal reproducible? | Yes |
| Were the characteristics and results of the individual studies summarised? | Yes |
| Were the methods for pooling the data appropriate? | Yes |
| Were sources of heterogeneity explored? | Yes |
| Was a summary of the main results and precision estimates reported? | Yes |

# Appendix D Literature search strategies

**Table 109 Endoscopic ultrasound Cochrane search strategy—August 4, 2005**

| Search history | | References retrieved |
|---|---|---|
| 1 | ENDOSONOGRAPHY explode all trees (MeSH) | 132 |
| 2 | endosonograph* or echo*endoscop* or eus | 190 |
| 3 | endoscop* next (echo*, ultrason*, ultrasound) | 94 |
| 4 | interventional next (ultrason*, ultrasound) | 5 |
| 5 | #1 or #2 or #3 or #4 | 223 |
| 6 | NEOPLASMS explode all trees (MeSH) | 27725 |
| 7 | cancer or malignan* or tumo*r* or neoplasm* | 46397 |
| 8 | #6 or #7 | 49057 |
| 9 | #5 and #8 | 112 |

## Management and health outcomes

### Medline search strategy

The search strategy used to identify relevant studies of endoscopic ultrasound for management and outcomes in Medline is presented in **Table 110**.

**Table 110 Endoscopic ultrasound management and outcomes Medline search strategy—1966 to May Week 1 2005**

| Search history | | References retrieved |
|---|---|---|
| 1 | endosonography/ | 3216 |
| 2 | endoscopy/ and ultrasonography/ | 470 |
| 3 | ultrasonics/ and endoscop$.ti,ab. | 89 |
| 4 | (endosonograph$ or echo?endoscop$ or eus).ti,ab. | 2687 |
| 5 | (endoscop$ adj (echo$ or ultrason$ or ultrasound)).ti,ab. | 2496 |
| 6 | (interventional adj (ultrason$ or ultrasound)).ti,ab. | 62 |
| 7 | or/1-6 | 5963 |
| 8 | exp decision making/ | 57165 |
| 9 | disease management/ | 3948 |
| 10 | (impact adj5 management).ti,ab. | 3119 |
| 11 | management plan$1.ti,ab. | 1438 |
| 12 | ((management or diagnosis) adj3 (change$1 or alter$)).ti,ab. | 12694 |
| 13 | or/8-12 | 77468 |
| 14 | 7 and 13 | 118 |
| 15 | survival/ | 1879 |
| 16 | exp survival analysis/ | 59699 |
| 17 | exp mortality/ | 151319 |
| 18 | fatal outcome/ | 24393 |
| 19 | mo.fs. | 238791 |
| 20 | prognosis/ | 213171 |
| 21 | (endosonograph$ adj3 outcome).ti,ab. | 7 |
| 22 | (survival or mortality or death).ti,ab. | 599726 |
| 23 | or/15-22 | 878978 |
| 24 | 7 and 23 | 690 |
| 25 | 24 and exp digestive system diseases/ | 571 |
| 26 | or/14,25 | 677 |
| 27 | 25 and exp digestive system neoplasms/ | 488 |
| 28 | 25 and exp gastrointestinal diseases/ | 387 |
| 29 | 25 and exp biliary tract diseases/ | 61 |
| 30 | 25 and exp pancreatic diseases/ | 145 |
| 31 | or/28-30 | 553 |
| 32 | 27 and exp gastrointestinal neoplasms/ | 335 |
| 33 | 27 and exp biliary tract neoplasms/ | 36 |
| 34 | 27 and exp pancreatic neoplasms/ | 123 |
| 35 | or/32-34 | 475 |
| 36 | 32 and esophageal neoplasms/ | 140 |
| 37 | 32 and stomach neoplasms/ | 98 |
| 38 | or/33-34,36-37 | 369 |
| 39 | or/14,38 | 475 |

## EMBASE search strategy

The search strategy used to identify relevant studies of endoscopic ultrasound for management and outcomes in EMBASE is presented in **Table 111**.

**Table 111 Endoscopic ultrasound management and outcomes EMBASE search strategy—1980 to 2005 Week 20**

| Search history | | References retrieved |
|---|---|---|
| 1 | endoscopic echography/ | 3419 |
| 2 | echography/ and endoscop$.ti,ab. | 2544 |
| 3 | (endosonograph$ or echo?endoscop$ or eus).ti,ab. | 2793 |
| 4 | (endoscop$ adj (echo$ or ultrason$ or ultrasound)).ti,ab. | 2659 |
| 5 | (interventional adj (ultrason$ or ultrasound)).ti,ab. | 61 |
| 6 | or/1-5 | 7218 |
| 7 | medical decision making/ | 31086 |
| 8 | exp disease management/ | 469457 |
| 9 | dm.fs. | 48864 |
| 10 | (impact adj5 management).ti,ab. | 3028 |
| 11 | management plan$1.ti,ab. | 1396 |
| 12 | ((management or diagnosis) adj3 (change$1 or alter$)).ti,ab. | 10986 |
| 13 | or/7-12 | 512030 |
| 14 | 6 and 13 | 1056 |
| 15 | exp survival/ | 150581 |
| 16 | exp mortality/ | 152203 |
| 17 | fatality/ | 36127 |
| 18 | prognosis/ | 122233 |
| 19 | (endosonograph$ adj3 outcome).ti,ab. | 8 |
| 20 | (survival or mortality or death).ti,ab. | 498728 |
| 21 | or/15-20 | 668815 |
| 22 | 6 and 21 | 897 |
| 23 | 22 and exp digestive system tumor/ | 632 |
| 24 | 23 and exp gastrointestinal tumor/ | 17 |
| 25 | 23 and exp esophagus tumor/ | 207 |
| 26 | 23 and exp stomach tumor/ | 126 |
| 27 | 23 and exp biliary tract tumor/ | 58 |
| 28 | 23 and exp pancreas tumor/ | 158 |
| 29 | or/24-28 | 496 |
| 30 | or/14,29 | 1404 |

## PreMedline search strategy

The search strategy used to identify relevant studies of endoscopic ultrasound for management and outcomes in PreMedline is presented in **Table 112**.

**Table 112 Endoscopic ultrasound management and outcomes PreMedline search strategy—May 13 2005**

| Search history | | References retrieved |
|---|---|---|
| 1 | (endosonograph$ or echo?endoscop$ or eus).ti,ab. | 106 |
| 2 | (endoscop$ adj (echo$ or ultrason$ or ultrasound)).ti,ab. | 103 |
| 3 | (interventional adj (ultrason$ or ultrasound)).ti,ab. | 0 |
| 4 | or/1-3 | 160 |
| 5 | (impact adj5 management).ti,ab. | 121 |
| 6 | management plan$1.ti,ab. | 45 |
| 7 | ((management or diagnosis) adj3 (change$1 or alter$)).ti,ab. | 303 |
| 8 | or/5-7 | 457 |
| 9 | 4 and 8 | 1 |
| 10 | (endosonograph$ adj3 outcome).ti,ab. | 1 |
| 11 | (survival or mortality or death).ti,ab. | 17101 |
| 12 | or/10-11 | 17102 |
| 13 | 4 and 12 | 17 |
| 14 | or/9,13 | 18 |

# Oesophageal neoplasia

## Medline search strategy

The search strategy used to identify relevant studies of endoscopic ultrasound for oesophageal neoplasia in Medline is presented in **Table 113**.

**Table 113 Endoscopic ultrasound oesophageal Medline search strategy—1966 to February Week 3 2005**

| Search history | | References retrieved |
|---|---|---|
| 1 | endosonography/ | 3129 |
| 2 | (endosonograph$ or echo?endoscop$ or eus).ti,ab. | 2632 |
| 3 | (endoscop$ adj (echo$ or ultrason$ or ultrasound)).ti,ab. | 2440 |
| 4 | (interventional adj (ultrason$ or ultrasound)).ti,ab. | 61 |
| 5 | or/1-4 | 5426 |
| 6 | esophageal neoplasms/ | 22355 |
| 7 | ((esophag$ or oesophag$) adj3 (cancer or neoplasm$1 or tumo?r$1)).ti,ab. | 11390 |
| 8 | ((esophag$ or oesophag$) adj3 (carcinoma$1 or adenocarcinoma$1)).ti,ab. | 9361 |
| 9 | or/6-8 | 25227 |
| 10 | 5 and 9 | 725 |
| 11 | exp tomography/ | 294840 |
| 12 | (ct or comput$ tomogra$ or cat scan$).ti,ab. | 152594 |
| 13 | (pet or (positron adj3 tomogra$)).ti,ab. | 24094 |
| 14 | or/11-13 | 352925 |
| 15 | 10 and 14 | 255 |

## EMBASE search strategy

The search strategy used to identify relevant studies of endoscopic ultrasound for oesophageal neoplasia in EMBASE is presented in **Table 114**.

**Table 114 Endoscopic ultrasound oesophageal EMBASE search strategy—1980 to 2005 Week 9**

| Search history | | References retrieved |
|---|---|---|
| 1 | endoscopic echography/ | 3297 |
| 2 | (endosonograph$ or echo?endoscop$ or eus).ti,ab. | 2712 |
| 3 | (endoscop$ adj (echo$ or ultrason$ or ultrasound)).ti,ab. | 2583 |
| 4 | (interventional adj (ultrason$ or ultrasound)).ti,ab. | 60 |
| 5 | or/1-4 | 5187 |
| 6 | exp esophagus tumor/ | 16166 |
| 7 | ((esophag$ or oesophag$) adj3 (cancer or neoplasm$1 or tumo?r$1)).ti,ab. | 8545 |
| 8 | ((esophag$ or oesophag$) adj3 (carcinoma$1 or adenocarcinoma$1)).ti,ab. | 7980 |
| 9 | or/6-8 | 18553 |
| 10 | 5 and 9 | 816 |
| 11 | exp computer assisted tomography/ | 190148 |
| 12 | (ct or comput$ tomogra$ or cat scan$).ti,ab. | 136854 |
| 13 | exp emission tomography/ | 39354 |
| 14 | (pet or (positron adj3 tomogra$)).ti,ab. | 23461 |
| 15 | or/11-14 | 247811 |
| 16 | 10 and 15 | 298 |

## PreMedline search strategy

The search strategy used to identify relevant studies of endoscopic ultrasound for oesophageal neoplasia in PreMedline is presented in **Table 115**.

**Table 115 Endoscopic ultrasound oesophageal PreMedline search strategy—February 28 2005**

| Search history | | References retrieved |
|---|---|---|
| 1 | (endosonograph$ or echo?endoscop$ or eus).ti,ab. | 97 |
| 2 | (endoscop$ adj (echo$ or ultrason$ or ultrasound)).ti,ab. | 94 |
| 3 | (interventional adj (ultrason$ or ultrasound)).ti,ab. | 1 |
| 4 | or/1-3 | 146 |
| 5 | ((esophag$ or oesophag$) adj3 (cancer or neoplasm$1 or tumo?r$1)).ti,ab. | 205 |
| 6 | ((esophag$ or oesophag$) adj3 (carcinoma$1 or adenocarcinoma$1)).ti,ab. | 191 |
| 7 | or/5-6 | 330 |
| 8 | 4 and 7 | 21 |
| 9 | (ct or comput$ tomogra$ or cat scan$).ti,ab. | 3635 |
| 10 | (pet or (positron adj3 tomogra$)).ti,ab. | 1023 |
| 11 | or/9-10 | 4419 |
| 12 | 8 and 11 | 13 |

# Gastric neoplasia

## Medline search strategy

The search strategy used to identify relevant studies of endoscopic ultrasound for gastric neoplasia in Medline is presented in **Table 116**.

**Table 116 Endoscopic ultrasound gastric Medline search strategy—1966 to February Week 3 2005**

| Search history | | References retrieved |
|---|---|---|
| 1 | endosonography/ | 3129 |
| 2 | (endosonograph$ or echo?endoscop$ or eus).ti,ab. | 2632 |
| 3 | (endoscop$ adj (echo$ or ultrason$ or ultrasound)).ti,ab. | 2440 |
| 4 | (interventional adj (ultrason$ or ultrasound)).ti,ab. | 61 |
| 5 | or/1-4 | 5426 |
| 6 | stomach neoplasms/ | 44338 |
| 7 | (stomach adj3 (cancer or carcinoma$1 or neoplasm$1 or tumo?r$1)).ti,ab. | 10512 |
| 8 | (gastr$ adj3 (cancer or carcinoma$1 or neoplasm$1 or tumo?r$1)).ti,ab. | 32458 |
| 9 | (gastr$ adj3 (adenoma$1 or carcinoid$1 or polyp$1)).ti,ab. | 2420 |
| 10 | (cardia adj (cancer or carcinoma$1 or neoplasm$1 or tumo?r$1)).ti,ab. | 258 |
| 11 | (cardio?esophageal adj (cancer or neoplasm$1 or tumo?r$1)).ti,ab. | 17 |
| 12 | (gastric cardia).ti,ab. | 743 |
| 13 | or/6-12 | 57603 |
| 14 | 5 and 13 | 816 |

## EMBASE search strategy

The search strategy used to identify relevant studies of endoscopic ultrasound for gastric neoplasia in EMBASE is presented in **Table 117**.

**Table 117 Endoscopic ultrasound gastric EMBASE search strategy—1980 to 2005 Week 9**

| Search history | | References retrieved |
|---|---|---|
| 1 | endoscopic echography/ | 3297 |
| 2 | (endosonograph$ or echo?endoscop$ or eus).ti,ab. | 2712 |
| 3 | (endoscop$ adj (echo$ or ultrason$ or ultrasound)).ti,ab. | 2583 |
| 4 | (interventional adj (ultrason$ or ultrasound)).ti,ab. | 60 |
| 5 | or/1-4 | 5187 |
| 6 | exp stomach tumor/ | 29695 |
| 7 | (stomach adj3 (cancer or carcinoma$1 or neoplasm$1 or tumo?r$1)).ti,ab. | 5569 |
| 8 | (gastr$ adj3 (cancer or carcinoma$1 or neoplasm$1 or tumo?r$1)).ti,ab. | 26887 |
| 9 | (gastr$ adj3 (adenoma$1 or carcinoid$1 or polyp$1)).ti,ab. | 1920 |
| 10 | (cardia adj (cancer or carcinoma$1 or neoplasm$1 or tumo?r$1)).ti,ab. | 195 |
| 11 | (cardio?esophageal adj (cancer or neoplasm$1 or tumo?r$1)).ti,ab. | 5 |
| 12 | (gastric cardia).ti,ab. | 630 |
| 13 | or/6-12 | 40641 |
| 14 | 5 and 13 | 916 |

## PreMedline search strategy

The search strategy used to identify relevant studies of endoscopic ultrasound for gastric neoplasia in PreMedline is presented in **Table 118**.

**Table 118 Endoscopic ultrasound gastric PreMedline search strategy—February 28 2005**

| Search history | | References retrieved |
|---|---|---|
| 1 | (endosonograph$ or echo?endoscop$ or eus).ti,ab. | 97 |
| 2 | (endoscop$ adj (echo$ or ultrason$ or ultrasound)).ti,ab. | 94 |
| 3 | (interventional adj (ultrason$ or ultrasound)).ti,ab. | 1 |
| 4 | or/1-3 | 146 |
| 5 | (stomach adj3 (cancer or carcinoma$1 or neoplasm$1 or tumo?r$1)).ti,ab. | 92 |
| 6 | (gastr$ adj3 (cancer or carcinoma$1 or neoplasm$1 or tumo?r$1)).ti,ab. | 759 |
| 7 | (gastr$ adj3 (adenoma$1 or carcinoid$1 or polyp$1)).ti,ab. | 39 |
| 8 | (cardia adj (cancer or carcinoma$1 or neoplasm$1 or tumo?r$1)).ti,ab. | 5 |
| 9 | (cardio?esophageal adj (cancer or neoplasm$1 or tumo?r$1)).ti,ab. | 0 |
| 10 | (gastric cardia or high?grade dysplasia$1).ti,ab. | 15 |
| 11 | or/5-10 | 845 |
| 12 | 4 and 11 | 14 |

# Pancreatic neoplasia

## Medline search strategy

The search strategy used to identify relevant studies of endoscopic ultrasound for pancreatic neoplasia in Medline is presented in **Table 119**.

**Table 119 Endoscopic ultrasound pancreatic Medline search strategy—1966 to February Week 2 2005**

| Search history | | References retrieved |
|---|---|---|
| 1 | endosonography/ | 3116 |
| 2 | (endosonograph$ or echo?endoscop$ or eus).ti,ab. | 2625 |
| 3 | (endoscop$ adj (echo$ or ultrason$ or ultrasound)).ti,ab. | 2436 |
| 4 | (interventional adj (ultrason$ or ultrasound)).ti,ab. | 61 |
| 5 | or/1-4 | 5411 |
| 6 | exp pancreatic neoplasms/ | 31104 |
| 7 | exp pancreatic cyst/ | 4295 |
| 8 | exp vater's ampulla/ | 5904 |
| 9 | insulinoma/ | 2753 |
| 10 | (pancrea$ adj3 (cancer or adenocarcinoma$1 or neoplasm$1 or tumo?r$1)).ti,ab. | 18580 |
| 11 | pancrea$ cyst$1.ti,ab. | 655 |
| 12 | (solid pancrea$ mass$2).ti,ab. | 19 |
| 13 | (pancrea$ adj3 (adenoma or insulinoma)).ti,ab. | 657 |
| 14 | ((pancrea$ or periampullary) adj (carcinoma$ or lesion$1)).ti,ab. | 5192 |
| 15 | ((ampulla or papilla) adj3 vater$2).ti,ab. | 1914 |
| 16 | (duoden$2 adj papilla).ti,ab. | 409 |
| 17 | exp cysts/ | 64798 |
| 18 | exp cystadenocarcinoma/ | 3644 |
| 19 | exp cystadenoma/ | 3841 |
| 20 | (cyst$1 or cystadenocarcinoma or pseudocyst$1).ti,ab. | 58069 |
| 21 | (cystic adj3 (lesion$1 or mass or tumo?r$1)).ti,ab. | 8384 |
| 22 | or/17-21 | 97651 |
| 23 | 22 and exp pancreas/ | 2102 |
| 24 | 22 and pancreas.ti,ab. | 3318 |
| 25 | ca-19-9 antigen/ | 912 |
| 26 | antigens, tumor-associated, carbohydrate/ | 4124 |
| 27 | (antigen 19-9 or gastrointestinal cancer antigen).ti,ab. | 323 |
| 28 | (ca 19-9 or ca 19 9 or ca19-9 or ca19 9 or ca-19-9).ti,ab. | 2171 |
| 29 | or/6-16,23-24 | 45612 |
| 30 | or/25-28 | 5640 |
| 31 | 5 and 29 | 1010 |
| 32 | 5 and 30 | 26 |
| 33 | jaundice, obstructive/ | 193 |
| 34 | cholestasis/ | 13224 |
| 35 | ((cholestatic or mechanical or obstructive or retention) adj jaundice).ti,ab. | 5021 |
| 36 | ((cholestatic or mechanical or obstructive or retention) adj icterus).ti,ab. | 145 |
| 37 | (extrahepatic cholestasis or cholestatic hepatobiliary disease).ti,ab. | 420 |
| 38 | (nonhaemolytic adj3 (bilirubinemia or icterus or jaundice)).ti,ab. | 27 |
| 39 | or/33-38 | 15463 |

| Search history | | References retrieved |
|---|---|---|
| 40 | 5 and 39 | 83 |
| 41 | exp tomography/ | 294315 |
| 42 | (ct or comput$ tomogra$ or cat scan$).ti,ab. | 152323 |
| 43 | (pentetreotide or octreoscan$ or octreotide).ti,ab,nm. | 5233 |
| 44 | indium radioisotopes/ and somatostatin/ | 273 |
| 45 | octreotide/ | 4131 |
| 46 | (scintigra$ or srs or scintiscan$).ti,ab. | 33948 |
| 47 | or/41-46 | 376107 |
| 48 | 31 and 47 | 486 |
| 49 | 32 and 47 | 18 |
| 50 | 40 and 47 | 41 |
| 51 | or/48-50 | 502 |

## EMBASE search strategy

The search strategy used to identify relevant studies of endoscopic ultrasound for pancreatic neoplasia in EMBASE is presented in **Table 120**.

**Table 120 Endoscopic ultrasound pancreatic EMBASE search strategy—1980 to 2005 Week 8**

| Search history | | References retrieved |
|---|---|---|
| 1 | endoscopic echography/ | 3295 |
| 2 | (endosonograph$ or echo?endoscop$ or eus).ti,ab. | 2709 |
| 3 | (endoscop$ adj (echo$ or ultrason$ or ultrasound)).ti,ab. | 2579 |
| 4 | (interventional adj (ultrason$ or ultrasound)).ti,ab. | 60 |
| 5 | or/1-4 | 5180 |
| 6 | exp pancreas tumor/ | 24651 |
| 7 | exp pancreas cyst/ | 2704 |
| 8 | vater papilla/ | 947 |
| 9 | vater papilla carcinoma/ | 740 |
| 10 | vater papilla tumor/ | 289 |
| 11 | (pancrea$ adj3 (cancer or adenocarcinoma$1 or neoplasm$1 or tumo?r$1)).ti,ab. | 15415 |
| 12 | pancrea$ cyst$1.ti,ab. | 367 |
| 13 | solid pancrea$ mass$2.ti,ab. | 20 |
| 14 | (pancrea$ adj3 (adenoma or insulinoma)).ti,ab. | 490 |
| 15 | ((pancrea$ or periampullary) adj (carcinoma$ or lesion$1)).ti,ab. | 4389 |
| 16 | ((ampulla or papilla) adj3 vater$2).ti,ab. | 1384 |
| 17 | (duoden$2 adj papilla).ti,ab. | 196 |
| 18 | exp cyst/ | 47267 |
| 19 | exp cystadenocarcinoma/ | 1351 |
| 20 | exp cystadenoma/ | 1652 |
| 21 | (cyst$1 or cystadenocarcinoma or pseudocyst$1).ti,ab. | 40261 |
| 22 | (cystic adj3 (lesion$1 or mass or tumo?r$1)).ti,ab. | 7272 |
| 23 | or/18-22 | 68978 |
| 24 | 23 and exp pancreas/ | 1598 |
| 25 | 23 and pancreas.ti,ab. | 2347 |
| 26 | ca 19 9 antigen/ | 2023 |
| 27 | (antigen 19-9 or gastrointestinal cancer antigen).ti,ab. | 291 |
| 28 | (ca 19-9 or ca 19 9 or ca19-9 or ca19 9 or ca-19-9).ti,ab. | 1797 |
| 29 | or/6-17,24-25 | 32916 |
| 30 | or/26-28 | 2660 |
| 31 | 5 and 29 | 1140 |
| 32 | 5 and 30 | 41 |
| 33 | obstructive jaundice/ | 3368 |
| 34 | (extrahepatic cholestasis or cholestatic hepatobiliary disease).ti,ab. | 276 |
| 35 | (nonhaemolytic adj3 (bilirubinemia or icterus or jaundice)).ti,ab. | 7 |
| 36 | ((cholestatic or mechanical or obstructive or retention) adj jaundice).ti,ab. | 3236 |
| 37 | ((cholestatic or mechanical or obstructive or retention) adj icterus).ti,ab. | 60 |
| 38 | or/31-35 | 4660 |
| 39 | 5 and 36 | 75 |

| Search history | | References retrieved |
|---|---|---|
| 40 | exp computer assisted tomography/ | 189799 |
| 41 | (ct or comput$ tomogra$ or cat scan$).ti,ab. | 136660 |
| 42 | pentetreotide/ or pentetreotide in 111/ | 1000 |
| 43 | (pentetreotide or octreoscan$ or octreotide).ti,ab,tn. | 4049 |
| 44 | exp scintiscanning/ | 62174 |
| 45 | (scintigra$ or srs or scintiscan$).ti,ab. | 27931 |
| 46 | or/39-44 | 281255 |
| 47 | 31 and 46 | 560 |
| 48 | 32 and 46 | 33 |
| 49 | 39 and 46 | 37 |
| 50 | or/47-49 | 577 |

## PreMedline search strategy

The search strategy used to identify relevant studies of endoscopic ultrasound for pancreatic neoplasia in PreMedline is presented in **Table 121**.

