CEA-Scan® for imaging recurrence &/or metastases in patients with histologically demonstrated carcinoma of the colon or rectum

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

MSAC recommendations do not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

This report was prepared by the Medical Services Advisory Committee with the assistance of Pam Smartt (Senior Research Fellow), Ray Kirk (Director until February 2005), Margaret Paterson (Information Specialist), Ian Sheerin (Health Economist), Sarah Hogan (Health Economist) and Robert Weir (Acting Director from February 2005) from the New Zealand Health Technology Assessment unit, University of Otago, and recommendations made by the MSAC Advisory Panel for CEA-Scan®. This report was edited by Ms Carol Webb. The report was endorsed by the Commonwealth Minister for Health and Ageing on 31 August 2004.

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Rationale

An application was made to MSAC for funding of a novel functional imaging technique to be used as diagnostic test for recurrent colorectal cancer. The test comprised a radiolabelled anti-carcinoembryonic monoclonal antibody (CEA-Scan®) used to detect recurrent colorectal cancer. An expert advisory panel under the stewardship of MSAC determined the most appropriate comparator for the assessment of the new service. Evaluators from the New Zealand Health Technology Assessment unit carried out a systematic review of the evidence for the effectiveness of CEA-Scan® compared to the chosen comparator, fluorine-18 labelled 2-fluoro-2-deoxyglucose, positron emission tomography (FDG-PET). A number of research questions were formulated to guide the review process and determine if there was sufficient evidence to support the funding of CEA-Scan® for the approved indications.

The procedure

CEA-Scan® (Immunomedics Inc., Morris Plains, New Jersey, USA) is a functional imaging technique for the detection of recurrent colorectal cancer. It is employed as a second-line diagnostic agent in cases where anatomical imaging techniques have failed or are equivocal.

CEA-Scan® comprises a murine monoclonal antibody fragment joined to a radioactive label. The antibody target is carcinoembryonic antigen (CEA) secreted by the tumour cell. The active component of CEA-Scan® is the Fab' fragment of the murine anti-CEA monoclonal antibody IMMU-4, also known as Arcitumomab. This fragment is a small, easily distributed molecule that is devoid of the most immunogenic portion of the antibody and has a half-life of four hours. In the body, IMMU-4 binds to the surface of tumour cells secreting CEA, providing a marker for imaging the distribution of these cells. The radiolabel is technetium 99m (^{99m}Tc), which is a short-lived radionuclide with a half-life of 6.02 hours that emits gamma rays as it decays. Visualisation of the distribution of the antibody in the patient is achieved using a gamma camera.

CEA-Scan® is administered by intravenous injection or intravenous infusion over a period of 5-20 minutes. Venous access may best be established by cannulation with a saline flush. Pre- and post-infusion serum samples are required for human anti-mouse antibody (HAMA) determination and patients' vital signs need to be monitored for at least one hour after infusion for acute allergic reaction. Imaging with both planar scintigraphy and single photon emission computed tomography (SPECT) is usually carried out 2-5 hours after Arcitumomab infusion and further planar imaging at 18-24 hours. Whole body planar scintigraphy is used to establish anatomical landmarks and SPECT of the chest, abdomen and pelvis is used to obtain the diagnostic images.

Medical Services Advisory Committee – role and approach

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

A rigorous assessment of the available evidence is thus the basis of decision making when funding is sought under Medicare. A team from the New Zealand Health Technology Assessment unit was engaged to conduct a systematic review of literature on CEA-Scan®. An Advisory Panel with expertise in this area then evaluated the evidence and provided advice to MSAC.

MSAC's assessment of CEA-Scan®

Clinical need

Colorectal cancer (CRC) is a major public health problem in Australia. It is associated with significant mortality and morbidity, with one in 17 Australian men and one in 26 Australian women likely to develop the disease before the age of 75 years. In 2000 it was the most common cancer reported in Australia with 12,405 cases accounting for 14.6 per cent of all new cancer registrations. The risk of colon cancer increases with age; most cases are diagnosed at age 60 years and over.

Colorectal cancer was the second biggest cause of cancer deaths after lung cancer with 4,718 deaths (13.3 per cent of all cancer deaths) and an estimated 30,225 person years of life lost (PYLL) before the age of 75 years in 2000. The average time from diagnosis to death was 2.3 years with an average premature loss of life of 6.3 years. In the same year the case fatality rate (mortality to incidence ratio) and number of hospitalisations for colorectal cancer was higher than breast or prostate cancer. Most patients (93 per cent) required acute hospital care with an average length of stay of 11.7 days. Disseminated colorectal disease is associated with considerable morbidity.

Comparator

The expert advisory panel under the stewardship of MSAC determined that the most appropriate comparator for the assessment of CEA-Scan® was fluorine-18 labelled 2-fluoro-2-deoxyglucose, positron emission tomography (FDG-PET).

Reference standard

The diagnostic accuracy of CEA-Scan® and the comparator FDG-PET was assessed against tumour histopathology obtained from biopsy or surgery. The true disease status of patients who were not eligible for surgery was determined by clinical follow-up of at least one year.

Safety

CEA-Scan® is administered as a single injection and requires no blood handling. The main safety concerns relating to the routine use of CEA-Scan® in clinical practice are allergic reaction to the mouse antibody, exposure to radiation and the increased risks associated with repeat tests.

Murine antibodies

The monoclonal antibody used in CEA-Scan® has been used for more than 20 years and its safety has been demonstrated in clinical trials. However, murine antibodies can provoke an allergic response which may result in anaphylactic and other hypersensitivity reactions that can be life threatening. The monoclonal antibody used in CEA-Scan® has been modified to lower the probability of a serious immune response in the patient and the reported incidence of allergic reactions is low (<1 per cent).

Adverse events

Reported adverse events and side effects include eosinophilia and pruritus (allergic reactions) and other non-specific events which include transient headache, minor gastro-intestinal upset, fever, bursitis and subdermal induration. One unwitnessed seizure was reported. Overall, of 453 patients receiving CEA-Scan® in nine clinical studies, 3 per cent were reported to have had untoward effects which may have been attributable to CEA-Scan®. A severe reaction to CEA-Scan® is therefore likely to be a rare event.

Repeat testing

A previous immune response to mouse antibodies increases the chance of serious immune reactions or immune complex disease as well as potentially interfering with the imaging efficiency of CEA-Scan®. High assays of human anti-mouse antibodies (HAMA) may also interfere with laboratory tests that are based on murine monoclonal antibodies such as serum CEA and CA-15. These reactions are more likely to occur with whole mouse monoclonal antibodies than monoclonal antibody fragments such as CEA-Scan®.

Exposure to radiation

The radiolabel employed in CEA-Scan® has a half-life of six hours and emits low energy radiation with very limited destructive ability. A single dose of CEA-Scan® delivers an effective radiation dose[1] of 9.1 :Sv/MBq to an adult patient. Two published studies of CEA-Scan® were identified that reported on the pharmacodynamics of the radiolabel. No adverse reactions during, or after, a single infusion of CEA-Scan® were reported and no changes related to the radiolabelled antibody were detected in haematological, liver and renal function tests. Overall, technetium is one of the safest radiolabels used in routine clinical practice. There is the possibility of adverse effects with repeated administration, however CEA-Scan® is currently only registered for single dose use in 0Australia.

[1] Effective radiation dose = a weighted average of the equivalent doses measured in millisieverts (mSv) or microsieverts (:Sv) received by each organ or tissue in the irradiated patient.

Diagnostic accuracy of the tests

The comparator for the assessment of the diagnostic accuracy of CEA-Scan® was FDG-PET, which is the test that CEA-Scan® would be most likely to replace or supplement. The gold standard or reference test for the assessment was histopathology for patients eligible for surgery, and clinical follow-up of at least one year for patients who were not eligible for surgery.

Only two studies were identified that directly compared CEA-Scan® and the comparator FDG-PET. Further information on the diagnostic accuracy of the tests was sought in publications reporting the accuracy of the tests separately against the chosen reference standard. None of the studies examined provide high quality evidence and all had more than one source of bias with the potential to impact on the validity of the results.

The use of CEA-Scan® as a third-line imaging technique

No studies were identified that considered the use of CEA-Scan® as a third-line imaging technique in patients with a negative or equivocal FDG-PET scans. Hence we were unable to assess the use of CEA-Scan® in this circumstance.

CEA-Scan®

Estimates of the accuracy of CEA-Scan® varied widely, making a precise estimate of test performance difficult. Small study size and selection bias are likely to have strongly influenced the results in a significant number of the studies. The reported accuracy of CEA-Scan® was generally low. It was more accurate in the small, highly selected study populations than the single large clinical trial. This trial reported an overall accuracy for CEA-Scan® of 70 per cent (sensitivity 71 per cent, specificity 63 per cent). When accuracy was assessed by disease site, CEA-Scan® more accurately identified local recurrence and extra-hepatic disease than liver metastases. The ability of CEA-Scan® to correctly identify patients with liver disease was poor.

FDG-PET

Estimates of the accuracy of the comparator FDG-PET against the gold standard were less variable and a larger number of studies were eligible for review. In addition, a number of health technology assessments were identified, including an MSAC report published in March 2000, and a report of the Australian review of PET published in 2001. Twelve post-2000 clinical studies that met the eligibility criteria for review were also identified. The overall accuracy of FDG-PET reported in all of these studies was high. Two systematic reviews summarised the evidence up to part of the year 2000. These studies reported overall sensitivities for FDG-PET of 92-100 per cent and overall specificities of 76-100 per cent. Twelve more recent, individual clinical studies had a median sensitivity of 97 per cent (range 71-100 per cent), median specificity 94 per cent (range 43-100 per cent) and median accuracy 94 per cent (range 74-100 per cent).

Although FDG-PET performed well overall, not all patients benefited. Patients with uncontrolled diabetes or acute inflammation were excluded from PET imaging in some studies. False positive diagnoses arose in patients with high physiologic uptake of FDG in the urinary tract, reactive lymph nodes, sites of pulmonary infection/inflammation, and in patients who had been treated with radiotherapy. False negative diagnoses were less common but were reported for mucinous colorectal cancer and in patients who had

undergone chemotherapy. In some cases, tumour lesions were mistaken for physiological uptake of FDG-PET.

Head-to-head studies of CEA-Scan® and FDG-PET

CEA-Scan® and FDG-PET were compared head to head in two small studies. Both studies included patients with known recurrence and asymptomatic patients; each group comprising fewer than 20 patients. CEA-Scan® was less accurate (median 80 per cent, range 21-96 per cent) than FDG-PET (median 98 per cent, range 86-100 per cent) across all patient-based analyses. Sensitivity values followed the same general pattern but with particularly low values for CEA-Scan® in the detection of liver lesions and distant metastases. In one of the studies, CEA-Scan® and FDG-PET were both able to identify patients without disease with high accuracy (95-100 per cent). In one group of patients with local disease recurrence, CEA-Scan® had a higher specificity (100 per cent) than FDG-PET (95 per cent). Because of the small number of patients involved in these studies, all patient-based estimates had wide confidence intervals. In an analysis based on lesions, CEA-Scan® was again less sensitive and less accurate than FDG-PET but more specific.

Economic considerations

In the assessment of a new service, MSAC is required to consider not only the effectiveness of the service but also its cost. If the new service is more effective than the current service standard, a cost-effectiveness analysis of the new service is also required.

At present there is no evidence to suggest that CEA-Scan® is as accurate as the comparator FDG-PET or that it leads to an improved long-term outcome for patients. There is therefore no justification for a full health economic analysis of CEA-Scan®. There is also a lack of empirical evidence on both outcomes and costs of FDG-PET and CEA-Scan®.

CEA-Scan® is reportedly less costly per test than FDG-PET ($779.35 and $953-$975 respectively), however the cost of CEA-Scan® is likely to have been under-estimated in the application. A more realistic estimate of the test cost suggests that CEA-Scan® would be more expensive to deliver than FDG-PET. In addition, indirect and flow-on costs are likely to be higher for CEA-Scan® than for the comparator.

The applicant's estimate of the total cost to the Australian health system of implementing CEA-Scan® of $130,000 is also likely to be an under-estimate. It is based on an assumption that only 5 per cent of patients with recurrence will receive the test and that only one test will be administered. Using more realistic estimates of test uptake and test cost, a revised total annual direct cost to the Australian health system of a single CEA-Scan®, administered to the relevant test population as a second-line imaging test, is estimated to be $477,593. If the cost of testing for HAMA and monitoring for potential allergic reactions to CEA-Scan® is included, the total annual cost could be as high as $1,075,886.

There is currently insufficient evidence to conduct an appraisal of CEA-Scan® as a third-line imaging technique when FDG-PET fails or is unavailable.

Conclusions

CEA-Scan® may generally be considered to be safe for administration as a single dose. However, patients receiving murine antibodies should be monitored for acute sensitivity reactions during and immediately after infusion with CEA-Scan®. There is an increased risk of adverse reaction with repeated dosage and the long-term safety of CEA-Scan® requires further study. A precise estimate of the accuracy of CEA-Scan® was hampered by the heterogeneity of the reported clinical results of the test and by methodological weaknesses in the reported studies. Nevertheless, the overall diagnostic accuracy of CEA-Scan® when analysed by patient was generally low. When the accuracy of CEA-Scan® was assessed by disease site and lesions, CEA-Scan® more accurately identified local recurrence and extra hepatic disease than liver metastases. The ability of CEA-Scan® to correctly identify patients with liver disease, which is the most common site of recurrence, was poor. When CEA-Scan® was compared to FDG-PET in two head-to-head studies, it was generally less accurate than FDG-PET for the diagnosis of recurrent colorectal cancer. However, not all patients benefit from FDG-PET and CEA-Scan® may be useful in selected patients.

Recommendation

The safety and effectiveness of CEA-Scan® has been assessed for imaging of recurrence and/or metastases in patients with histologically proven carcinoma of the colon or rectum. The procedure appears to be safe. However, on the strength of evidence pertaining to the effectiveness and cost-effectiveness of CEA-Scan®, public funding should not be supported for this procedure.

- The Minister for Health and Ageing accepted this recommendation on 31 August 2004 -

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of CEA-Scan®, which is a second-line diagnostic test for recurrent or metastatic disease in patients with previously diagnosed and treated colorectal cancer. This test uses functional characteristics of the tumour to provide imaging information which is additional to that provided by the standard anatomical imaging techniques.

MSAC evaluates new and existing health 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 presented in Appendix A. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

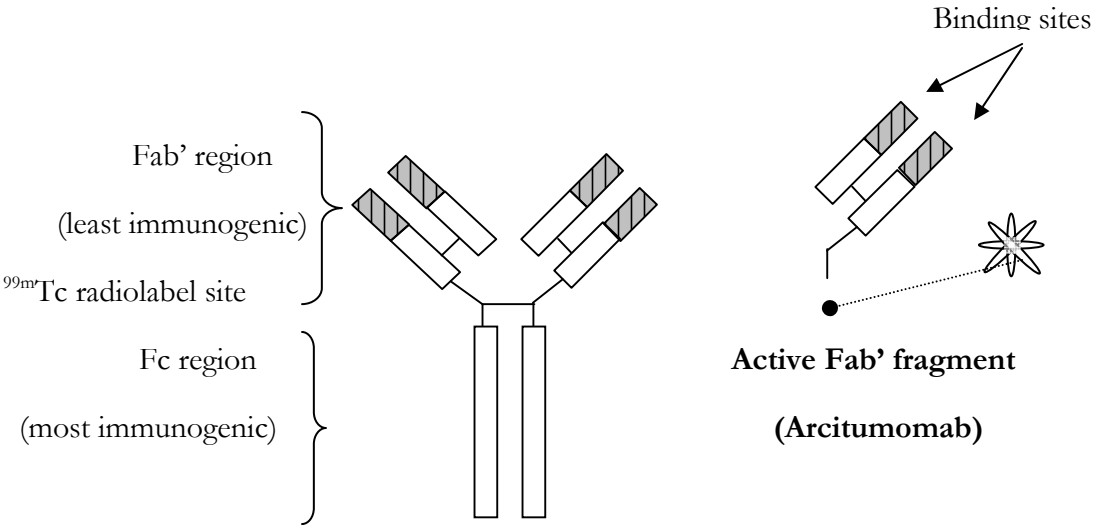
This report summarises the assessment of current evidence for CEA-Scan® for recurrent colorectal disease in patients with previously diagnosed and treated colorectal cancer.

Background

The procedure

CEA-Scan® (Immunomedics Inc., Morris Plains, New Jersey, USA) is a functional imaging technique for the detection of recurrent colorectal cancer. It is employed when other imaging techniques have failed or are equivocal. CEA-Scan® comprises a murine monoclonal antibody fragment joined to a radioactive label. The antibody target is carcinoembryonic antigen (CEA) secreted by the tumour cell. The active component of CEA-Scan® is the Fab' fragment of the murine anti-CEA monoclonal antibody IMMU-4, previously known as NP-4 and also known as Arcitumomab. This fragment is a small, easily distributed molecule which is devoid of the most immunogenic portion of the antibody (Goldenberg et al., 1997), see Figure 1. In the body, IMMU-4 binds to the surface of CEA-secreting cells, providing a marker for imaging the distribution of these cells.

Figure 1 Monoclonal antibody



Whole monoclonal antibody (IMMU-4)

The monoclonal antibody Fab' fragment is formulated to be labelled with technetium 99m (^{99m}Tc), a short-lived gamma ray emitting, radionuclide with a half-life of 6.02 hours. Visualisation of the distribution of the antibody in the patient is achieved using a gamma camera (Immunomedics, 1999). One injection of CEA-Scan® delivers an effective radiation dose[2] of 9.1 :Sv/MBq to an adult patient.

[2] See footnote 1

CEA-Scan® is supplied as a vial containing 1.25 mg of sterile lyophilised powder containing the Fab' fragment. This is reconstituted immediately prior to administration with 1,110 MBq/mL of ^{99m}Tc sodium pertechnetate in 1.0 ml of sodium chloride for intravenous injection, or diluted to a volume of 30 ml with saline for intravenous infusion over a period of 5-20 minutes. Standard precautions for handling radionuclides apply and there must be less than 10 per cent free technetium prior to injection (Immunomedics, 1999). Patients are normally well hydrated the day prior to infusion and under fluid restriction a few hours before the injection to reduce non-specific uptake of CEA-Scan® in the bladder. Venous access may best be established by a butterfly infusion set with a saline flush (Erb and Nabi, 2000). Pre- and post-infusion serum samples are required for human anti-mouse antibody (HAMA) determination and patients' vital signs need to be monitored for at least one hour after infusion for acute allergic reaction. Patients should urinate prior to imaging to reduce radiation dose to the bladder. Catheterisation may be required in patients with difficulties emptying their bladder.

Imaging with both planar scintigraphy and single photon emission computed tomography (SPECT) is usually carried out 2-5 hours after Arcitumomab infusion and further planar imaging at 18-24 hours. Whole body planar scintigraphy is used to establish anatomical landmarks and SPECT of the chest, abdomen and pelvis for diagnostic images (Moffat et al., 1996). For optimum results, imaging should commence 2.5 hours post-infusion with SPECT imaging of the pelvis followed immediately by a whole-body planar image and SPECT imaging of the abdomen centred upon the liver. Chest imaging using SPECT should be carried out 8-18 hours post-infusion (Immunomedics, 2002). Delayed planar imaging (18-24 hours) should be compared with earlier images (2-5 hours) as normal intestinal and gall bladder activity may interfere with tumour imaging.