**Table 121 Endoscopic ultrasound pancreatic PreMedline search strategy—February 18 2005**

| Search history | | References retrieved |
|---|---|---|
| 1 | (endosonograph$ or ech?endoscop$ or eus).ti,ab. | 88 |
| 2 | (endoscop$ adj (echo$ or ultrason$ or ultrasound)). ti, ab. | 85 |
| 3 | (interventional adj (ultrason$ or ultrasound)). ti, ab. | 1 |
| 4 | or/1-3 | 133 |
| 5 | (pancrea$ adj3 (cancer or adenocarcinoma$1 or neoplasm$1 or tumo?r$1)). ti, ab. | 386 |
| 6 | pancrea$ cyst$1. ti, ab. | 6 |
| 7 | solid pancrea$ mass$2. ti, ab. | 1 |
| 8 | (pancrea$ adj3 (adenoma or insulinoma)) ti, ab. | 6 |
| 9 | ((pancrea$ or periampullary) adj (carcinoma$ or lesion$1)). ti, ab. | 80 |
| 10 | ((ampulla or papilla) adj3 vater$2). ti, ab. | 22 |
| 11 | (duoden$2 adj papilla). ti, ab. | 7 |
| 12 | (cyst$1 or cystadenocarcinoma or pseudocyst$1). ti, ab. | 841 |
| 13 | (cystic adj3 (lesion$1 or mass or tumo?r$1)). ti, ab. | 179 |
| 14 | or/12-13 | 951 |
| 15 | 14 and pancreas. ti, ab. | 39 |
| 16 | (antigen 19-9 or gastrointestinal cancer antigen).ti,ab. | 4 |
| 17 | (ca 19-9 or ca 19 9 or ca19-9 or ca19 9 or ca-19-9).ti,ab. | 39 |
| 18 | ((cholestatic or mechanical or obstructive or retention) adj jaundice).ti,ab. | 54 |
| 19 | (extrahepatic cholestasis or cholestatic hepatobiliary disease).ti,ab. | 5 |
| 20 | ((cholestatic or mechanical or obstructive or retention) adj icterus).ti,ab. | 0 |
| 21 | (nonhaemolytic adj3 (bilirubinemia or icterus or jaundice)).ti,ab. | 0 |
| 22 | or/5-11,15-21 | 538 |
| 23 | 4 and 22 | 22 |
| 24 | (ct or comput$ tomogra$).ti,ab. | 3563 |
| 25 | (pentetreotide or octreoscan$ or octreotide).ti,ab. | 112 |
| 26 | (scintigra$ or srs or scintiscan$).ti,ab. | 539 |
| 27 | or/24-26 | 4082 |
| 28 | 23 and 27 | 9 |

# Pancreatic solid mass: single arm EUS

## Medline search strategy

The search strategy used to identify relevant studies of single arm endoscopic ultrasound in Medline is presented in **Table 122**.

**Table 122 Endoscopic ultrasound search Medline search strategy—1966 to May Week 2 2005**

| Search history | | References retrieved |
|---|---|---|
| 1 | endosonography/ | 3227 |
| 2 | (endosonograph$ or echo?endoscop$ or eus).ti,ab. | 2693 |
| 3 | (endoscop$ adj (echo$ or ultrason$ or ultrasound)).ti,ab. | 2503 |
| 4 | (interventional adj (ultrason$ or ultrasound)).ti,ab. | 62 |
| 5 | or/1-4 | 5566 |
| 6 | exp pancreatic neoplasms/ | 31603 |
| 7 | exp vater's ampulla/ | 5948 |
| 8 | (pancrea$ adj3 (cancer or adenocarcinoma$1 or neoplasm$1 or tumo?r$1)).ti,ab. | 18999 |
| 9 | (solid pancrea$ mass$2).ti,ab. | 20 |
| 10 | pancrea$ adj3 adenoma.ti,ab. | 339 |
| 11 | ((pancrea$ or periampullary) adj (carcinoma$ or lesion$1)).ti,ab. | 5286 |
| 12 | ((ampulla or papilla) adj3 vater$2).ti,ab. | 1935 |
| 13 | (duoden$2 adj papilla).ti,ab. | 412 |
| 14 | or/6-13 | 41955 |
| 15 | 5 and 14 | 943 |

## EMBASE search strategy

The search strategy used to identify relevant studies of single arm endoscopic ultrasound in EMBASE is presented in **Table 123**.

**Table 123 Endoscopic ultrasound search EMBASE search strategy—1980 to 2005 week 21**

| Search history | | References retrieved |
|---|---|---|
| 1 | endoscopic echography/ | 3419 |
| 2 | (endosonograph$ or echo?endoscop$ or eus).ti,ab. | 2796 |
| 3 | (endoscop$ adj (echo$ or ultrason$ or ultrasound)).ti,ab. | 2667 |
| 4 | (interventional adj (ultrason$ or ultrasound)).ti,ab. | 61 |
| 5 | or/1-4 | 5358 |
| 6 | exp pancreas tumor/ | 25213 |
| 7 | vater papilla/ | 968 |
| 8 | vater papilla carcinoma/ | 767 |
| 9 | vater papilla tumor/ | 292 |
| 10 | (pancrea$ adj3 (cancer or adenocarcinoma$1 or neoplasm$1 or tumo?r$1)).ti,ab. | 15768 |
| 11 | (solid pancrea$ mass$2).ti,ab. | 20 |
| 12 | (pancrea$ adj3 adenoma).ti,ab. | 224 |
| 13 | ((pancrea$ or periampullary) adj (carcinoma$ or lesion$1)).ti,ab. | 4462 |
| 14 | ((ampulla or papilla) adj3 vater$2).ti,ab. | 1409 |
| 15 | (duoden$2 adj papilla).ti,ab. | 202 |
| 16 | or/6-15 | 30692 |
| 17 | 5 and 16 | 1058 |

## PreMedline search strategy

The search strategy used to identify relevant studies of single arm endoscopic ultrasound in PreMedline is presented in **Table 124**.

**Table 124 Endoscopic ultrasound PreMedline search strategy—May 24 2005**

| Search history | | References retrieved |
|---|---|---|
| 1 | (endosonograph$ or echo?endoscop$ or eus).ti,ab. | 110 |
| 2 | (endoscop$ adj (echo$ or ultrason$ or ultrasound)).ti,ab. | 102 |
| 3 | (interventional adj (ultrason$ or ultrasound)).ti,ab. | 0 |
| 4 | or/1-3 | 161 |
| 5 | (pancrea$ adj3 (cancer or adenocarcinoma$1 or neoplasm$1 or tumo?r$1)).ti,ab. | 484 |
| 6 | solid pancrea$ mass$2.ti,ab. | 1 |
| 7 | (pancrea$ adj3 adenoma).ti,ab. | 3 |
| 8 | ((pancrea$ or periampullary) adj (carcinoma$ or lesion$1)).ti,ab. | 99 |
| 9 | ((ampulla or papilla) adj3 vater$2).ti,ab. | 32 |
| 10 | (duoden$2 adj papilla).ti,ab. | 15 |
| 11 | or/5-10 | 560 |
| 12 | 4 and 11 | 30 |

# Pancreatic solid mass: single arm CT-guided biopsy

## Medline search strategy

The search strategy used to identify relevant studies of single arm CT-guided biopsy in Medline is presented in **Table 125**.

**Table 125 CT-guided biopsy search Medline search strategy—1966 to February Week 3 2005**

| Search history | | References retrieved |
|---|---|---|
| 1 | exp pancreatic neoplasms/ | 31139 |
| 2 | (pancrea$ adj3 (cancer or adenocarcinoma$1 or neoplasm$1 or tumo?r$1)).ti,ab. | 18610 |
| 3 | solid pancrea$ mass$2.ti,ab. | 19 |
| 4 | (pancrea$ adj3 adenoma).ti,ab. | 339 |
| 5 | ((pancrea$ or periampullary) adj (carcinoma$ or lesion$1)).ti,ab. | 5200 |
| 6 | or/1-5 | 35947 |
| 7 | exp biopsy, needle/ | 32317 |
| 8 | ((aspiration or puncture or suction) adj biops$3).ti,ab. | 6396 |
| 9 | ((needle or fine needle) adj3 (biops$3 or aspiration)).ti,ab. | 21126 |
| 10 | ((guided adj3 (biops$3 or aspiration)) or fna$1).ti,ab. | 9960 |
| 11 | or/7-10 | 43269 |
| 12 | exp tomography/294840 | 294840 |
| 13 | (ct or comput$ tomogra$ or cat scan$).ti,ab. | 152594 |
| 14 | or/12-13 | 346651 |
| 15 | (ct-guided or ct guided or guidance).ti,ab. | 22452 |
| 16 | or/11,15 | 63146 |
| 17 | 6 and 14 and 16 | 25503 |
| 18 | exp "sensitivity and specificity"/ | 173799 |
| 19 | likelihood functions/ | 6867 |
| 20 | area under curve/ | 8894 |
| 21 | reproducibility of results/ | 101474 |
| 22 | (specificity or screening or sensitiv$ or accuracy).ti,ab. | 806999 |
| 23 | (false adj (positive$1 or negative$1)).ti,ab. | 30618 |
| 24 | ((predictive or reference) adj value$1).ti,ab. | 35862 |
| 25 | (roc or receiver operat$).ti,ab. | 9682 |
| 26 | likelihood ratio$1.ti,ab. | 2722 |
| 27 | or/18-26 | 995771 |
| 20 | 17 and 27 | 159 |

## EMBASE search strategy

The search strategy used to identify relevant studies of single arm CT-guided biopsy in EMBASE is presented in **Table 126**.

**Table 126 CT-guided biopsy search EMBASE search strategy—1980 to 2005 Week 9**

| Search history | | References retrieved |
|---|---|---|
| 1 | exp pancreas tumor/ | 24674 |
| 2 | (pancrea$ adj3 (cancer or adenocarcinoma$1 or neoplasm$1 or tumo?r$1)).ti,ab. | 15431 |
| 3 | solid pancrea$ mass$2.ti,ab. | 20 |
| 4 | (pancrea$ adj3 adenoma).ti,ab. | 223 |
| 5 | ((pancrea$ or periampullary) adj (carcinoma$ or lesion$1)).ti,ab. | 4391 |
| 6 | or/1-5 | 28309 |
| 7 | aspiration biopsy/ | 10647 |
| 8 | needle biopsy/ | 7323 |
| 9 | ((aspiration or puncture or suction) adj biops$3).ti,ab. | 4680 |
| 10 | ((needle or fine needle) adj3 (biops$3 or aspiration)).ti,ab. | 17818 |
| 11 | ((guided adj3 (biops$3 or aspiration)) or fna$1).ti,ab. | 9274 |
| 12 | exp computer assisted tomography/ | 190148 |
| 13 | (ct or comput$ tomogra$ or cat scan$).ti,ab. | 136854 |
| 14 | or/12-13 | 225361 |
| 15 | (ct-guided or ct guided or guidance).ti,ab. | 18985 |
| 16 | or/7-11,28 | 44196 |
| 17 | 6 and 14 and 15 | 442 |
| 18 | diagnostic accuracy/ | 82557 |
| 19 | "sensitivity and specificity"/ | 18093 |
| 20 | receiver operating characteristic/ | 3488 |
| 21 | exp "prediction and forecasting"/ | 187194 |
| 22 | statistical model/ | 10668 |
| 23 | area under the curve/ | 18971 |
| 24 | reproducibility/ | 21958 |
| 25 | (specificity or screening or sensitiv$ or accuracy).ti,ab. | 693790 |
| 26 | (false adj (positive$1 or negative$1)).ti,ab. | 26084 |
| 27 | ((predictive or reference) adj value$1).ti,ab. | 33213 |
| 28 | (roc or receiver operat$).ti,ab. | 8962 |
| 29 | likelihood ratio$1.ti,ab. | 2473 |
| 30 | or/18-29 | 961429 |
| 31 | 17 and 30 | 183 |

## PreMedline search strategy

The search strategy used to identify relevant studies of single arm CT-guided biopsy search in PreMedline is presented in **Table 127**.

**Table 127 CT-guided biopsy search PreMedline search strategy—February 28 2005**

| Search history | | References retrieved |
|---|---|---|
| 1 | (endosonograph$ or echo?endoscop$ or eus).ti,ab. | 97 |
| 2 | (endoscop$ adj (echo$ or ultrason$ or ultrasound)).ti,ab. | 94 |
| 3 | (interventional adj (ultrason$ or ultrasound)).ti,ab. | 1 |
| 4 | or/1-3 | 146 |
| 5 | (pancrea$ adj3 (cancer or adenocarcinoma$1 or neoplasm$1 or tumo?r$1)).ti,ab. | 410 |
| 6 | solid pancrea$ mass$2.ti,ab. | 1 |
| 7 | (pancrea$ adj3 adenoma).ti,ab. | 2 |
| 8 | ((pancrea$ or periampullary) adj (carcinoma$ or lesion$1)).ti,ab. | 85 |
| 9 | or/5-8 | 442 |
| 10 | ((aspiration or puncture or suction) adj biops$3).ti,ab. | 87 |
| 11 | ((needle or fine needle) adj3 (biops$3 or aspiration)).ti,ab. | 410 |
| 12 | ((guided adj3 (biops$3 or aspiration)) or fna$1).ti,ab. | 299 |
| 13 | or/10-12 | 542 |
| 14 | 4 and 13 | 40 |
| 15 | (eus-fna or eus fna or eus-guided).ti,ab. | 28 |
| 16 | or/14-15 | 43 |
| 17 | 9 and 16 | 9 |
| 18 | (ct or comput$ tomogra$).ti,ab. | 3621 |
| 19 | (ct-guided or ct guided or guidance).ti,ab. | 794 |
| 20 | or/13,19 | 1285 |
| 21 | 9 and 18 and 20 | 7 |
| 22 | or/17,21 | 11 |

# Biliary tract neoplasia

## Medline search strategy

The search strategy used to identify relevant studies of endoscopic ultrasound for biliary tract neoplasia in Medline is presented in **Table 128**.

**Table 128 Endoscopic ultrasound biliary tract Medline search strategy—1966 to February Week 2 2005**

| Search history | | References retrieved |
|---|---|---|
| 1 | endosonography/ | 3116 |
| 2 | endoscopy/ and ultrasonography/ | 469 |
| 3 | ultrasonics/ and endoscop$.ti,ab. | 85 |
| 4 | (endosonograph$ or echo?endoscop$ or eus).ti,ab. | 2625 |
| 5 | (endoscop$ adj (echo$ or ultrason$ or ultrasound)).ti,ab. | 2436 |
| 6 | (interventional adj (ultrason$ or ultrasound).ti,ab. | 61 |
| 7 | or/1–6 | 5820 |
| 8 | exp biliary tract neoplasms/ | 13045 |
| 9 | bile duct obstruction, extrahepatic/ | 2547 |
| 10 | (bil$ adj3 (cancer or carcinoma$1 or neoplasm$1 or tumo?r$1)).ti,ab. | 8623 |
| 11 | (bil$ adj3 (stricture$1 or obstruct$)).ti,ab. | 7296 |
| 12 | (gallbladder adj (cancer or carcinoma$1 or neoplasm$1 or tumo?r$1)).ti,ab. | 1731 |
| 13 | ((gall?bladder adj polyp$1) or (choledoch$ adj (cancer or tumo?r))).ti,ab. | 114 |
| 14 | or/8-13 | 26275 |
| 15 | 7 and 14 | 345 |
| 16 | exp vater's ampulla/ | 5904 |
| 17 | ((ampulla or papilla) adj3 vater$2).ti,ab. | 1914 |
| 18 | (duoden$2 adj papilla).ti,ab. | 409 |
| 19 | or/16-18 | 6645 |
| 20 | 7 and 19 | 137 |
| 21 | exp cholangiography/ | 15894 |
| 22 | (cholangio$ or ercp or ptc or mrcp).ti,ab. | 17412 |
| 23 | (pancreatocholangio$ or endoscopic pancreato$).ti,ab. | 212 |
| 24 | (bil$ duct radiogra$).ti,ab. | 3 |
| 25 | or/21-24 | 25054 |
| 26 | 15 and 25 | 157 |
| 27 | 20 and 25 | 53 |
| 28 | or/26-27 | 180 |

## EMBASE search strategy

The search strategy used to identify relevant studies of endoscopic ultrasound for biliary tract neoplasia in EMBASE is presented in **Table 129**.

**Table 129 Endoscopic ultrasound biliary tract EMBASE search strategy—1980 to 2005 Week 8**

| Search history | | References retrieved |
|---|---|---|
| 1 | endoscopic echography/ | 3295 |
| 2 | echography/ and endoscop$.ti,ab. | 2474 |
| 3 | (endosonograph$ or echo?endoscop$ or eus).ti,ab. | 2709 |
| 4 | (endoscop$ adj (echo$ or ultrason$ or ultrasound)).ti,ab. | 2579 |
| 5 | (interventional adj (ultrason$ or ultrasound)).ti,ab. | 60 |
| 6 | or/1-5 | 7001 |
| 7 | exp biliary tract tumor/ | 8437 |
| 8 | exp obstructive bile duct disease/ | 17468 |
| 9 | (bil$ adj3 (cancer or carcinoma$1 or neoplasm$1 or tumo?r$1)).ti,ab. | 6854 |
| 10 | (bil$ adj3 (stricture$1 or obstruct$)).ti,ab. | 5828 |
| 11 | (gallbladder adj (cancer or carcinoma$1 or neoplasm$1 or tumo?r$1)).ti,ab. | 1315 |
| 12 | ((gall?bladder adj polyp$1) or (choledoch$ adj (cancer or tumo?r))).ti,ab. | 110 |
| 13 | or/7-12 | 30981 |
| 14 | 6 and 13 | 876 |
| 15 | vater papilla/ | 947 |
| 16 | vater papilla carcinoma/ | 740 |
| 17 | vater papilla tumor/ | 289 |
| 18 | ((ampulla or papilla) adj3 vater$2).ti,ab. | 1384 |
| 19 | (duoden$2 adj papilla).ti,ab. | 196 |
| 20 | or/15-19 | 2461 |
| 21 | 6 and 20 | 171 |
| 22 | exp cholangiography/ | 13159 |
| 23 | exp pancreatography/ | 9787 |
| 24 | (cholangio$ or ercp or ptc or mrcp).ti,ab. | 13781 |
| 25 | (pancreatocholangio$ or pancreaticocholangio$).ti,ab. | 26 |
| 26 | (bil$ duct radiogra$ or endoscopic pancreato$).ti,ab. | 75 |
| 27 | or/22-26 | 19850 |
| 28 | 14 and 27 | 618 |
| 29 | 21 and 27 | 90 |
| 30 | or/28-29 | 657 |

## PreMedline search strategy

The search strategy used to identify relevant studies of endoscopic ultrasound for biliary tract neoplasia in PreMedline is presented in **Table 130**.

**Table 130 Endoscopic ultrasound biliary tract PreMedline search strategy—February 18 2005**

| Search history | | References retrieved |
|---|---|---|
| 1 | endoscop$.ti,ab. | 1431 |
| 2 | (endosonograph$ or echo?endoscop$ or eus).ti,ab. | 88 |
| 3 | (endoscop$ adj (echo$ or ultrason$ or ultrasound)).ti,ab. | 85 |
| 4 | (interventional adj (ultrason$ or ultrasound)).ti,ab. | 1 |
| 5 | or/1-4 | 1473 |
| 6 | (bil$ adj3 (cancer or carcinoma$1 or neoplasm$1 or tumo?r$1)).ti,ab. | 139 |
| 7 | (bil$ adj3 (stricture$1 or obstruct$)).ti,ab. | 114 |
| 8 | (gallbladder adj (cancer or carcinoma$1 or neoplasm$1 or tumo?r$1)).ti,ab. | 47 |
| 9 | ((gall?bladder adj polyp$1) or (choledoch$ adj (cancer or tumo?r))).ti,ab. | 3 |
| 10 | ((ampulla or papilla) adj3 vater$2).ti,ab. | 22 |
| 11 | (duoden$2 adj papilla).ti,ab. | 7 |
| 12 | or/6-11 | 313 |
| 13 | 5 and 12 | 59 |
| 14 | (cholangio$ or ercp or ptc or mrcp).ti,ab. | 364 |
| 15 | 13 and 14 | 34 |

# Appendix E Included studies

## Health outcomes

**Table 131 Included studies comparing EUS and CT for staging on health outcomes in oesophageal cancer evaluation**

| Study author/s | Population, treatment | Test characteristics | Study outcomes | Level of evidence |
|---|---|---|---|---|
| Harewood and Kumar (2004)<br>Retrospective interrupted time series without a parallel control group (1998, 2000) | **Patient inclusion:** Histopathologically confirmed oesophageal cancer<br>**Treatment:** Presumed resectable: surgery, Adjuvant therapy: chemoradiation | **EUS characteristics:** Radial echoendoscopes (Olympus GF-UM30, GF-UM20), Operator: 1 of 4 experienced endosonographers<br>**CT characteristics:** Slice thickness (5–7 mm) and scanning time remained unchanged over time (1998) | **Cox proportional hazard for mortality—EUS vs. non-EUS**: HR: 0.66; 95% CI: 0.47, 0.90; *p* value: 0.008<br>**Cox proportional hazard for tumour recurrence rate—EUS vs. non-EUS**: HR: 0.63; 95% CI: 0.43, 0.87; *p* value: 0.004 | III-3<br>High potential for bias, clearly reported |
| van Westreenen (2005)<br>Retrospective interrupted time series without a parallel control group (1992–2002) | **Patient inclusion:** Biopsy-proven malignancy of the oesophagus or gastro-oesophageal junction<br>**Treatment**: Patients staged as T1-3 N0 M0: oesophagectomy as curative treatment, Resection abandoned if staged as T4, N1 or M1 | **EUS characteristics:** Radial scanner (Olympus GF-UM20) for EUS, linear-array scanner (Pentax FGUX-36) for EUS-FNA, Operator: 1 well trained endoscopist (1997)<br>**CT characteristics:** NR (1992–1996) | **Kaplan-Meier survival analysis—CT alone vs CT + EUS**: HR: 0.98; 95% CI: 0.48, 2.00; *p* value: NS | III-3<br>High potential for bias, clearly reported |

Abbreviations: CI; confidence intervals; CT, computed tomography; EUS, endoscopic ultrasound; HR, hazard ratio; NS, not significant

**Table 132 Included study comparing EUS-FNA and CT-FNA/Bx effects on health outcomes in pancreatic mass diagnosis**

| Study author/s | Population, treatment | Test characteristics | Study outcomes | Level of evidence |
|---|---|---|---|---|
| Erickson and Garza (2000)<br>Retrospective interrupted time series without a parallel control group (1993–1997) | **Patient inclusion:** Diagnosed with pancreatic carcinoma<br>**Treatment:** Operable and staged as resectable: surgery, fluorouracil, gemcitabine in some from May 1997 | **EUS-FNA characteristics:** NR (1995–1997)<br>**CT-FNA/Bx characteristics:** NR (1993–1995) | **EUS-FNA**: 14% (NS) of patients undergoing surgical resection; Median survival of 205 days ($p < 0.02$)[a] with pancreatic cancer without liver metastases<br>**CT-FNA/Bx**: 13% of patients undergoing surgical resection; Median survival of 102 days with pancreatic cancer without liver metastases | III-3<br>High potential for bias, clearly reported |

Abbreviations: Bx, biopsy; CI; confidence intervals; CT, computed tomography; EUS, endoscopic ultrasound; FNA, fine needle aspiration; NR, not reported; NS, not significant

[a] log rank test

# Oesophageal neoplasia

**Table 133 Included studies for the assessment of the incremental value of EUS over CT in oesophageal neoplasm staging**

| Study author/s | Population, prevalence, prior tests | Test characteristics | Study outcomes | Study quality |
|---|---|---|---|---|
| Botet et al (1991a)<br>Prospective, consecutive patients, inclusion based on clinical presentation<br>Incremental data, EUS for TN staging, CT for M staging<br>Dec 1986–Dec 1988 | **Patient inclusion:** Patients with epidermoid carcinoma or adenocarcinoma of the oesophagus planned for palliative or curative surgery<br>**Prevalence**: Stage III or IV 33/42 (21.4%); Stage IV 16/42 (38.1%)<br>**Prior tests:** Endoscopy | **EUS characteristics:** Olympus GF-UM2, GF-UM3, Operator: radiologist<br>**CT characteristics:** Dynamic CT, 1200SX Picker Int or GE9800 GE Medical Systems, 10 mm slices. Multiple radiologists of comparable experience. Performed after EUS<br>**Reference standard:** Surgery (100%) | Non-traversable tumours: 0/42 (0%)<br>**CT**: Stage III or IV, Sn 78.8%, Sp 66.7%, Acc 76.2%; Stage IV, Sn 75.0%, Sp 100%, Acc 90.5%<br>**CT+EUS**: Stage III or IV, Sn 97.0%, Sp 77.8%, Acc 92.9%; Stage IV, Sn 81.3%, Sp 100%, Acc 92.9% | C1 P2 Q1<br>*Quality*: high<br>*Applicability*: limited<br>Outdated technology, not either positive approach, patient group applicable |
| Choi et al (2000)<br>Prospective, reference standard-based inclusion<br>Individual patient data<br>Feb 1997–Dec 1998 | **Patient selection**: Patients with biopsy-proven oesophageal cancer undergoing oesophagectomy with 2- or 3-field lymph node dissection<br>**Prevalence**: N1 (per patient) 32/48 (66.7%); N1 (per node) 32/48 (66.7%)<br>**Prior tests:** Bone scintigraphy, oesophagogastro-duodenoscopy, bronchoscopy, abdominal and neck sonography within 3 weeks of PET | **EUS characteristics:** Olympus GF-UM20 radial scanner. Operator: one gastroenterologist. Blinded to other imaging modalities<br>**CT characteristics:** Helical CT, 5 mm or 7 mm collimation, Interpreted before surgery by 1 radiologist<br>**PET characteristics**: Advance PET scanner, General Electric Medical Systems, 5 minutes/frame<br>**Reference standard:** Surgery (100%) | Non-traversable tumours: 12/45[b] (25.0%)<br>**CT**: N1 (per patient), Sn 40.6%, Sp 100%, Acc 60.4%<br>**CT+EUS**: N1 (per patient), Sn 68.8%, Sp 75.0%, Acc 70.8%<br>**CT+PET**: N1 (per node), Sn 84.4%, Sp 87.5%, Acc 85.4%<br>**CT+PET+EUS**: N1 (per node), Sn 87.5%, Sp 62.5%, Acc 79.2% | C1 P2 Q2<br>*Quality*: medium<br>Selection bias<br>*Applicability*: limited<br>Resected patients only |
| Date et al (1990)<br>Unclear direction, reference-standard-based inclusion<br>Individual patient data<br>1985–1988 | **Patient selection** Patients with squamous cell carcinoma of the oesophagus, undergoing subtotal oesophagectomy<br>**Prevalence**: T4 11/20 (55.0%)<br>**Prior tests:** Barium swallow and endoscopic evaluation | **EUS characteristics**: Olympus GF-UM2 radial system fibrescope, with balloon-filling technique<br>**CT characteristics:** NR<br>**Reference standard:** Surgery (100%) | Non-traversable tumours: 4/20 (20.0%)<br>**CT**: T4, Sn 90.9%, Sp 44.4%, Acc 70.0%<br>**CT+EUS**: T4, Sn 100%, Sp 44.4%, Acc 75.0% | C1 P2 Q2<br>*Quality*: medium<br>Selection bias<br>*Applicability*: limited<br>Resected patients only, outdated technology |

| Study author/s | Population, prevalence, prior tests | Test characteristics | Study outcomes | Study quality |
|---|---|---|---|---|
| Flamen et al (2000)<br>Prospective, consecutive patients, inclusion based on clinical presentation<br>Incremental data, either positive<br>Oct 1997–Dec 1998 | **Patient inclusion:** Mixed population of oesophageal and GOJ biopsy-proven cancer patients evaluated for resectability<br>**Prevalence**: Stage IV 34/74 (45.9%)<br>**Prior tests:** Laboratory tests, neck US, barium oesophagogram, bronchoscopy | **EUS characteristics:** Olympus UM-20 radial scanner, Pentax linear sector scan. Operator: 1–3 examiners with 4–12 years of experience. Blinded to other imaging modalities<br>**CT characteristics:** Spiral CT; 5 mm slices<br>**PET characteristics**: CTI-Siemens 931/08/12 scanner<br>**Reference standard:** Surgery (68%), dedicated radiographic techniques (NR) or clinical and radiographic follow up (NR) | Non-traversable tumours: 19/74 (25.7%)<br>**CT**: Stage IV, Sn 41.2%, Sp 82.5%, Acc 63.5%<br>**CT+EUS**: Stage IV, Sn 47.1%, Sp 77.5%, Acc 63.5% | C1 P1 Q2<br>*Quality*: medium<br>Differential verification bias<br>*Applicability*: applicable (stage IV)<br>limited (nodes) |
| Lerut et al (2000)<br>Substudy of Flamen et al (2000)<br>Prospective, reference-standard-based inclusion<br>Individual patient data<br>Oct 1997–Dec 1998 | **Patient inclusion:** Mixed population of oesophageal and GOJ biopsy-proven cancer patients undergoing primary curative surgery with 2- or 3-field lymphadenectomy<br>**Prevalence**: M1a 10/39 (25.6%); N1 (per patient) 21/32 (65.6%); N1 (per node) 15/25 (60%)<br>**Prior tests:** Laboratory tests, neck US, barium oesophagogram, bronchoscopy | **EUS characteristics:** EUS: Olympus UM-20 radial scanner, Pentax linear sector scan. Operator: 1–3 examiners with 4–12 years of experience<br>**CT characteristics:** Spiral CT; 5 mm slices<br>**PET characteristics**: CTI-Siemens 931/08/12 scanner<br>**Reference standard:** Surgery (100%) | Non-traversable tumours: M1a 5/39 (12.8%); N1 (per patient) 4/32 (12.5%); N1 (per node) 2/25 (8.0%)<br>**CT**: M1a, Sn 20.0%, Sp 82.8%, Acc 66.7%; N1 (per patient), Sn 42.9%, Sp 90.9%, Acc 59.4%<br>**CT+EUS**: M1a, Sn 60.0%, Sp 72.4%, Acc 69.2%; N1 (per patient), Sn 81.0%, Sp 45.5%, Acc 68.8%<br>**CT+PET**: N1 (per node), Sn 53.3%, Sp 80.0%, Acc 64.0%<br>**CT+PET+EUS**: N1 (per node), Sn 86.7%, Sp 40.0%, Acc 68.0% | C1 P2 Q2<br>*Quality*: medium<br>Selection bias<br>*Applicability*: limited<br>Resected patients only |

| Study author/s | Population, prevalence, prior tests | Test characteristics | Study outcomes | Study quality |
|---|---|---|---|---|
| Heeren et al (2004)<br>Prospective, test-based inclusion<br>Incremental data, either positive<br>Jan 1996–Jan 2002 | **Patient inclusion:** Mixed population of patients with resectable carcinoma of the thoracic oesophagus and GOJ based on CT, EUS and US<br>**Prevalence**: M1a 24/72 (33.3%)<br>**Prior tests:** Neck ultrasonography | **EUS characteristics:** Olympus GF-UM20 radial scanner (n = 46) or Olympus MH-908 small-calibre probe (n = 8); inadequate EUS in 20 patients. Blinded to other staging methods<br>**CT characteristics:** Fourth generation units (SR7000 Philips Medical Systems), or spiral Siemens Somatron Plus 4. Operator: experienced oncological radiologist.<br>**PET characteristics**: Siemens ECAT HR+ positron camera<br>**Reference standard:** Surgical resection with curative attempt (56%), explorative laparotomy (39%), FNA biopsy (6%) | Non-traversable tumours: NR<br>**CT**: M1a, Sn 20.8%, Sp 97.9%, Acc 72.2%<br>**CT+EUS**: M1a, Sn 29.2%, Sp 95.8%, Acc 73.6% | C1 P2 Q2<br>*Quality*: medium<br>Selection bias<br>*Applicability*: limited<br>Potentially excluded patients determined unresectable by EUS. 15% patients mini-probe |
| Hordijk et al (1993a)<br>Prospective study, non-consecutive, inclusion based on clinical presentation<br>Individual patient data<br>Jan 1990–Jun 1991 | **Patient inclusion:** Mixed population of patients with carcinoma of the oesophagus or GOJ proven by endoscopic biopsy undergoing transhiatal oesophagectomy<br>**Prevalence**: T4 1/41 (2.4%); T3 or T4 29/41 (70.7%)<br>**Prior tests:** Endoscopy, neck US, guided cytological needle aspiration biopsy | **EUS characteristics:** Olympus GF-UM3/EUM3<br>**CT characteristics:** Somatom Plus<br>**Reference standard:** Surgery (100%)<br>Time lag 2 weeks | Non-traversable tumours: 15/41 (36.6%)<br>**CT**: T4, Sn 100%, Sp 70.0%, Acc 70.7%; T3 or T4, Sn 100%, Sp 41.7%, Acc 82.9%<br>**CT+EUS**: T4, Sn 100%, Sp 67.5%, Acc 68.3%; T3 or T4, Sn 100%, Sp 33.3%, Acc 80.5% | C1 P2 Q2<br>*Quality*: medium<br>Selection bias<br>*Applicability*: limited<br>Outdated technology, patient group applicable |
| Hordijk et al (1993b)<br>Prospective study, non-consecutive, inclusion based on clinical presentation<br>Individual patient data<br>Jan 1990–Sep 1992 | **Patient inclusion:** Patients with resectable squamous cell carcinoma of the oesophagus undergoing transhiatal oesophagectomy following induction chemotherapy<br>**Prevalence**: T3 or T4 3/10[c] (30.0%)<br>**Prior tests:** Endoscopy, neck US, guided cytological needle aspiration biopsy | **EUS characteristics:** Olympus GF-UM3 EUM3<br>**CT characteristics:** Third-generation Somatom plus<br>**Reference standard:** Surgery (100%) | Non-traversable tumours: 1/11 (9.1)<br>**CT**: T3 or T4, Sn 100%, Sp 28.6%, Acc 50.0%<br>**CT+EUS**: T3 or T4, Sn 100%, Sp 28.6%, Acc 50.0% | C1 P2 Q2<br>*Quality*: medium<br>Selection bias<br>*Applicability*: limited<br>Post-induction chemotherapy resectable patients only, outdated technology |

| Study author/s | Population, prevalence, prior tests | Test characteristics | Study outcomes | Study quality |
|---|---|---|---|---|
| Luketich et al (2000)<br>Prospective study, reference standard-based inclusion<br>Incremental data, method not reported<br>May 1995–Sep 1998 | **Patient selection**<br>Patients with potentially resectable oesophageal cancer<br>**Prevalence**:<br>N1, 36/53 (67.9%)<br>**Prior tests:**<br>NR | **EUS characteristics:**<br>NR<br>**CT characteristics:**<br>NR<br>**Reference standard:**<br>Laparoscopic staging with intraoperative ultrasound (83%) and video-thoracoscopy (79%) | Non-traversable tumours: 13/47[d] (27.7)<br>**CT**:<br>N1, Sn 33.3%, Sp 88.2%, Acc, 50.9%<br>**CT+EUS**:<br>N1, Sn 86.1%, Sp 41.2%, Acc 71.7% | C1 P2 Q2<br>*Quality*: medium<br>Selection bias, differential verification bias<br>*Applicability*: limited<br>Potentially excluded patients determined unresectable by EUS, potentially outdated technology |
| Sihvo et al (2004)<br>Prospective study, reference-standard-based inclusion<br>Incremental data, method not reported<br>Dec 1998–Oct 2003 | **Patient inclusion:**<br>Mixed population of patients with histologically proved adenocarcinoma of the oesophagus (36%) or GOJ (64%) undergoing radical oesophagectomy and lymphadenectomy<br>**Prevalence**:<br>Stage IV 19/55 (34.5%); N1 (per patient) 26/43 (60.5%); N1 (per node) 26/43 (60.5%)<br>**Prior tests:**<br>Endoscopy | **EUS characteristics:**<br>NR<br>**CT characteristics:**<br>NR<br>**PET characteristics**:<br>Advance PET scanner, General Electric Medical Systems, 5 minutes/frame<br>**Reference standard:**<br>Primary surgery with 2 field lymphadenectomy (78%), explorative surgery with palliative treatment (22%) | Non-traversable tumours: Stage IV 7/55 (12.7%); N1 (per patient) 7/43 (16.3%); N1 (per node) 7/43 (16.3%)<br>**CT**:<br>Stage IV, Sn 31.6%, Sp 97.2%, Acc 74.5%; N1 (per patient), Sn 42.3%, Sp 82.4%, Acc 58.1%<br>**CT+EUS**:<br>Stage IV, Sn 42.1%, Sp 100%, Acc 80%; N1 (per patient), Sn 84.6%, Sp 82.4%, Acc 83.7%<br>**CT+PET**:<br>N1 (per node), Sn 50.0%, Sp 100%, Acc 69.8%<br>**CT+PET+EUS**:<br>N1 (per node), Sn 84.6%, Sp 100%, Acc 90.7% | C1 P2 Q2<br>*Quality*: medium<br>Selection bias<br>*Applicability*: limited<br>Resected patients only |
| Ziegler et al (1991)<br>Prospective study, reference-standard-based inclusion<br>Individual patient data<br>Jan 1986–Jul 1988 | **Patient inclusion:**<br>Patients with histologically proven squamous cell carcinoma of the oesophagus undergoing subtotal oesophageal resection<br>**Prevalence**:<br>T4 20/37 (54.1%); N1 25/37 (67.6%)<br>**Prior tests:**<br>NR | **EUS characteristics:**<br>Siemens linear array scanner. Operator: fully trained endoscopist<br>**CT characteristics:**<br>Siemens Somatom DRG or DRH, 8–10 mm section distance<br>**Reference standard:**<br>Surgery (92%), necropsy (8%)<br>Time lag 2 weeks | Non-traversable tumours: 7/37 (18.9%)<br>**CT**:<br>T4, Sn 55.0%, Sp 76.5%, Acc 64.9%; N1, Sn 40.0%, Sp 66.7%, Acc 48.6%<br>**CT+EUS**:<br>T4, Sn 95.0%, Sp 76.5%, Acc 86.5%; N1, Sn 72.0%, Sp 50.0%, Acc 64.9% | C1 P2 Q2<br>*Quality*: medium<br>Selection bias<br>*Applicability*: limited<br>Resected patients only, potentially excluded patients determined unresectable by EUS, outdated technology |

Abbreviations: Acc, accuracy; CT, computed tomography; EUS, endoscopic ultrasound; GOJ; gastro-oesophageal junction; NR, not reported; PET, positron emission tomography; Sn, sensitivity; Sp, specificity; US, ultrasound

[a] Includes coeliac nodes

[b] Excludes three patients who were unable to tolerate EUS

[c] Excludes one patient with unpassable tumour stenosis

[d] EUS was not performed in six patients

[e] Authors' method for combining data is unclear, but cannot be either positive for stage IV approach

# Gastric neoplasia

**Table 134 Included studies for the assessment of the incremental value of EUS over CT in gastric neoplasm staging**

| Study author/s | Population, prevalence, prior tests | Test characteristics | Study outcomes (gastric neoplasm staging) | Study quality |
|---|---|---|---|---|
| Botet et al (1991b)[a]<br>Unclear direction, consecutive patients, inclusion based on clinical presentation<br>Dec 1986–Dec 1988 | **Patient inclusion:** Histologically proven gastric adenocarcinoma planned for palliative or curative surgery<br>**Prevalence**: Stage IV11/33[b] (33.3%)<br>**Prior tests:** Biopsy | **EUS characteristics:** Olympus GFUM2, GFUM3; stomach water-filled electively. Blinded to CT<br>**CT characteristics:** Dynamic CT, 1200SX Picker Int or GE9800 GE Medical Systems; 10 mm slices. Multiple radiologists. Performed after EUS<br>**Reference standard:** Pathological examination of resected tumours and perigastric lymph nodes (100%) | **CT**: Stage IV, Sn 72.7%, Sp 72.7%, Acc 72.7%<br>**CT+EUS**: Stage IV, Sn 90.9%, Sp 77.3%, Acc 81.8% | C1 P2 Q1<br>*Quality*: high<br>*Applicability*: limited<br>Outdated technology, patient group applicable |

Abbreviations: Acc, accuracy; AJCC, American Joint Committee on Cancer; CT, computed tomography; EUS, endoscopic ultrasound; GOJ; gastro-oesophageal junction; NR, not reported; PET, positron emission tomography; Sn, sensitivity; Sp, specificity; US, ultrasound
[a] Not an either test positive approach: Likely to be EUS for TN and CT for M based on Botet et al (1991a)
[b] Number of tumours

**Table 135 Included studies for the assessment of the replacement value of EUS compared with CT in gastric neoplasm staging**

| Study author/s | Population, prevalence, prior tests | Test characteristics | Study outcomes (gastric neoplasm staging) | Study quality |
|---|---|---|---|---|
| Habermann et al (2004)<br>Prospective, consecutive patients, inclusion based on clinical presentation<br>Feb 1998–Mar 2000 | **Patient inclusion:** Patients with gastric cancer<br>**Prevalence**: T4 3/51 (5.9%); T3 or T4 22/51 (43.1%); N1 or N2 31/50 (62.0%); N2 19/50 (38.0%)<br>**Prior tests:** Endoscopic biopsy | **EUS characteristics:** Olympus GF-UM2, GF-UM3 radial sector scan. Operator: single endoscopist with 8 years of experience. Blinded to CT. Performed within 3 days of CT<br>**CT characteristics:** Siemens single-detector row CT scanner, Somatom Plus 4. Operator: two radiologists, both with 7 years of experience. Performed within 3 days of EUS<br>**Reference standard:** Partial or complete gastrectomy with D1 or D2 lymphadenectomy (100%)[a] | **EUS**: T4, Sn 100%, Sp 100%, Acc 100%; T3 or T4, Sn 81.8%, Sp 89.7%, Acc, 86.3%; N1 or N2, Sn 96.8%, Sp 100%, Acc 98.0%; N2, Sn 84.2%, Sp 93.5%, Acc 90.0%<br>**CT**: T4, Sn 100%, Sp 95.8%, Acc 96.1%; T3 or T4, Sn 77.3%, Sp 82.8%, Acc 80.4%; N1 or N2, Sn 74.2%, Sp 84.2%, Acc 78.0%; N2, Sn 73.7%, Sp 77.4%, Acc 76.0% | C1 P2 Q1<br>*Quality*: high<br>*Applicability*: limited<br>Outdated technology, patient group applicable |
| Perng et al (2004)<br>Prospective, consecutive patients, inclusion based on clinical presentation<br>Nov 1989–Dec 1993 | **Patient inclusion:** Patients with gastric adenocarcinoma<br>**Prevalence**: T4 23/69 (33.3%); N1 or N2 37/69 (53.6%); N2 20/69 (29.0%)<br>**Prior tests:** NR | **EUS characteristics** Olympus EU-M3 radial mechanical sector scan<br>**CT characteristics:** Siemens Somatom DRH, 8 mm section intervals<br>**Reference standard:** Surgery (100%)<br>Time lag: 12 days from CT | **EUS**: T4, Sn 82.6%, Sp 95.7%, Acc 91.3%; N1 or N2, Sn 67.6%, Sp 75.0%, Acc 71.0%; N2, Sn 60.0%, Sp 91.8%, Acc 82.6%<br>**CT**: T4, Sn 52.2%, Sp 91.3%, Acc 78.3%; N1 or N2, Sn 27.0%, Sp 81.3%, Acc 52.2%; N2, Sn 30.0%, Sp 91.8%, Acc 73.9% | C1 P2 Q1<br>*Quality*: high<br>*Applicability*: limited<br>Outdated technology, patient group applicable |

Abbreviations: Acc, accuracy; CT, computed tomography; EUS, endoscopic ultrasound; Sn, sensitivity; Sp, specificity
[a] D1 lymphadenectomy denotes that all N1 nodes are removed en bloc with the stomach; D2 lymphadenectomy denotes that all N1 and N2 nodes are removed en bloc with the stomach

**Table 136 Studies considering the value of EUS in gastric submucosal tumour diagnosis (non-comparative studies)**

| Study author/s | Population, prevalence, prior tests | Test characteristics | Study outcomes (diagnosis of gastric malignancy/ outcomes) | Study quality |
|---|---|---|---|---|
| Ando et al (2002)<br>Prospective, reference standard-based inclusion<br>Oct 1993–Mar 2000) | **Patient selection:** Patients who underwent resection of SMTs diagnosed by EUS (22 gastric, 1 duodenal)<br>**Prevalence:** 6/23 (26.1%)<br>**Prior tests:** NR | **EUS characteristics:** Olympus GF-UM20 radial scanner<br>**EUS-FNA characteristics**: Convex Array, Pentax FG-32UA or FG36UX Needle 22 G, average passes 2.83 (range 1–5)<br>**Reference standard:** Surgery (100%)<br>**Definition of malignancy**: EUS, tumour > 5 cm, irregular border, cystic spaces; EUS-FNA, high number of mitotic figures; high cellularity; severe nuclear atypia | **EUS**: Sn 83.3%, Sp 76.5%, Acc 78.3%<br>**EUS-FNA**: Sn 66.7%, Sp 100%, Acc 91.3% | P2 Q2<br>*Quality*: medium<br>Selection bias<br>*Applicability:* limited<br>Resected patients only |
| Caletti et al (1989)<br>Prospective, consecutive patients<br>Jan 1986–April 1988 | **Patient selection:** Patients from a group of 25 with endoscopically proven gastric SMTs[a]<br>**Prevalence:** 13/24[b] (54%)<br>**Prior tests:** Abdominal ultrasound; Multiple forceps biopsy; Endoscopy | **EUS characteristics:** Olympus GF-UM2/EUM2 with rotating transducer<br>**Reference standard:** Surgery (58%); abdominal ultrasound (42%); follow up (13%), time period not reported[c]<br>**Definition of outcomes**: Differentiation of gastric SMT from extramural compression | **EUS**: Sn 100%, Sp 100%, Acc 100% | P2 Q2<br>*Quality*: medium<br>Differential verification bias<br>*Applicability*: limited<br>Outdated technology |
| Caletti et al (1991)<br>Unclear direction, test-based inclusion<br>Jan 1989–Oct 1990 | **Patient selection:** Patients with gastric SMTs with solid intramural growth detected by EUS<br>**Prevalence:** 2/21 (9.5%)<br>**Prior tests:** NR | **EUS characteristics:** Olympus GF-UM3/EUM3 radial scanner<br>**Reference standard:** Surgery (76%); follow up (6-month intervals) by EUS and guillotine needle biopsy (24%)<br>**Definition of malignancy**: NR | **EUS**: Sn 0%, Sp 94.7%, Acc 85.7% | P2 Q2<br>*Quality*: medium<br>Potential selection bias<br>*Applicability:* limited<br>Outdated histological classification |
| Kwon et al (2005)<br>Retrospective, reference-standard-based inclusion<br>Aug 2001–Sept 2003 | **Patient selection:** Patients with gastric SMTs confirmed by histology or cytology<br>**Prevalence:** 8/34 (23.5%)<br>**Prior tests:** NR | **EUS characteristics:** Olympus GF-UM240, UM-2R/3R, EU-M30 radial scanner<br>**Reference standard:** Histological diagnosis by endoscopic resection (NR); surgery (NR); or core needle biopsy(NR); FNA cytology (NR)[d]<br>**Definition of malignancy**: Tumour ≥ 3 cm, echoinhomogenicity, irregular borders, stippled high echo, cystic structure | **EUS**: 75.0%, Sp 96.2%, Acc 91.2%, DOR 75.0, LR+ 19.5, LR- 0.26 | P2 Q2<br>*Quality*: medium<br>Differential verification bias<br>Potential selection bias<br>*Applicability*: limited<br>SMT confirmed by reference standard |

| Study author/s | Population, prevalence, prior tests | Test characteristics | Study outcomes (diagnosis of gastric malignancy/ outcomes) | Study quality |
|---|---|---|---|---|
| Matsui et al (1998)<br>Unclear direction, test-based inclusion<br>Oct 1993–May 1997 | **Patient selection:** Patients from group of 174 presenting with upper gastrointestinal SMTs diagnosed by EUS[e]<br>**Prevalence:** 3/20 (15%)<br>**Prior tests:** NR | **EUS characteristics:** Olympus GF-UM20 radial scanner<br>**EUS-FNA characteristics**: Convex array, Pentax FG-32UA or FG-36UX. Pentax needle 22 G, average passes 4.3<br>**Reference standard:** Surgical resection (65%); clinical follow up (35%) by repeated endoscopy and EUS at 6-month intervals, mean 14-month period (range 9–28 months)<br>**Definition of malignancy**: EUS, tumour > 3 cm echoinhomogenicity, irregular borders; EUS-FNA, mitotic figures; high cellularity; nuclear atypia | **EUS**: Sn 66.7%, Sp 82.4%, Acc 80.0%<br>**EUS-FNA**: Sn 100%, Sp 100%, Acc 100% | P2 Q2<br>*Quality*: medium<br>Potential selection bias<br>*Applicability*: limited<br>Outdated histological classification |
| Okubo et al (2004)<br>Unclear direction, test-based inclusion<br>Jan 1997–Mar 2002 | **Patient selection:** Patients with resected GIST confirmed by IHC<br>**Prevalence:** 5/14 (36%)<br>**Prior tests:** EUS | **EUS-FNA characteristics:** Olympus GF-UCT 240, 22 G needle, 1–4 passes (average of 2.4 passes), NA-10J-KB or NA-11J-KB (Olympus) Cytologist present<br>**Reference standard:** Surgery (100%)<br>**Definition of malignancy**: High-grade malignancy: 1/5 HPF mitotic figure; high cellularity; severe nuclear atypia | **EUS-FNA**: Sn 40%, Sp 100%, Acc 78.6% | P2 Q2<br>*Quality*: medium<br>Potential selection bias<br>*Applicability*: limited<br>Resected patients only |
| Tsai et al (2001)<br>Unclear direction, reference-standard-based inclusion<br>Oct 1994–Mar 2000 | **Patient selection:** Patients with histologically proven gastric GIST undergoing resection or biopsy<br>**Prevalence:** 11/52 (21.2%)<br>**Prior tests:** Endoscopy | **EUS characteristics:** Olympus EU-M3, radial scanner<br>**Reference standard:** Surgery (98%); biopsy (2%)<br>**Definition of malignancy**: Tumour > 3 cm sonolucence, irregular margin | **EUS**: Sn 72.7%, Sp 90.2%, Acc 86.5% | P2 Q2<br>*Quality*: medium<br>Selection bias<br>*Applicability:* limited<br>Resected patients only |