The recommended order of imaging is SPECT imaging of the pelvis, whole-body planar imaging, SPECT imaging of the abdomen/liver and SPECT of the chest 8-18 hours after administration. The images are read and interpreted by a nuclear medicine physician and any abnormally distributed ^{99m}Tc-IMMU-4 activity may be considered positive for recurrent or metastatic tumour (Immunomedics, 2002).

The target

CEA-Scan® targets carcinoembryonic antibody (CEA) that is normally expressed during the embryonic development of the large intestine and in low concentrations in certain tissues of healthy adults. CEA may be abnormally expressed in colorectal and other cancers, inflammatory bowel disease and post-radiation therapy to the bowel (Fletcher 1986). The majority of colorectal cancers, particularly those with mucinous histology, have been found to express large quantities of CEA. Most of the antigen is retained and accumulated in the tumour (Mattes et al., 1990), providing a target for radioimmunodetection agents such as CEA-Scan®; the rest is released into the bloodstream where it can be detected as serum CEA. Accordingly, CEA is not a tumour-specific antigen but rather a tumour-associated antigen that is more abundant in tumours than normal tissue.

Serum CEA levels and the diagnostic properties of CEA-Scan®

The upper limit of normal for plasma CEA varies with the assay method used but generally lies between 2.5 –5.0 ng/ml (Stevens, 1975). Serum CEA levels in patients with recurrent CRC commonly vary between 5-200 ng/ml (Watine et al., 2001). Levels of more than 1000 ng/ml have been reported, however such extreme values are rare in this patient population. CEA-Scan® is designed to bind to the 200-kilodalton CEA molecule on the cell membrane and has only weak binding to circulating CEA at levels below 500 ng/ml (Goldenberg et al., 1990, Eccles, 1999, Hansen et al., 1990). At blood titres greater than 2000 ng/ml approximately 50 per cent complex formation has been reported (Anonymous, 2002b). However, even at this level imaging was not prohibited and it would appear that elevated circulating CEA levels are not detrimental to successful tumour imaging with CEA-Scan® (Goldenberg et al., 1978). No correlation has been found between serum CEA levels and the results of CEA-Scan®.

Intended purpose

CEA-Scan® is designed to exploit functional differences between normal and malignant tissue. It is considered for use only in patients with histologically demonstrated colorectal cancer to complement anatomical imaging which is heavily reliant upon morphological rather than functional change. It is registered for use in Australia for the following approved indications:

"CEA-Scan® is indicated only in patients with histologically demonstrated carcinoma of the colon or rectum for imaging of recurrence and/or metastases.

CEA-Scan® is employed for diagnostic use only in the above-mentioned patients as an adjunct to standard diagnostic techniques in the following situations:

- patients with evidence of recurrence and/or metastatic carcinoma of the colon or rectum, who are undergoing an evaluation for extent of disease, such as prior to surgical resection and/or other therapy;

- patients with suspected recurrence and/or metastatic carcinoma of the colon or rectum in association with rising levels of carcinoembryonic antigen (CEA)."

Second and subsequent doses may be considered in patients who do not develop human anti-mouse antibodies (HAMA) after the first dose (Wegener, et al., 2000). However, CEA-Scan® is not registered for repeat administration in Australia.

CEA-Scan® is not intended to be used to diagnose colorectal cancer and is contraindicated in patients with known allergies or hypersensitivity to mouse protein, pregnant or breastfeeding women, and in children (Immunomedics, 1999).

Colorectal cancer

Colorectal cancer (CRC) starts in the colon or rectum and spreads to other parts of the body, notably the lymph nodes, liver and lungs. It is often confined to the bowel for a relatively long period before metastasising. Colorectal cancer cases detected at this early stage are potentially curable with surgical resection. The classification of colorectal cancers follows the WHO International Classification of Tumours (Hamilton and Aaltonen, 2000). The most common type of colorectal cancer is adenocarcinoma (95 per cent), which develops in the glands of the inner lining (mucosa) of the intestine (Hermanek, 1989). Management of the disease has improved, with the five-year overall survival rising from 50 per cent for the period 1977 to 1985 to 56 per cent for the period 1986 to 1994 (National Health and Medical Research Council, 2000).

Staging of disease and prognosis

Pathological staging of colorectal cancers in Australia follows the Australian clinicopathological staging system (ACPS), based on the degree of penetration of the bowel wall and the extent of metastatic spread (Davis and Newland, 1983).

Table 1 Australian clinicopathological staging system for colorectal cancer (Davis and Newland, 1983).

Stage	Definition	Proportion of patients at presentation*	5 year survival
A	Localised within the bowel	10%	88%
B	Penetrates the bowel wall	36%	70%
C	Regional nodal involvement	29%	43%
D	Distant metastases	25%	7%

* Figures based on the Concord Hospital Sydney experience

Prognosis is closely linked to stage (Table 1) with the local extent of tumour and regional lymph node invasion considered to be the most important prognostic factor, together with surgical margin status and pre-operative CEA levels (Compton et al., 2000, Gennari et al., 2000).

Clinical need and burden of disease

Colorectal cancer (CRC) is a major public health problem in Australia. It is associated with significant mortality and morbidity, with one in 17 Australian men and one in 26 Australian women likely to develop the disease before the age of 75 years (Australian Institute of Health and Welfare, 2001). The risk of colon cancer increases with age; most cases are diagnosed at age 60 years and over. Risk of colorectal cancer is also increased in people with certain inherited conditions, notably familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC). Hereditary colorectal cancer accounts for up to 5 per cent of all cases of the disease. These high-risk patients are closely monitored with annual follow-up and colonoscopy (National Health and Medical Research Council, 2000). Colorectal cancer was the most common cancer

reported in Australia in 2000 with 12,405 cases accounting for 14.6 per cent of all new cancer registrations.

Australian incidence rates are high by international standards with a standardised rate (world population) of 46.5 per 100,000 in 2000. Incidence rates were higher for males than females with rates of 56.3 and 38.0 per 100,000 respectively (Australian Institute of Health and Welfare, 2001). Colorectal cancer was the second biggest cause of cancer deaths after lung cancer with 4,718 deaths (13.3 per cent of all cancer deaths) and an estimated 30,225 person years of life lost (PYLL) before the age of 75 years in 2000. The average time from diagnosis to death was 2.3 years with an average premature loss of life of 6.3 years. The case fatality rate (mortality to incidence ratio) for colorectal cancer in 2000 was 0.38 compared with 0.22 for breast cancer, 0.25 for prostate cancer and 0.86 for lung cancer (Australian Institute of Health and Welfare, 2001).

In 2000-01, there were more hospital separations for colorectal cancer (25,238) than breast cancer (20,527) or lung cancer (17,086) and overall, 217,421 patient days were attributed to colorectal cancer in that year. Most patients (93 per cent) received acute hospital care with an average length of stay of 11.7 days (Australian Institute of Health and Welfare, 2001). Disability weights[4] attributed to colorectal cancer in the Australian Burden of Disease Study (Mathers et al., 2000), acknowledge the considerable morbidity associated with this disease at diagnosis (disability weight of 43 per cent or 0.43) and for patients with non-resectable and disseminated disease (disability weight of 83 per cent or 0.83), see Table 2.

Table 2 Disability weighting for colorectal cancer (Australian Burden of Disease Study, 1999)

Sequalae	Disability Weight
Diagnosis and primary therapy and remission	0.43
State after intentionally curative primary therapy	0.20
State after radically removed or disseminated cancer	0.83
Terminal stage	0.93

Existing procedures

After potentially curable resection for colorectal cancer, most patients with suspected recurrence undergo CT scan and/or colonoscopy to locate and characterise the lesions. These first-line imaging techniques provide essential anatomical information relating to recurrence. If further evaluation for disease recurrence or spread is required, second or third-line imaging techniques may be used. These technologies target biological properties of the tumour such as glucose metabolism, gallium accumulation and antigen-antibody interaction. FDG-PET and gallium scans are currently employed as second line imaging techniques for colorectal cancer. Should gallium scan go into the generic management flow chart?

[4] Disability weight: 0 = no disability and 1= dead

Computed tomography (CT scan)

The international literature reports CT scan as the most commonly used first-line imaging technique for the identification and localisation of recurrent colorectal cancer. It is an anatomical imaging technique that can detect extensive tumour recurrence and morphological changes in malignant tissue. A CT scan of the liver, the most common site of spread, will be necessary to accurately stage the tumour prior to treatment decisions. Recent enhancements, such as contrast-enhanced spiral CT, have improved definition of liver lesions with an average sensitivity of 73 per cent, specificity 99 per cent (Freeny et al., 1986). Moreover, with helical multi-slice CT and IV contrast, patients can be scanned in a single breath-hold (Bruzzi et al., 2001) and targets of 2-3mm in diameter detected.

Although CT scan is the anatomical imaging technique of choice for the initial assessment of recurrent and metastatic colorectal disease, high rates of false positive, false negative and equivocal scans occur in some patient groups. Small liver and lymph node metastases are the most frequently missed lesions because, although modern CT scans can detect small structures, it is unable to characterise them. Moreover, benign lesions, scar and fibrotic tissue, and inflammatory changes are not easily distinguished from malignant masses.

Colonoscopy

Colonoscopy is a procedure for direct visual examination of the interior lining of the colon. A thin, flexible fibre-optic tube or colonoscope is inserted into the anus or stoma and advanced through the colon under visual control. The image from the colonoscope is projected onto a video monitor and viewed through the proximal eyepiece. Tissue samples may be taken using tiny forceps and polyps removed using snare wire through the scope. The ability to take samples is one of the benefits of conventional colonoscopy over virtual colonoscopy.

The reported sensitivity of diagnostic colonoscopy is 95 per cent (range 70-95 per cent), however detection rates depend on the size and location of the tumour and the training and experience of the endoscopist. The sensitivity of colonoscopy is lowest in the splenic flexure, hepatic flexure and caecum. This is due to failure to reach or examine fully these areas (Hixson et al., 1990, Rex et al., 1997). While the technique is very specific, there are problems with sensitivity for local recurrence (Kievit and Bruinvels, 1995, Longo and Johnson, 2002). Complication rates of 0.14 per cent have been reported for diagnostic colonoscopy and two per cent for therapeutic colonoscopy. According to Australian figures, approximately one in 2,000 patients undergoing a colonoscopy suffers bowel perforation, one in 1,000 a major haemorrhage, and one in 10,000 dies as a result of the procedure (Irwig et al., 1994). Conventional colonoscopy uses a colonoscope to screen for polyps or tumours in the colon. The current status of a possible alternative, virtual colonoscopy, was recently assessed by the Medical Services Advisory Committee (Medical Services Advisory Committee, 2002).

FDG-PET

Positron emission tomography (PET) is a non-invasive nuclear imaging technique that exploits metabolic differences between normal and malignant tissue. Physiologically active molecules are tagged with positron emitting radionuclides to form radiotracers that can be detected by a PET scanner. The most widely used radiotracer is fluorine-18-labelled 2-fluoro-2-deoxy-glucose (FDG), which is a glucose analogue tagged with fluorine-18. FDG has a half-life of 90 minutes.

When injected intravenously, FDG concentrates preferentially in certain cells including cancer cells. These cells have higher levels of glucose metabolism than normal cells due to increased expression of glucose transporter proteins in their cell membranes. As FDG decays gamma rays are emitted that are detected by a PET camera to give a very precise indication of the site of accumulation. The effective radiation dose to the body delivered by FDG-PET is 7.2 milliseiverts which is less than that of a CT scan of the pelvis and thorax which has a combined effective radiation dose[5] to the body of 10-12 milliseiverts.

Patients fast for five to six hours on the day of their scan. Upon arrival, FDG is injected via a drip in the arm. In some cases, patients may also receive an injection of the diuretic frusemide, or a muscle relaxant, midazolam. After the injection of FDG, the patient rests up to an hour before undergoing the scan. This allows the FDG tracer to accumulate in areas with increased metabolic rates, including tumours. The patient is then placed on a bed in the scanner with the scan taking between 30 minutes and two hours to be completed. Approximately an hour after an injection of FDG the radiotracer is sufficiently well distributed throughout the body to allow imaging.

32denomatous colorectal tumours accumulate high levels of FDG after infusion, allowing good imaging (high tumour-to-background ratio). The whole body can be imaged after a single injection of FDG.

The kidneys excrete FDG, leading to accumulation in the renal pelvis, ureter and bladder. Highly variable FDG accumulation in the colon requires experienced interpretation to distinguish normal variation from disease. (Flamen et al., 2000).

The imaging technique used in PET has a much higher resolution than standard imaging techniques. Nevertheless, spatial resolution is still limited and lesions smaller than 1.0 cm may be under-estimated, as they merge with background uptake. Moreover, since the visibility of the tumour depends not only upon the size of the lesion but also on the level of metabolic activity, large moderately active or necrotic tumour masses with small active rims may be less visible than small lesions with high metabolic activity levels.

The effectiveness of FDG-PET in colorectal cancer has been the subject of a number of recent Health Technology Assessment (HTA) evaluations and reviews in Europe and the USA (Adams et al., 1999, Adams and Flynn, 1998, Dussault et al., 2003, Institute for Clinical Evaluative Sciences, 2001, Muller et al., 2000, Morland, 2003) and in Australia (Department of Health and Ageing, 2001). The findings of the MSAC report were largely consistent with other reviews which concluded that FDG-PET had superior diagnostic

[5] See footnote 1

accuracy over conventional anatomical diagnostic imaging techniques for some indications, including recurrent colorectal cancer. The evidence suggested that PET was safe, potentially clinically effective and potentially cost-effective for imaging recurrent colorectal cancer (Department of Health and Ageing, 2001, Medical Services Advisory Committee, 2001). While the evidence did not support unrestricted Medicare Benefits Schedule (MBS) funding, MSAC recommended interim funding for a range of indications, including colorectal cancer, to enable the further evaluation of PET's clinical effectiveness and cost effectiveness.

Limitations of FDG-PET

FDG is not tumour specific. It can be accumulated by the cells involved in reactive processes such as inflammatory bowel disease (Flamen et al., 2000), healing bones and joints (Shreve et al., 1999) and in the cells of the heart muscle and neural tissue (Department of Health and Ageing, 2001).

Patients with diabetes and patients treated with granulocyte colony stimulating factor (G-CSF) after high dose chemotherapy may be difficult to image (Abdel-Dayem et al., 1999) and FDG-PET imaging of slow growing mucinous tumours may be poor (Whiteford et al., 2000).

There is also some limitation to the present coverage of FDG-PET in Australia, however, most patients requiring surgery for metastatic disease would be referred to a tertiary centre where FDG-PET is likely to be available. A detailed discussion of the extent of the PET technology, and PET use in Australia is available in the MSAC report titled "Review of positron emission tomography" (Department of Health and Ageing, 2001).

Gallium scan

A gallium scan may be used to evaluate recurrent colorectal cancer. Gallium-67 citrate (^{67}Ga citrate) is a gamma emitting radioactive tracer which is taken up by most primary tumours. It has a half-life of three days and an effective dose of 0.10 mSv/Mbq and an absorbed dose[6] of 30 mSv. Patients may be imaged at 24, 48 and 72 hours post injection. Abnormal accumulation may be difficult to distinguish from physiological excretion in the stools.

The comparator

The comparator is the current service most likely to be replaced or supplemented by the new service. For the detection of recurrent or metastatic colorectal cancer in previously diagnosed and treated colorectal cancer patients after the failure of conventional anatomical diagnostic tests, supplemental functional imaging by FDG-PET may be considered the current service most likely to be replaced by CEA-Scan®.

[6] Absorbed dose = the amount of energy from the radiolabel which is deposited per unit mass of absorbing tissue.

Both CEA-Scan® and FDG-PET are indicated for second-line imaging of colorectal cancer when first-line anatomical imaging has failed or is equivocal. CEA-Scan® may also be indicated when FDG-PET has failed or is equivocal. For the purposes of this review, therefore, functional imaging by CEA-Scan® will be compared to functional imaging by FDG-PET.

The reference standard

An assessment of the comparative diagnostic accuracy of CEA-Scan® and FDG-PET requires the determination of the true disease status of patients, using an appropriate reference standard. For the purposes of this review, the true disease status of patients with operable/resectable disease must be determined by tumour histopathology obtained from biopsy or surgery. The true disease status of patients with inoperable/unresectable disease must be determined by long-term clinical follow-up, ie, follow-up of one year or more.

Additional or replacement test?

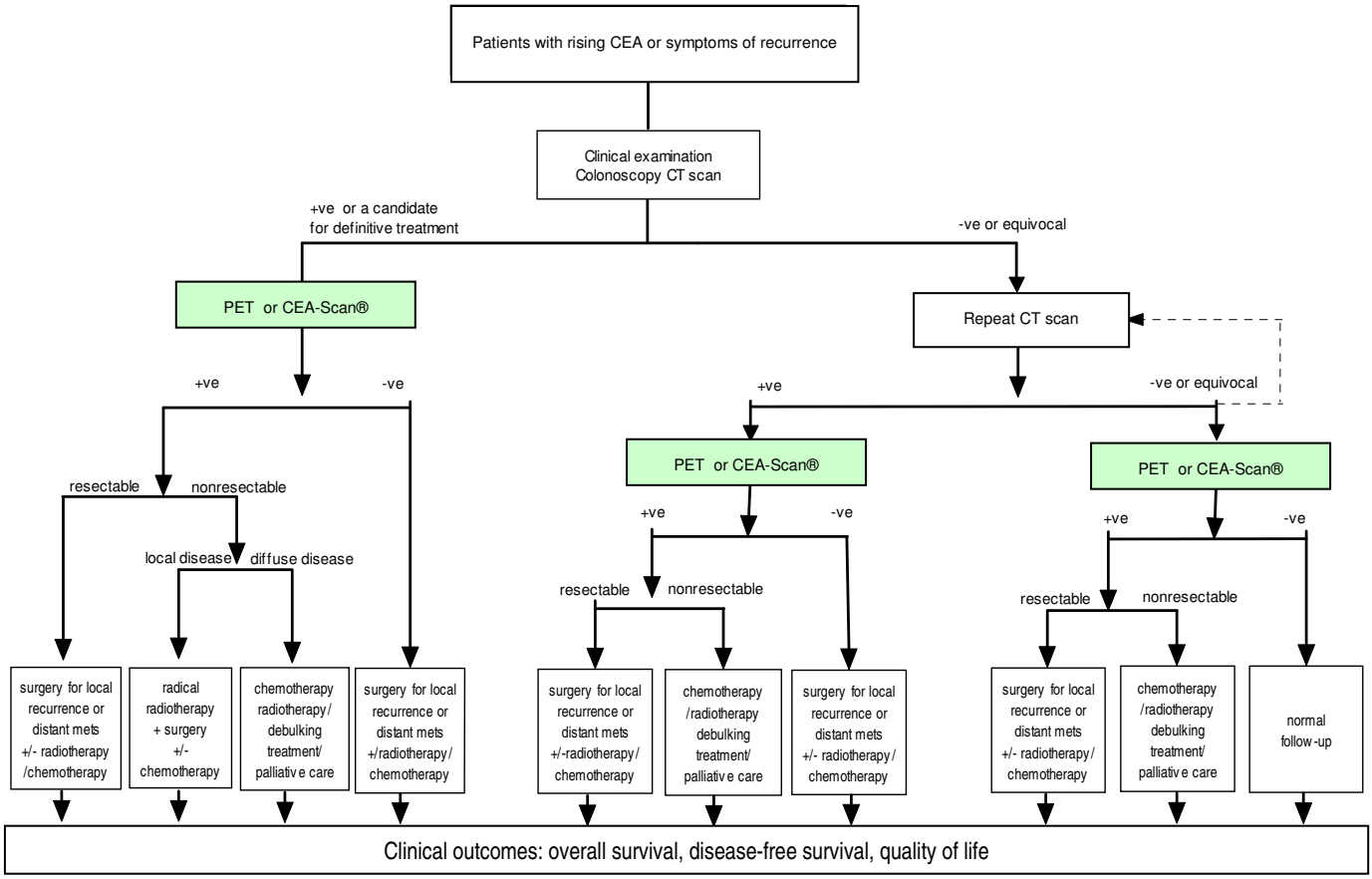
CEA-Scan® is perceived as an adjunct to first-line anatomical diagnostic modalities for the detection, location and extent of recurrent or metastatic disease in patients with previously diagnosed and treated colorectal cancer. It may also be considered when other functional imaging techniques are unhelpful or unavailable.