Abbreviations: Acc, accurate; EUS, endoscopic ultrasound; EUS-FNA, endoscopic ultrasound guided fine needle aspiration; IHC; immunohistochemistry; LR+, positive likelihood ratio; LR–, negative likelihood ratio; NR, not reported; SMT, submucosal tumour; Sn, sensitivity; Sp, specificity

[a] EUS failed in one patient with a small SMT (0.5 cm) located on the prepyloric antral region

[b] One case of retroperitoneal haematoma was counted as an extrinsic compression

[c] Some patients had more than one reference standard

[d] The number of patients receiving each reference standard was not reported

[e] Data from two duodenal patients were excluded. The reason for exclusion of the remaining 152 patients was not reported. Specimens for cytological diagnosis were inadequate in three cases. These specimens were counted as true negatives as there was no change in tumour size and echo characteristics during follow up.

# Pancreatic neoplasia

**Table 137 Studies considering the diagnostic value of EUS in pancreatic neoplasia in absence of a solid mass (exocrine)**

| Study author/s | Population, prevalence, Prior tests | Test characteristics | Study outcomes (diagnosis of pancreatic neoplasia) | Study quality |
|---|---|---|---|---|
| Agarwal et al (2004)<br>Retrospective test-based inclusion<br>Replacement study, reported subgroup EUS in those negative on CT<br>Nov 2000–Nov 2001 | **Patient selection**: Patients with obstructive jaundice + biliary stricture on ERCP; suspected pancreatic mass on CT; > 2 episodes pancreatitis in 6 months<br>Subgroup with no identifiable mass on spiral CT (25/81)<br>**Prevalence**: 71/81 (88%)<br>**Prior tests**: ERCP, CT | **EUS characteristics**: Olympus EUM-30, radial scanner<br>**EUS-FNA characteristics**: Pentax FG-32A linear scanner, echo-tip FNA, 1-7 passes<br>**CT characteristics**: GE Medical Systems Lightspeed CT multidetector spiral CT with multiphasic pancreas protocol<br>**Reference standard**: Pathology, cytology or > 1 year clinical follow up (100%) | **CT**: Uncertain/negative 18/81, Sn 75%, Sp 70%, Acc 74%<br>**CT+EUS**: uncertain/negative 18/81, Sn 100%, Sp 50%, Acc 94%<br>**CT+EUS-FNA**: uncertain/negative 18/81, Sn 97%, Sp 70%, Acc 94% | C1 P2 Q2<br>*Quality*: medium<br>Potential selection bias,<br>differential verification bias<br>*Applicability*: limited<br>Referral bias, some patients with suspected mass on CT |
| Harrison et al (1999)<br>Retrospective, likely reference standard-based inclusion (possibly test referent)<br>Replacement study but reported individual patient data | **Patient selection**: Patients with obstructive jaundice; abdominal pain and weight loss; incidental CT finding<br>Undergoing exploratory surgery<br>No mass on CT (6)<br>**Prevalence**: 15[a]/18 (79%)<br>**Prior tests**: NR | **EUS characteristics**: Olympus UM20, radial scanner, single endoscopist<br>**CT characteristics**: NR<br>**Reference standard**: Surgery (100%) | **CT**: Uncertain/negative 8/18, Sn 53%, Sp 33%, Acc 50%<br>**CT+EUS**: uncertain/negative 8/18, Sn 100%, Sp 0%, Acc 83% | C1, P2, Q3<br>*Quality*: poor<br>Insufficient information on inclusion, possibly test referent<br>*Applicability*: limited<br>Surgical exploration, prior tests NR |
| Snady et al (1992)<br>Design unclear, non-consecutive<br>Replacement value, EUS compare with CT+ERCP knowledge<br>May 1998–Feb 1990 | **Patient selection**: Diagnostically problematic patients; most abnormality on US; obstructive jaundice; pancreatic mass < 5 cm on CT + pain, jaundice or abnormal duct; pain + abnormal pancreatogram; no evidence of metastases<br>**Prevalence**: 40/60 (66%)<br>**Prior tests**: US + CT and/or ERCP | **EUS characteristics**: Olympus UM2, radial scanner, unblinded<br>**CT characteristics**: Described elsewhere, 7 patients received repeat CT<br>**ERCP characteristics**: Olympus JF10 or JFV10<br>**Reference standard**: Surgery (53%), biopsy (17%), > 6 months clinical follow up (30%) | **CT+ERCP**: Sn 75%, Sp 65%, Acc 72%<br>**CT+ERCP+EUS**: Sn 85%, Sp 80%, Acc 83% | C1 P2 Q3<br>*Quality*: poor<br>Selection bias, no 2 x 2,<br>poor reporting<br>*Applicability*: limited<br>CT results pooled with ERCP, outdated technology, some patients lesions < 5 cm on CT, 12% received repeat CT |

Abbreviations: Acc, accuracy; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; EUS-FNA, endoscopic ultrasound guided fine needle aspiration; NR, not reported; Sn, sensitivity; Sp, specificity.
[a] Including one ampullary carcinoma.

**Table 138 Studies concerning the value of EUS in pancreatic neoplasia diagnosis in the absence of a solid mass (neuroendocrine)**

| Study author/s | Population, prevalence, Prior tests | Test characteristics | Study outcomes (correct localisation of neuroendocrine tumours) | Study quality |
|---|---|---|---|---|
| De Angelis et al (1999)<br>Study subset<br>Unclear direction, reference standard-based inclusion<br>1991–1998 | **Patient selection**: Patients with suspected PETs undergoing resection, 42 tumours–23 pancreatic, 8 duodenal, 11 lymph nodes; MEN-1 or Werner's syndrome<br>**Prevalence**: Pancreatic insulinomas and gastrinomas EUS 23/19[a]; SRS 13/9[a]; duodenal gastrinomas 8/4[a]<br>**Prior tests**: Biochemistry; comparison with CT, US and angiography | **EUS characteristics**: Olympus GF-UM2/GF-UM3, radial scanner, single investigator (n = 19)<br>**SRS characteristics**: 111-In-octreotide, 4- and 24-hour SPECT images (n = 9)<br>47% of patients had both tests<br>**Reference standard**: Surgery (100%) | **EUS**: Pancreatic insulinomas and gastrinomas, 87%; duodenal gastrinomas 38%<br>**SRS**: Pancreatic insulinomas and gastrinomas, 15%; duodenal gastrinomas 0% | CX P2 Q2<br>*Quality*: medium<br>Selection bias, detection bias, insufficient information on negative tests<br>*Applicability*: limited<br>Surgical series, no prior CT or US, outdated technology, not all pancreatic, results per tumour |
| Fendrich et al (1996)<br>Retrospective reference standard-based inclusion<br>1987–2003 | **Patient selection**: Patients with sporadic insulinomas undergoing surgery<br>**Prevalence**: EUS 23[a], SRS 14[a]<br>**Prior tests**: Biochemistry, fasting test, comparison with CT, US, MRI and angiography | **EUS characteristics**: NR (n = 23)<br>**SRS characteristics**: NR (n = 14)<br>**Reference standard**: Surgery (100%) | **EUS**: 65%<br>**SRS**: 0% | CX P2 Q2<br>*Quality*: medium<br>Selection bias, detection bias, insufficient information on negative tests<br>*Applicability*: limited<br>Surgical series, results per tumour, no prior CT or US |
| Mirallie et al (2002)<br>Retrospective reference standard-based inclusion<br>Individual patient data presented<br>1991–2000 | **Patient selection**: PETs; insulinomas; gastrinomas; MEN-1<br>**Prevalence**: Insulinomas 14/16 (88%)[b]; gastrinomas 16/18 (89%)[b]<br>**Prior tests**: Biochemistry | **EUS characteristics**: Olympus 7.5 MHz, experienced operator<br>**SRS characteristics**: 111-In-pentreotide, octreoscan, 111-185 MBq, 4- and 24-hour and 48-hour images (2 cases)<br>100% patients had both tests<br>**Reference standard**: Surgery (100%) | **EUS**: Insulinomas 79%; gastrinomas 56%<br>**SRS**: Insulinomas 50%, gastrinomas 56% | C1 P2 Q2<br>*Quality*: medium<br>Selection bias, insufficient information on negative tests<br>*Applicability*: limited<br>Spectrum bias, prior US & CT not reported, EUS model not reported |
| Proye et al (1998)<br>Retrospective reference standard-based-inclusion<br>Duplicate series to Mirallie et al (2002) | **Patient selection**: Insulinomas; gastrinomas; MEN-1<br>**Prevalence**: N/A<br>**Prior tests**: Biochemistry | **EUS characteristics**: Olympus 7.5 MHz, experienced operator<br>**SRS characteristics**: 111-In-pentreotide, octreoscan, 111-185 MBq, 4- and 24-hour images<br>100% patients had both tests<br>**Reference standard**: Surgery (100%) | N/A | C1 P2 Q2<br>*Quality*: medium<br>Selection bias, insufficient information on negative tests<br>*Applicability*: limited<br>Surgical series, prior US & CT not reported |

| Study author/s | Population, prevalence, Prior tests | Test characteristics | Study outcomes (correct localisation of neuroendocrine tumours) | Study quality |
|---|---|---|---|---|
| Zimmer et al (2000)<br>Unclear direction, reference standard-based inclusion<br>1990–1997 | **Patient selection**: Pancreatic insulinomas, gastrinomas and non-functional gastropancreatic NETs; MEN-1<br>**Prevalence**: Insulinomas 17/11[a], gastrinomas 15/11[a]<br>**Prior tests**: Comparison with CT, US and MRI | **EUS characteristics**: Olympus GF-UM3/GF-UM20, test within 4 weeks, experienced operator<br>**SRS characteristics**: 100–200 MBq 111-In-labelled pentetreotide, Octreoscan 111, 4- 24- 48- planar images, 24-hour SPECT images, test within 4 weeks, experienced operator<br>**Reference standard**: Surgery (100%) | **EUS**: Insulinomas 94%, gastrinomas 80%<br>**SRS**: Insulinomas 12%, gastrinomas 87% | C1 P2 Q2<br>*Quality*: medium<br>Selection bias<br>*Applicability*: limited<br>Surgical series, no prior CT or US, not all pancreatic, results per tumour |
| Zimmer et al (1994)<br>Prospective consecutive patients<br>1991–1993<br>Duplicate series to Zimmer et al (2000) | **Patient selection**: Confirmed or suspected NETs of the stomach, duodenum, pancreas or liver<br>**Prevalence**: N/A<br>**Prior tests**: Comparison with CT, US and MRI | **EUS characteristics**: Olympus GF-UM3<br>**SRS characteristics**: 100–200 MBq 111-In-labelled pentetreotide, Siemens Orbiter 7500 gamma camera, 4- 24- 48-hour images, 24-hour SPECT images<br>**Reference standard**: Surgery (78%), US-guided biopsy (11%), endoscopic biopsy (11%) | N/A | C1 P2 Q1<br>*Quality*: high<br>Consecutive patients, valid reference standard<br>*Applicability*: limited<br>No prior US or CT, outdated technology |
| Zimmer et al (1998)<br>Prospective non-consecutive<br>1991–1994<br>Duplicate series to Zimmer et al (2000) | **Patient selection**: Patients with insulinomas or gastrinomas; MEN-1<br>**Prevalence**: N/A<br>**Prior tests**: Comparison with CT, US and MRI | **EUS characteristics**: Olympus GF-UM3/GF-UM20<br>**SRS characteristics**: 100–200 MBq 111-In-labelled pentetreotide, Siemens Orbiter 7500 gamma camera, 4- 24- 48-hour images, 24-hour SPECT images, test within 4 weeks, experienced operator<br>**Reference standard**: Surgery (85%), US-guided or CT-guided biopsy (15%) | N/A | C1 P2<br>*Quality*: not assessed<br>Foreign language, potential selection bias<br>*Applicability*: limited<br>No prior US or CT, some outdated technology |

| | | | | |
|---|---|---|---|---|
| Zimmer et al (1999)<br>Prospective non-consecutive<br>1991–1993<br>Duplicate series to Zimmer et al (2000) | **Patient selection**:<br>Patients with insulinomas or gastrinomas;<br>MEN-1<br>**Prevalence**:<br>N/A<br>**Prior tests**:<br>Serum calcium, PTH, PLH; comparison with CT, US and MRI | **EUS characteristics**:<br>Olympus GF-UM3/GF-UM20<br>**SRS characteristics**:<br>100–200 MBq 111-In-labelled pentetreotide, Siemens Orbiter 7500 gamma camera, 4- 24- 48-hour images, 24-hour SPECT images, test within 4 weeks, experienced operator<br>**Reference standard**:<br>Surgery (90%), US-guided or<br>CT-guided biopsy (10%) | N/A | C1 P2 Q2<br>*Quality*: medium<br>Potential selection bias<br>*Applicability*: limited<br>No prior US or CT, some outdated technology |

Abbreviations: Acc, accuracy; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; MEN-1, multiple endocrine neoplasia; MRI, magnetic resonance imaging; N/A, not applicable; NET, neuroendocrine tumour; NR, not reported; PET, pancreatic endocrine tumour; PLH, prolactin hormone; PTH, parathyroid hormone; Sn, sensitivity; Sp, specificity; SPECT, Single Photon Emission Computed Tomography; SRS, somatostatin receptor scintigraphy

[a] n (tumours)/N (patients)

[b] Per patient, not per tumour

**Table 139 Studies concerning the value of EUS versus CT in pancreatic solid mass diagnosis**

| Study author/s | Population, prevalence, prior tests | Test characteristics | Study outcomes (pancreatic neoplasia diagnosis) | Study quality |
|---|---|---|---|---|
| Okai et al (1999)<br>Prospective test-based inclusion<br>Individual patient data | **Patient selection**:<br>Patients evaluated for pancreatic disease with a pancreatic mass lesion detected by US, CT or EUS<br>**Prevalence**:<br>19/36 (52.8%)<br>**Prior tests**: Comparison with US | **EUS characteristics**:<br>Olympus GF-UM3, GF-UM20 or<br>JF-UM200 radial scanner<br>**CT characteristics**:<br>CT/T 9800 System with intravenous contrast agent with 5mm section at 5mm intervals<br>**Reference standard**:<br>Surgery, autopsy, cytology, clinical follow up with imaging | **CT**:<br>Sn 78.9%, Sp 88.2%,<br>Acc 83.3%<br>**CT+EUS**:<br>Sn 100%, Sp 76.5%,<br>Acc 88.9% | C1 P1 Q2<br>*Quality*: medium<br>Selection bias, inadequate reference standard<br>*Applicability*: Applicable |
| Harrison et al (1999)<br>Retrospective test-based inclusion<br>Individual patient data | **Patient selection**:<br>Patients evaluated pre-operatively with EUS, with a mass lesion detected on CT[a]<br>**Prevalence**:<br>9/11 (81.8%)<br>**Prior tests**:<br>NR | **EUS characteristics**:<br>Olympus GF-UM20 radial scanner<br>**CT characteristics**:<br>Spiral and non-spiral CT<br>**Reference standard**:<br>Surgery | **CT**:<br>Sn 100%, Sp 0%,<br>Acc 81.8%<br>**CT+EUS**:<br>Sn 100%, Sp 0%,<br>Acc 81.8% | C1, P2, Q2<br>*Quality*: medium<br>Selection bias<br>*Applicability*: limited<br>Different CT technology, surgical exploration series |

Abbreviations: Acc, accuracy; CT, computed tomography; EUS, endoscopic ultrasound; NR, not reported; US, ultrasound; Sn, sensitivity; Sp, specificity

[a] The patients reported in this comparison are a subgroup of the entire study population.

**Table 140 Studies concerning the value of EUS-FNA in pancreatic solid mass diagnosis**

| Study author/s | Population, prevalence, prior tests | Test characteristics | Study outcomes (pancreatic neoplasia diagnosis) | Study quality |
|---|---|---|---|---|
| Harewood and Wiersema (1994)<br>Prospective, test-based inclusion<br>Incremental value study, replacement value calculable | **Patient selection:**<br>Known or suspected solid pancreatic mass, with previous CT-guided biopsy, excluding diagnosed metastatic[a]<br>**Prevalence:**<br>53/61 (87)<br>**Prior tests:**<br>CT | **EUS characteristics:**<br>EUS: Olympus GF-UM20 or GF-UM30 radial scanner<br>**EUS-FNA characteristics**:<br>Olympus GF-UC30P or Pentax FG-32UA linear array, 22 G Wilson Cook needle, median of five passes<br>**CT characteristics:**<br>CT-guided biopsy: 18–20 G guiding needle with 22 G aspiration needle<br>Median of three passes, range 2–5<br>Cytopathologist present (84%)<br>**Reference standard (%):**<br>Surgery, > 12-month clinical and imaging follow up, cytology and compatible clinical course | **EUS-FNA**:<br>Sn 91%, Sp 100%, Acc 92%<br>**CT-Bx/FNA**:<br>Sn 6%, Sp 100%, Acc 18% | C1, P1, Q2<br>*Quality*: medium<br>Selection bias<br>*Applicability*: applicable |
| Qian and Hecht (2003)<br>Retrospective reference-test-based inclusion<br>Parallel test application Jan 1995–Jun 2001 | **Patient selection:**<br>Patient population characteristics not reported (includes solid and cystic lesions)[a]<br>**Prevalence:**<br>EUS-FNA**:** 38/63 (67%); CT-FNA: 35/47 (74%)<br>**Prior tests:**<br>NR | **EUS characteristics**:<br>NR<br>**EUS-FNA characteristics:**<br>EUS-FNA: uncontrolled with respect to needle size, number of passes or presence of cytologist. Generally, 2–3 passes, 22 G needle<br>**CT-FNA characteristics**:<br>NR<br>**Reference standard (%):**<br>Surgery, clinical/radiographic (CT) data, > 2 years follow up | **EUS-FNA**:<br>Sn 34%, Sp 100%, Acc 60%<br>**CT-FNA**:<br>Sn 69%, Sp 100%, Acc 77% | CX, P2, Q3<br>*Quality*: poor<br>Potential selection bias, retrospective. detection/ spectrum bias, tests not in same patients. Differential verification bias. Poor reporting<br>*Applicability*: limited<br>Poor reporting |

Abbreviations*:* Acc, accuracy; Bx, biopsy; CT, computed tomography; EUS, endoscopic ultrasound; FNA, fine needle aspiration; NR, not reported, Sn, sensitivity; Sp, specificity.

[a] The patients reported in this comparison are a subgroup of the entire study population.