CEA-Scan® provides additional functional information in patients with negative, inconclusive or equivocal first-line imaging results[7]. Thus a CEA-Scan® is indicated after conventional anatomical diagnostic modalities (minimally consisting of physical examination, colonoscopy and CT scan) have failed in previously treated patients with confirmed or suspected recurrent or metastatic disease. In these circumstances, the incremental value of CEA-Scan® is of interest and it may be viewed as an additional test.

FDG-PET is currently the second-line imaging technique of choice in Australia when conventional or first-line anatomical diagnostic imaging has failed. CEA-Scan® could potentially perform the same function in these patient groups, see Figure 2, and may therefore be viewed as a potential replacement or alternative functional imaging technique to FDG-PET.

[7] CEA-Scan® application to MSAC for funding by Australian Radioisotopes, October 2002.

Figure 2 Generic flow chart for the management of patients with suspected recurrent colorectal cancer (Australia).



Not all patients can benefit from FDG-PET, because of local unavailability of the technology or because of co-morbidities or physiological states that may interfere with FDG-PET imaging. CEA-Scan® may also be considered for imaging recurrent disease in such patients.

For the purposes of this review, therefore, CEA-Scan® will be assessed as an additional test and the incremental value of CEA-Scan® assessed in relation to patient management and health outcomes when conventional anatomical diagnostic modalities, including FDG-PET have failed or are unavailable or equivocal.

Marketing status of the technology

CEA-Scan® Arcitumomab is a registered radiopharmaceutical in the USA (1996), Canada (1997) and the European Union (1996). It was evaluated in 2002 by the Australian Drug Evaluation Committee (ADEC) for the sponsor and importer,

Australian Radioisotopes (ARI), and registered on the Australian Register of Therapeutic goods for approved indications[8] in November 2002.

Current reimbursement arrangement

CEA-Scan® is not currently supported by Medicare. FDG-PET has interim funding, dependent upon data collection relating to its clinical and cost effectiveness, and its provision to a central coordinating body (Medical Services Advisory Committee 2001, Department of Health and Ageing, 2001). Medicare rebates are currently available for specific PET indications performed at seven designated PET facilities nationally: the Royal Prince Alfred and Liverpool hospitals in New South Wales, the Peter MacCallum Cancer Centre and Monash Medical Centre in Victoria, the Royal Adelaide Hospital (South Australia), the Wesley Hospital (Queensland) and the Sir Charles Gardiner Hospital (Western Australia). In addition, the Commonwealth funds PET scans at Austin Health, Melbourne, through a grant arrangement.

[8] See page 4

Approach to assessment

Research questions

A number of research questions were formulated to guide the review process. The questions were developed using the PICO[9] process and information on current clinical practice for the diagnosis and management of colorectal cancer in Australia supplied by the CEA-Scan® advisory panel.

Safety

Is CEA-Scan® safe?

What are the safety issues/adverse events associated with CEA-Scan® for (a) a single administration, and (b) repeat administrations?

Diagnostic test performance

Is CEA-Scan® a reliable and accurate diagnostic test for the defined indications?

How well does the test perform in the clinical setting?

Patient management/Health outcomes

What is the incremental value of CEA-Scan® compared with FDG-PET in relation to patient management and health outcomes in asymptomatic patients with suspected recurrence of colon or rectal cancer based on rising serum CEA, when conventional anatomical diagnostic modalities have failed or are equivocal?

What is the incremental value of CEA-Scan® compared with FDG-PET in relation to patient management and health outcomes in symptomatic patients with suspected recurrence of colon or rectal cancer based on clinical symptoms, when conventional anatomical diagnostic modalities have failed or are equivocal?

What is the incremental value of CEA-Scan® compared with FDG-PET in relation to patient management and health outcomes in the assessment of the extent of disease in patients with proven recurrence, when conventional anatomical diagnostic modalities have failed or are equivocal?

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[9] PICO criteria are used to develop precise clinical questions for each indication, focused around: **P**atient group(s) or problem(s) to be addressed, **I**ntervention(s) or test(s) being considered, **C**omparison test(s) reference standard(s) and clinical **O**utcome(s) of interest. Richardson, W. S., Wilson, M., C, Nishikawa, J. and Hayward, R. S. (1995). *ACP Journal Club* **123**(3): A12-3.

For each of the indications above:

Does clinical decision-making change as a result of the use of CEA-Scan®?

Do patients who have received CEA-Scan® have better health outcomes in terms of improved survival, lower morbidity or better quality of life as a result of the test?

Does CEA-Scan® have a role to play where FDG-PET fails or is unavailable?

Economic evaluation

What are the cost implications of replacing FDG-PET scan with CEA-Scan® in the indications being considered?

What are the cost implications of adding CEA-Scan® as a third-line imaging agent when FDG-PET is negative or equivocal?

Review of literature

Search strategy

The medical literature was searched to identify all studies relevant to the review questions for the period 1996-January 2004. Searches were conducted via the databases listed in Appendix C and using the search terms shown in Table 3.

Table 3 Search terms used in the primary and secondary database searches

Element of clinical question	Search terms
Patient	Exp colorectal neoplasms/, ((colorectal or colon$ or rectal) adj2 (cancer or carcinoma or tumour$ or tumor$ or neoplasm$))
Intervention / test	Carcinoembryonic antigen/, or carcinoembryonic antigen/, or carcinoembryonic antigen$, or immu 4, immu4, arcitumomab, cea adj3 scan$
Comparator	Exp tomography, emission-computed/, pet, positron emission tomography, fdg, 18F, 18-F
Effectiveness of comparator	Exp sensitivity and specificity, exp diagnostic errors, reproducibility of results, false negative results, false positive results, positive predictive value, negative predictive value, ppv, npv

A core strategy was developed and implemented by an information specialist. The strategy was used in Medline and CancerLit to identify relevant publications on the use of CEA to identify recurrence or metastases of colorectal cancer. The strategy was adapted for Embase using relevant subject headings and simplified for use in databases without indexing. The search was broad in scope and incorporated sub-sets relating to safety and cost-effectiveness. The core search for CEA-Scan® is shown in Table 4.

Table 4 CEA-Scan® core search strategy

Search Area	Search terms
1.	immu 4 OR immu4
2.	arcitumomab
3.	CEA adj3 scan$
4.	1 or 2 or 3
5.	exp colorectal neoplasms
6.	(colorectal or colon$ or rectal) adj2 (cancer$ or carcinoma$ or tumour$ or tumor$ or neoplasm$)
7.	5 or 6
8.	carcinoembryonic antigen$
9.	carcinoembryonic antigen/
10.	cd66e
11.	cea
12.	8 or 9 or 10
13.	7 and 11
14.	di.fs
15.	ri.fs
16.	rt.fs
17.	exp 'sensitivity and specificity'/
18.	sensitivity
19.	specificity
20.	exp diagnosis/
21.	exp pathology/
22.	exp diagnosis/
23.	(pretest or pre test) adj probability
24.	post test probability
25.	or/17-24
26.	neoplasm recurrence, local/
27.	exp neoplasm metastasis/
28.	recurren$
29.	metastas$
30.	secondary
31.	or/26-30
32.	4 or (13 and 25 and 31)

Table 4 CEA-Scan® core search strategy (continued)

13.	7 and 11
14.	di.fs
15.	ri.fs
16.	rt.fs
17.	exp 'sensitivity and specificity'/
18.	sensitivity
19.	specificity
20.	exp diagnosis/
21.	exp pathology/
22.	exp diagnosis/
23.	(pretest or pre test) adj probability
24.	post test probability
25.	or/17-24
26.	neoplasm recurrence, local/
27.	exp neoplasm metastasis/
28.	recurren$
29.	metastas$
30.	secondary
31.	or/26-30
32.	4 or (13 and 25 and 31)

Additional searches were undertaken for colorectal cancer therapy (Appendix D) and for the comparator FDG-PET (Appendix E).

A separate search of Health Technology Assessment agency websites was undertaken to locate any systematic reviews, meta-analyses or health technology assessments not uncovered by the core searches of the medical databases. The HTA organisations that were included in the search are shown in Appendix F.

Search results

The initial scoping search[10], which was restricted to Medline and Embase databases, identified 1,759 papers. The comprehensive searches that followed covered a much larger number of databases and retrieved a further 1,515 papers. The additional searches to locate relevant papers relating to the treatment of recurrent colorectal cancer and the comparator FDG-PET identified a further 255 and 395 papers respectively. In all, a total of 3,944 abstracts and titles were retrieved and examined, see Table 5.

[10] CEA-Scan® Protocol, 2003

Table 5 Results of search for review literature

Search	Number of papers identified
A. Initial scoping search	1,759
B. Additional PET search	395
C. Additional comprehensive search	1,515
D. Effective therapy search	255
E. Health technology assessment search	20
Total number of abstracts/titles examined	**3,944**

No health technology assessments of CEA-Scan® were located, but nine health technology assessment groups had published reports assessing the use of FDG-PET in colorectal cancer. Four reports were published after MSAC's assessment report of positron emission tomography in March 2000, see Table 6.

Table 6 Health technology assessment sites providing assessment reports of FDG-PET post-2000

HTA organisations	Authors/date	Website
Agence d'Evaluation des Technologies et des Modes d'Intervention (AETMIS)	Dussault et al., 2003	www.aetmis.gouv.qc.ca
Norwegian Centre for Health Technology Assessment (SMM)*	Morland et al., 2003	http://www.oslo.sintef.no/smm/
Institute for Clinical Systems Improvement (ICSI)	Smith et al., 2001	http://www.icsi.org
Health Technology Board for Scotland	Bradbury et al., 2002	http://www.htbs.org.uk/
*English translation available from the Department of Veterans' Affairs		

Study selection

All studies examining the validity, reliability, effectiveness, safety and cost-effectiveness of CEA-Scan® for the agreed indications were identified. In addition, all studies relating to the effectiveness of therapy for these indications were identified. Two reviewers assessed study eligibility. Emphasis was placed on identifying high quality studies for each indication and outcome to be evaluated. The following selection criteria were applied to the articles identified by the literature search in order to identify relevant studies for assessment and critical appraisal.

Inclusion criteria

- Studies which include CEA-Scan® and are relevant to the review questions.
- Studies which include FDG-PET and are relevant to the review questions.
- Clinical studies relevant to the review questions.
- Studies where CEA-Scan® is compared with a suitable reference standard.

- Studies with one or more of the following patient groups: (a) Asymptomatic patients with histologically confirmed and treated cancer of the colon or rectum with rising serum CEA; (b) Patients with histologically confirmed and treated cancer of the colon or rectum with symptoms of recurrence; and (c) Patients with histologically confirmed recurrent cancer of the colon or rectum.

- Studies with an overall sample size of 10 or more were included to maintain parity with a previous MSAC assessment report on the utility of PET Scan for colorectal cancer (Medical Services Advisory Committee, 2001).

- Studies corresponding to NHMRC (2000) evidence levels I-IV for therapy intervention studies and (Anonymous, 2002) evidence levels I-IV for diagnostic studies.

- Confidential material supplied specifically for the review by the applicant.

Exclusion criteria

- Non-published work except where confidential material is supplied specifically for the review by the applicant.

- Studies which report no clinical results.

- Non-English language articles (due to time constraints).

- Non-systematic reviews, letters, editorials, expert opinion/viewpoint articles, comments, overviews, articles published in abstract form only, conference proceedings and studies on animal subjects.

- Studies which duplicate or precede a subsequent study addressing the same question from the same institution(s).

- Fewer than 10 cases reported overall.

- Reports based on expert opinion only.

Evaluation of diagnostic tests

The evaluation of a diagnostic test requires the assessment of how well the test performs in the clinical setting, i.e. (i) its accuracy, sensitivity and specificity in the diagnosis of disease; (ii) impact of the test results on clinical practice; and (iii) the effect of any changes in clinical management arising from the results of the test on the health outcome for the patient.

Test performance

The assessment of the performance of CEA-Scan® includes consideration of its validity and reliability as a diagnostic test in the clinical setting.

Test validity

The validity of CEA-Scan® as a diagnostic test for recurrent colorectal cancer was measured by comparing the results of the test against the reference test or gold standard in a two-by-two table, see Table 7. The input values for the calculation of test sensitivity and specificity, and the derived likelihood ratios were taken from this table.

Table 7 Two-by-two table for the calculation of sensitivity and specificity

		Reference test	
		Positive	**Negative**
Diagnostic test	Positive	**a** (true positive)	**b** (false positive)
	Negative	**c** (false negative)	**d** (true negative)
	Total sample size	n_1 (total number patients with the disease)	n_2 (total number of patients without the disease)

Test sensitivity, specificity and the derived test likelihood ratios were defined and calculated as shown in Table 8.

Table 8 Measures used to assess the accuracy of diagnostic tests

Definition	Measure	95% Confidence interval§	Notes
Sensitivity (Se): The proportion of patients with the disease that are correctly identified	a/(a+c) = a/n_1	$p \pm 1.96(pq/n_1)^{1/2}$ where p = a/(a+c) q = c/(a+c)	If either n*p or n(1-p) were less than five, exact methods based on the binomial distribution were used to calculate the confidence interval
Specificity (Sp): The proportion of patients who do not have the disease that are correctly identified	d/(b+d) = d/n_2	$p \pm 1.96(pq/n_2)^{1/2}$ where p = d/(b+d) q = b/(b+d)	

Definition	Measure	95% Confidence intervals	Notes
Positive likelihood ratio (LR+): The ratio of the likelihood of a positive test in a patient with the disease to the likelihood of a positive test in a patient without the disease	sensitivity / (1-specificity)	Exp{ln[sensitivity/(1-specificity) $\pm 1.96[(sensitivity/c) + (specificity/b)]^{1/2}$}	Simel et al., 1991
Negative likelihood ratio (LR-):S The ratio of the likelihood of a negative test in a patient with the disease to the likelihood of a positive test in a patient without the disease	(1- sensitivity)/ specificity	Exp{ln[(1sensitivity)/(specificity)] $\pm 1.96[(sensitivity/c) + (1-specificity)/d]^{1/2}$}	Simel et al., 1991

Test reliability

The methods used for the performance of the test must be described in sufficient detail to allow replication of the test in routine clinical practice. This should include the preparation of the materials used in the test, the preparation of the patient, the delivery of the test, post-test precautions and monitoring, and the analysis and interpretation of results (Jaeschke et al., 1994).

Quality of the evidence

Published studies assessing diagnostic tests vary considerably in study design (Knottnerus, 1987). Many of these designs are prone to a number of biases which may influence their estimates of test sensitivity and specificity (Deeks 2001, Lijmer et al., 1999, Reid et al., 1995). Whilst biases theoretically may work in either direction, in practice most tend to result in over-estimation of test accuracy (Whiting 2003, Lijmer, et al., 1999).

The most common biases are:

Selection bias: This can occur when the study group is very different from the patient population or the healthcare setting in which the test will be applied. This can lead to both under- or over-estimation of test accuracy.

Verification bias: This can occur if the reference test confirming or denying the test results is only performed on patients with a positive test result. This can lead to both under- and over-estimation of the test's specificity and sensitivity. Verification bias is avoided when the reference standard is measured in consecutive patients (Cochrane Methods Group on Systematic Review of Screening and Diagnostic Tests, 1996).

Review bias: This can occur if the test is interpreted with foreknowledge of the results of the reference test or the comparator, and the test evaluation is influenced by this knowledge. This most often results in over-estimation of the test's accuracy.

Studies that have been designed to eliminate or minimise bias arising from these and other sources are most likely to provide a valid estimate of the sensitivity and specificity CEA-Scan®. The concept of "levels of evidence" was developed in this context and study designs graded to reflect their ability to eliminate or minimise serious bias.

Levels of evidence for diagnostic tests

The quality of studies assessing the accuracy of diagnostic tests is often poor (Reid et al., 1995) and appropriate levels of evidence for studies of diagnostic performance have yet to be established[11] (Irwig et al., 1994). However, there are a number of indicative studies (Lijmer et al., 1999, Bossuyt et al., 2003), guidelines (Jaeschke et al., 1994, Sackett and Haynes, 2002), and provisional instruments (Anonymous, 2002) that may be used to inform judgements relating to the level of evidence provided by a particular study reporting diagnostic test performance.

[11] MSAC evaluators meeting, November 2001, Sydney

The most rigorous study design for assessing the validity of a diagnostic test is generally considered to be a prospective, blinded comparative study of the test and a reference test or gold standard in a consecutive series of patients from a relevant clinical population (Jaeschke et al., 1994, Sackett and Haynes, 2002, Irwig et al., 2002, Irwig et al., 1994). Levels of evidence were assigned to studies assessed in this review based on this standard and by the provisional instrument provided by Bandolier (Anonymous, 2002), see Table 9.

Table 9 Levels of evidence for studies of diagnostic tests adapted from Bandolier (Anonymous 2002)

Level of evidence	Criteria for inclusion in level
LEVEL ONE	Independent masked comparison with reference standard
	Appropriate clinical population
	Consecutive patients
LEVEL TWO	Independent masked comparison with reference standard
	Appropriate clinical population
	Non-consecutive patients or confined to a narrow spectrum of patients
LEVEL THREE	Independent masked comparison with reference standard
	Appropriate clinical population
	Reference standard not applied to all study patients
LEVEL FOUR	Reference standard not applied independently or masked
LEVEL FIVE	Expert opinion with no explicitly critical appraisal, based on physiology, bench research or first principles

The highest available level of evidence available was used for decision-making.

Impact on clinical management

The therapeutic impact of CEA-Scan® was measured as the change in treatment decisions made by clinicians in response to information provided by the test.

Improved health outcomes

The effect of CEA-Scan® on health outcomes would ideally be reported in a randomised study assigning patients to CEA-Scan® or PET, treating both patient groups in the same way and evaluating the health outcomes (Van Tinteren and Hoekstra, 2003). There are very real difficulties in establishing randomised controlled trials in rapidly evolving technologies (Hojgaard, 2003).