**Table 141 Single arm studies concerning the value of EUS or CT-FNA/guided biopsy in pancreatic solid mass diagnosis**

| Study author/s | Population, prevalence, prior tests | Test characteristics | Study outcomes (pancreatic neoplasia diagnosis) | Study quality |
|---|---|---|---|---|
| Becker et al (2000)<br>Unclear direction consecutive patients | **Patient selection:** Patients with solid pancreatic masses; excluding cystic and solid/cystic masses<br>**Prevalence:**<br>16/23 (69.6%)<br>**Prior tests:**<br>US, CT | **EUS characteristics:**<br>EUS: Pentax FG32-UA<br>Intravenous contrast agent (Optison FS069)<br>**Reference standard:**<br>Surgery (NR), histology (NR),<br>6 months clinical follow up (NR) | **EUS**:<br>Uninterpretable NR,<br>Sn 93.8%, Sp 100%,<br>Acc 95.7% | P2, Q1<br>*Quality*: high<br>*Applicability*: limited<br>EUS used with a contrast agent |
| Brand et al (2000)<br>Prospective, test-based inclusion | **Patient selection:** Focal pancreatic mass; excluding uncomplicated cystic mass and patients with inadequate histology<br>**Prevalence:**<br>81/115 (70.4%)<br>**Prior tests:**<br>US, CT, ERCP | **EUS characteristics:**<br>EUS: Olympus GF-UM3, GF-UM 20, GF-UM200<br>**Reference standard:**<br>Histopathology (100%) | **EUS**:<br>Uninterpretable NR,<br>Sn 95.1%, Sp 52.9%,<br>Acc 82.6% | P1, Q2<br>*Quality*: Medium<br>Selection bias<br>*Applicability*:<br>Applicable |
| Geng et al (1987)<br>Unclear direction, test-based inclusion | **Patient selection:** Patients with known pancreatic neoplasms undergoing surgery, excluding patients with other biliopancreatic lesions<br>**Prevalence:**<br>18/20 (90.0%)<br>**Prior tests:**<br>NR | **CT-FNA characteristics:**<br>Unknown device using a 22 G Franseen needle<br>**Reference standard:**<br>Surgery (100%) | **EUS**:<br>Uninterpretable NR,<br>Sn 100%, Sp 100%,<br>Acc 100% | P2, Q2<br>*Quality:* medium<br>Potential selection bias<br>*Applicability:* limited<br>Unknown whether a mass identified previously |
| Luning et al (2001)<br>Unclear direction, test-based inclusion<br>Duplicate of Luning et al (1985) | **Patient selection:** Pancreatic mass or to confirm suspected carcinoma<br>**Prevalence**:<br>N/A<br>**Prior tests:**<br>NR | **CT-FNA characteristics:**<br>Unknown device using a 22 G needle<br>**Reference standard:**<br>Surgery (NR), clinical and imaging follow up (NR), five months of follow up | N/A | P2, Q2<br>*Quality*: medium<br>Potential selection bias<br>*Applicability*: limited<br>Data are presented for samples not patients |
| Luning et al (1985)<br>Unclear direction, test-based inclusion | **Patient selection:** Pancreatic mass or to confirm suspected carcinoma, excluding pseudocysts<br>**Prevalence:**<br>41/124 (36.3%)<br>**Prior tests:** CT | **CT-FNA characteristics:**<br>Unknown device using a 22 G needle, 1–6 passes were used to obtain the sample<br>**Reference standard:**<br>Surgery (36%), clinical and imaging follow up (64%) | **EUS**:<br>Uninterpretable 15/124, Sn 71.1%, Sp 83.5%,<br>Acc 79.0% | P2, Q2<br>*Quality*: medium<br>Potential selection bias<br>*Applicability*: limited<br>Data are presented for samples not patients |
| Mitchell et al (1988)<br>Retrospective, test-based inclusion | **Patient selection:** Precise criteria unknown; most patients had abdominal pain and radiographic evidence of a pancreatic mass; patients excluded for inadequate follow up<br>**Prevalence:**<br>38/41 (92.7%)<br>**Prior tests:** NR | **CT-FNA characteristics:**<br>Unknown device using a 22 G needle<br>**Reference standard:**<br>Surgery (NR), clinical and imaging follow up (NR) | **EUS**:<br>Uninterpretable NR, Sn 73.7%, Sp 100%,<br>Acc 75.6% | P2, Q2<br>*Quality*: medium<br>Potential selection bias<br>*Applicability*: limited<br>Inclusion criteria were not limited to previously detected mass |

| Study author/s | Population, prevalence, prior tests | Test characteristics | Study outcomes (diagnosis of pancreatic neoplasia) | Study quality |
|---|---|---|---|---|
| Robins et al (1995)<br>Retrospective, test-based inclusion | **Patient selection:** Pancreatic lesions, excluding inadequate reference standard<br>**Prevalence:**<br>63/90 (70.0%)<br>**Prior tests:**<br>NR | **CT-FNA characteristics:**<br>Unknown device using a 22 G needle<br>**Reference standard:**<br>Surgery and autopsy (68%),<br>18 months of clinical and imaging follow up (32%) | **EUS**:<br>Uninterpretable NR,<br>Sn 85.7%, Sp 100%,<br>Acc 88.9% | P2, Q2<br>*Quality*: medium<br>Potential selection bias<br>*Applicability*: limited<br>Inclusion criteria were not limited to previously detected mass |
| Rodriguez et al (1992)<br>Retrospective, test-based inclusion | **Patient selection:** Recently diagnosed pancreatic mass with adequate follow up<br>**Prevalence:**<br>29/41 (70.7%)<br>**Prior tests:** CT or US | **CT-Bx characteristics:**<br>Siemens Somatom DRH scanner using a 16.5 G Lee needle, with one or two passes to obtain the sample<br>**Reference standard:**<br>Surgery (NR) autopsy (NR), six months of clinical and imaging follow up (NR) | **EUS**:<br>Uninterpretable 8/41,<br>Sn 44.8%, Sp 100%,<br>Acc 61.0% | P1, Q2<br>*Quality*: medium<br>Potential selection bias<br>*Applicability*: applicable |
| Sperti et al (1994)<br>Retrospective, test-based inclusion | **Patient selection:** Recently diagnosed solid pancreatic mass<br>**Prevalence:**<br>54/58 (93.0%)<br>**Prior tests:**<br>US | **CT-FNA characteristics:**<br>Unknown device using a 22 G needle<br>**Reference standard:**<br>Surgery (NR), autopsy (NR), 12 months of clinical follow up (NR) | **EUS**:<br>Uninterpretable 0/54,<br>Sn 98.1%, Sp 100%,<br>Acc 98.3% | P1, Q2<br>*Quality*: medium<br>Potential selection bias<br>*Applicability*: applicable |

Abbreviations: Acc, accuracy; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; FNA, fine needle aspiration; N/A, not applicable; NR, not reported; US, ultrasound; Sn, sensitivity; Sp, specificity

**Table 142 Studies concerning EUS and CT in pancreatic cystic lesion diagnosis**

| Study author/s | Population, prevalence (%), prior tests (%) | Test characteristics | Study outcomes (pancreatic neoplasia diagnosis) | Study quality |
|---|---|---|---|---|
| Baba et al (2004)[a]<br>Retrospective, reference standard-based inclusion<br>Jun 1988–Feb 2002 | Patient selection: Patients with IPMT diagnosed by histopathology<br>Prevalence: 74/121[b] (61%)<br>Prior tests: Unclear, possibly ERCP | EUS characteristics: Radial scan type (brand not reported) (n = 49)<br>CT characteristics: NR (n = 121)<br>Reference standard: Histopathology (100%) | EUS: Cyst diameter, Sn 54.1%, Sp 85.8%, Acc 68.2%; Main pancreatic duct diameter[d], Sn 40.4%, Sp 74.9%, Acc 53%; Height of protruding lesion[e], Sn 67.7%, Sp 87.9%, Acc 76.4%<br>CT: Cyst diameter[c], Sn 46%, Sp 76.9%, Acc 60.4%; Main pancreatic duct diameter[d], Sn 50.5%, Sp 81%, Acc 61.6%; Height of protruding lesion[e], Sn 52.7%, Sp 95.7%, Acc 69.4% | CX P2 Q2<br>Quality: medium<br>Potential selection bias<br>Applicability: limited<br>Histologically proven IPMT |
| Cellier et al (1998)<br>Retrospective, reference standard-based inclusion<br>1980–1995 | Patient selection: Patients who had surgical resection for pathologically diagnosed IPMT<br>Prevalence: EUS 9/21 (43%); CT 13/25 (52%)<br>Prior tests: Unclear, possibly ERCP | EUS characteristics: Olympus GFUM3 (n = 11); GFUM20 (n = 10) (between 1990 and 1995) (n = 21)<br>CT characteristics: Various generations of conventional imagers used; Spiral CT not used (n = 25) 10 patients also received EUS<br>Reference standard: Surgery (100%) | EUS: Rupture and invasion, Sn 77.8%, Sp 75.0%, Acc 76.2%<br>CT: Rupture and invasion, Sn 69.2%, 83.3%, Acc 76.0% | CX P2 Q2<br>Quality: medium Selection bias<br>Applicability: limited Resected patients only |
| Levy et al (1995)<br>Retrospective, consecutive patients<br>1988–1993 | Patient selection: Patients with cystic pancreatic tumours; excluded patients with cystic papillary and cystic endocrine tumours and non-tumoral cystic lesions<br>Prevalence: Adenocarcinoma: CT, 7/35 (20%); EUS, 6/31 (19%); Cystic neoplasms: CT, 16/35 (46%); EUS, 14/31 (45%)<br>Prior tests: NR | EUS characteristics: Olympus CF UM3/EUM3 and CFUM20/EUM20 (N = 31)<br>CT characteristics: NR (N = 35)<br>Reference standard: Surgery (83%); other tests (clinical follow up, radiological or cytological) (17%) | EUS: Adenocarcinoma: presence of vegetations, spread, dilated ducts, Sn 100, Sp 96, Acc 96.8; Adenocarcinoma and adenoma: usually anechoic, wall thickening, intracystic partitions[f], Sn 86%, Sp 59%, Acc 71%<br>CT: Adenocarcinoma: presence of vegetations, spread, dilated ducts, Sn 100, Sp 100, Acc 100; Adenocarcinoma and adenoma: usually anechoic, wall thickening, intracystic partitions[f], Sn 75%, Sp 95%, Acc 86% | CX P2 Q2<br>Quality: medium Differential verification bias<br>Applicability: limited Outdated technology |
| Yamao et al (2001)<br>Unclear direction, reference-standard-based inclusion<br>Sept 1991–Oct 1999 | Patient selection: Patients who had resection of IPMT<br>Prevalence: Neoplasia outcome: 42/49 (86%); Invasive carcinoma outcome: 12/49 (25%)<br>Prior tests: Unclear, possibly US and IDUS | EUS characteristics: JF-UM20 (7.5 MHz) and GF-UM240 (7.5 and 12 MHz) with ultrasound processors EU-M20 and M240 (N = 49)<br>CT characteristics: Yokogawa CT 9200 and General Electronics Hi-speed advantage (Helical CT) (N = 49)<br>Reference standard: Surgery (100%) | EUS: Neoplasia[g,i], Sn 88%, Sp 71%, Acc 86%; Invasive carcinoma[h,i], Sn 50%, Sp 97%, Acc 86%<br>CT: Neoplasia[g,i], Sn 36%, Sp 100%, Acc 45%; Invasive carcinoma[h,i], Sn 33%, Sp 100%, Acc 84% | C1 P2 Q2<br>Quality: medium; selection bias<br>Applicability: limited; Resected patients only |

Abbreviations: Acc, Accuracy; CT, computed tomography; EUS, endoscopic ultrasound; ERP, endoscopic retrograde pancreatography; ERCP, endoscopic retrograde cholangiopancreatography; IDUS, intraductal ultrasonography; IPMT, intraductal papillary-mucinous tumour; NR, not reported; Sens, sensitivity; Spec, specificity; US, ultrasonography.

[a] Receiver operating characteristic (ROC) curves were used to establish optimal cut-off values (mm) to distinguish benign from malignant tumours; cyst diameter: CT = 33.7, EUS = 33.9; main pancreatic duct diameter: CT = 8.2, EUS = 11.4; height of protruding lesion: CT = 2.9, EUS = 5.4.

[b] For total of 121 patients.

[c] CT in 77 patients, EUS in 38 patients; unclear how many received both tests.

[d] CT in 44 patients, EUS in 21 patients; unclear how many received both tests.

[e] CT was performed in all (121) patients, EUS in 49 patients.

[f] Differentiation of cystic from serous neoplasms.

[g] Thickening and protrusion.

[h] Heterogeneous pattern or interruption of duct wall.

[i] Tumour not delineated in one case each for CT and EUS. For CT, the final diagnosis of this tumour was hyperplasia, so was counted here as a true negative. For EUS, final diagnosis was invasive adenocarcinoma, so counted here as a false negative.

**Table 143 Studies concerning the value of EUS in pancreatic neoplasia staging**

| Study author/s | Population, prevalence, prior tests | Test characteristics | Study outcomes (pancreatic neoplasia staging) | Study quality |
|---|---|---|---|---|
| Awad et al (1997)<br>Unclear direction, comparator-based inclusion<br>Incremental value<br>1992–1996 | **Patient selection**: Histologically proven pancreatic or ampullary adenocarcinoma<br>Basis for EUS unclear<br>**Prevalence**: Liver metastases, occlusion or encasement of coeliac artery[a], SMA, SMV, portal vein 15/30 (50%)<br>**Prior tests**: NR | **EUS characteristics**: Olympus EM-20 scanner (n = 16)<br>**CT characteristics**: 150 mL Omnipaque contrast (n = 30)<br>**Reference standard**: Exploratory laparotomy (100%) | **CT**: Sn 13%, Sp 100%, Acc 57%<br>**CT+EUS**: Sn 63%, Sp 63%, Acc 63% | C1 P2 Q2<br>*Quality*: medium<br>No 2 x 2 data, basis for receiving EUS unclear<br>*Applicability*: limited<br>EUS performed in some patients with metastases on CT, EUS selection unclear |
| Harrison et al (1999)<br>Retrospective reference standard-based inclusion<br>Replacement study with individual patient data | **Patient selection**: Suspected pancreatic carcinoma undergoing pre-operative assessment<br>**Prevalence**: Stage III or IV 3/18 (16%), N-stage 6/16 (38%)<br>**Prior tests**: NR | **EUS characteristics**: Olympus UM-20 radial scanner, single endoscopist<br>**CT characterisitics**: NR<br>**Reference standard**: Exploratory laparotomy (100%) with 30 days | **CT**: Stage III or IV Sn 0%, Sp 100%, Acc 83%; N-Stage Sn 0%, Sp 100%, Acc 63%<br>**CT+EUS**: Stage III or IV Sn 0%, Sp 100%, Acc 83%; N-Stage Sn 100%, Sp 60%, Acc 75% | C1 P2 Q2<br>*Quality*: medium<br>Potential for selection bias, poor reporting<br>*Applicability*: limited<br>Insufficient information on patient selection, all operative patients |
| Mertz et al (2000)<br>Unclear direction, reference standard-based inclusion<br>Replacement study with test agreement<br>Aug 1996–Jan 1999 | **Patient selection**: Resectable pancreatic adenocarcinoma (abnormal prior imaging), confirmed diagnosis; subset with surgical confirmation of vascular invasion<br>**Prevalence**: Invasion of a major vessel 6/16 (38%)<br>**Prior tests**: CT and/or US, ERCP | **EUS characteristics**: Pentax FG-32UA<br>**EUS-FNA characteristics**: 22G GIP needle; > 3 passes; cytopathologist present, single examiner, prior experience 257 cases<br>**CT characteristics**: Helical CT; Somatom Plus Siemens Medical Systems; or Tomoscan AV scanner Phillips Medical Systems; 5 mm collination, senior radiologist, blinding NR<br>**Reference standard**: Subset data—surgery 100% | **CT**: Sn 50%, Sp 100%, Acc 81%<br>**CT+EUS**: Sn 100%, Sp 100%, Acc 100% | C1 P2 Q2<br>*Quality*: medium<br>Selection bias<br>*Applicability*: limited<br>Surgical series, ERCP in some patients, outdated technology |
| Tomazic and Pegan (2000)<br>Unclear direction, likely reference standard-based inclusion<br>Incremental value | **Patient selection**: Undergoing surgical resection for pancreatic, ampullary and duodenal carcinoma<br>**Prevalence**: Liver or peritoneal metastases, invasion of SMA, SMV, portal vein 34/43 (56%)<br>**Prior tests**: NR | **EUS characteristics**: NR<br>**CT characteristics**: NR<br>**Reference standard**: Surgical resection (100%) | **CT**: Sn 46%[b], Acc 70%<br>**CT+EUS**: Sn 75%[b] | C1 P2 Q3<br>*Quality*: poor<br>Poor reporting, selection bias, no 2 x 2 verification<br>*Applicability*: limited<br>Referral pattern unclear, surgical resection series |

Abbreviations: Acc, accuracy; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; EUS-FNA, endoscopic ultrasound guided fine needle aspiration; NR, not reported; SMA, superior mesenteric artery; SMV, superior mesenteric vein. Sn, sensitivity; Sp, specificity; US, ultrasound

[a] Coeliac artery and major branches

[b] Data were estimated from figures 2 and 3 of Tomazic and Pegan (2000)

# Biliary tract neoplasia

**Table 144 Studies concerning the value of EUS in biliary tract neoplasia diagnosis**

| Study author/s | Population, prevalence, prior tests | Test characteristics | Study outcomes (biliary tract neoplasia diagnosis) | Study quality |
|---|---|---|---|---|
| Rosch et al (2002b)<br>Prospective non-consecutive; retrospective blinded image review<br>Replacement value (additional value reported)<br>1995–1997 | **Patient selection**: Patients with suspected biliary strictures, presenting with jaundice or cholestasis, no pain<br>**Prevalence**: 26/50 (53%)<br>**Prior tests**: Serological testing, US | **EUS characteristics**: Olympus GF-UM20 and GF-UM30 sector scanners<br>**MRI characteristics**: 1.5T Glyroscan ASCII Phillips Medical Systems, standard body coil<br>**MRCP characteristics**: 3D multichunk, TR 5500, TE300, slice 1.2 mm<br>**Reference standard**: Surgery (26%), biopsy/cytology (16%), > 12 months clinical follow up (58%) | **MRCP**: Sn 85%, Sp 71%<br>**MRCP+EUS**: Sn 85%, Sp 88% | C1 P2 Q2<br>*Quality*: medium<br>Differential verification bias, cannot reconstruct 2 x 2<br>*Applicability*: limited<br>No prior CT, many patients had surgically altered anatomy, accuracy for tests in agreement |
| Rosch et al (2004)<br>Prospective consecutive patients<br>Replacement value<br>1998–2000 | **Patient selection**: Patients with indeterminate biliary stricture or pancreatic head mass<br>**Prevalence**: EUS 26/47 (55%); ERCP 28/50 (56%)<br>**Prior tests**: US, CT | **EUS characteristics**: Olympus GF-UM20 and GF-UM30 radial scanner<br>**EUS-FNA characteristics**: NR, experienced operator, no cytopathologist present<br>**ERCP characteristics**: ERCP + cytology by over-the-guidewire brush, spiral brush and interbiliary forceps, experienced operator<br>**Reference standard**: Surgery (NR), biopsy (NR), > 12 months clinical follow up (NR) | **ERCP+cytology**: Sn 54%, Sp 100%, Acc 74%<br>**ERCP+cytology+EUS-FNA**: Sn 71%, Sp 100%, Acc 86% | C1 P2 Q1<br>*Quality*: high<br>*Applicability*: limited<br>ERCP result for three combined tissue sampling methods |
| Wierzbicka-Paczos and Butkiewicz (1999b)<br>Prospective non-consecutive inclusion<br>Incremental value<br>1994–1997 | **Patient selection**: Patients with extrahepatic cholestasis unexplained by US, ERCP and CT<br>**Prevalence**: N/A<br>**Prior tests**: Clinical examination and biochemistry, US, CT, ERCP | **EUS characteristics**: Pentax FG-32UA or Hitachi 405EUB linear scanner<br>**ERCP characteristics**: NR<br>**Reference standard**: Surgery (NR) | N/A | C1 P2 Q3<br>*Quality*: poor<br>Accuracy outcomes not clearly reported<br>*Applicability*: limited<br>Some patient had no structural abnormality identified, most no prior CT, many pancreatic patients |

Abbreviations: Acc, accuracy; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; EUS-FNA, endoscopic ultrasound guided fine needle aspiration; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; N/A, not applicable; NR, not reported; Sn, sensitivity; Sp, specificity

[a] The patients reported in this comparison are a subgroup of the entire study population

# Management studies

**Table 145 Management studies concerning the value of EUS**

| Study author/s | Population, physician | Test characteristics | Study outcomes | Study quality |
|---|---|---|---|---|
| Chong et al (2005)<br>Prospective pre-test, post-test case series in consecutive patients<br>Aug 2002–June 2004 | **Patient selection**: Mixed indications, including oesophageal, gastric and pancreaticobiliary, lung mediastinal disease and duodenal<br>**Physician determining management**: Referring doctors—physicians or surgeons | **Test characteristics**: Olympus GF-UM20, GF-UM160 or GF-UC140P radial scanner, experienced operator | **EUS**: Accuracy 84%<br>**Oesophageal**: Cancer diagnosis and staging: EUS change in management 23/72 (31.9%); EUS-FNA change in management 1/3 (33.3%); imaging/therapy changed to clinical follow up 25/75 (33.3%) Cancer staging: EUS/EUS-FNA change in management 15/48 (31.3%)<br>**Gastric**: Gastric masses; EUS change in management 19/34 (55.9%); imaging/therapy changed to clinical follow up 16/35 (6.9%); Gastric masses (diagnosis); EUS/EUS-FNA change in management 16/29 (55.2%); Gastric masses (staging), EUS/EUS-FNA change in management 3/6 (50%)<br>**Pancreaticobiliary**: Pancreaticobiliary, EUS change in management 11/21 (52.4%), EUS-FNA change in management 22/51 (43.1%), Imaging/therapy changed to clinical follow up 41/72 (56.9%); Pancreatic masses or bile duct strictures (diagnosis), EUS/EUS-FNA change in management 29/68 (42.6%); Periampullary carcinomas (staging), EUS/EUS-FNA change in management 2/3 (66.7%)<br>**Mixed Indication**: EUS change in management 47/69 (68.1%), EUS-FNA change in management 64/162 (39.5%), surgery avoided 39/231 (17%), Imaging/therapy changed to clinical follow up 115/231 (50%) | P1 Q1<br>*Quality*: high<br>*Applicability*: applicable |
| Jafri et al (1996)<br>Prospective pre-test, post-test case series | **Patient selection**: Mixed indications, including oesophageal, gastric and pancreatic<br>**Physician determining management**: Referring physician | **Test characteristics**: OlympusGF-UM3 radial scanner | **EUS**: Accuracy NR<br>**Mixed indication**: EUS change in management 29/63 (46%), surgery avoided 8/63 (12.7%), Imaging/therapy changed to clinical follow up 16/63 (25.4%) | P2 Q2<br>*Quality*: medium<br>Selection bias<br>*Applicability*: limited<br>Mixed indication |

| Study author/s | Population, physician | Test characteristics | Study outcomes | Study quality |
|---|---|---|---|---|
| Nickl et al (1996)<br>Prospective pre-test, post-test case series in consecutive patients<br>Apr 1992–Feb 1995 | **Patient selection**: Mixed indications, including oesophageal, gastric, pancreatic and biliary<br>**Physician determining management**: Endosonographer (completed < 6 hours following EUS) | **Test characteristics**: 15 sonographers, seniors at 10 centres experienced in an average of 628 each (range 100-2000) for 5.2 (1-14) years | **EUS**: Accuracy NR<br>**Oesophageal**: Oesophageal cancer (staging), EUS change in management 10/43 (24%)<br>**Gastric**: Gastric cancer (staging), EUS change in management (31%); Gastric submucosal tumour (diagnosis), EUS change in management (67%)<br>**Pancreaticobiliary**: Pancreatic mass, EUS change in management 9/34 (26%)<br>**Mixed indication**: EUS change in management 291/393 (74%), surgery avoided 41/393 (10%), Imaging/therapy changed to clinical follow up 87/386 (22.5%) | P2 Q2<br>*Quality*: high<br>*Applicability*: limited<br>Plans by endosonographers |
| Preston et al (2003)<br>Blinded reassessment of consecutive patients with pre-test, post-test plan<br>June 1996–June 1999 | **Patient selection**: Patients with oesophageal or oesophagogastric junction carcinoma<br>**Physician determining management**: Consultant oesophagogastric surgeon<br>Blinded to outcomes | **Test characteristics**: Olympus GF-UM20 radial scanner, no dilatation | **EUS**: T Staging, Sn 76.4%, Sp 75.0%, Acc 75.9%; N Staging, Sn 83.3%, Sp 87.5%, Acc 85.7% | P1 Q1<br>*Quality*: high<br>*Applicability*: limited<br>Outcomes reported in different manner to other studies |
| Shah et al (2004)<br>Prospective pre-rest, post-test case series<br>Mar 2002–Aug 2002 | **Patient selection**: Mixed indications, including oesophageal, gastric, pancreatic and rectal<br>**Physician determining management**: Surgeons (33%); non-EUS gastroenterologists (58%), oncologists (3%), internists (4%), pulmonologist (1%) | **Test characteristics**: Operator blinded to pre-test management plan | **EUS**: Accuracy NR<br>**Oesophageal**: Oesophageal cancer or mediastinal masses (diagnosis and staging), EUS change in management 12/22 (56%), EUS-FNA change in management 4/4 (100%), surgery avoided 4/22 (18.2%), Imaging/therapy changed to clinical follow up 3/22 (13.6%)<br>**Gastric**: Gastric cancer or SM masses (diagnosis and staging), EUS change in management 9/15 (60%), EUS-FNA change in management 0/1 (0%), surgery avoided 2/15 (13.3%), Imaging/therapy changed to clinical follow up 6/15 (40%)<br>**Pancreaticobiliary**: Pancreatic masses (diagnosis), EUS change in management 21/43 (49%), EUS-FNA change in management 4/13 (31%), surgery avoided 7/43 (16.3%), Imaging/therapy changed to clinical follow up 6/43 (14.0%) | P2 Q1<br>*Quality*: high<br>*Applicability*: limited<br>Mixed indications |

Abbreviations: Acc, accuracy; EUS, endoscopic ultrasound; EUS-FNA, endoscopic ultrasound guided fine needle aspiration, NR, not reported; SM, submucosal; Sn, sensitivity; Sp, specificity

[a] The patients reported in this comparison are a subgroup of the entire study population.