In the absence of a randomised trial, improved health outcomes may be inferred if there is clear evidence of improved diagnostic accuracy leading to a change in patient management, supported by evidence of effective treatment for the indication. There are two considerations here: firstly that there is effective treatment for the indications of interest and secondly that early diagnosis and treatment leads to improved health outcomes for patients. Studies that have been designed to eliminate or minimise various forms of bias are most likely to provide reliable estimates of treatment effect. Therapeutic study designs vary considerably in their ability to eliminate bias and a number of different grading systems have been developed.

Levels of evidence for effectiveness

Evidence presented in therapeutic studies (Appendix K) was assessed and classified using the dimensions of evidence defined by the National Health and Medical Research Council (National Health and Medical Research Council, 2000), which include an assessment of strength of the evidence, size of the effect and relevance of the evidence, see Table 10. For surgical interventions, systematic reviews (Level I) and randomised controlled trials (Level II) are rare, and evidence of successful patient outcomes from well-designed case series (Level III) was accepted as evidence of treatment effectiveness for recurrent or metastatic colorectal cancer. For chemotherapy and radiotherapy, studies providing Level I or Level II evidence of treatment efficacy were used to evaluate the impact of therapy. Evidence of effective treatment by these modalities assessed in systematic reviews or randomised controlled clinical trials (RCTs) was used to evaluate the potential effect of CEA-Scan® on patient outcomes.

Table 10 Dimensions and levels of evidence for studies addressing the efficacy of treatment for recurrent colorectal cancer

Type of evidence	Definition
Strength of the evidence	The study design used, as an indicator of the degree to which bias has been eliminated by design:
Level	**I** Evidence obtained from a systematic review of all relevant randomised controlled trials
	II Evidence obtained from at least one properly-designed randomised controlled trial
	III-1 Evidence obtained from well-designed pseudorandomised controlled trials (alternate allocation or some other method)
	III-2 Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group
	III-3 Evidence obtained from comparative studies with historical control, 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
Quality	The methods used by investigators to minimise bias within a study design.
Statistical precision	The *p*-value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect.
Size of effect	The distance of the study estimate from the "null" value and the inclusion of only clinically important effects in the confidence interval.
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used.

Data extraction and analysis

Data were extracted from the articles selected for appraisal using a datasheet designed for the review. Study quality was assessed against predefined criteria that included a checklist developed from the STARD protocol (Bossuyt et al., 2003) and the accompanying flow diagram. Data were extracted independently by two reviewers (PS and RK).

Expert advice

An Advisory Panel with expertise in surgery, medical oncology, radiology and nuclear medicine was established to evaluate the evidence and provide advice to MSAC from a clinical perspective. In selecting members for Advisory Panels, MSAC's practice is to approach the appropriate medical colleges, specialist societies, associations, and consumer bodies for nominees. Membership of the Advisory Panel is provided at Appendix B.

Results of assessment

Overall, 31 papers were appraised in the assessment of CEA-Scan®. These comprised eligible clinical studies and reviews of the safety and effectiveness of CEA-Scan® employed as an imaging technique for the assessment of recurrent or metastatic disease in patients previously treated for primary colorectal cancer.

Is CEA-Scan® safe?

CEA-Scan® is manufactured by Immunomedics Inc., Morris Plains, New Jersey, USA and supplied in Australia by the Australian Nuclear Science and Technology organisation trading under the name Australian Radioisotopes (ARI). It comprises a radioactive tracer attached to a mouse antibody fragment. The recommended dose of CEA-Scan® is 1.0 mg of the antibody fragment (Arcitumomab) labelled with 740-1100 MBq of pertechnetate [99m Tc], which is administered after dilution with 1.0 ml of sodium chloride by slow intravenous injection (Immunomedics, 2002). This delivers an effective radiation dose[12] of 9.1 :Sv/MBq to an adult patient. In terms of radiation equivalence CEA-Scan® delivers a similar radiation dose to FDG-PET (8.2 mSv versus 7.4 mSv) and a much lower equivalent dose[13] than a CT or gallium scan at 10-12 mSv and 30 mSv respectively.

General precautions and problems noted by the manufacturer

The patient information sheet for CEA-Scan® presented to the TGA for registration (revision 25 October 2002) recognised that:

- the carcinogenic potential of CEA-Scan® had not been established in long-term animal studies;
- the effect on male and female fertility had not been established in long-term animal studies;
- the safety of the product in children below 18 years had not been established;
- safety in patients with renal or hepatic impairment had not been established;
- no data were available on possible drug interactions.

[12] Effective radiation dose = a weighted average of the equivalent doses measured in millisieverts (mSv) or microsieverts (:Sv) received by each organ or tissue in the irradiated patient.

[13] Equivalent dose = the amount of radiation absorbed by the tissue, weighted by a factor that takes into account the biological effectiveness of each type of radiation.

Safety concerns in routine clinical practice

Radiation dose

The amount of the radiopharmaceutical given to the patient is the minimal amount required to obtain the required imaging information before it decays. Although high doses of radiation have been linked with adverse health effects, the low doses associated with diagnostic imaging are medically insignificant.

The radiolabel used in CEA-Scan® emits low energy radiation with very limited destructive ability. This, together with a short physical half-life (6.02 hours) and emission of radiation suitable for imaging by gamma cameras, has made it the isotope of choice for radioimmunoscintigraphy (Potamianos et al., 2000). Technetium is excreted in the urine and the highest absorbed doses[14] of the radionuclide are in the kidney (100.3 :Gy/MBq) and the bladder (16.6 :Gy/MBq) followed by the spleen (15.9 :Gy/MBq) and bone surface (13.6 :Gy/MBq) (Immunomedics, 2002).

In an early study of 18 colorectal cancer patients (Goldenberg et al., 1990), a single dose of CEA-Scan® had a median elimination time of 13.2 hours. No adverse reactions were reported and no changes related to the radiolabelled antibody were detected in haematological, liver and renal function tests. In a more recent study, 44 patients undergoing repeat administration of CEA-Scan® had no clinically significant changes in blood and serum chemistry tests at 24 hours and one week post-infusion (Wegener et al., 2000).

Allergic reaction

IMMU-4 is a murine anti-CEA monoclonal antibody (MOAB) that has been used for more than 20 years in studies evaluating immunoscintigraphic imaging of colorectal cancer. The relative safety of infused murine monoclonal antibodies has been demonstrated in trials (Nabi and Doerr, 1992). However, murine MOABs may be perceived as foreign proteins that can provoke an allergic response from the patient's immune system, leading to the production of human anti-mouse antibodies (HAMA). The possibility of HAMA is a serious concern (Potamianos et al., 2000) as it may increase the chance of a severe allergic reaction to further mouse protein products, which can be life threatening.

The development of CEA-Scan® has been concentrated on refinement of the product to reduce immunogenicity and only a small fragment of the original IMMU-4 antibody is used in CEA-Scan®. This significantly reduces the chance of a severe immune reaction (see Figure 1). Nevertheless, anaphylactic and other hypersensitivity reactions have been reported following the administration of CEA-Scan® and appropriate facilities should be available during infusion in case the patient experiences a severe adverse reaction to CEA-Scan®.

[14] See footnote 6

Risks associated with repeated testing with CEA-Scan®

There are a number of potential risks associated with repeat testing with CEA-Scan®. As the administered dose of CEA-Scan® is increased through multiple injections there is an increased risk of the production of human anti-mouse antibodies in the individual patient and potentially an increased number of patients with circulating HAMA. A previous immune response increases the chance of serious immune reactions or immune complex disease as well as potentially interfering with the imaging efficiency of CEA-Scan®. High HAMA assays may also interfere with laboratory tests which are based on murine monoclonal antibodies such as serum CEA and CA-15 (Tempero, 1993, Moffat et al., 1996). These reactions are more likely to occur with whole mouse monoclonal antibodies than with monoclonal antibody fragments such as CEA-Scan®.

Studies reporting HAMA and adverse events

The literature search identified 48 studies reporting on CEA-Scan®, with 15 studies reporting on safety issues. The quality of the overall reporting of safety in the clinical studies detailing the use of CEA-Scan® was variable and mostly related to reporting the incidence of HAMA and short-term events in small groups of highly selected patients.

The reported incidence of raised HAMA was very low, with only two studies (Moffat et al., 1996, Wegner et al., 2000) reporting incidents after one CEA-Scan® injection and no studies reporting HAMA response to multiple doses. However, only HAMA non-responders would have had a repeat CEA-Scan® and many studies routinely screen for previous HAMA before administration of CEA-Scan®.

The most commonly reported adverse events and side effects were allergic reactions such as eosinophilia and pruritus and other non-specific events including transient headache, minor gastro-intestinal upset, fever, bursitis and subdermal induration. One unwitnessed seizure was reported (Moffat et al., 1996). Overall, of 453 patients receiving CEA-Scan® in these studies only three per cent were reported to have had any untoward effects from the administration of CEA-Scan®.

Reporting issues

There are a number of issues to keep in mind when reading the review, including:

- **Lack of evidence** regarding long-term data for single and repeat injections
- **Severe reaction to Arcitumomab is likely to be rare**. The study populations for the most part were small selected groups of patients who are unlikely to be representative of the larger patient populations that the test will be used in if funded.

- **For the radioactive agent there is lack of long-term follow-up** for both single and repeat injections. The amount of radioactivity is small but the effects are cumulative.

- **Adverse reactions versus side effects.** Both are reported and it is unclear when no adverse effects are reported if side effects have been included.

- **Conflict of interest**. Immunomedics, the manufacturer of CEA-Scan®, sponsored most of the 10 studies reporting on safety or had a member of the company as a co-author.

Potential value of CEA-Scan®

CEA-Scan® has a number of potential advantages when employed as a second-line or third line imaging technique for recurrent colorectal cancer. For example, CEA-Scan® may be helpful in the:

- identification of occult disease in patients with rising serum CEA who may benefit from surgery with curative extent;

- identification of patients who are not suitable for surgery because of extensive or distant lesions reducing morbidity and hospital costs that may be associated with unnecessary surgery;

- allocation of appropriate treatment through a more accurate determination of the extent of recurrent disease.

CEA-Scan® may also be useful in selected patients when FDG-PET is available but has provided negative or equivocal results as for example in:

- patients who are asymptomatic but with rising serum CEA;

- patients who have a high risk of relapse who require further imaging;

- patients with benign or therapy induced physiological conditions that are likely to interfere with FDG uptake;

- patients with slow growing tumours that may not absorb enough FDG for successful imaging.

Patients who fall into these latter categories include patients with uncontrolled diabetes, patients with inflammatory disease, patients who have been treated with G-CSF chemotherapy, patients who have been treated with aggressive radiotherapy and patients with mucinous histological sub-types.

Is CEA-Scan® effective?

The effectiveness of a diagnostic test depends not only on its diagnostic efficacy but also on the availability of effective treatment for the condition. In many cases recurrent

colorectal cancer can be effectively treated provided it is diagnosed early enough and the exact location and true extent of the recurrence can be determined (see Appendix K).

Diagnostic efficacy

Three search strategies were designed which were sensitive to studies reporting safety, effectiveness and economic analyses of CEA-Scan® and/or FDG-PET. Of the 3,944 published studies and abstracts identified by these searches, 34 reported on the use of CEA-Scan® in colorectal cancer (Appendix G, Appendix H), 130 reported on FDG-PET and two studies compared CEA-Scan® and the chosen comparator, FDG-PET. Twenty health technology assessments (HTAs) were identified, all reporting on FDG-PET. There were no published health technology assessments or systematic reviews of CEA-Scan®. No randomised controlled trials reporting on the use of CEA-Scan® or FDG-PET in colorectal cancer were identified.

Of the 20 HTAs reporting on the use of PET in cancer, three reported after the MSAC review of FDG-PET (March 2000). In addition, two systematic reviews of PET published in peer-reviewed journals were identified, one assessing whole-body PET in recurrent colorectal cancer (Huebner et al., 2000) and one assessing the comparative performance of PET for the detection of liver metastases in gastro-intestinal cancers (Kinkel et al., 2002).

Because only two comparative studies of CEA-Scan® and FDG-PET were identified, an initial indication of the level of accuracy achieved by the two imaging techniques in separate studies was sought. Only studies that fulfilled the eligibility criteria set for review papers were included and all papers assessed had to include an evaluation of FDG-PET or CEA-Scan® against histologically confirmed disease.

Diagnostic accuracy of the comparator FDG-PET

This assessment was restricted to recent and relevant health technology assessments, systematic reviews or clinical studies assessing imaging accuracy of FDG-PET against histopathology or clinical follow-up. Only clinically relevant populations were included.

Existing FDG-PET reviews

An MSAC assessment of positron emission tomography reported on the value of PET in recurrent and metastatic colorectal cancer in March 2000 (Department of Health and Ageing, 2001, Medical Services Advisory Committee, 2001). This report examined seven previous reviews published between 1997 and 1999, and 50 additional publications to establish the incremental value of PET over computed tomography.

Since the MSAC review there have been a further three health technology assessments reporting on the use of PET in recurrent or metastatic colorectal cancer (Institute for Clinical Evaluative Sciences, 2001, Smith, et al., 2001, Dussault et al., 2003) and two systematic reviews (Huebner et al., 2000, Kinkel et al., 2002). Two of these publications (Huebner et al., 2000, Dussault et al., 2003) included all but one of the studies assessed in the MSAC, ICES and ICSI reviews.

Huebner (2000) reported an overall FDG-PET sensitivity of 97 per cent (95 per cent CI, 95-99 per cent calculated over all patients) and specificity of 76 per cent (95 per cent CI,

63-88 per cent) in the imaging of recurrent colorectal cancer. The overall accuracy of FDG-PET was 94 per cent (95 per cent CI, 90-96 per cent). An additional sub-group analysis reported sensitivities and specificities of 96 per cent (95 per cent CI, 94-99 per cent) and 99 per cent (95 per cent CI, 98-100 per cent) for the detection of hepatic involvement and 95 per cent (95 per cent CI, 91-98 per cent) and 98 per cent (95 per cent CI, 96-100 per cent) for the detection of local or pelvic recurrence.

The AETMIS health technology assessment of PET (Dussault et al., 2003) commissioned for the Quebec government identified a further three high-quality studies that were eligible for review (Zhuang et al., 2000, Staib et al., 2000, Imdahl et al., 2000). These studies confirmed the high accuracy of PET for the detection of recurrent or metastatic colorectal found in the other reviews with reported sensitivity values between 92 and 100 per cent and specificity values between 98-99 per cent in reported studies. A search of the literature conducted for the current review identified 48 publications reporting on the use of PET in recurrent or metastatic CRC; 12 pre-2000 and 36 post-2000 clinical studies (Appendix I). Twenty-two studies failed to meet the eligibility criteria. Twelve of the clinical studies examined the accuracy of PET against histopathology and long-term clinical follow-up (see Table 11), while two studies compared FDG-PET and CEA-Scan, see Table 17.

Studies comparing FDG-PET with the gold standard varied in size, quality and indication; most comprised selected patients, non-blinded image assessment and varying proportions of patients assessed against the gold standard. The median sensitivity across these studies was 95 per cent (range 71-100 per cent), median specificity 94 per cent (43-100 per cent) and median accuracy 94 per cent (74-100 per cent). The results of these studies broadly confirmed the high levels of sensitivity and specificity of PET scans reported in the earlier reviews.

Although FDG-PET performed well overall, not all patients benefited. Patients with uncontrolled diabetes or acute inflammation were excluded from PET imaging in some studies (Staib et al., 2000), while in other studies physiological uptake of FDG impaired visualisation of the tumour or led to a false positive diagnosis (Flamen et al., 2001, Moore et al., 2003, Tanaka et al., 2002). False positive diagnoses also arose in patients with reactive lymph nodes, pulmonary infections and inflammation, and in patients who had been treated with radiotherapy (Lonneux et al., 2002, Arulampalam et al., 2001, Hung et al., 2001, Selvaggi et al., 2003). False negative diagnoses were less common but were reported for a mucinous CRC (Lonneux et al., 2002), for mistaken physiological uptake in the bladder, and in patients who had undergone chemotherapy (Flamen et al., 2001).

Table 11 Diagnostic accuracy of FDG-PET 2000-2003

Author	Patients	Indication	Sensitivity % (95 per cent CI)	Specificity% (95 per cent CI)	Accuracy % (95 per cent CI)
Arulampalam et al., 2001	42	Detection of recurrence/ metastases	93 (79-98)	58 (32-81)	83 (69-92)
	15	Determination of the extent of local recurrence	100 (68-100)	86 (49-97)	100 (80-100)
	15	Determination of the extent of liver metastases	100 (74-100)	100 (51-100)	100 (80-100)
Even-Sapir et al., 2002[16]	56	Recurrent or metastatic disease	91 (81-96)	73 (43-90)	88 (78-94)
Flamen et al., 2001	50	Unexplained CEA rise	79 (65-89)	43 (16-75)	74 (60-84)
Hung et al., 2001	33	Detection of recurrence of CRC	100 (80-100)	83 (61-94)	91 (76-97)
Johnson et al., 2001[17]	123	Detection of recurrence all sites	87 (NAC)	96 (NAC)	NAC
	41	Detection of recurrence in liver region	100 (NAC)	100 (NAC)	NAC
	41	Detection of recurrence in extrahepatic region	90 (NAC)	95 (NAC)	NAC
	41	Detection of recurrence in the pelvis	87 (NAC)	94 (NAC)	NAC
Lonneux et al., 2002	79**	Detection of known /suspected recurrence	97 (90-99)	72(43-90)	94 (86-97)
	79	Detection of liver metastases	97 (85-99)	100 (92-100)	99 (93-100)
	79	Detection of lung metastases	92 (74-98)	95 (85-98)	94 (86-97)
	79	Detection of local recurrence	100 (80-100)	98 (92-100)	99 (93-100)
	79	Detection of other metastases	90 (60-98)	94 (86-98)	94 (86-97)
Moore et al., 2003	60*	Detection of recurrence rectal ca	84 (62-95)	88 (75-95)	87 (76-93)
Selvaggi et al., 2003	31	Detection of asymptomatic recurrence	100 (51-100)	96 (82-99)	97 (84-99)
Simo et al., 2002	58	Unexplained CEA rise	92 (79-97)	100 (85-100)	95 (86-98)
	31	Inconclusive CDM	100 (86-100)	100 (65-100)	100 (89-100)
Staib et al., 2000	100	Detection of recurrent CRC	98 (91-100)	90 (78-96)	95 (89-98)
Tanaka et al., 2002	18	Detection of suspected peritoneal recurrence	100 (51-100)	93 (69-99)	94 (74-99)
Yang et al., 2003[18]	30	Detection of liver metastases	71 (45-88)	94 (72-99)	83 (66-93)

NAC= not able to calculate * 19 cases and 41 controls ** 122 patients reviewed

Overall summary of FDG-PET results

The overall diagnostic performance of FDG-PET reported in health technology assessments, meta-analyses and recent clinical studies is summarised in Table 12.

[16] Even-Sapir, E., Lerman, H., Figer, A., Rabau, M., Livshitz, G., Inbar, M. and Gutman, M. (2002). *Journal of Nuclear Medicine* **43**(5): 603-609.

[17] Johnson, K., Bakhsh, A., Young, D., Martin, T. E., Jr and Arnold, M. (2001). *Diseases of the Colon & Rectum* **44**(3): 354-357.

[18] Yang, M., Martin, D. R., Karabulut, N. and Frick, M. P. (2003). *Journal of Magnetic Resonance Imaging* **17**(3): 343-349.

Table 12 Summary of the sensitivity and specificity of PET in recurrent colorectal cancer

Source	Year	Type	Sensitivity % (95 % CI)	Specificity % (95% CI)
Huebner	2000	Meta-analysis	97 (95-99)	76 (63-88)
AETMIS	2001	HTA	95-100 (NAC)	92-95 (NAC)
Post 2000 studies	2001-2004	Clinical studies	95 median*	94 median**

* range 71-100, ** range 43-100, NAC = not able to calculate CIs

Overall, the reported accuracy of FDG-PET was high. The ability of PET to correctly identify patients with recurrent or metastatic lesions (sensitivity) was 95 per cent or above in most studies; estimates of the ability of PET to correctly identify patients who did not have recurrent cancer (specificity) were generally lower and more variable. Inflammatory response, infections and high physiological uptake of FDG in the urinary tract were the main cause of false positive test results. False negative diagnoses were less common but were reported for a patient with mucinous colorectal cancer, mistaken physiological FDG uptake and patients who had undergone chemotherapy.

Diagnostic accuracy of CEA-Scan®

A search of all literature reporting the use of CEA-Scan® conducted for the current review identified 48 publications reporting on CEA-Scan® (Appendix H). After screening, 34 studies were excluded (Table 13).

Table 13 Reasons for exclusion of CEA-Scan® papers examined in full text

Reason for exclusion	Number of papers excluded
Not CEA-Scan®	2
Non-systematic review	9
Not recurrent CRC	2
Not a clinical study	1
Reference standard problems	2
Sample size <10	11
Abstract	7
Total	**34**

The remaining 14 studies were potentially eligible for review. However, in one study (Hladik et al., 2001) it was not possible to extract data on recurrence from mixed primary and recurrent disease patients, and three studies (Patt et al., 1993, Lechner et al., 2000b, Moffat et al., 1994) duplicated or preceded a subsequent study addressing the same question from the same institution. The remaining 10 papers formed the basis of the review. These papers are summarised in the evidence tables in Appendix J and the full selection process for CEA-Scan® literature is summarised in a flow diagram in Appendix G.

Methodological issues in CEA-Scan® studies

The most rigorous study design for assessing the validity of a diagnostic test is generally considered to be a prospective, blinded comparative study of the test and a reference test or gold standard in a consecutive series of patients from a relevant clinical population (Jaeschke et al., 1994, Sackett and Haynes, 2002, Irwig et al., 2002, Irwig et al., 1994). These criteria have been applied in a quality assessment of the studies reporting on the accuracy of CEA-Scan® for the study indications.

None of the studies reported matched this specification completely and all studies were subject to potential bias from one or more of the main sources that are known to influence the estimation of accuracy of a diagnostic test.

In addition, a number of other shortcomings had the potential to impact on the quality of some of the studies and influence the estimates of accuracy reported. These included:

- lack of detail on patient follow-up or consistency of follow-up in patients who did not have surgery;
- lack of appropriate sub-set analysis;
- combining results for occult disease, known recurrence and suspected recurrence with symptoms and/or failure to report important disease sub-groups separately, i.e. colon cancer and rectal cancer;
- lack of detail relating to histopathology results and surgical exploration;
- variation in reporting where results were reported by scans, lesions sites and patients.

Diagnostic accuracy of CEA-Scan®

A summary of the relevant findings relating to the accuracy of CEA-Scan®, based on results per patient, is given in Table 14. Additional summaries for individual disease sites are given in Table 15 and the overall diagnostic accuracy of CEA-Scan® for all sites and indications is summarised in Table 16. Detailed evidence tables that include accuracy estimates reported by lesion for each of the studies can be found in Appendix J.

Table 14 The estimated accuracy of CEA-Scan® reported by patients

Publication/ Patients	Indication	Sensitivity % (95%CI)	Specificity % (95%CI)	Accuracy % (95 % CI)	PPV %	NPV %	LR+	LR-
Baulieu et al., 2001 N=40	Suspected recurrence	Not reported separately or not able to calculate						
	Confirmed recurrence							
	Liver metastases	53(36-70)	100(72-100)	65(50-78)	100	42	∝	0.47
	Extra-hepatic abdominal metastases	100(76-100)	82(64-92)	88(74-95)	71	100	5.6	0.0
Fuster et al., 2003 N=51 8 patient repeat scans	Suspected recurrence (all sites) †	48(33-63)	97(93-99)	86(75-93)	83	87	17.3	0.54
	Liver metastases	27(10-57)	100(93-100)	86(75-93)	100	86	∝	0.72
	Extra-hepatic abdo/pelvic metastases	78(55-91)	90(77-96)	86(75-93)	NC	NC	7.97	0.25
	Thorax	22(6-55)	100(93-100)	88(77-94)	100	88	∝	0.78
Hughes et al., 1997 N=209	Known recurrence	Not reported separately or not able to calculate						
	Suspected recurrence							
	Overall disease groups	52(45-60)	72(58-83)	57(50-63)	84	33	1.90	0.66
	Liver metastases (n=100)	43(33-53)	43(16-75)	43(34-53)	NC	NC	0.75	1.33
	Overall resectability	64(53-73)	52(43-61)	57(50-63)	49	67	1.33	0.70
	Liver metastases resectability (n=100)	47(32-63)	41(30-53)	43(33-53)	29	61	0.75	1.33
Lechner 2000 N=40	All patients except those with Duke's A CRC were monitored for recurrence	100(81-100)	79(60-91)	88(74-95)	76	100	4.8	NC
Lechner 1993	Suspected recurrence (n-=15) † ‡	100(76-100)	88(69-96)	92(78-97)	80	100	8.0	0.0
Libutti 2001 N=28	Known recurrence (n=15)	Not reported separately or not able to calculate						
	Suspected recurrence rising CEA (n=15)							
	All patients	18(7-39)	33(10-70)	21(10-40)	50	10	0.27	2.45
Moffat 1996 N=210	Know recurrence/ metastases(n=122) §	78(70-85)	86(49-97)	79(71-85)	97	36	5.48	0.25
	Suspected recurrence (n=88)	Not reported separately or not able to calculate						
	All patients	71(64-78)	63(44-79)	70(63-76)	91	28	1.90	0.46
Patt 1994	Suspected recurrence † (n=15)	100(76-100)	67(21-94)	93(70-99)	92	100	3.00	0.00
Sirisriro 1996 N=24	Known recurrence (n=10)	Not reported separately or not able to calculate						
	Suspected recurrence (n=14)							
	Patients all sites (n=24)	95(75-99)	60(23-88)	88(69-96)	90	75	2.37	0.09
	Liver (n=24)	71(35-92)	100(81-100)	92(74-98)	100	89	∝	0.29
	Abdomen (n=23)	93(69-99)	89(57-98)	91(73-98)	93	89	8.36	0.08
	Pelvis (n=24)	70((40-89)	79(52-92)	75(55-88)	70	79	3.27	0.38
Willkomm 2000 Asymptomatic N=13	Asymptomatic local recurrence †	100(44-100)	100(73-100)	100(77-100)	100	100	∝	∝
	Asymptomatic liver metastases †	0(0-39)	100(65-100)	54(29-77)	NC	54	∝	1.00
	Asymptomatic distant metastases †	33(6-79)	100(73-100)	85(58-96)	100	78	∝	0.67
Symptomatic N=15	Symptomatic local recurrence	83(44-97)	100(71-100)	93(70-99)	100	90	∝	0.17
	Symptomatic liver metastases	33(6-79)	100(76-100)	87(62-96)	100	86	∝	0.67
	Symptomatic distance metastases	0(0-79)	100(78-100)	93(70-99)	NC	93	∝	100

† Based on rising CEA and clinical suspicion of disease ‡ based on number of scans not patients § 20 per cent of patients had primary disease, 9 per cent with metastases. NC = not able to calculate, ∝ = infinity, PPV = positive predicative value, NPV = negative predictive value LR+ = positive likelihood ratio, LR- = negative likelihood ratio.

Study heterogeneity

The reported accuracy of CEA-Scan® varied widely over the appraised studies. The poorest results overall were reported by Libutti et al., (2000) in a comparative study of CEA-Scan® and FDG-PET, while the most favourable results were also reported in a

comparative study of CEA-Scan® and FDG-PET (Willkomm et al., 2000), for patients with asymptomatic local recurrence. All of the studies included symptomatic or asymptomatic patients with rising serum CEA. However, the accuracy of CEA-Scan® was generally reported either for both groups combined or for individual disease sites. Where patients with symptomatic and asymptomatic disease were reported separately (Willkomm et al., 2000, Lechner et al., 1993, Patt et al., 1994, Fuster et al., 2003, Moffat et al., 1996), the accuracy of CEA-Scan® again showed wide variation.

The overall heterogeneity of estimates of the diagnostic accuracy of CEA-Scan® was of some concern. There were a number of potential sources of bias that may have impacted on the estimates of accuracy and contributed to the observed heterogeneity of the estimates:

Small study size: Most of the studies reviewed were small. Only three studies had a sample size larger than 50 (Hughes et al., 1997, Moffat et al., 1996, Fuster et al., 2003) and two of these studies reported on different outcomes in the same large group of patients (Hughes et al., 1997, Moffat et al., 1996). Random effects, which may result in over- or under-estimation of estimates, are highly likely in small studies.

Selection bias: Only four of the studies reported on a consecutive patient population (Baulieu et al., 2001, Fuster et al., 2003, Lechner et al., 2000a, Sirisriro et al., 1996). In the remainder, patients were either selected on the basis of strict entry criteria (Willkomm et al., 2000) or the selection process was unclear. Patient selection often may lead to the over-estimation of diagnostic accuracy, while unselected series often report much lower estimates. The external validity or general applicability of the results of studies reporting on selected patients may also be limited.

Review bias: In all except two studies (Willkomm et al., 2000, Lechner et al., 1993) CEA-Scan® was interpreted without knowledge of the results of the reference test. However, in the two unblinded studies it was not clear if test evaluation was influenced by foreknowledge of the results of the reference test, one study (Lechner et al., 1993), reported 100 per cent sensitivity and the other (Willkomm et al., 2000), 100 per cent specificity for CEA-Scan®. Review bias most commonly results in an over-estimation of test accuracy.

Verification bias: In five studies (Baulieu et al., 2001, Fuster et al., 2003, Hughes et al., 1997, Lechner et al., 2000a, Sirisriro et al., 1996) full surgical exploration and verification of the imaging results was only performed on patients with positive imaging results. As error arising from this type of bias may lead to both under- and over-estimation of test accuracy, potential verification bias in a large proportion (50 per cent) of the studies could have contributed significantly to the observed heterogeneity in the results.

In four out of the 10 CEA-Scan® studies reviewed (Lechner et al., 2000a, Hughes et al., 1997, Moffat et al., 1996, Patt et al., 1994) there appeared to be potential for a conflict of interest with one or more authors either shareholders or on the board of the manufacturer of CEA-Scan®. All four studies were supported financially by the manufacturer of CEA-Scan®.

Asymptomatic patients with rising serum CEA

CEA-Scan® results were reported separately for asymptomatic patients with rising serum CEA and/or clinical suspicion of disease in four studies. In the largest study (Fuster et al., 2003) the sensitivity of CEA-Scan® was 48 per cent and the specificity 97 per cent with an overall accuracy of 86 per cent. In the smallest study (Willkomm et al., 2000) the specificity of CEA-Scan® was 100 per cent for asymptomatic local recurrence, liver and distant metastases. However, sensitivity varied from 0 per cent for asymptomatic liver lesions through 33 per cent for asymptomatic distant metastases to 100 per cent for asymptomatic local recurrence, see Table 14.

Symptomatic patients

CEA-Scan® results were only reported separately for this group of patients in one study (Willkomm et al., 2000). For 15 patients with symptomatic disease the sensitivity of CEA-Scan® varied between 0 per cent for the detection of symptomatic distant metastases, through 33 per cent for symptomatic liver metastases to 83 per cent for patients with symptomatic local recurrence. Specificity for all sites was 100 per cent with this small study group.

Sites of recurrence (local, liver, extra-hepatic/distant sites)

All accuracy estimates varied widely and summaries in Table 15 have been based on median estimates to moderate the effect of extreme values.

Table 15 Diagnostic accuracy of CEA-Scan® for individual disease sites

Disease site	Group size range	Number of studies	Number of patients	Average study size	Median sensitivity† (range)	Median specificity§ (range)	Median accuracy‡ (range)
Local recurrence	13-24	4	75	19	88%(70-100)	95%(79-100)	92%(75-100)
Liver	13-100	6	251	42	38%(0-71)	100%(43-100)	76%(43-92)
Extra-hepatic/distant sites	13-59	5	186	37	33%(0-100)	100%(82-100)	87%(85-93)

‡ proportion of all test results, both positive and negative, that are correct † proportion of patients with the disease that are correctly identified; § proportion of patients who do not have the disease that are correctly identified.

CEA-Scan® was most accurate for the determination of local recurrence (median 92 per cent, range 75-100 per cent) and least accurate for the detection of liver metastases (median 76 per cent, range 43-92 per cent). Sensitivity scores were lower than overall accuracy scores for all disease sites. Specificity scores, i.e. the ability of CEA-Scan® to rule out disease at a specific site, were generally higher than sensitivity or overall accuracy for local recurrence, liver and extra-hepatic metastases.

Overall diagnostic accuracy and study size

The number of patients in each study varied from 15 to 210, see Table 16. Small studies tended to have the highest accuracy scores. The single large study (n=210) reported an accuracy of 70 per cent with a sensitivity of 71 per cent and a specificity of 63 per cent. Studies with fewer than 100 patients and an average study size of 29 reported rather higher scores, with a median accuracy of 88 per cent, a median sensitivity of 98 per cent and a median specificity of 73 per cent.

Table 16 Overall diagnostic accuracy of CEA-Scan® for all disease sites

Study type	Group size range	Number of studies	Number of patients	Average study size	Median sensitivity† (range)	Median specificity§ (range)	Median accuracy‡ (range)
All studies	15-210	7**	383	55	95% (18-100)	67% (33-97)	88% (21-93)
Study size <100	15-51	6	173	29	98% (18-100)	73% (33-97)	88% (21-93)
Study size >= 100	210	1*	210	210	71%	63%	70%

* Hughes et al., 1997 not included (duplicate population) ** Hughes et al., 1997, Bauleiu et al., 2001, Willkomm et al., 2000 only reported by disease site. ‡ proportion of all test results, both positive and negative, that are correct † proportion of patients with the disease that are correctly identified; § proportion of patients who do not have the disease that are correctly identified.

Summary of the accuracy of CEA-Scan®

The estimates of accuracy for CEA-Scan® in the reported studies varied widely, making a precise estimate of test performance difficult. The studies were also subject to a number of weaknesses and biases that are likely to have contributed to the observed heterogeneity and compromised the validity of a number of studies. Small study size and selection bias are likely to have strongly influenced the results in a significant number of studies.

Despite these difficulties, a number of general statements are possible about the accuracy of CEA-Scan®. The overall accuracy of CEA-Scan® in the reported studies is low and the ability of CEA-Scan® to correctly identify patients with liver disease poor. CEA-Scan® has a better ability to rule out (specificity) than rule in (sensitivity) recurrence at particular disease sites. However, overall accuracy may be increased through careful selection of individual patients and in particular patient groups notably;

- asymptomatic patients with rising serum CEA;
- patients with local recurrence;
- patients with extrahepatic abdominal recurrence.

Comparison of CEA-Scan® and FDG-PET

Only two studies (Libutti et al., 2001, Willkomm et al., 2000) compared CEA-Scan® and FDG-PET in the same patient population. Both were prospective case series carried out on a small, selected population of patients with known or suspected recurrent colorectal cancer. The diagnostic performance of CEA-Scan® and FDG-PET in both studies is summarised in Table 17 and reported in full in the evidence tables in Appendix J.

Table 17 Head-to-head studies of CEA-Scan® and FDG-PET

Study	Site	N	Imaging technique	Sensitivity % (95% CI)	Specificity % (95% CI)	Accuracy % (95 % CI)
Libutti et al., 2001	All sites	28 patients	CEA-Scan®	18 (7-39)	33 (10-70)	21 (10-40)
			FDG-PET	88 (71-96)	50 (9-91)	86 (69-94)
		119 lesions	CEA-Scan®	5 (2-12)	86 (72-94)	30 (23-39)
			FDG-PET	57 (47-67)	65 (49-78)	60 (51-68)
Willkomm et al., 2000	Local	28 patients	CEA-Scan®	89 (56-98)	100 (83-100)	96 (82-99)
			FDG-PET	100 (70-100)	95 (75-99)	96 (82-99)
	Liver	28 patients	CEA-Scan®	11 (2-44)	100 (83-100)	71 (53-85)
			FDG-PET	100 (70-100)	100 (83-100)	100 (88-100)
	Distant	28 patients	CEA-Scan®	25 (5-70)	100 (86-100)	89 (73-96)
			FDG-PET	100 (51-100)	100 (86-100)	100 (88-100)
	All sites	140 lesions	CEA-Scan®	42 (24-61)	100 (97-100)	90 (84-94)
			FDG-PET	100 (86-100)	99 (95-100)	99 (96-100)

Libutti et al., (2001) studied 30 colorectal cancer patients with rising serum CEA but without evidence of disease on standard imaging[19] (arm one) and patients with evidence of resectable disease on conventional anatomical imaging who were thought to have further occult disease which may make surgical resection less effective (arm two). Two patients were found to have extra abdominal disease on FDG-PET and were excluded; 28 patients were eligible for study.

Both CEA-Scan® and PET were assessed independently of each other and blind to the results of surgery. CEA-Scan®, FDG-PET and blind second-look surgery were compared with the results of a second unblinded surgical exploration. This exploration was carried out with full knowledge of the results of the definitive pathology and the advanced imaging studies. These results, together with close follow-up of the patients post-operatively, served as the gold standard against which CEA-Scan® and FDG-PET results were judged.

The accuracy of CEA-Scan® and FDG-PET was reported by patient (n=28) and lesion (n=119) and compared with the gold standard. CEA-Scan® had a reported accuracy over all patients of 21 per cent, a sensitivity of 18 per cent, a specificity of 33 per cent, a PPV of 50 per cent and a NPV of 10 per cent. FDG-PET accuracy was 86 per cent, with a reported sensitivity of 88 per cent, a specificity of 50 per cent, a PPV of 96 per cent and a NPV of 25 per cent. The reported accuracy for lesions was generally lower with a sensitivity of 57 per cent reported for FDG-PET against a sensitivity of 5 per cent for CEA-Scan®. However, CEA-Scan® had a higher specificity than FDG-PET in identifying 32 true negative and five false positive lesions against 24 true negative and 13 false positive lesions recorded for FDG-PET.

FDG-PET predicted unresectable disease in nine out of 10 patients, while CEA-Scan® failed to predict unresectable disease in any patient that was explored. In 16 patients with

[19] All patients had previously had CT, bone scan, MRI and a total colonoscopy.

resectable disease FDG-PET made correct predictions in 13 cases (81 per cent), CEA-Scan® correctly predicted two cases (13 per cent).

There are a number of methodological problems with this study that may affect the validity of these results. CEA-Scan® and FDG-PET were assessed against a standard that included knowledge of the results of both advanced imaging techniques. Moreover, although FDG-PET scans were read independently of any other imaging, an observer who had also reviewed the patients' CT scans evaluated the CEA-Scans®. The main surgical exploration was also unblinded to the results of the two advanced imaging studies. In addition, there was considerable scope for bias in the selection of the study patients, which comprised a non-consecutive group of relatively young and fit patients.