# Appendix F Staging classification

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

## Oesophageal and gastric cancer

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 (FAP). Gastric polyps may be: neoplastic or non-neoplastic; hamartomatous; related to polyposis syndromes; arising 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 146,** and the stage classification is shown in **Table 147**. The Japanese staging system is different from the American Joint Committee on Cancer (AJCC) staging system.

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

**Table 146 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 | Tumor 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 |
| *Tumours of the lower thoracic oesophagus* | | |
| M1a | Metastasis in coeliac lymph nodes | |
| M1b | Other distant metastasis | |
| *Tumours of mid thoracic oesophagus* | | |
| M1a | Not applicable | |
| M1b | Non-regional lymph nodes and/or other distant metastasis | |
| *Tumours of upper thoracic oesophagus* | | |
| 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 147 Oesophageal and gastric cancer staging by TNM grouping**

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

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 146 for explanation of T, N and M notation

# Pancreatic neoplasia

The TNM staging of pancreatic carcinoma, as described by the American Joint Committee on Cancer (AJCC) is presented in **Table 148**, and the stage classification is shown in **Table 149**.

**Table 148 TNM classification of pancreatic cancer**

| Classification | Pancreas |
|---|---|
| **Tumour** | |
| TX | Primary tumour cannot be assessed |
| T0 | No evidence of primary tumour |
| Tis | Carcinoma *in situ* |
| T1 | Tumour limited to the pancreas: 2 cm or less in greatest dimension |
| T2 | Tumour limited to the pancreas: more than 2 cm in greatest dimension |
| T3 | Tumour extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery |
| T4 | Tumour involves the celiac axis or the superior mesenteric artery (unresectable primary tumour) |
| **Node** | |
| NX | Regional lymph nodes cannot be assessed |
| N0 | No regional node metastases |
| N1 | Regional node metastases |
| **Metastasis** | |
| MX | Distant metastases cannot be assessed |
| M0 | No distant metastases |
| M1 | Distant metastasis |

Source: Exocrine pancreas. In American Joint Committee on Cancer: AJCC Staging Manual. 6th ed. New York, NY: Springer, 2002, pp157–164

**Table 149 Pancreatic cancer staging by TNM grouping**

| Stage | TNM grouping |
|---|---|
| 0 | Tis, N0, M0 |
| IA | T1, N0, M0 |
| IB | T2, N0, M0 |
| IIA | T3, N0, M0 |
| IIB | T1, N1, M0<br>T2, N1, M0<br>T3, N1, M0 |
| III | T4, any N, M0 |
| IV | Any T, any N, M1 |

Source: Exocrine pancreas. In American Joint Committee on Cancer: AJCC Staging Manual. 6th ed. New York, NY: Springer, 2002, pp157–164

# Biliary cancer

The TNM staging system for extra-hepatic biliary carcinoma is presented in **Table 150**, and the stage classification is shown in **Table 151** and **Table 152**.

**Table 150 TNM classification of biliary tract cancer**

| Classification | Extrahepatic bile ducts | Gallbladder |
|---|---|---|
| **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* |
| T1 | Tumour confined to bile duct histology | Tumour invades lamina propria or muscle layer |
| T1a | – | Tumour invades lamina propria |
| T1b | – | Tumour invades the muscle layer |
| T2 | Tumour invades beyond the wall of the bile duct | Tumour invades the peri-muscular connective tissue; no extension beyond the serosa or into the liver |
| T3 | Tumour invades the liver, gallbladder, pancreas, and/or unilateral branches of the portal vein (right or left) or hepatic artery (right or left) | Tumour perforates the serosa (visceral peritoneum) or directly invades one adjacent organ, or both (extension 2 cm or less into the liver) |
| T4 | Tumour invades any of the following: main portal vein or its branches bilaterally, common hepatic artery, or other adjacent structures, such as the colon, stomach, duodenum, or abdominal wall | Tumour extends more than 2 cm into the liver, and/or into two or more adjacent organs (stomach, duodenum, colon, pancreas, omentum, extrahepatic bile ducts, any involvement of the liver) |
| **Node** | | |
| NX | Regional lymph nodes cannot be assessed | Regional lymph nodes cannot be assessed |
| N0 | No regional node metastases | No regional node metastases |
| N1 | Regional node metastases | Metastasis in cystic duct, peri-choledochal, and/or hilar lymph nodes (ie in the hepatoduodenal ligament) |
| **Metastasis** | | |
| MX | Distant metastases cannot be assessed | Distant metastases cannot be assessed |
| M0 | No distant metastases | No distant metastases |
| M1 | Distant metastasis | Distant metastasis |

Source: Extrahepatic Bile Ducts. In American Joint Committee on Cancer: AJCC Staging Manual. 6th ed. New York, NY: Springer, 2002, pp145–150. Gallbladder. In American Joint Committee on Cancer: AJCC Staging Manual. 6th ed. New York, NY: Springer, 2002, pp139–144

**Table 151 Extrahepatic bile duct cancer staging by TNM grouping**

| Stage | TNM grouping |
|---|---|
| 0 | Tis, N0, M0 |
| IA | T1, N0, M0 |
| IB | T2, N0, M0 |
| IIA | T3, N0, M0 |
| IIB | T1, N1, M0 |
| | T2, N1, M0 |
| | T3, N1, M0 |
| III | T4, Any N, M0 |
| IV | Any T, Any N, M1 |

Source: Extrahepatic Bile Ducts. In American Joint Committee on Cancer: AJCC Staging Manual. 6th ed. New York, NY: Springer, 2002, pp145–150

**Table 152 Gallbladder cancer staging by TNM grouping**

| Stage | TNM grouping |
|---|---|
| 0 | Tis, N0, M0 |
| IA | T1, N0, M0 |
| IB | T2, N0, M0 |
| IIA | T3, N0, M0 |
| IIB | T1, N1, M0 |
| | T2, N1, M0 |
| | T3, N1, M0 |
| III | T4, Any N, M0 |
| IV | Any T, Any N, M1 |

Source: Gallbladder. In American Joint Committee on Cancer: AJCC Staging Manual. 6th ed. New York, NY: Springer, 2002, pp139–144

# Appendix G Management

Flowcharts depicting the standard Australian clinical management strategies for oesophageal, gastric, pancreatic and biliary tract cancers are presented in **Figure 18–Figure 21**. These charts have been developed in consultation with the Advisory panel.

## Management of oesophageal cancer

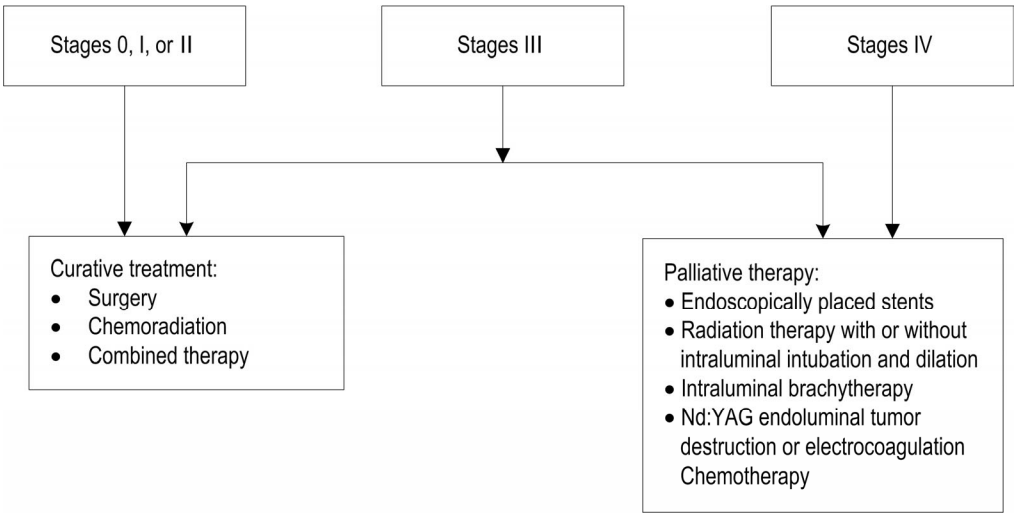



**Figure 18 Downstream management pathway for oesophageal cancer**

## Management of gastric cancer

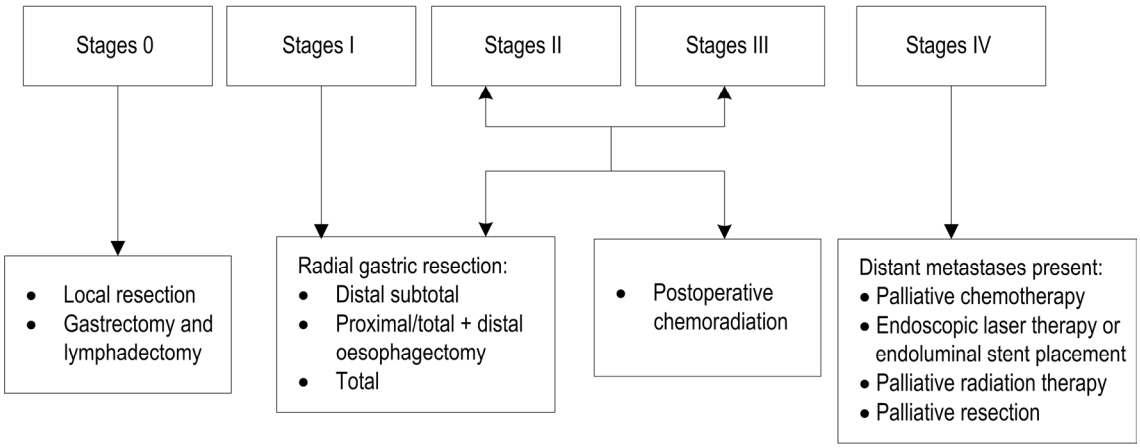



**Figure 19 Downstream management pathway for gastric cancer**

## Management of pancreatic cancer

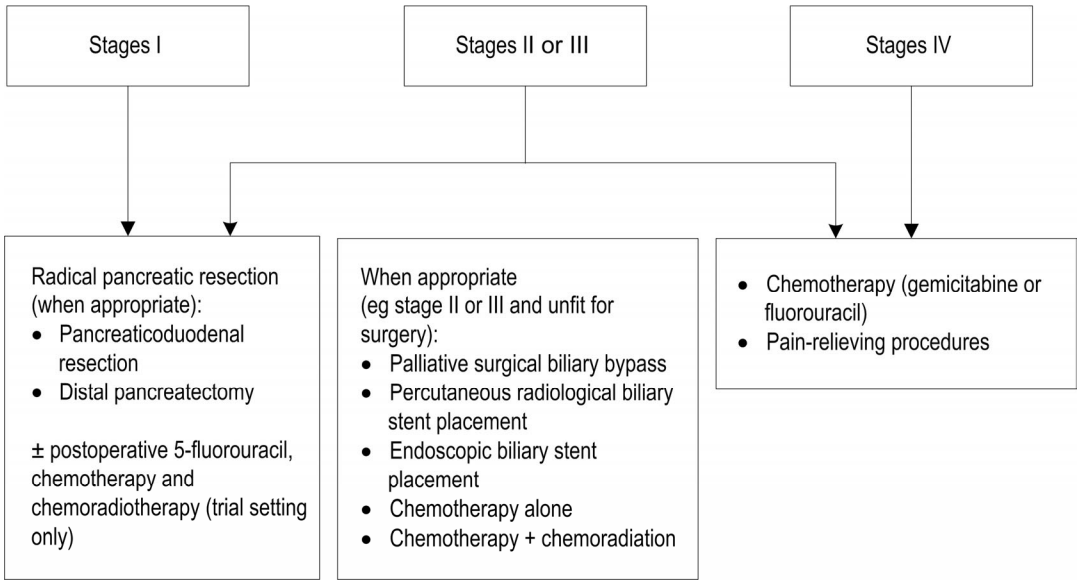



**Figure 20 Downstream management pathway for pancreatic cancer**

# Management of biliary tract cancer

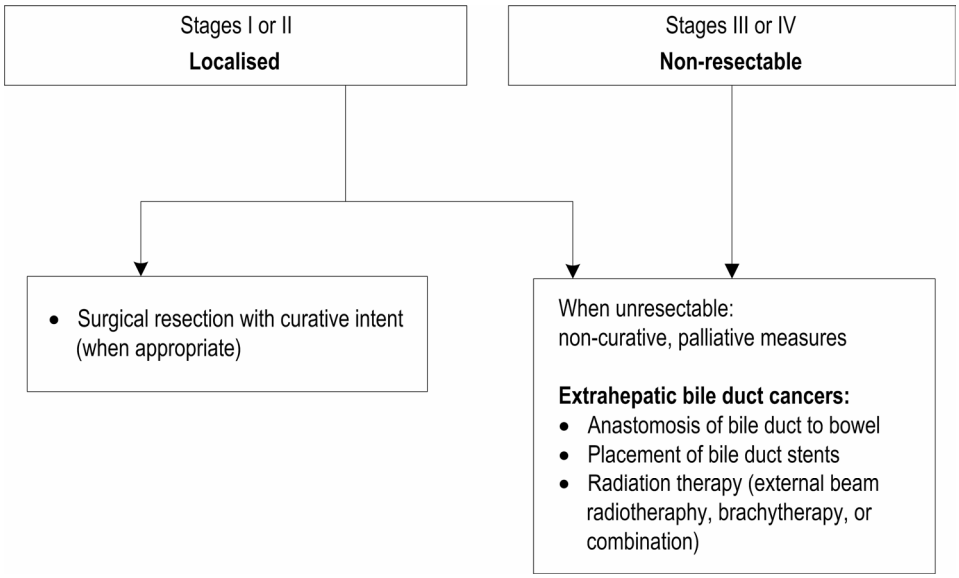
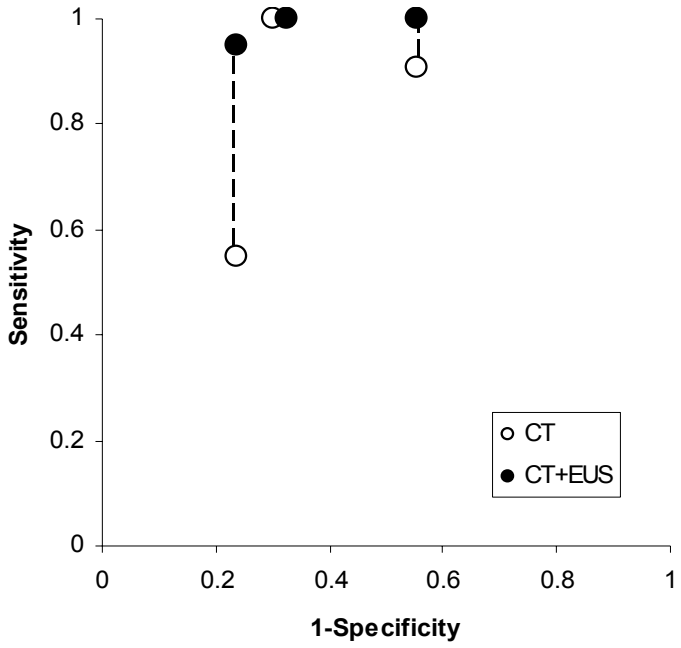


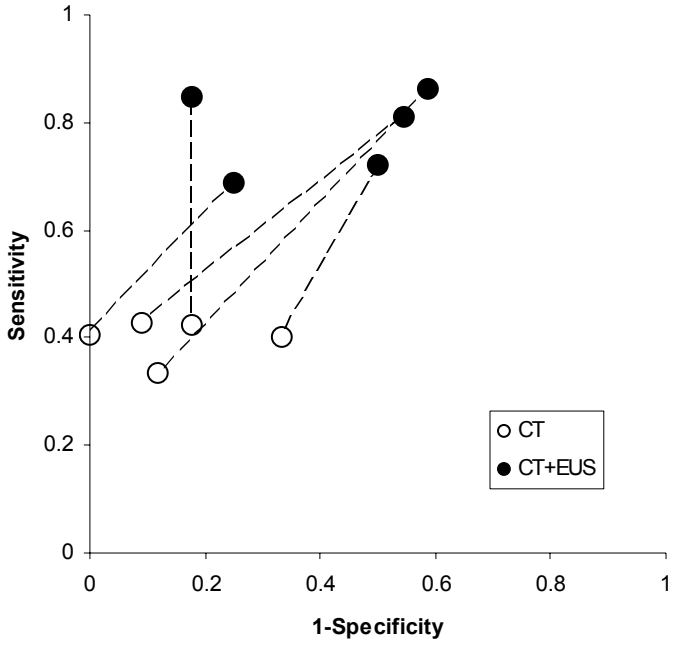

**Figure 21 Downstream management pathway for biliary tract cancer**

# Appendix H ROC plots



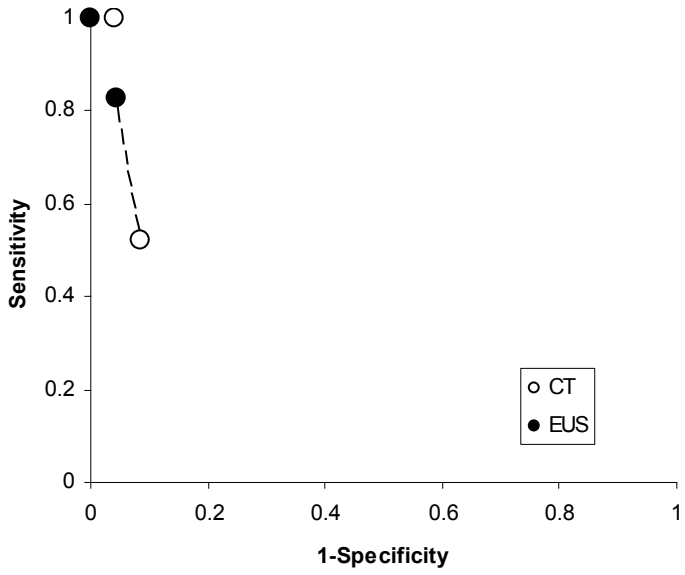

Abbreviations: CT, computed tomography; EUS, endoscopic ultrasound

**Figure 22 T-staging of oesophageal cancer—detection of T4**



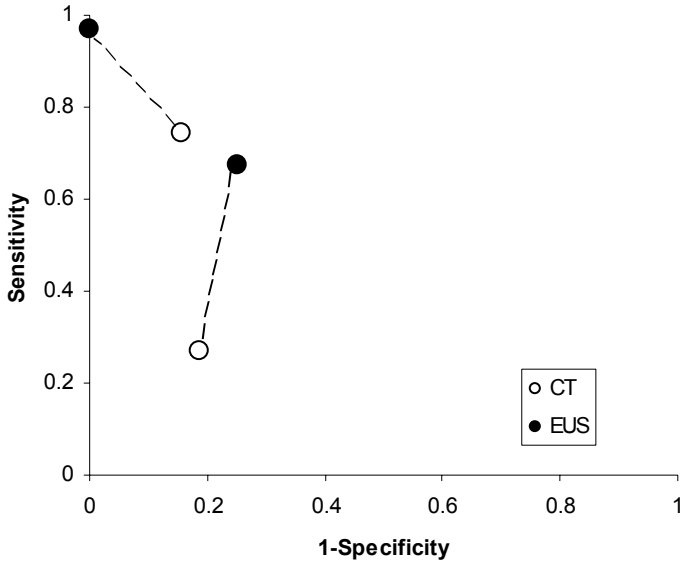

Abbreviations: CT, computed tomography; EUS, endoscopic ultrasound

**Figure 23 N-staging of oesophageal cancer (incremental value of EUS over CT)**



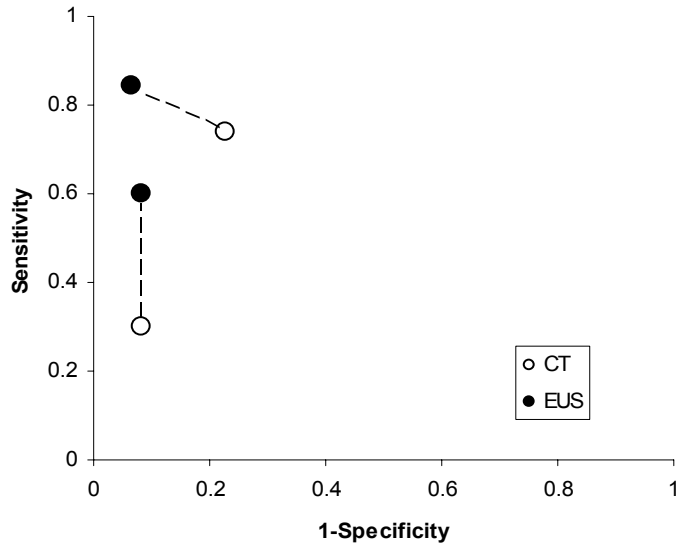

Abbreviations: CT, computed tomography; EUS, endoscopic ultrasound; PET, positron emission tomography

**Figure 24 T-staging for gastric cancer in replacement studies—detection of T4**



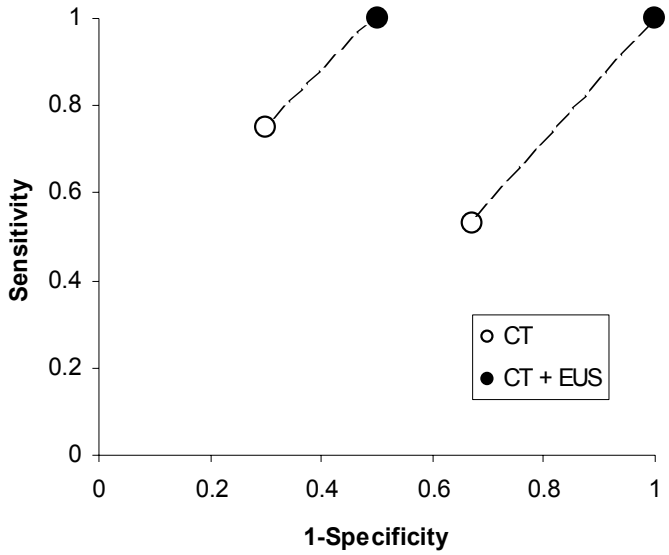

Abbreviations: CT, computed tomography; EUS, endoscopic ultrasound

**Figure 25 N-staging for gastric cancer in replacement studies—detection of N1 or N2**




Abbreviations: CT, computed tomography; EUS, endoscopic ultrasound.