It is not clear why CEA-Scan® performed so poorly in this study and no explanation was put forward by the authors. However, there were a number of factors that may have impacted on the CEA-Scan® results: (i) random effects resulting from a small study population; (ii) selection bias arising from the exclusion of patients with extra abdominal or visible abdominal disease; (iii) an imperfect or biased reference standard due to the incorporation of advanced imaging (CEA-Scan® and FDG-PET) into the gold standard and (iv) inappropriate interpretation criteria. It is not clear, for example, what degree of uptake was considered positive; too high a threshold may have lead to the very high false negative rates for CEA-Scan® observed in this study. Each of these features can result in under-estimation of diagnostic accuracy and the combined effect could lead to significant bias in the estimation of test accuracy.

The second head-to-head study (Willkomm et al., 2000) was also a small prospective study of 28 selected patients. A large proportion (79 per cent) of the relatively young patient group had rectal cancer. All patients underwent CEA-Scan® and FDG-PET imaging and all scans were compared to the reference standard. Only patients eligible for surgery were confirmed by histology the remainder were verified by clinical follow-up. CEA-Scan® and FDG-PET images were assessed independently but further blinding was not reported. Accuracy results were reported by site of recurrence for 28 patients and 140 lesions.

The overall accuracy of CEA-Scan® for patients with local recurrence, liver and distant metastases was 96 per cent, 71 per cent and 89 per cent respectively, while overall accuracy of FDG-PET for the same sites was 96 per cent, 100 per cent, 100 per cent, see Table 17. The sensitivity of CEA-Scan® was 89 per cent for local recurrence, 11 per cent for liver metastases and 25 per cent for distant metastases; the sensitivity of PET for all sites was 100 per cent. Specificity values varied little between the two tests with CEA-Scan® reported at 100 per cent for all sites and FDG-PET at 100 per cent for liver and distant metastases and 95 per cent for local recurrence. When the accuracy of CEA-Scan and FDG-PET were compared across all 140 lesions the same trends were apparent. CEA-Scan® and FDG-PET both correctly determined the status of 125 of 140 lesions. In the 15 discordant lesions CEA-Scan® correctly determined the status of a single local lesion, FDG-PET correctly determined the status of the remaining 14 lesions which included eight liver, one local, one bone, two lung and two lymph node metastases.

Sub-set analysis for asymptomatic patients (n=13) revealed perfect scores for FDG-PET imaging of all sites, generally low scores for CEA-Scan® in the detection of liver metastases, and a low sensitivity for distant metastases (evidence tables, Appendix J). This pattern was repeated for symptomatic patients with FDG-PET accuracy higher than that of CEA-Scan® and the latter failing to identify liver and distant metastases. These

sub-set analyses, however, are likely to be subject to the vagrancies of small sample size and low event rates.

Overall, both imaging techniques showed high accuracy, sensitivity and specificity for local recurrence but only FDG-PET appeared to have the ability to detect liver and distant metastases with the same high degree of accuracy. The 95 per cent confidence limits for all estimates were wide due to the small sample size.

The authors concluded that both FDG-PET and CEA-Scan® could detect local recurrence of colorectal carcinoma, that CEA-Scan® showed a high sensitivity for scarring or relapse of CT-proven lesions and FDG-PET was better able to determine the extent of recurrence due to higher sensitivity for lymph node and distant metastases.

There were a number of methodological weaknesses in the study that may have impacted on the validity of the results. Within the CEA-Scan® study, population selection bias was apparent. Four patients with liver metastases greater than 1.0 cm did not have SPECT imaging of the upper abdomen. The low accuracy of CEA-Scan® in this group of patients may have been due to reliance on planar imaging, which is known to perform poorly in this area. In an unknown number of cases, the length of follow-up fell short of the required 12-month minimum, partially invalidating the gold standard in these patients. The small study population contained a high proportion of rectal cancer patients, which may limit the applicability of the results to routine practice. Finally, although CEA-Scan® and PET were reviewed independently of each other, it was not clear if they were reviewed blind to the results of surgery or other imaging.

The use of CEA-Scan® in patients with negative or equivocal FDG-PET scans

All clinical studies reporting on CEA-Scan® were examined for information relating to the use of CEA-Scan® in cases where FDG-PET scans were negative or unhelpful. No studies were identified in which CEA-Scan® had been employed as a third-line imaging technique. However, three studies (Libutti et al., 2001, Baulieu et al., 2001, Willkomm et al., 2000) discussed the relative merits of CEA-Scan® and FDG-PET. All three studies discussed the limited availability and expense of FDG-PET compared with CEA-Scan® and Willkomm et al., (2000) noted that FDG was unspecific tracer. In a comparative study of CEA-Scan® and FDG-PET, Libutti et al., (2001) recommended selective repeat imaging at 3-6 months for patients with negative FDG-PET scans but did not specify which tests should be used. Baulieu et al., (2001), in a discussion of immunoscintigraphy and FDG-PET, also noted that in some instances FDG-PET lacked specificity and that antibodies were the theoretical paradigm of high affinity, specific targeting molecules.

Summary

CEA-Scan® and FDG-PET were compared head to head in two small studies. Both studies included a group of patients with known recurrence and a group of asymptomatic patients, each group comprising fewer than 20 patients. Because of the small number of patients involved in these studies, all patient-based estimates had wide confidence intervals.

CEA-Scan® was less accurate than FDG-PET across all analyses (CEA-Scan® median 80 per cent, range 21-96 per cent; FGD-PET median 98 per cent, range 60-100 per cent). Sensitivity values followed the same general pattern but with particularly low values for

CEA-Scan® in the detection of liver and distant metastases. However, in one study CEA-Scan® and FDG-PET were both able to identify patients without disease with high accuracy (95-100 per cent) and in one group of patients, CEA-Scan® correctly identified eight out of nine patients with local disease recurrence. It also had a higher specificity (100 per cent) than FDG-PET (95 per cent). In the same study, CEA-Scan® and FDG-PET both correctly determined the status of 125 of 140 lesions. Five studies reported clinical benefits for patients receiving CEA-Scan®, see Table 19. No studies reported on the use or potential of CEA-Scan® imaging of patients after negative or equivocal FDG-PET.

Change in management and health outcomes

Demonstration of high diagnostic accuracy alone is not sufficient to establish a diagnostic test in routine clinical practice. The test must demonstrate that its use will impact significantly on the management of patients and result in worthwhile improvements in patients' health or quality of life.

FDG-PET management and outcome changes

In August 2000, the steering committee overseeing a review of the use of FDG-PET in Australia (Department of Health and Ageing, 2001) recommended that further evaluation of the clinical and cost-effectiveness of PET for recurrent colorectal cancer should be carried out. Lack of outcome data at this time (MSAC report 2000) prohibited a recommendation for unrestricted funding of FDG-PET for recurrent colorectal cancer through the Medicare Benefits Schedule.

Since that time, a number of studies have been published examining or reporting on the effect of FDG-PET on clinical practice that has the potential to change patient outcome. Of the 12 clinical studies of FDG-PET evaluated for accuracy in this review, six reported the effect of FDG-PET on the management of study patients.

Arulampalam et al., (2001) reported that 27 per cent of 30 patients with recurrence were upstaged and 47 per cent had significant and beneficial change in management as a result of the use of FDG-PET. Two patients (7 per cent) in this study had non-productive surgery. The diagnostic impact of FDG-PET in recurrent CRC was also reported by Flamen (2001). Surgery was avoided and chemotherapy initiated in 20 patients (47 per cent) with a positive PET finding. Dedicated diagnostic procedures based on the results of PET imaging led to resection with curative intent in 33 per cent of the study population. The effect on patient management of four incorrect diagnoses based on PET was not reported.

In a retrospective study of the effect of FDG-PET on the re-staging of patients with suspected recurrent CRC, Lonneux (2002) found that in 42 per cent of patients the stage was correctly modified, and seven (9 per cent) of these patients were spared surgery. Most (70 per cent) of the staging changes effected by PET resulted in patients being upstaged because more extensive disease was discovered, sparing some patients unnecessary surgery and leading to more patients going to surgery with chance of cure (truly limited disease). Overall, management changes were reported in 48 per cent of patients, and patients operated on with curative intent had a higher three-year survival than the rest of the study patients (78 per cent, P=0.06, non-significant). Lead-time bias,

ie, earlier diagnosis, was not thought to fully explain the increase, as a group of asymptomatic patients with early diagnosis showed no survival benefit.

In another study (Selvaggi et al., 2003), the use of FDG-PET in the follow-up of 31 disease-free, non-diabetic patients after curative surgery resulted in upstaging of eight (27 per cent) patients and altered the management in 16 (38 per cent). One FDG-PET positive patient underwent surgery with no evidence of disease.

Two papers (Simo et al., 2002, Staib et al., 2000) indicated that the aim of the study was to evaluate the contribution of FDG-PET to the management of recurrent colorectal patients. Simo et al., (2002) evaluated the effect of FDG-PET on patient management for 120 cases of suspected recurrent CRC presenting to the CWTIR PET Center in Barcelona, Spain. The use of FDG-PET resulted in major management change in 58 (48 per cent) patients, minor changes in four (3 per cent) and no change in 54 (45 per cent) of patients. Of 25 patients undergoing pre-operative assessment, management was changed from surgery to chemotherapy in eight (32 per cent) and of 31 patients evaluated because of inconclusive conventional diagnostic tests, 14 (45 per cent) were changed from local to systemic therapy because of the detection of disseminated disease by FDG-PET. PET also led to a major management change in 34 (59 per cent) of 58 patients with raised serum CEA and 18 (53 per cent) of these patients were treated with potentially curative surgery. Negative impact of FDG-PET was not reported.

Staib et al., (2000) reported that FDG-PET influenced surgical decisions in 61 (61 per cent) cases. None of the false PET results was reported to have had a serious negative consequence for surgical decision-making.

Summary

All six studies reported a change in management in a substantial proportion of patients as a result of the use of FDG-PET. In half of the studies, PET identified more extensive disease than conventional anatomical imaging (see Table 18), and these changes impacted on treatment decisions mostly, resulting in sparing patients unnecessary surgery.

Table 18 Studies reporting the clinical benefits of FDG-PET between 2000-2004

Reported item	Patients upstaged	Stage modified	Management change	Non-productive
Patients affected, median per cent (range)	27%(27-29)	44%(42-45)	47%(38-61)	3%(0-7)
Number of studies reporting	3	2	6	3

CEA-Scan® management and outcome changes

Of the 10 clinical studies of CEA-Scan® evaluated for accuracy in this review, five reported the effect of CEA-Scan® on the management or outcome of study patients.

Baulieu et al., (2001) reported an undefined "beneficial impact" on the surgical management of 15 patients (37 per cent) with suspected liver metastases. A reported NPV of 100 per cent for CEA-Scan® in the detection of extra-hepatic lesions allowed the surgeons to propose major surgery when required.

Serial CEA-Scan® was reported to have had a therapeutic impact in six (38 per cent) of 16 patients with recurrent rectal cancer (Lechner et al., 2000a), with four (25 per cent) of these patients undergoing potentially curative second-look surgery. These six patients had a mean disease-free survival of at least 35 months and one patient was alive without evidence of disease seven years after resection. A further five (31 per cent) patients were reported to have received palliative procedures that led to marked symptomatic relief. Three patients (19 per cent) had no operation and two (13 per cent) had an exploratory laparotomy with no influence on symptoms or prognosis.

In an early study by Moffat et al., (1996), the managing clinicians of patients with known disease reported changes in the assessment of the extent of disease in 64 (61 per cent) patients and "potential" changes in clinical management in 64 (61 per cent) patients.

Immuomedics[20] medical personnel reported "potential" clinical benefit in 40 (33 per cent) patients. Additional information was obtained from CEA-Scan® in 70 (67 per cent) of patients with known disease. Patients with occult disease were reported to have had a change in assessment of disease extent in 61 (81 per cent) cases, a presumed change in therapy in 61 (81 per cent) and potential clinical benefit in 49 (56 per cent) cases.

The overall effect of CEA-Scan® was not separated from that of laparotomy by Patt (1994), who reported that in 15 patients with recurrent rectal cancer, the "total impact" of CEA-Scan® and laparotomy on patient management was 80 per cent; cancer treatment was changed to chemotherapy in five (33 per cent) patients, complete tumour resection accomplished in five (33 per cent) patients and a negative disease status recorded for two (13 per cent) patients. For five (33 per cent) patients who were reported to have had "optimal" results from CEA-Scan® imaging (exploratory laparotomy and potentially curative resection), survival ranged from at least 12 months to at least 33 months; however, only two patients were disease free at the time of reporting. In a study of the surgical management of 24 consecutive colorectal patients, the surgeon judged CEA-Scan® to be "helpful" in six (24 per cent) patients and "neutral" in 18 (74 per cent) (Sirisriro et al., 1996).

Summary

Change in the assessment of disease extent was reported in only one study (Moffat et al., 1996). However, in this study 81 per cent of patients with occult disease had their disease status changed as a result of CEA-Scan®. All studies reported clinical benefits and all but one study reported change, or the potential for management change, as a result of CEA-Scan®. Deleterious or non-productive interventions were reported in four studies, see Table 19.

[20] Manufacturers of CEA-Scan

Table 19 Studies reporting the clinical benefits of CEA-Scan®

Reported item	Changed assessment of disease extent	Management change*	Clinical benefit or impact*	Non-productive*
Patients affected, median per cent (range)	74(67-81)†	38(33-81)‡	37(24-80)‡	7(0-13)
Number of studies reporting	1	4	5	4

† Known disease and occult disease sub-sets ‡ includes known disease and occult disease sub-sets *one study reported the potential for change if the test had been part of routine work-up

The reported changes impacted on treatment decisions in four main areas:

- resection with curative intent, particularly decisions relating to hepatectomy, ie, the exclusion of extra-hepatic disease;
- avoidance of unnecessary surgery;
- instigation of systemic chemotherapy;
- identification of new disease leading to extended surgical exploration.

No papers reported the effect of CEA-Scan® on the overall survival of patients, although all reported on the potential for change in outcome. It is not yet clear if patients receiving CEA-Scan® benefit in terms of recurrence rate and survival.

Limitations of the review

- since only English language literature was reviewed, relevant articles in other languages may have been missed;
- quality assessment of non-comparative studies for diagnostic accuracy;
- large volume of literature on CRC and FDG-PET;
- small volume of literature on CEA-Scan®;
- quality of the reference standard: verification bias (van Erkel et al., 2002) is likely to over-estimate the detection rates for lesions as small lesions are not uncovered by the reference standard.

Economic considerations

The purpose of an economic assessment of a new health technology is to determine its value for money, to identify and compare the direct, indirect, and flow-on costs of the technology and its comparator, and to balance these against the evidence of effectiveness.

Because a technology which is less effective than the comparator would not generally be considered for funding, even if a cost saving were possible, new technologies which cannot demonstrate a level of effectiveness that is at least equivalent to that of the comparator do not warrant a full cost-effectiveness analysis. Although the data presented in this review suggests that at present there is no direct evidence that CEA-Scan® is more accurate than the comparator, or that it leads to an improved outcome for patients when used as an alternative diagnostic technique, the limited data do provide an indication that CEA-Scan® is not likely to be as accurate as the comparator. There is therefore no justification for a full health economic analysis of CEA-Scan®.

During the course of this review, no studies were identified in the literature search that compared the cost of implementing CEA-Scan® to that of implementing FDG-PET. This review of the potential costs associated with use of CEA-Scan® was therefore limited to a critique of the economic analysis of CEA-Scan® presented to MSAC in the applicant's submission for funding. As this is only a limited review of the cost implications of these imaging techniques, and due to the lack of available cost data, details as to the indirect and flow-on costs of these services are incomplete.

Decision tree

A simple decision tree, mapping the clinical choices and events in chronological order for a patient presenting with recurrent CRC in Australia is presented in Figure 3. This tree, which is derived from the flow chart shown in Figure 2, has been used to assist in the analysis of the economic arguments presented in the CEA-Scan® submission. It assumes that CEA-Scan® would be used for patients with suspected recurrent or metastatic colorectal cancer after conventional diagnostic methods had been used. For patients with liver metastases, CEA-Scan® is significantly less sensitive than FDG-PET (Willkomm et al., 2000), resulting in a larger number of negative scans. This would result in more patients undergoing repeat testing and fewer patients treated with potentially curative resection.

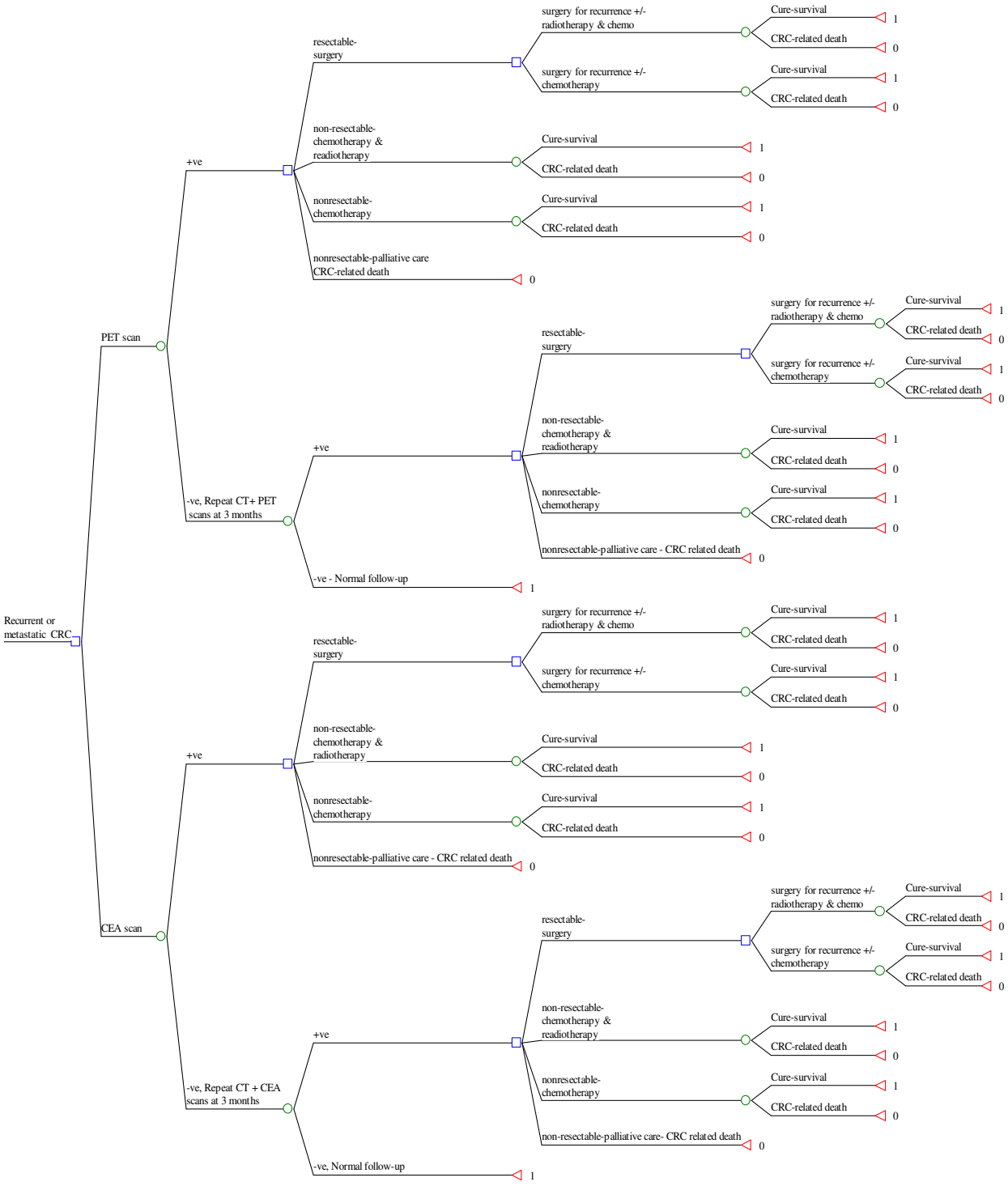


Figure 3 Decision-tree model for CEA-Scan® compared with FDG-PET

Economic aspects of the submission for funding of CEA-Scan®

The cost per patient of CEA-Scan®

In order to generate an estimate of the cost of a health technology, the direct cost must be added to estimates of indirect costs, (such as the costs of associated procedures, drugs, other health services), and of flow-on costs such as increased hospitalisation or other procedures, the need for which is a consequence of the effectiveness of the technology being evaluated.