**Figure 26 N-staging for gastric cancer in replacement studies—detection of N2**




Abbreviations: CT, computed tomography; EUS, endoscopic ultrasound

**Figure 27 Diagnosis of pancreatic cancer—diagnoses in patients with no pancreatic mass identified**

# Appendix I Safety using studies with mixed tumour types

**Table 153 Adverse events reported in association with tests performed for diagnosis of pancreatic and biliary tract neoplasia from mixed tumour types studies**

| | EUS | | | EUS-FNA | | | CT-FNA/GB | | | Total EUS | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **n/368** | **%** | **Exact 95% CI** | **n/2010** | **%** | **Exact 95% CI** | n/ 117 | **%** | **Exact 95% CI** | n/ 2378 | **%** | **Exact 95% CI** |
| **Total events** | 112 | 30.43 | 25.77, 35.42 | 15 | 0.75**, *** | 0.42, 1.23 | 5 | 4.27*, *** | 1.40, 9.69 | 127 | 5.34 | 4.47, 6.32 |
| ***Serious adverse events*** | | | | | | | | | | | | |
| Perforation | 0 | 0.00 | 0.00, 1.00Ŧ | 1 | 0.05 | 0.00, 0.28 | 0 | 0.00 | 0.00, 3.10Ŧ | 1 | 0.04 | 0.00, 0.23 |
| Bleeding | 0 | 0.00 | 0.00, 1.00Ŧ | 1 | 0.05 | 0.00, 0.28 | 0 | 0.00 | 0.00, 3.10Ŧ | 1 | 0.04 | 0.00, 0.23 |
| ***Adverse events*** | | | | | | | | | | | | |
| Pancreatitis | 0 | 0.00 | 0.00, 1.00Ŧ | 3 | 0.15 | 0.03, 0.44 | 0 | 0.00 | 0.00, 3.10Ŧ | 3 | 0.12 | 0.03, 0.37 |
| Fever | 0 | 0.00 | 0.00, 1.00Ŧ | 2 | 0.10 | 0.01, 0.36 | 0 | 0.00 | 0.00, 3.10Ŧ | 2 | 0.08 | 0.01, 0.30 |
| Abdominal pain | 25 | 6.79 | 4.44, 9.87 | 7 | 0.35*** | 0.14, 0.72 | 2 | 1.71 | 0.21, 6.04 | 32 | 1.35 | 0.92, 1.89 |
| Cholangitis | 1 | 0.27 | 0.01, 1.50 | 0 | 0.00 | 0.00, 0.18Ŧ | 0 | 0.00 | 0.00, 3.10Ŧ | 1 | 0.04 | 0.00, 0.23 |
| Infection | 0 | 0.00 | 0.00, 1.00Ŧ | 1 | 0.05 | 0.00, 0.28 | 0 | 0.00 | 0.00, 3.10Ŧ | 1 | 0.04 | 0.00, 0.23 |
| Cardiorespiratory events | 0 | 0.00 | 0.00, 1.00Ŧ | 0 | 0.00 | 0.00, 0.18Ŧ | 0 | 0.00 | 0.00, 3.10Ŧ | 0 | 0.00 | 0.00, 0.16Ŧ |
| Over-sedation | 0 | 0.00 | 0.00, 1.00Ŧ | 0 | 0.00 | 0.00, 0.18Ŧ | 0 | 0.00 | 0.00, 3.10Ŧ | 0 | 0.00 | 0.00, 0.16Ŧ |
| Hypotension | 0 | 0.00 | 0.00, 1.00Ŧ | 0 | 0.00 | 0.00, 0.18Ŧ | 0 | 0.00 | 0.00, 3.10Ŧ | 00 | 0.00 | 0.00, 0.16Ŧ |
| Haematoma | 0 | 0.00 | 0.00, 1.00Ŧ | 0 | 0.00** | 0.00, 0.18Ŧ | 2 | 1.71[a] | 0.21, 6.04 | 0 | 0.00 | 0.00, 0.16Ŧ |
| Vasovagal events | 0 | 0.00 | 0.00, 1.00Ŧ | 0 | 0.00 | 0.00, 0.18Ŧ | 0 | 0.00 | 0.00, 3.10Ŧ | 0 | 0.00 | 0.00, 0.16Ŧ |
| Hypoxia | 0 | 0.00 | 0.00, 1.00Ŧ | 0 | 0.00 | 0.00, 0.18Ŧ | 0 | 0.00 | 0.00, 3.10Ŧ | 0 | 0.00 | 0.00, 0.16Ŧ |
| Other | 74[a] | 20.11 | 16.13, 24.57 | 0 | 0.00* | 0.00, 0.18Ŧ | 1[b] | 0.85*** | 0.02, 4.67 | 74 | 3.11 | 2.45, 3.89 |
| **No complications** | 256 | 69.57 | 64.58, 74.23 | 1995 | 99.25**, *** | 98.77, 99.58 | 112 | 95.73*, *** | 90.31, 98.60 | 2251 | 94.66 | 93.68, 95.53 |

Abbreviations: CI, confidence interval, EUS, endoscopic ultrasound; EUS-FNA, endoscopic ultrasound guided fine needle aspiration; CI, confidence interval; CT-FNA, computed tomography guided fine needle aspiration

*$p < 0.05/3$, significantly different from EUS-FNA; **$p < 0.05/3$, significantly different from CT-FNA/biopsy; ***$p < 0.05/3$, significantly different from EUS

[a] 61 with sore throat, 4 vomiting, 9 discomfort

[b] 1 pneumothorax

Ŧ One-sided 95% computed CI

# Appendix J Calculation of capital costs per endoscopic ultrasound procedure

**Table 154 Calculation of capital costs per endoscopic ultrasound procedure**

| Cost of investment | Year 1 | Year 2 | Year 3 | Year 4 |
|---|---|---|---|---|
| Undepreciated value of equipment[a] | $236,667 | $177,500 | $118,333 | $59,167 |
| Depreciation over a year[b] | $59,167 | $59,167 | $59,167 | $59,167 |
| Maintenance cost[c] | $31,915 | $31,915 | $31,915 | $31,915 |
| Opportunity cost of investment and maintenance expenditure[d] | $23,674 | $18,459 | $13,244 | $8,028 |
| Total cost per year | $114,756 | $109,540 | $104,325 | $99,110 |
| Present value of cost stream[e] | $105,460 | $92,512 | $80,970 | $70,691 |
| Total present value of cost stream[f] | | $349,634 | | |
| **Return on investment** | | | | |
| Number of procedures performed annually[g] | 200 | 200 | 200 | 200 |
| Present value of procedures performed[h] | 182 | 166 | 152 | 138 |
| Total present value of number of procedures performed[i] | | 639 | | |
| Calculated capital cost per procedure[j] | | $547.52 | | |

| Component costs of proposed MBS fee for EUS | | Source |
|---|---|---|
| Capital cost | $547.52 | Based on calculated cost per procedure |
| Proposed professional fee[k] | $283.65 | Expert opinion |
| Cost of associated medical services[l] | $1.10 | Cost of sedative—PharmacyDirect |
| Total direct medical cost | $284.75 | |
| Total cost per service | **$832.27** | |

| Component costs of proposed MBS fee for EUS-FNA | | Source |
|---|---|---|
| Capital cost | $547.52 | Based on calculated cost per procedure |
| Proposed professional fee[m] | $790.95 | Expert opinion |
| Ultrasound needle | $200.00 | Based on cost of NA-200H-8022 Olympus Fine Aspiration Needle, 22 gauge, 8 mm |
| Pre-anaesthesia consultation | $36.40 | MBS Item 17603 |
| Anaesthesia for a gastrointestinal endoscopic procedure | $84.25 | MBS Item 20740 |
| Time (60 minutes) | $67.40 | MBS Item 23043 |
| Total direct medical cost | $979.00 | |
| Total cost per service[n] | **$1,726.52** | |

Note: Figures are based on 2004 costings

[a] Cost of equipment ($355,000) supplied by applicant. Undepreciated value of equipment based on assumption that 300 procedures performed annually per machine and 200 only of those procedures are for the indication examined in this analysis

[b] Assumes straight-line depreciation, 4-year equipment lifetime & $0 residual value. $59,167 = ($236,667-0)/4

[c] Proposed by applicant

[d] Opportunity cost measured as the rate of borrowing (8.8%). This rate of return is assumed to capture the risk of investment. Annual maintenance expenditures & the undepreciated value of the capital equipment accrue opportunity cost $23,674 = [($236,667 / $31,915) x 8.8%]

[e] Present value represents the total value costs that need to be reimbursed to the investor to justify their investment

[f] This value represents the total value of costs that needs to be reimbursed to the investor to justify their investment

[g] Expert opinion

[h] A procedure performed in 4 years time has less 'value' to the investor than one performed now. Therefore, the effective number of procedures is estimated by discounting at 8.8%.
[i] Sum of the discounted number of procedures
[j] Cost of 2.5 mg Midazolam [$1.10 = ($32.99/ (15 mg x 5) x 2.5)]. *Guidelines on Sedation for Gastrointestinal Endoscopic Procedures.* Australia and New Zealand College of Anaesthetists 2004
[k] Total present value of cost stream divided by the total present value of procedures performed
[l] Professional fee based on cost of colonoscopy (MBS No. 32090)
[m] Professional fee based on cost of therapeutic ERCP = [(MBS No 30485 ($477.95 for sphincterotomy in same procedure to facilitate stenting) + 30491 x half ($471.20/2 = $235.60 to place stent) + 30484 x ¼ ($309.60/4) = $77.40 to do diagnostic ERCP

# Abbreviations

| | |
|---|---|
| AACR | Australian Association of Cancer Registries |
| AIHW | Australian Institute of Health And Welfare |
| AJCC | American Joint Committee On Cancer |
| AR-DRG | Australian Refined Diagnosis Related Groups |
| ARTG | Australian Registry of Therapeutic Goods |
| ASCO | American Society of Clinical Oncology |
| Bx | biopsy |
| CA | carbohydrate antigen |
| CAT scan | computed axial tomography scan |
| CBD | common bile duct |
| CCOHTA | Canadian Co-Ordinating Office for Health Technology Assessment |
| CEA | carcinoembryonic antigen |
| CT | computed tomography |
| DACEHTA | Danish Centre for Evaluation and Health Technology Assessment |
| ERCP | endoscopic retrograde cholangiopancreatography |
| EUS | endoscopic ultrasound |
| FDA | Food and Drug Administration |
| FNA | fine needle aspiration |
| GEP | gastro-enteropancreatic |
| GI | gastrointestinal |
| GIST | gastrointestinal stromal tumour |
| HASTE | half-Fourier acquisition single shot turbo-spin-echo |
| HCFA | Health Care Financing Administration |
| HIRU | Health Information Research Unit |
| HSTAT | Health Services Research and Health Care Technology |

| | |
|---|---|
| IDUS | intraductal ultrasound |
| INAHTA | International Network of Agencies for Health Technology Assessment |
| IPMT | intraductal papillary-mucinous tumor |
| MBS | Medicare Benefits Schedule |
| MCN | mucinous cystic neoplasms |
| MEN-1 | multiple endocrine neoplasia type-1 |
| MRCP | magnetic resonance cholangiopancreatography |
| MRI | magnetic resonance imaging |
| MSAC | Medical Services Advisory Committee |
| NCI | National Cancer Institute |
| NET | neuroendocrine tumours |
| NHMRC | National Health and Medical Research Council |
| NPV | negative predictive value |
| PET | positron emission tomography |
| PET | pancreatic endocrine tumours |
| PPICO | population, prior tests, index test, comparator, outcomes |
| PPV | positive predictive value |
| PTC | percutaneous transhepatic cholangiography |
| RARE | rapid acquisition in relaxation enhancement |
| ROC | receiver operating characteristic |
| SBU | Swedish Council on Technology Assessment in Health Care |
| SEER | Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute |
| SMT | submucosal tumour |
| SPECT | single-photon emission computed tomography |
| SRS | somatostatin receptor scintigraphy |
| TGA | Therapeutic Goods Administration |
| US | ultrasound |

# References


Agarwal B, Abu-Hamda E, Molke KL, Correa AM, Ho L (2004). 'Endoscopic ultrasound-guided fine needle aspiration and multidetector spiral CT in the diagnosis of pancreatic cancer'. *American Journal of Gastroenterology*. 99: 844–850.

Allum WH, Griffin SM, Watson A, Colin-Jones D (2002). 'Guidelines for the management of oesophageal and gastric cancer.' *Gut*. 50 (Suppl 5): v1–v23.

American Joint Committee on Cancer (2002a). 'Soft tissue sarcoma'. In: Greene FL, Page DL, Fleming ID, Fritz AG, Balch CM, Haller DG, Morrow M (eds). *AJCC Staging Manual*. Springer, New York, NY. 6th ed: 193–200.

American Joint Committee on Cancer (2002b). 'Small intestine'. In: Greene FL, Page DL, Fleming ID, Fritz AG, Balch CM, Haller DG, Morrow M (eds). *AJCC Staging Manual*. Springer, New York, NY. 6th ed: 107–112.

American Society for Gastrointestinal Endoscopy (2005a). *Guidelines for training in endoscopic ultrasound*. Available from: http://www.asge.org/nspages/education/training/t-ultrasound.cfm [Accessed 20 April 2005].

American Society for Gastrointestinal Endoscopy (2005b). *Role of endoscopic ultrasonography*. Available from: http://www.asge.org [Accessed 13 September 2005].

American Society for Gastrointestinal Endoscopy Standards Practice Committee (2003). 'Complications of ERCP'. *Gastrointestinal Endoscopy*. 57: 633–638.

Ando N, Goto H, Niwa Y, Hirooka Y, Ohmiya N, Nagasaka T, Hayakawa T (2002). 'The diagnosis of GI stromal tumors with EUS-guided fine needle aspiration with immunohistochemical analysis'. *Gastrointestinal Endoscopy*. 55: 37–43.

Australian Bureau of Statistics (2005). *National Statistics: Australia's Population*. Available from: http://www.abs.gov.au [Accessed 5 August 2005].

Australian Institute of Health and Welfare (2005a). *AIHW Interactive National Hospital Morbidity Data*. Available from: http://www.aihw.gov.au/hospitals/datacubes/index.cfm [Accessed 24 January 2005].

Australian Institute of Health and Welfare (2005b). *AIHW Interactive Cancer Data*. Available from: http://www.aihw.gov.au/cancer/datacubes/index.cfm [Accessed 1 September 2005].

Australian Institute of Health and Welfare and Australasian Association of Cancer Registries (2004). *Cancer in Australia 2001*. Australian Institute of Health and Welfare, Canberra.

Australian Institute of Health and Welfare and Australasian Association of Cancer Registries (2005). *Cancer survival in Australia, 2001. Part 1: National summary statistics*. Australian Institute of Health and Welfare, Canberra.

Awad SS, Colletti L, Mulholland M, Knol J, Rothman ED, Scheiman J, Eckhauser FE, Hoffman JP, Stellato TA (1997). 'Multimodality staging optimizes resectability in patients with pancreatic and ampullary cancer'. *American Surgeon*. 63: 634–638.

Baba T, Yamaguchi T, Ishihara T, Kobayashi A, Oshima T, Sakaue N, Kato K, Ebara M, Saisho H (2004). 'Distinguishing benign from malignant intraductal papillary mucinous tumors of the pancreas by imaging techniques'. *Pancreas*. 29: 212–217.

Barawi M, Gottlieb K, Cunha B, Portis M, Gress F (2001). 'A prospective evaluation of the incidence of bacteremia associated with EUS-guided fine needle aspiration'. *Gastrointestinal Endoscopy*. 53: 189–192.

Becker D, Strobel D, Bernatik T, Hahn EG (2001). 'Echo-enhanced color- and power-Doppler EUS for the discrimination between focal pancreatitis and pancreatic carcinoma'. *Gastrointestinal Endoscopy*. 53: 784–789.

Botet JF, Lightdale CJ, Zauber AG, Gerdes H, Urmacher C, Brennan MF (1991a). 'Preoperative staging of esophageal cancer: Comparison of endoscopic US and dynamic CT'. *Radiology*. 181: 419–425.

Botet JF, Lightdale CJ, Zauber AG, Gerdes H, Winawer SJ, Urmacher C, Brennan MF (1991b). 'Preoperative staging of gastric cancer: Comparison of endoscopic US and dynamic CT'. *Radiology*. 181: 426–432.

Brand B, Pfaff T, Binmoeller KF, Sriram PV, Fritscher-Ravens A, Knofel WT, Jackle S, Soehendra N (2000). 'Endoscopic ultrasound for differential diagnosis of focal pancreatic lesions, confirmed by surgery'. *Scandinavian Journal of Gastroenterology*. 35: 1221–1228.

Braunwald E, Fauci, AS, Kasper DL, Hauser SL, Longo DL, Jameson JL (2001). *Harrison's Principles of Internal Medicine*. 15th edition. CD-ROM Version 1.0. McGraw-Hill, New York, NY.

Caletti G, Zani L, Bolondi L, Brocchi E, Rollo V, Barbara L (1989). 'Endoscopic ultrasonography in the diagnosis of gastric submucosal tumor'. *Gastrointestinal Endoscopy*. 35: 413–418.

Caletti GC, Brocchi E, Ferrari A, Bonora G, Santini D, Mazzoleni G, Barbara L (1991). 'Guillotine needle biopsy as a supplement to endosonography in the diagnosis of gastric submucosal tumors'. *Endoscopy*. 23: 251–254.

Catalano M, Hoffman B, Bhutani M, et al. (1997). 'Endoscopic ultrasound (EUS) guided fine needle aspiration (FNA) of gastrointestinal (GI) tract lesions: multicenter assessment of accuracy, complication rate and technical competence.' *Gastrointestinal Endoscopy*. 45: AB26.

Cellier C, Cuillerier E, Palazzo L, Rickaert F, Flejou JF, Napoleon B, Van G, Bely N, Ponsot P, Partensky C, Cugnenc PH, Barbier JP, Deviere J, Cremer M (1998). 'Intraductal papillary and mucinous tumors of the pancreas: Accuracy of pre-operative computed tomography, endoscopic retrograde pancreatography and endoscopic ultrasonography, and long-term outcome in a large surgical series'. *Gastrointestinal Endoscopy*. 47: 42–49.

Chaturvedi P, Chamberlain RS, Chaturvedi U, Kuwajerwala NK, Goswami G (2004). Carcinoma of the ampulla of Vater. Available from: http://www.emedicine.com/MED/topic2676.htm [Accessed 8 March 2005].

Chen F, Ni YC, Zheng KE, Ju SH, Sun J, Ou XL, Xu MH, Zhang H, Marchal G (2003). 'Spiral CT in gastric carcinoma: comparison with barium study, fiberoptic gastroscopy and histopathology'. *World Journal of Gastroenterology*. 9: 1404–1408.

Choi JY, Lee KH, Shim YM, Lee KS, Kim JJ, Kim SE, Kim BT (2000). 'Improved detection of individual nodal involvement in squamous cell carcinoma of the esophagus by FDG PET'. *Journal of Nuclear Medicine*. 41: 808–815.

Chong AK, Caddy GR, Desmond PV, Chen RY (2005). 'Prospective study of the clinical impact of endoscopic ultrasound'. *Gastrointestinal Endoscopy*. In press.

Conlon KC (2005). 'Intraductal papillary mucinous tumors of the pancreas'. *Journal of Clinical Oncology*. 23: 4518–4523.

Cunningham D, Allum WH, Stenning SP, Weeden S, for the NCRI Upper GI Cancer Clinical Studies Group (2005). 'Perioperative chemotherapy in operable gastric and lower oesophageal cancer: final results of a randomised controlled trial (the MAGIC trial, ISRCTN 93793971)'. Abstract No: 4001–*Proceedings of the American Society of Clinical Oncology*.

Date H, Miyashita M, Sasajima K, Toba M, Yamashita K, Takubo K, Onda M (1990). 'Assessment of adventitial involvement of esophageal carcinoma by endoscopic ultrasonography'. *Surgical Endoscopy*. 4: 195–197.

De Angelis C, Carucci P, Repici A, Rizzetto M (1999). 'Endosonography in decision making and management of gastrointestinal endocrine tumors'. *European Journal of Ultrasound*. 10: 139–3.

De Ledinghen V, Lecesne R, Raymond JM, Gense V, Amouretti M, Drouillard J, Couzigou P, Silvain C (1999). 'Diagnosis of choledocholithiasis: EUS or magnetic resonance cholangiography? A prospective controlled study'. *Gastrointestinal Endoscopy*. 49: 26–31.

Dematteo RP, Heinrich MC, El Rifai WM, Demetri G (2002). 'Clinical management of gastrointestinal stromal tumors: before and after STI-571'. *Human Pathology*. 33: 466–477.

Di Magno EP (1999). 'Pancreatic cancer: clinical presentation, pitfalls and early clues'. *Annals of Oncology*. 10 Suppl 4: 140–142.

Erickson RA (2002). *Endoscopic ultrasound-guided fine needle aspiration of the pancreas*. Available from: http://www.vhjoe.com/Volume1Issue4/1-4-3.htm [Accessed 9 September 2005].

Erickson RA (2004). *Pancreatic cancer*. Available from: http://www.emedicine.com/med/topic1712.htm [Accessed 17 February 2005].

Erickson RA, Garza AA (2000). 'Impact of endoscopic ultrasound on the management and outcome of pancreatic carcinoma'. *American Journal of Gastroenterology*. 95: 2248–2254.

Falconi M, Salvia R, Bassi C, Zamboni G, Talamini G, Pederzoli P (2001). 'Clinicopathological features and treatment of intraductal papillary mucinous tumour of the pancreas'. *British Journal of Surgery*. 88: 376–381.

Fendrich V, Bartsch DK, Langer P, Zielke A, Rothmund M (2004). 'Diagnosis and surgical treatment of insulinoma: Report of 40 cases'. [German]. *Deutsche Medizinische Wochenschrift* 129: 941–946.

Fiorica F, Di Bona D, Schepis F, Licata A, Shahied L, Venturi A, Falchi AM, Craxi A, Camma C (2004). 'Preoperative chemoradiotherapy for oesophageal cancer: a systematic review and meta-analysis'. *Gut*. 53: 925–930.

Flamen P, Lerut A, Van C, De W, Peeters M, Stroobants S, Dupont P, Bormans G, Hiele M, De L, Van R, Coosemans W, Ectors N, Haustermans K, Mortelmans L (2000). 'Utility of positron emission tomography for the staging of patients with potentially operable esophageal carcinoma'. *Journal of Clinical Oncology*. 18: 3202–3210.

Fletcher CD, Berman JJ, Corless C, Gorstein F, Lasota J, Longley BJ, Miettinen M, O'Leary TJ, Remotti H, Rubin BP, Shmookler B, Sobin LH, Weiss SW (2002). 'Diagnosis of gastrointestinal stromal tumors: A consensus approach'. *Human Pathology*. 33: 459–465.

Fong Y, Kemeny N, Lawrence TS (2001). Cancer of the liver and biliary tree. In: Devita Jr VT, Hellman S, Rosenberg SA (eds). *Cancer: Principles and Practice of Oncology*. Lippincot, Williams & Wilkins, Philadelphia. pp. 1162–1342.

Freeman ML, DiSario JA, Nelson DB, Fennerty MB, Lee JG, Bjorkman DJ, Overby CS, Aas J, Ryan ME, Bochna GS, Shaw MJ, Snady HW, Erickson RV, Moore JP, Roel JP (2001). 'Risk factors for post-ERCP pancreatitis: a prospective, multicenter study'. *Gastrointestinal Endoscopy*. 54: 425–434.

Freeman ML, Nelson DB, Sherman S, Haber GB, Herman ME, Dorsher PJ, Moore JP, Fennerty MB, Ryan ME, Shaw MJ, Lande JD, Pheley AM (1996). 'Complications of endoscopic biliary sphincterotomy'. *New England Journal of Medicine*. 335: 909–918.

Freeny PC, Traverso LW, Ryan JA (1993). 'Diagnosis and staging of pancreatic adenocarcinoma with dynamic computed tomography'. *American Journal of Surgery*. 165: 600–606.

Fusaroli P, Caletti G (2005). 'Endoscopic ultrasonography: current clinical role'. *European Journal of Gastroenterology and Hepatology* 17: 293–301.

Geng JZ, Qin PR, Hui LD, Po PD (1987). 'CT guided fine needle aspiration biopsy of biliopancreatic lesions: report of 30 cases'. *Japanese Journal of Surgery*. 17: 461–464.

Habermann CR, Weiss F, Riecken R, Honarpisheh H, Bohnacker S, Staedtler C, Dieckmann C, Schoder V, Adam G (2004). 'Pre-operative staging of gastric adenocarcinoma: comparison of helical CT and endoscopic US'. *Radiology*. 230: 465–471.

Harewood GC, Kumar KS (2004). 'Assessment of clinical impact of endoscopic ultrasound on esophageal cancer'. *Journal of Gastroenterology and Hepatology*. 19: 433–439.

Harewood GC, Wiersma MJ (2001). 'A cost analysis of endoscopic ultrasound in the evaluation of pancreatic head adenocarcinoma.' *American Journal of Gastroenterology*. 96: 2651–2656.

Harewood GC, Wiersema MJ (2002). 'Endosonography-guided fine needle aspiration biopsy in the evaluation of pancreatic masses'. *American Journal of Gastroenterology*. 97: 1386–1391.

Harris KM, Kelly S, Berry E, Hutton J, Roderick P, Cullingworth J, Gathercole L, O'Connor PJ, Boyce JC, Smith MA (1998). 'Systematic review of endoscopic ultrasound in gastro-oesophageal cancer'. *Health Technology Assessment*. 2: iii–129.

Harrison JL, Millikan KW, Prinz RA, Zaidi S, Hoffman JP, Aranha GV, Smith S, Leibold WC (1999). 'Endoscopic ultrasound for diagnosis and staging of pancreatic tumors'. *American Surgeon*. 65: 659–665.

Heeren PA, Jager PL, Bongaerts F, van D, Sluiter W, Plukker JT (2004). 'Detection of distant metastases in esophageal cancer with (18)F-FDG PET'. *Journal of Nuclear Medicine*. 45: 980–987.

Henson DE, Albores-Saavedra J, Corle D (1992). 'Carcinoma of the extrahepatic bile ducts. Histologic types, stage of disease, grade, and survival rates'. *Cancer*. 70: 1498–1501.

Hordijk ML, Kok TC, Wilson JHP, Mulder AH (1993a). 'Assessment of response of esophageal carcinoma to induction chemotherapy'. *Endoscopy*. 25: 592–596.

Hordijk ML, Zander H, Van B, Tilanus HW (1993b). 'Influence of tumor stenosis on the accuracy of endosonography in pre-operative T staging of esophageal cancer'. *Endoscopy*. 25: 171–175.

Jafri IH, Saltzman JR, Colby JM, Krims PE (1996). 'Evaluation of the clinical impact of endoscopic ultrasonography in gastrointestinal disease'. *Gastrointestinal Endoscopy*. 44: 367–370.

Janssen J, Konig K, Knop-Hammad V, Johanns W, Greiner L (2004). 'Frequency of bacteremia after linear EUS of the upper GI tract with and without FNA'. *Gastrointestinal Endoscopy*. 59: 339–344.

Jong K, Goumas XYC, O'Connell D, Armstrong B, Smith D (2002). 'Remoteness and cancer incidence, mortality and survival in New South Wales 1992 to 1996'. NSW Cancer Council NSW. Sydney.

Kaffes AJ, Mishra A, Simpson SB, Jones DB (2002). 'Upper gastrointestinal endoscopic ultrasound and its impact on patient management: 1990–2000'. *Internal Medicine Journal*. 32: 372–378.

Kaklamanos IG, Walker GR, Ferry K, Franceschi D, Livingstone AS (2003). 'Neoadjuvant treatment for resectable cancer of the esophagus and the gastroesophageal junction: a meta-analysis of randomized clinical trials'. *Annals of Surgical Oncology*. 10: 754–761.

Kato H, Miyazaki T, Nakajima M, Takita J, Kimura H, Faried A, Sohda M, Fukai Y, Masuda N, Fukuchi M, Manda R, Ojima H, Tsukada K, Kuwano H, Oriuchi N, Endo K (2005). 'The incremental effect of positron emission tomography on diagnostic accuracy in the initial staging of esophageal carcinoma'. *Cancer*. 103: 148–156.

Kayaalp C, Arda K, Orug T, Ozcay N (2002). 'Value of computed tomography in addition to ultrasound for pre-operative staging of gastric cancer'. *European Journal of Surgical Oncology*. 28: 540–543.

Keogh GW, Pirola RC (1999). 'Pancreatic disease'. *Medical Journal of Australia*. 170: 228–234.

Kwon JG, Kim EY, Kim YS, Chun JW, Chung JT, You SS, Ha HK, Lee CH, Kim HG, Cho CH (2005). 'Accuracy of endoscopic ultrasonographic impression compared with pathologic diagnosis in gastrointestinal submucosal tumors'. [Korean]. *Korean Journal of Gastroenterology/Taehan Sohwagi Hakhoe Chi*. 45: 88–96.

Le Borgne J, de Calan L, Parensky C (1999). 'Cystadenomas and cystadenocarcinomas of the pancreas: a multi-institutional retrospective study of 398 cases. French Surgical Association'. *Annals of Surgery*. 230: 152–61.

Lerut T, Flamen P, Ectors N, Van C, Peeters M, Hiele M, De W, Coosemans W, Decker G, De L, Deneffe G, Van R, Mortelmans L (2000). 'Histopathologic validation of lymph node staging with FDG-PET scan in cancer of the esophagus and gastroesophageal junction: A prospective study based on primary surgery with extensive lymphadenectomy'. *Annals of Surgery*. 232: 743–752.

Levy M, Levy P, Hammel P, Zins M, Vilgrain V, Amouyal G, Amouyal P, Molas G, Flejou JF, Voitot H, Sauvanet A, Bara J, Menu Y, Belghiti J, Bernades P (1995). 'Diagnosis of cystadenomas and cystadenocarcinomas of the pancreas: A study of 35 cases'. [French]. *Gastroenterologie Clinique et Biologique*. 19: 189–196.

Levy MJ, Clain JE (2004). 'Evaluation and management of cystic pancreatic tumors: emphasis on the role of EUS FNA'. *Clinical Gastroenterology and Hepatology*. 2: 639–653.

Luketich JD, Meehan M, Nguyen NT, Christie N, Weigel T, Yousem S, Keenan RJ, Schauer PR (2000). 'Minimally invasive surgical staging for esophageal cancer'. *Surgical Endoscopy*. 14: 700–702.

Luning M, Kursawe R, Lorenz D, et al (1984). 'Reduction of diagnostics of space occupying processes of the pancreas by CT-guided fine needle biopsy'. [German]. *Radiologia Diagnostica*. 25: 701–717.

Luning M, Kursawe R, Schopke W, Lorenz D, Menzel A, Hoppe E, Meyer R (1985). 'CT guided percutaneous fine needle biopsy of the pancreas'. *European Journal of Radiology*. 5: 104–108.

Macaskill P, Walter SD, Irwig L, Franco EL (2002). 'Assessing the gain in diagnostic performance when combining two diagnostic tests'. *Statistics in Medicine*. 21: 2527–2546.

Malka D, Hammel P, Maire F, Rufat P, Madeira I, Pessione F, Levy P, Ruszniewski P (2002). 'Risk of pancreatic adenocarcinoma in chronic pancreatitis'. *Gut*. 51: 849–852.

Masci E, Toti G, Mariani A, Curioni S, Lomazzi A, Dinelli M, Minoli G, Crosta C, Comin U, Fertitta A, Prada A, Passoni GR, Testoni PA (2001). 'Complications of diagnostic and therapeutic ERCP: a prospective multicenter study'. *American Journal of Gastroenterology*. 96: 417–423.

Matsui M, Goto H, Niwa Y, Arisawa T, Hirooka Y, Hayakawa T (1998). 'Preliminary results of fine needle aspiration biopsy histology in upper gastrointestinal submucosal tumors'. *Endoscopy*. 30: 750–755.

Medical Services Advisory Committee (MSAC) (1999). *OctreoScan scintigraphy for gastro-entero-pancreatic neuroendocrine tumours*. Commonwealth of Australia, Canberra.

Medical Services Advisory Committee (MSAC) (2002). *Positron emission tomography (PET) for a number of services*. Commonwealth of Australia, Canberra.

Medical Services Advisory Committee (MSAC) (2004). *Guidelines for the Assessment of Diagnostic Technologies*. Commonwealth of Australia, Canberra.

Medical Services Advisory Committee (MSAC) (2005). *Magnetic resonance cholangiopancreatography*. Commonwealth of Australia, Canberra.

Mertz HR, Sechopoulos P, Delbeke D, Leach SD (2000). 'EUS, PET, and CT scanning for evaluation of pancreatic adenocarcinoma'. *Gastrointestinal Endoscopy*. 52: 367–371.

Micames C, Jowell PS, White R, Paulson E, Nelson R, Morse M, Hurwitz H, Pappas T, Tyler D, McGrath K (2003). 'Lower frequency of peritoneal carcinomatosis in patients with pancreatic cancer diagnosed by EUS-guided FNA versus percutaneous FNA.' *Gastrointestinal Endoscopy*. 58: 690–695.

Mirallie E, Pattou F, Malvaux P, Filoche B, Godchaux JM, Maunoury V, Palazzo L, Lefebvre J, Huglo D, Paris JC, Carnaille B, Proye C (2002). 'Value of endoscopic ultrasonography and somatostatin receptor scintigraphy in the pre-operative localization of insulinomas and gastrinomas. Experience of 54 cases'. [French]. *Gastroenterologie Clinique et Biologique*. 26: 360–366.

Mitchell ML, Bittner CA, Wills JS, Parker FP (1988). 'Fine needle aspiration cytology of the pancreas. A retrospective study of 73 cases'. *Acta Cytologica*. 32: 447–451.

Murr MM (2005). *Gallbladder tumours*. Available from: http://www.emedicine.com/med/topic2711.htm [Accessed 22 July 2005].

Nachimuthu SFM (2002). *Gastrinomas*. Available from: http://www.emedicine.com/MED/topic2678.htm [Accessed 17 February 2005].

National Cancer Institute (2003a). *Islet cell carcinoma: Treatment*. Available from: http://www.cancer.gov/cancertopics/pdq/treatment/isletcell/HealthProfessional [Accessed 24 January 2005b].

National Cancer Institute (2003b). *Gallbladder cancer: Treatment*. Available from: http://www.cancer.gov/cancertopics/pdq/treatment/gallbladder/HealthProfessional [Accessed 24 January 2005a].

National Cancer Institute (2004a). *Oesophageal cancer: Treatment*. Available from: http://www.cancer.gov/cancertopics/pdq/treatment/esophageal/HealthProfessional [Accessed 28 February 2005].

National Cancer Institute (2004b). *Gastric cancer: Treatment*. Available from: http://www.cancer.gov/cancertopics/pdq/treatment/gastric/HealthProfessional [Accessed 28 February 2005].

National Cancer Institute (2004c). *Extrahepatic bile duct cancer: Treatment*. Available from: http://www.cancer.gov/cancertopics/pdq/treatment/bileduct/HealthProfessional [Accessed 24 January 2005].

National Cancer Institute (2004d). *Pancreatic cancer: Treatment*. Available from: http:www.cancer.gov/cancertopics/pdq/treatment/pancreatic/HealthProfessional [Accessed 24 January 2005].

National Cancer Institute (2005). *Adult soft tissue sarcoma: Treatment*. Available from: http://www.cancer.gov/cancertopics/pdq/treatment/adult-soft-tissue-sarcoma/HealthProfessional/page1 [Accessed 31 August 2005].

National Comprehensive Cancer Network (2004). *Clinical practice guidelines in oncology*. Available from: www.nccn.com [Accessed 15 September 2005].

Nguyen V (2004). *Gastrointestinal stromal tumours–leiomyoma/leiomyosarcoma*. Available from: http://www.emedicine.com/radio/topic388.htm [Accessed 20 April 2005].

NHMRC (2005). *NHMRC additional levels of evidence and grades for recommendations for developers of guidelines. Pilot Program 2005*. National Health and Medical Research Council, Canberra. Available from: www.nhmrc.gov.au/publications/_files/levels_grades05.pdf

NHS (2001). *Guidance on commissioning cancer health services: improving outcomes in gastro-intestinal cancers*. Department of Health, London. Available from: http://www.dh.gov.uk/assetRoot/04/08/02/78/04080278.pdf

Nickl NJ, Bhutani MS, Catalano M, Hoffman B, Hawes R, Chak A, Roubein LD, Kimmey M, Johnson M, Affronti J, Canto M, Sivak M, Boyce HW, Lightdale CJ, Stevens P, Schmitt C (1996). 'Clinical implications of endoscopic ultrasound: the American Endosonography Club Study'. *Gastrointestinal Endoscopy*. 44: 371–377.

Nilsson B, Bumming P, Meis-Kindblom JM, Oden A, Dortok A, Gustavsson B, Sablinska K, Kindblom LG (2005). 'Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era– a population-based study in western Sweden'. *Cancer*. 103: 821–829.

Okai T, Watanabe H, Yamaguchi Y, Mouri I, Motoo Y, Sawabu N (1999). 'EUS and K-ras analysis of pure pancreatic juice collected via a duodenoscope after secretin stimulation for diagnosis of pancreatic mass lesion: a prospective study'. *Gastrointestinal Endoscopy*. 50: 797–803.

Okubo K, Yamao K, Nakamura T, Tajika M, Sawaki A, Hara K, Kawai H, Yamamura Y, Mochizuki Y, Koshikawa T, Inada KI (2004). 'Endoscopic ultrasound-guided fine needle aspiration biopsy for the diagnosis of gastrointestinal stromal tumors in the stomach'. *Journal of Gastroenterology*. 39: 747–753.

Pancreatic Section of the British Society of Gastroenterology, Pancreatic Society of Great Britain and Ireland, Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland, Royal College of Pathologists, Special Interest Group for Gastro-Intestinal Radiology (2005). 'Guidelines for the management of patients with pancreatic cancer peri-ampullary and ampullary carcinomas'. *Gut.* 54 (Suppl V): v1–v16.

Parada KS, Peng R, Erickson RA, Hawes R, Sahai AV, Ziogas A, Chang KJ (2002). 'A resource utilization projection study of EUS'. *Gastrointestinal Endoscopy.* 55: 328–334.

Partensky C (2004). 'Surgical management of cystic pancreatic tumours'. *Acta Chirurgica Belgica.* 104: 618–621.

Perng DS, Jan CM, Wang WM, Chen LT, Su YC, Liu GC, Lin HJ, Huang TJ, Chen CY (1996). 'Computed tomography, endoscopic ultrasonography and intraoperative assessment in TN staging of gastric carcinoma'. *Journal of the Formosan Medical Association.* 95: 378–385.

Prat F, Amouyal G, Amouyal P, Pelletier G, Fritsch J, Choury AD, Buffet C, Etienne JP (1996). 'Prospective controlled study of endoscopic ultrasonography and endoscopic retrograde cholangiography in patients with suspected common-bileduct lithiasis'. *Lancet.* 347: 75–79.

Prat F, Edery J, Meduri B, Chiche R, Ayoun C, Bodart M, Grange D, Loison F, Nedelec P, Sbai-Idrissi MS, Valverde A, Vergeau B (2001). 'Early EUS of the bile duct before endoscopic sphincterotomy for acute biliary pancreatitis'. *Gastrointestinal Endoscopy.* 54: 724–729.

Preston SR, Clark GW, Martin IG, Ling HM, Harris KM (2003). 'Effect of endoscopic ultrasonography on the management of 100 consecutive patients with oesophageal and junctional carcinoma'. *British Journal of Surgery.* 90: 1220–1224.

Proye C, Malvaux P, Pattou F, Filoche B, Godchaux JM, Maunoury V, Palazzo L, Huglo D, Lefebvre J, Paris JC, Thompson NW (1998). 'Noninvasive imaging of insulinomas and gastrinomas with endoscopic ultrasonography and somatostatin receptor scintigraphy'. *Surgery.*124: 1134–1144.

Qian X, Hecht JL (2003). 'Pancreatic fine needle aspiration: A comparison of computed tomographic and endoscopic ultrasonographic guidance'. *Acta Cytologica.* 47: 723–726.

Radebold K (2001). *Insulinomas.* Available from: http://www.emedicine.com/MED/topic2677.htm [Accessed 17 February 2005].

Recine M, Kaw M, Evans DB, Krishnamurthy S (2004). 'Fine needle aspiration cytology of mucinous tumors of the pancreas'. *Cancer.* 102: 92–99.

Remer EM, Baker ME (2002). 'Imaging of chronic pancreatitis'. *Radiologic Clinics of North America.* 40: 1229–1242.

Robins DB, Katz RL, Evans DB, Atkinson EN, Green L (1995). 'Fine needle aspiration of the pancreas. In quest of accuracy'. *Acta Cytologica.* 39: 1–10.

Rodriguez J, Kasberg C, Nipper M, Schoolar J, Riggs MW, Dyck WP (1992). 'CT-guided needle biopsy of the pancreas: A retrospective analysis of diagnostic accuracy'. *American Journal of Gastroenterology* 87: 1610–1613.

Rosch T, Hofrichter K, Frimberger E, Meining A, Born P, Weigert N, Allescher HD, Classen M, Barbur M, Schenck U, Werner M (2004). 'ERCP or EUS for tissue diagnosis of biliary strictures? A prospective comparative study'. *Gastrointestinal Endoscopy.* 60: 390–396.

Rosch T, Meining A, Fruhmorgen S, Zillinger C, Schusdziarra V, Hellerhoff K, Classen M, Helmberger H (2002). 'A prospective comparison of the diagnostic accuracy of ERCP, MRCP, CT, and EUS in biliary strictures'. *Gastrointestinal Endoscopy.* 55: 870–876.

Scarpignato C, Pelosini I (2001). 'Somatostatin analogs for cancer treatment and diagnosis: an overview'. *Chemotherapy.* 47 Suppl 2: 1–29.

Sedlack R, Affi A, Vazquez-Sequeiros E, Norton ID, Clain JE, Wiersema MJ (2002). 'Utility of EUS in the evaluation of cystic pancreatic lesions'. *Gastrointestinal Endoscopy.* 56: 543–547.

Shah JN, Ahmad NA, Beilstein MC, Ginsberg GG, Kochman ML (2004). 'Clinical impact of endoscopic ultrasonography on the management of malignancies'. *Clinical Gastroenterology and Hepatology.* 2: 1069–1073.

Sihvo EI, Rasanen JV, Knuuti MJ, Minn HR, Luostarinen ME, Viljanen T, Farkkila MA, Salo JA (2004). 'Adenocarcinoma of the esophagus and the esophagogastric junction: positron emission tomography improves staging and prediction of survival in distant but not in locoregional disease'. *Journal of Gastrointestinal Surgery.* 8: 988–996.

Snady H, Cooperman A, Siegel J (1992). 'Endoscopic ultrasonography compared with computed tomography with ERCP in patients with obstructive jaundice or small peri-pancreatic mass'. *Gastrointestinal Endoscopy.* 38: 27–34.

Soriano A, Castells A, Ayuso C, Ayuso JR, de Caralt MT, Gines MA, Real MI, Gilabert R, Quinto L, Trilla A, Feu F, Montanya X, Fernandez-Cruz L, Navarro S (2004). 'Preoperative staging and tumor resectability assessment of pancreatic cancer: prospective study comparing endoscopic ultrasonography, helical computed tomography, magnetic resonance imaging, and angiography'. *American Journal of Gastroenterology.* 99: 492–501.

Sperti C, Pasquali C, Di P, Rugge M, Petrin P, Costantino V, Canton A, Pedrazzoli S (1994). 'Percutaneous CT-guided fine needle aspiration cytology in the differential diagnosis of pancreatic lesions'. *Italian Journal of Gastroenterology.* 26: 126–131.

Spinelli KS, Fromwiller TE, Daniel RA, Kiely JM, Nakeeb A, Komorowski PA, Wilson SD, Pitt AA (2004). 'Cystic pancreatic neoplasms: observe or operat'e. *Annals of Surgery.* 239: 651–657.

Supramaniam R, Smith DP, Coates MS, Armstrong BK (1998). 'Survival from cancer in New South Wales in 1980 to 1995'. NSW Cancer Council, Sydney, NSW.

Takhar AS, Palaniappan P, Dhingsa R, Lobo DN (2004). 'Recent developments in diagnosis of pancreatic cancer'. *Bristish Medical Journal.* 329: 668–673.

Taylor AC, Little AF, Hennessy OF, Banting SW, Smith PJ, Desmond PV (2002). 'Prospective assessment of magnetic resonance cholangiopancreatography for noninvasive imaging of the biliary tree'. *Gastrointestinal Endoscopy*. 55: 17–22.

Tomazic A, Pegan V (2000). 'Preoperative staging of periampullar cancer with US, CT, EUS and CA 19-9'. *Hepato-Gastroenterology*. 47: 1135–1137.

Tsai TL, Changchien CS, Hu TH, Hsiaw CM, Hsieh KC (2001). 'Differentiation of benign and malignant gastric stromal tumors using endoscopic ultrasonography'. *Chang Gung Medical Journal*. 24: 167–173.

van Westreenen HL, Heeren PA, van Dulleman HM, van der Jagt EJ, Jager PL, Groen H, Plukker JT (2005). 'Positron emission tomography with F-18-fluorodeoxyglucose in a combined staging strategy of esophageal cancer prevents unnecessary surgical explorations'. *Journal of Gastrointestinal Surgery*. 9: 54–61.

Varadarajulu S, Eloubeidi MA (2004). 'Frequency and significance of acute intracystic hemorrhage during EUS-FNA of cystic lesions of the pancreas'. *Gastrointestinal Endoscopy*. 60: 631–635.

Wiersema MJ, Schwartz SM, Hawes RH, Rex DK (1993). 'Abnormalities of pancreas parenchymal and ductular features detected by endosonography in asymptomatic subjects with a history of moderate to heavy alcohol use'. *Gastrointestinal Endoscopy*. 39: 336–336.

Wierzbicka-Paczos E, Butkiewicz J (1999). 'Endoscopic ultrasonography in the diagnosis of unexplained extrahepatic cholestasis'. [Polish]. *Polski Merkuriusz Lekarski*. 7: 175–179.

World Health Organization (2003). *International Statistical Classification of Diseases and Related Health Problem, Tenth Revision*. Available from: http://www3.who.int/icd/vol1htm2003/fr-icd.htm [Accessed 7 September 2005].

Yamao K, Ohashi K, Nakamura T, Suzuki T, Watanabe Y, Shimizu Y, Nakamura Y, Ozden I (2001). 'Evaluation of various imaging methods in the differential diagnosis of intraductal papillary-mucinous tumor (IPMT) of the pancreas'. *Hepato-Gastroenterology*. 48: 962–966.

Yip D, Karapetis C, Strickland A, Steer C, Goldstein D, Harper P (2000). Chemotherapy and radiotherapy for pancreatic cancer. Yip D, Karapetis C, Strickland A, Steer C, Goldstein D, Harper P. Chemotherapy and radiotherapy for pancreatic cancer. The Cochrane Database of Systematic Reviews: Protocols 2000. Issue 2. John Wiley & Sons, Ltd. Chichester, UK DOI 10. 1002. /14651858.

Yu XQ, O'Connell DL, Gibberd RW, Smith DP, Armstrong BK (2003). *Cancer survival, incidence and mortality by Area Health Service in NSW 1994 to 2000*. NSW Cancer Council, Sydney.

Zamboni G, Kloppel G, Hruban RH, Longnecker DS, Adler G (2000). Mucinous cystic neoplasms of the pancreas. In: Hamilton SR, Aaltonen LA (eds). *World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Digestive System*. IARC Press, Lyon. pp. 234–236.

Zamboni G, Scarpa A, Bogina G, Iacono C, Bassi C, Talamini G, Sessa F, Capella C, Solcia E, Rickaert F, Mariuzzi GM, Kloppel G (1999). 'Mucinous cystic tumors of the pancreas: clinicopathological features, prognosis, and relationship to other mucinous cystic tumors'. *American Journal of Surgical Pathology.* 23: 410–422.

Ziegler K, Sanft C, Friedrich M, Stein H, Haring R, Riecken EO (1991). 'Evaluation of endosonography in TN staging of oesophageal cancer'. *Gut.* 32: 16–20.

Zimmer T, Scherubl H, Faiss S, Stolzel U, Riecken EO, Wiedenmann B (2000). 'Endoscopic ultrasonography of neuroendocrine tumours'. *Digestion.* 62: 45–50.

Zimmer T, Stolzel U, Bader M, Koppenhagen K, Hamm B, Buhr H, Riecken EO, Wiedenmann B (1996). 'Endoscopic ultrasonography and somatostatin receptor scintigraphy in the pre-operative localisation of insulinomas and gastrinomas'. *Gut.* 39: 562–568.

Zimmer T, Stolzel U, Liehr RM, Bader M, Fett U, Hamm B, Wiedenmann B, Riecken EO (1995). 'Somatostatin receptor scintigraphy and endoscopic ultrasound for the diagnosis of insulinoma and gastrinoma'. [German]. *Deutsche Medizinische Wochenschrift.* 120: 87–93.

Zimmer T, Ziegler K, Bader M, Fett U, Hamm B, Riecken EO, Wiedenmann B (1994). 'Localisation of neuroendocrine tumours of the upper gastrointestinal tract'. *Gut.* 35: 471–475.