Direct cost

The price proposed by the applicant for CEA-Scan® is $779.35 per scan.[21] The current MBS fee for whole-body FDG-PET following therapy for CRC ranges from $953 to $975 per scan[22], suggesting a lower unit cost for CEA-Scan®. However, the applicant's proposed cost for CEA-Scan® is probably unrealistic. The current purchase cost of the CEA-Scan® antibody kit is $660, and the additional cost of the radioisotope and the associated costs of performing and interpreting the scan is likely to be more than the $119.35 allowed by the applicant in the submission. A recent economic analysis of CEA-Scan® by Bridwel and Thropay (2003) suggested that the cost of the antibody kit was approximately 60 per cent of the total cost of performing a single CEA-Scan®. Using this approximation, the true cost of CEA-Scan® is likely to be approximately $1,100, ie, $125 more than the current maximum cost of FDG-PET listed in the MBS.

Indirect and flow-on costs

With a higher direct cost per patient, CEA-Scans® would have to be associated with lower indirect and flow-on costs than the comparator if any cost-savings are to be realised. Given that CEA-Scan® also appears to be less effective than the comparator, indirect and flow-on costs would also have to be lower than for the comparator in order to generate a favourable cost-effectiveness ratio.

The indirect costs of CEA-Scan®, however, must include testing for HAMA and monitoring for anaphylactic and other hypersensitivity reactions during infusion due to the small but potentially serious risk posed to patients undergoing this procedure. HAMA testing and monitoring for allergic reaction are required only for CEA-Scan® and not for FDG-PET. In addition, although the risk of severe allergic reaction is small, there may be a need for additional equipment and an appropriate team to be available in the event that allergic reaction occurs. These factors clearly suggest that the per patient indirect costs would be higher for CEA-Scan® than for FDG-PET. A lack of data on the cost of these additional procedures prevents the reliable estimation of total costs, however, a HAMA kit

[21] CEA-Scan® application to MSAC

[22] Health Insurance Determination HS/6/01, 2002

alone would cost approximately $1,378 (based on an approximate cost of US$1000[23] and the exchange rate at the time this analysis was conducted).

The flow-on costs of these imaging techniques would include any cost related to the possible allergic reaction of patients and also any costs associated with increased hospitalisation as a result of lower effectiveness. It is likely that these costs would be higher for CEA-Scan® than for the comparator due to the higher accuracy of the comparator.

Even in the absence of reliable data for indirect costs, the need for additional procedures and the risks associated with CEA-Scan®, in part due to it being less effective than the comparator, suggest that even if the cost of a single CEA-Scan® were, as suggested by the

applicant, less than the cost of a single FDG-PET scan neither a prediction of net savings nor a favourable incremental cost-effectiveness ratio for CEA-scan are likely to be realistic.

Total Health System Cost

The applicant's total annual direct cost to the Australian health system is based on:

- the 1998 incidence of colorectal cancer in Australia (11,291 cases);
- an estimated proportion undergoing potentially curative resection (85 per cent or approximately 9,5976 cases);
- an estimated proportion with recurrence among those who have had potentially curative resection (the mid-point of the 30-40 per cent range or approximately 3,359 cases);
- an estimated uptake of CEA-Scan® based on CT-scan being equivocal or patients having extensive scarring (5% or approximately 168 cases).

The resulting number of patients per year is 168. Using the estimate of $779.35 per scan, the applicant's estimate of total annual direct cost is approximately $130,000. This figure is probably an underestimate of the true annual direct cost. In addition to the unrealistically low per unit cost, this estimate is based on a low uptake of the CEA-Scan® technology. A more realistic estimate may be obtained by using:

- a more recent incidence of colorectal cancer in Australia (12,405 cases in 2000);
- a more realistic estimate of the proportion undergoing potentially curative resection (70 per cent);
- a more realistic estimate of the proportion with recurrence among those who have had potentially curative resection (up to 50 per cent);

[23] Cost obtained from a direct inquiry to Immunomedics, Morris Plains, New Jersey, USA

- the current uptake of the comparator, FDG-PET, as an estimate of the uptake of CEA-Scan® (10 per cent).

The resulting number of patients per year is 434. Applying the more realistic estimate of per unit cost ($1,100) to these assumptions, the resulting total annual direct cost is up to $477,593. Adding to this what is known about indirect and flow-on costs ($1,378 for the HAMA kit, based on US$1,000 and the exchange rate at the time this analysis was conducted, assuming one kit per patient), the estimated total annual cost of CEA-Scan® rises to as much as $1,075,886.

The estimated total annual direct cost of the comparator, FDG-PET, is $413,774 to $423,326.

In the unlikely event that all patients with recurrent CRC received a CEA-Scan®, the total (including all known direct and indirect costs) cost to the Australian health system would be in the order of $10,758,980.

CEA-Scan® as a third-line imaging technique

In selected cases and where FDG-PET is unavailable or has failed, CEA-Scan® may provide useful additional information. Unfortunately, there is insufficient evidence as to the proportion of patients for whom FDG-PET fails or would be unavailable. There is also insufficient evidence as to the effectiveness of CEA-Scan® in these patients.

Some sense of cost can be gained by considering the potential incremental cost of the test. Negative initial imaging results for both CEA-Scan® and FDG-PET would result in repeat scans, see Figure 3. CEA-Scan® is likely to result in more repeat scans because of its low specificity for hepatic metastases, which is the major site of disease recurrence. Theoretically, as CEA-Scan® has not been approved for repeat use in Australia, the cost difference between CEA-Scan® and FDG-PET would be multiplied and the potential costs could be considerably greater than stated in the submission or estimated in this assessment, which is based on a single dose of CEA-Scan®. However, it should also be noted that the current licensing of CEA-Scan® by the TGA is for a single administration of the test.

Conclusions

Safety

CEA-Scan® is currently registered for a single administration dose in Australia and may generally be considered to be safe at this dosage level. Adverse events and side effects do occur in a small number of patients but they are generally mild and transient. There are a number of potential difficulties that may be associated with repeat scanning, including an increased risk of a serious immune reaction or immune complex disease, potential interference with imaging efficiency, and laboratory tests which are based on murine monoclonal antibodies. These reactions are however, more likely to occur with whole mouse monoclonal antibodies than monoclonal antibody fragments such as CEA-Scan®. The safety of CEA-Scan® in repeated applications and in particular the long-term effects of multiple doses, has not been fully explored. Patients receiving antibodies of murine origin should be monitored for acute sensitivity reactions during, and immediately after, infusion with CEA-Scan®.

Diagnostic accuracy of CEA-Scan®

A precise estimate of CEA-Scan® test performance is difficult due to heterogeneity of study results. The validity of the estimates of accuracy of the test made in a number of the studies may have been compromised by one or more methodological weaknesses. Even so, the reported accuracy of CEA-Scan® was generally low. It was more accurate in the small, highly selected populations than the single large clinical trial that reported an overall accuracy for CEA-Scan® in the detection of recurrent disease. In this trial the reported accuracy of CEA-Scan® was 70 per cent with a sensitivity of 71 per cent and a specificity of 63 per cent. When accuracy was assessed by disease site, CEA-Scan® more accurately identified local recurrence (median accuracy 92 per cent) and extra-hepatic disease (median accuracy 87 per cent) than liver metastases (median accuracy 76 per cent). The ability of CEA-Scan® to correctly identify patients with liver disease was poor.

Diagnostic accuracy of FDG-PET

Estimates of the accuracy of the comparator, FDG-PET, against the reference standard were less variable and a larger number of studies were eligible for review. In addition, a number of health technology assessments were identified, including an MSAC report published in March 2000, and a report of the Australian review of PET published in 2001. Thirteen post-2000 clinical studies also met the eligibility criteria for review.

The overall accuracy of FDG-PET reported in all of these studies was high. The ability of PET to correctly identify patients with recurrent or metastatic lesions was generally 95 per cent or greater. Estimates of the ability of PET to correctly identify patients who did not have recurrent cancer are generally lower and more variable.

Two systematic reviews summarised the evidence up to part of the year 2000. These studies reported overall sensitivities for FDG-PET of 92-100 per cent and overall specificities of 76-100 per cent. Twelve more recent individual clinical studies had a

median sensitivity of 95 per cent (range 71-100 per cent), median specificity 94 per cent (43-100 per cent) and median accuracy 94 per cent (74-100 per cent). The results of these studies broadly confirmed the high levels of sensitivity and specificity of PET scans reported in the earlier systematic reviews.

Although FDG-PET performed well overall, not all patients benefited. Patients with uncontrolled diabetes or acute inflammation/infection were excluded from some studies. False positive imaging occurred in patients with mucinous colorectal cancer, high physiologic uptake of FDG in the urinary tract, reactive lymph nodes and in patients who had been treated with radiotherapy. False negative imaging was reported for mucinous colorectal cancer, patients with mistaken physiological uptake of FDG, and patients treated with chemotherapy.

The accuracy of CEA-Scan® and FDG-PET in head-to-head studies

CEA-Scan® and FDG-PET were compared head to head in two small studies. Both studies included patients with known recurrence and asymptomatic patients. Each group comprised fewer than 20 patients. CEA-Scan® was less accurate (median 80 per cent, range 21-96 per cent) than FDG-PET (median 98 per cent, range 60-100 per cent) across all analyses. Sensitivity values followed the same general pattern, but with particularly low values for CEA-Scan® in the detection of liver lesions and distant metastases. In one of the studies, CEA-Scan® and FDG-PET were both able to identify patients without disease with high accuracy (95-100 per cent). In one group of patients with local disease recurrence, CEA-Scan® had a higher specificity (100 per cent) than FDG-PET (95 per cent). Because of the small number of patients involved in these studies, all patient-based estimates had wide confidence intervals. In one study, both CEA-Scan® and FDG-PET correctly determined the status of 125 out of 140 lesions.

The use of CEA-Scan® in patients with negative or equivocal FDG-PET Scans

No studies were identified in which CEA-Scan® had been employed as a third-line imaging technique when FDG-PET scans were negative or unhelpful. However, three studies discussed the relative merits of CEA-Scan® and FDG-PET. The limited availability and expense of FDG-PET compared to CEA-Scan® was noted, and the fact that FDG was an unspecific tracer. One study recommended selective repeat imaging at 3-6 months for patients with negative FDG-PET scans but did not specify which tests should be used. Attention was drawn to the fact that in some instances FDG-PET lacked specificity and that antibodies were the theoretical paradigm of high affinity, specific targeting molecules.

Impact on clinical decision-making and health outcomes

There was documented evidence of the effect of CEA-Scan® test results on patient management. CEA-Scan® was reported to have changed the assessment of disease extent which led to management change and significant clinical benefit or impact. In some studies, potential rather than actual management impact was reported. Non-

productive or adverse effects of false positive or negative test results were not well reported.

FDG-PET was reported to have modified the assessment of the extent of disease leading to management change in all of the studies reviewed. In most cases, FDG-PET imaging led to an upstaging of patients after the discovery of previously undiagnosed or unknown recurrence sites in a significant number of patients. The discovery of more extensive disease changed management and avoided unnecessary surgery in these patients.

It is not yet clear if changes in the clinical management of patients arising from the use of CEA-Scan® or FDG-PET will result in improved survival.

Economic considerations

At present there is no evidence to suggest that CEA-Scan® is as accurate as the comparator FDG-PET or that it leads to an improved long-term outcome for patients. There is therefore no justification for a full health economic analysis of CEA-Scan®. There is also a lack of empirical evidence on both outcomes and costs of FDG-PET and CEA-Scan®.

CEA-Scan® is reportedly less costly per test than FDG-PET ($779.35 and $953-$975 respectively), however the cost of CEA-Scan® is likely to have been under-estimated in the application. A more realistic estimate of the test cost suggests that CEA-Scan® would be more expensive to deliver than FDG-PET. In addition, indirect and flow-on costs are likely to be higher for CEA-Scan® than for the comparator.

The applicant's estimate of the total cost to the Australian health system of implementing CEA-Scan® of $130,000 is also likely to be an under-estimate. It is based on an assumption that only 5 per cent of patients with recurrence will receive the test and that only one test will be administered. Using more realistic estimates of test uptake and test cost, a revised total annual direct cost to the Australian health system of a single CEA-Scan® administered to the relevant test population as a second-line imaging test is estimated to be $477,593. If the cost of testing for HAMA and monitoring for potential allergic reactions to CEA-Scan® is included, the total annual cost could be as high as $1,075,886.

There is currently insufficient evidence to conduct an appraisal of CEA-Scan® as a third-line imaging technique when FDG-PET fails or is unavailable.

Recommendation

The safety and effectiveness of CEA-Scan® has been assessed for imaging of recurrence and/or metastases in patients with histologically proven carcinoma of the colon or rectum. The procedure appears to be safe. However, on the strength of evidence pertaining to the effectiveness and cost-effectiveness of CEA-Scan®, public funding should not be supported for this procedure.

- The Minister for Health and Ageing accepted this recommendation on 31 August 2004 -

Appendix A MSAC terms of reference and membership

The 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, effectiveness and cost-effectiveness and under what circumstances public funding should be supported;
- advise the Minister for Health and Ageing on which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness;
- advise the Minister for Health and Ageing on references related either to new and/or existing medical technologies and procedures; and
- undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC) and report its findings to AHMAC.

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

Member	Expertise or Affiliation
Dr Stephen Blamey (Chair)	general surgery
Associate Professor John Atherton	cardiology
Professor Bruce Barraclough	general surgery
Professor Syd Bell	pathology
Dr Michael Cleary	emergency medicine
Dr Paul Craft	clinical epidemiology and oncology
Dr Gerry FitzGerald	Australian Health Ministers' Advisory Council representative
Dr Kwun Fong	thoracic medicine
Dr Debra Graves	medical administrator
Professor Jane Hall	health economics
Professor John Horvath	Chief Medical Officer, Department of Health and Ageing
Ms Rosemary Huxtable	department representative
Dr Terri Jackson	health economics
Professor Brendon Kearney	health administration and planning
Associate Professor Donald Perry-Keene	endocrinology
Associate Professor Richard King	internal medicine
Dr Ray Kirk	health research
Dr Michael Kitchener	nuclear medicine

Professor Alan Lopez	medical statistics and population health
Dr Ewa Piejko	general practice
Ms Sheila Rimmer	consumer health issues
Professor Jeffrey Robinson	obstetrics and gynaecology
Professor John Simes	clinical epidemiology and clinical trials
Professor Michael Solomon	colorectal surgery, clinical epidemiology
Professor Bryant Stokes	neurological surgery
Professor Ken Thomson	radiology
Dr Douglas Travis	urology

Appendix B Advisory Panel

Advisory Panel for MSAC application 1062

Dr Paul Craft (Chair) Medical Oncology and Palliative Care Canberra Hospital, ACT	member of MSAC
Professor Bruce Barraclough Chair for Australian Council for Safety and Quality in Health Care/Director of Cancer Services Northern Sydney Area Health Service	member of MSAC
Dr Dylan Bartholomeusz Department of Nuclear Medicine, Royal Adelaide Hospital, SA	nominated by the Australian and New Zealand Association of Physicians in Nuclear Medicine
Associate Professor Stephen Clarke Department of Medical Oncology, Royal Prince Alfred Hospital, NSW	nominated by the Medical Oncology Group of Australia
Dr Robert Padbury Department of Surgery, Flinders Medical Centre, SA	nominated by the Gastroenterological Society of Australia
Dr Alex Pitman Diagnostic Imaging, Peter MacCallum Cancer Institute, VIC	nominated by the Royal Australian and New Zealand College of Radiologists
Dr Caroline Wright Department of Colorectal Surgery, Royal Prince Alfred Hospital, NSW.	nominated by the Colorectal Surgical Society of Australasia

Appendix C Bibliographic databases

Primary databases

Medline (includes HealthStar)

Embase

Cochrane Controlled Trials Register

Current Contents

CINAHL

Web of Science

ABI Inform

EconLit

Secondary databases

Cochrane Database of Systematic Reviews

Evidence-based reviews (Evidence-based Medicine, ACP Journal Club)

University of York databases (DARE, NHS EED, HTA)

Science Citation Index

Other sources

Websites of professional oncology associations

Websites and publications of HTA organisations, see Appendix F.

Reference lists of retrieved papers

Appendix D Search strategy for therapy for colorectal cancer therapy

1	immu 4.tw. (18)
2	immu4.tw. (1)
3	arcitumomab.tw. (11)
4	(CEA adj3 scan$).tw. (88)
5	or/1-4 (106)
6	exp colorectal neoplasms/ (77372)
7	((colorectal or colon$ or rectal) adj2 (cancer or carcinoma or tumour$ or tumor$ or neoplasm$)).tw. (54847)
8	Carcinoembryonic Antigen/ (10807)
9	carcinoembryonic antigen$.tw. (8097)
10	cd66e.tw. (17)
11	cea.tw. (10068)
12	or/8-11 (15663)
13	or/6-7 (88675)
14	13 and 12 (4369)
15	di.fs. (1161197)
16	ri.fs. (77807)
17	rt.fs. (98591)
18	exp "Sensitivity and Specificity"/ (156838)
19	sensitivity.tw. (249456)
20	specificity.tw. (169593)
21	exp diagnosis/ (3223804)
22	exp pathology/ (10217)
23	((pre test or pretest) adj probability).tw. (392)
24	post test probability.tw. (118)
25	or/15-24 (4005747)
26	14 and 25 (3082)
27	Neoplasm Recurrence, Local/ (45957)
28	exp Neoplasm Metastasis/ (95009)
29	recurren$.tw. (176709)
30	metastas$.tw. (104837)
31	secondary.tw. (198186)
32	sc.fs. (69029)
33	or/27-32 (535891)
34	26 and 33 (1593)
35	6 or 7 (88675)
36	meta-analysis/ (5297)
37	meta analy$.tw. (10588)
38	metaanaly$.tw. (399)
39	meta analysis.pt. (8848)
40	exp review, literature/ (1964)
41	(systematic adj (review$ or overview$)).tw. (5281)

42	randomized controlled trials/ (31513)
43	randomized controlled trial.pt. (186803)
44	random allocation/ (50295)
45	double blind method/ (77373)
46	case report.tw. (97669)
47	letter.pt. (500990)
48	editorial.pt. (159556)
49	or/46-48 (756657)
50	6 and 33 (20832)
51	or/36-45 (278530)
52	exp *colorectal neoplasms/ and 33 and 51 (950)
53	limit 52 to (human and english language and yr=2000-2004) (295)
54	53 not (34 or 49) (275)

Appendix E Search strategy for the comparator FDG-PET

1	exp colorectal neoplasms/ (75251)
2	((colorectal or colon$ or rectal) adj2 (cancer or carcinoma or tumour$ or tumor$ or neoplasm$)).tw. (52799)
3	1 or 2 (86001)
4	carcinoembryonic antigen/ (10373)
5	cd66e.mp. (14)
6	carcinoembryonic antigen$.mp. (12346)
7	cea.mp. (9608)
8	or/4-7 (15030)
9	pet.mp. (16087)
10	exp tomography, emission-computed/ (32749)
11	positron emission tomography.mp. (11680)
12	fdg.mp. (3857)
13	(18F or 18-F).mp. (4734)
14	or/9-13 (40047)
15	3 and 8 and 14 (122)
16	exp "Sensitivity and Specificity"/ (149939)
17	exp diagnostic errors/ (55304)
18	reproducibility of results/ (86249)
19	false negative reactions/ or false positive reactions/ (22808)
20	(positive predictive value or ppv).mp. (10447)
21	(negative predictive value or npv).mp. (7220)
22	or/16-21 (261843)
23	3 and 14 and 22 (138)
24	15 or 23 (217)

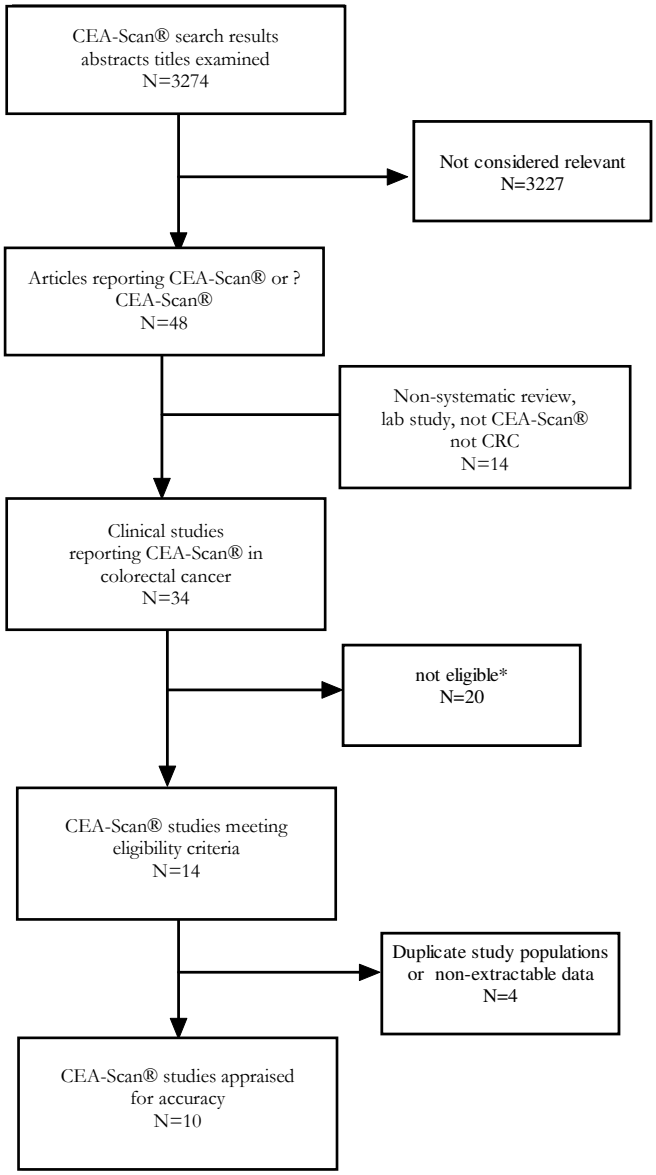
Appendix F Search websites

HTA Organisations	Website URL
Agencia de Evaluacion de Tecnologias Sanitarias (AETS)	http://www.isciii.es/unidad/aet/caet.html
Agencia de Evaluacion de Tecnologias Sanitarias de Andalucia (AETSA)	http://www.csalud.junta-andalucia.es/orgdep/AETSA/
Alberta Heritage Foundation for Medical Research (AHFMR)	http://www.ahfmr.ab.ca/
Agency for Health Research Quality (AHRQ)	http://www.ahrq.gov
L'Agence nationale d'Accréditation et d'Evaluation en Santé	http://www.anaes.fr
L'Agence Nationale pour le Developpement de l'Evaluation Medicale (ANDEM)	http://www.upml.fr/andem/andem.htm
British Columbia Office of Health Technology Assessment (BCOHTA)	http://www.chspr.ubc.edu.ca/bcohta
Catalan Agency for Health Technology Assessment (CAHTA)	http://www.aatm.es/
Canadian Coordinating Office for Health Technology Assessment (CCOHTA)	http://www.ccohta.ca
Centre for Clinical Effectiveness, Monash University	http://www.med.monash.edu.au/healthservices/cce/
Center for Medical Technology Assessment (CMT)	http://ghan.imt.liu.se/cmt/
College voor Zorgverzekeringen (CVZ)	
German Agency for Health Technology Assessment at the German Institute for Medical Documentation and Information (DIMDI)	http://www.dahta.dimdi.de/
Danish Centre for Evaluation and Health Technology Assessment (DACEHTA)	http://www.dihta.dk/
Danish Institute for Health Services Research (DSI)	http://www.dsi.dk/
ECRI (USA)	http://www.ecri.org
Unidad de Tecnologias de Salud (ETESA)	http://www.minisal.cl
EUROSCAN	http://www.ad.bham.ac.uk/euroscan/index.asp
Finnish Office for Health Care Technology Assessment (FinOHTA)	http://www.stakes.fi/finohta/
Health Council of the Netherlands (GR)	http://www.gr.nl/
Health Technology Board for Scotland	http://www.htbs.org.uk/
Minnesota Health Technology Advisory Committee (HTAC)	http://www.health.state.mn.us/htac/
Institute for Clinical Systems Improvement (ICSI)	http://www.icsi.org
Institute of Technology Assessment of the Austrian Academy of Science (ITA)	http://www.oeaw.ac.at/ita/hta/
International Network of Agencies for Health Technology Assessment (INAHTA)	http://www.inahta.org
International Society of Technology Assessment in Health Care	http://www.istahc.org
Medical Technology Assessment Group (M-TAG)	http://www.m-tag.net/
Medical Technology and Practice Patterns Institute	http://www.mtppi.org/
National Coordinating Centre for Health Technology Assessment (NCCHTA)	http://www.soton.ac.uk/~hta
National Horizon Scanning Centre (NHSC)	http://www.bham.ac.uk/PublicHealth/horizon
National Institute for Clinical Excellence (NICE)	http://www.nice.org.uk/
New Zealand Health Technology Assessment (NZHTA)	http://nzhta.chmeds.ac.nz

Medical and Health Research Council (MW-NWO)	http://www.nwo.nl
Basque Office for Health Technology Assessment (OSTEBA)	http://www.euskadi.net/sanidad/
Swedish Council on Technology Assessment in Health Care (SBU)	http://www.sbu.se
Norwegian Centre for Health Technology Assessment (SMM)	http://www.oslo.sintef.no/smm/
Swiss Science Council/Technology Assessment (SWISS/TA)	http://www.ta-swiss.ch/
TNO Prevention and Health (TNO)	http://www.tno.nl/homepage.html
University Health Consortium Technology Assessment Monitor	http://www.uhc.edu
Veterans' Affairs Technology Assessment Program (VATAP)	http://www.va.gov/vatap/
WHO Health Technology Assessment Programme (Collaborating Centres)	http://www.who.int/pht/technology_assessment/index.html
Other organisations	
Australian Institute of Health & Welfare (AIHW)	http://www.aihw.gov.au
Australian National Health & Medical Research Council	http://www.health.gov.au/nhmrc/index.htm
Commonwealth Department of Health and Aged Care	http://www.health.gov.au
Centres for Medicare and Medicaid Services (US Health Care Financing Administration)	http://www.hcfa.gov
Health Economics Research Group (Brunel University)	http:// www.brunel.ac.uk/depts/herg
US Federal Drug Administration	http://www.fda.gov
Health Canada	http://www.hc-sc.gc.ca/
UK Department of Health publications	http://www.doh.gov.uk/publications/index.html
US Centers for Disease Control	http://www.cdc.gov
Professional Associations/Societies (representative only)	
National Cancer Institute	http://www.cancer.gov/
American Association for Cancer Research	http://www.aacr.org/
American Cancer Society	http://www.cancer.org/docroot/home/index.asp
Canadian Cancer Society	http://www.cancer.ab.ca/
and other relevant associations	
World Health Organisation	http://www.who.int/
International Agency for Research on Cancer IARC	http://www.iarc.fr/
Controlled Clinical Trials	http://www.controlled-trials.com/
Clinicaltrials.gov	http://www.clinicaltrials.gov

Appendix G Selection process for CEA-Scan® papers

Flow chart of selection process for papers reporting on the effectiveness of CEA-Scan® for the detection of recurrent colorectal cancer.



*abstracts, small sample size, problematic reference standard

Appendix H Articles reporting CEA-Scan® in colorectal cancer[24]

Baulieu, F., Bourlier, P., Scotto, B., Mor, C., Eder, V., Picon, L., De Calan, L., et al. (2001) 'The value of immunoscintigraphy in the detection of recurrent colorectal cancer', *Nuclear Medicine Communications,* 22(12)**,** 1295-1304.

Behr, T., Becker, W., Hannappel, E., Goldenberg, D. M. and Wolf, F. (1995) 'Targeting of liver metastases of colorectal cancer with IgG, F(ab')2, and Fab' anti-carcinoembryonic antigen antibodies labeled with 99mTc: the role of metabolism and kinetics', *Cancer Research,* 55(23 Suppl)**,** 5777s-5785s.

Behr, T. M. B., W. S. Sharkey, R. M. Juweid, M. E. Dunn, R. M. Bair, H. J. Wolf, F. G. Goldenberg, D. M. (1996) 'Reduction of renal uptake of monoclonal antibody fragments by amino acid infusion', *Journal of Nuclear Medicine,* 37(5)**,** 829-833.

Bongers, V., Verhaar-Langereis, M. J., Hobbelink, M. G., Zonnenberg, B. A. and de Klerk, J. M. (2000) 'Bone metastases in a patient with colon cancer depicted by Tc-99m carcinoembryonic antigen scintigraphy', *Clinical Nuclear Medicine,* 25(10)**,** 817-818.

Bridwel, R. and Thropay, J. (2003) 'Economic Utility of CEA-Scan®; (arcitumomab) immunoscintigraphy in the evaluation of patients with colorectal cancer. A retrospective financial analysis based on published clinical studies', *Alasbimn Journal,* (No. 19)**.** Available from http://www2.alasbimnjournal.cl/alasbimn.

De la Guardia, M., Wegener, W., Rubinstein, M. and VanDaele, P. (2002) 'Impact of training on the interpretation of CEA-Scan (Arcitumomab)', *Radiology,* 225, 518.

Eccles, S. A. (1999) 'Technology evaluation: CEA-Scan, Immunomedics Inc', *Current Opinion in Molecular Therapeutics,* 1(6)**,** 737-744.

Erb, D. A. and Nabi, H. A. (2000) 'Clinical and technical considerations for imaging colorectal cancers with technetium-99m-labeled antiCEA Fab' fragment', *Journal of Nuclear Medicine Technology,* 28(1)**,** 12-18; quiz 21.

Fuster, D., Maurel, J., Muci, A., Setoain, X., Ayuso, C., Martin, F., Ortega, M. L., et al., (2003) 'Is there a role for Tc-99m-anti-CEA monoclonal antibody imaging in the diagnosis of recurrent colorectal carcinoma?' *Quarterly Journal of Nuclear Medicine,* 47(2)**,** 109-115.

Ghesani, M., A., B. and S., H. (2003) 'Carcinoembryonic antigen (CEA) scan in the diagnosis of recurrent colorectal carcinoma in a patient with increasing CEA levels and inconclusive computed tomographic findings', *Clinical Nuclear Medicine,* 28(7)**,** 608-609.

Goldenberg, D. M., Goldenberg, H., Sharkey, R. M., Higginbotham-Ford, E., Lee, R. E., Swayne, L. C., Burger, K. A., et al. (1990) 'Clinical studies of cancer radioimmunodetection with carcinoembryonic antigen monoclonal antibody fragments labeled with 123I or 99mTc', *Cancer Research,* 50(3 Suppl)**,** 909s-921s.

[24] Some studies in this appendix were retrieved as possibly included CEA-Scan®.

Goldenberg, D. M. (1997) 'Perspectives on oncologic imaging with radiolabeled antibodies', *Cancer,* 80(12 Suppl)**,** 2431-2435.

Goldenberg, D. M., Juweid, M., Dunn, R. M. and Sharkey, R. M. (1997) 'Cancer imaging with radiolabeled antibodies: new advances with technetium-99m-labeled monoclonal antibody Fab' fragments, especially CEA-Scan and prospects for therapy', *Journal of Nuclear Medicine Technology,* 25(1)**,** 18-23.

Griffiths, G. L., Goldenberg, D. M., Roesch, F. and Hansen, H. J. (1999) 'Radiolabeling of an anti-carcinoembryonic antigen antibody Fab' fragment (CEA-Scan) with the positron-emitting radionuclide Tc-94m', *Clinical Cancer Research,* 5(10 Suppl)**,** 3001s-3003s.

Hansen, H. J., Jones, A. L., Sharkey, R. M., Grebenau, R., Blazejewski, N., Kunz, A., Buckley, M. J., et al. (1990) 'Preclinical evaluation of an "instant" 99mTc-labeling kit for antibody imaging', *Cancer Research,* 50(3 Suppl)**,** 794s-798s.

Harwood, S. J., Fig, L. M., Wegener, W. A., Dove, D., Olsen, L., Chalam, G., Doronila, A. T., et al. (2003) 'Pharmacokinetics and biodistribution of multiple administrations of CEA-Scan (R) (arcitumomab) following complete resection of primary colorectal carcinoma', *Journal of Nuclear Medicine,* 44(5)**,** 27P-27P.

Heriot, A. G., Masoomi, M., McCready, V. R., Britton, A., Ganes, J., Biassoni, L. and Kumar, D. (1999) 'Assessment of spread of primary rectal carcinoma with radioimmunoscintigraphy using anti-CEA antibody (IMMU-4)', *Gut,* 44, A141-A141.

Hladik, P., Vizda, J., Bedrna, J., Simkovic, D., Strnad, L., Smejkal, K. and Voboril, Z. (2001) 'Immunoscintigraphy and intra-operative radioimmunodetection in the treatment of colorectal carcinoma', *Colorectal Disease,* 3(6)**,** 380-386.

Hughes, K., Pinsky, C. M., Petrelli, N. J., Moffat, F. L., Patt, Y. Z., Hammershaimb, L. and Goldenberg, D. M. (1997) 'Use of carcinoembryonic antigen radioimmunodetection and computed tomography for predicting the resectability of recurrent colorectal cancer', *Annals of Surgery,* 226(5)**,** 621-631.

Hwang, I., Kulas, P. M., Starnes, B. W., Balingit, A. G. and Shriver, C. D. (1999) 'Incidental detection of carcinoid with Tc-99m-labeled carcinoembryonic antigen monoclonal antibody scintigraphy during evaluation of metastatic colon cancer', *Clinical Nuclear Medicine,* 24(12)**,** 978-979.

Jarv, V., Blomqvist, L., Holm, T., Ringertz, H. and Jacobsson, H. (2000) 'Added value of CEA scintigraphy in the detection of recurrence of rectal carcinoma', *Acta Radiologica,* 41(6)**,** 629-633.

Kumar, D., Heriot, A. G., Masoomi, M., McCready, V. R., Britton, A., Ganes, J. and Biassoni, L. (1999) 'Assessment of spread of primary rectal carcinoma with radioimmunoscintigraphy using anti-CEA antibody (IMMU-4)', *Gastroenterology,* 116(4)**,** A445-A445.

Larson, S. M. (1995) 'Improving the balance between treatment and diagnosis: a role for radioimmunodetection', *Cancer Research,* 55(23 Suppl)**,** 5756s-5758s.

Laterza, C., Pons, F., Setoain, F. J., Mateos, J. J., Martin, F., Muxi, A. and Herranz, R. (1999) 'Immunoscintigraphy in the detection of recurrent colorectal cancer in patients with rising serum CEA levels', *European Journal of Nuclear Medicine,* 26(9)**,** 1151-1151.

Lechner, P., Lind, P., Binter, G. and Cesnik, H. (1993) 'Anticarcinoembryonic antigen immunoscintigraphy with a 99mTc-Fab' fragment (Immu 4) in primary and recurrent colorectal cancer. A prospective study', *Diseases of the Colon & Rectum,* 36(10)**,** 930-935.

Lechner, P., Lind, P. and Goldenberg, D. M. (2000a) 'Can postoperative surveillance with serial CEA immunoscintigraphy detect resectable rectal cancer recurrence and potentially improve tumor-free survival?' *Journal of the American College of Surgeons,* 191(5)**,** 511-518.

Lechner, P., Lind, P. and Golenbergh, D. M. (2000b) 'CEA immunoscintigraphy detects resectable rectal cancer recurrence and improves survival.' *Coloproctology,* 22(1)**,** 23-28.

Lechner, P., Lind, P., Snyder, M. and Haushofer, H. (2000c) 'Probe-guided surgery for colorectal cancer', *Recent Results in Cancer Research,* 157, 273-280.

Libutti, S. K., Alexander, H. R., Jr., Choyke, P., Bartlett, D. L., Bacharach, S. L., Whatley, M., Jousse, F., et al. (2001) 'A prospective study of 2-[18F] fluoro-2-deoxy-D-glucose/positron emission tomography scan, 99mTc-labeled arcitumomab (CEA-scan), and blind second-look laparotomy for detecting colon cancer recurrence in patients with increasing carcinoembryonic antigen levels.' *Annals of Surgical Oncology,* 8(10)**,** 779-786.

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Rodriguez-Bigas, M. A., Bakshi, S., Stomper, P., Blumenson, L. E. and Petrelli, N. J. (1992) '99mTc-IMMU-4 monoclonal antibody scan in colorectal cancer. A prospective study', *Archives of Surgery,* 127(11)**,** 1321-1324.

Serafini, A. N., Vargascuba, R., Benedetto, P., Ardalan, B., Garrido, J., Robinson, D., Moffat, F., et al. (1991) 'Tc-99m-labeled Fab' Fragment of Anti-CEA Monoclonal-antibody for the radioimmunodetection of colorectal adenocarcinoma ', *Antibody Immunoconjugates and Radiopharmaceuticals,*4(4), 561-568.

Sirisriro, R., Kim, E. E. and Podoloff, D. A. (1995) 'Radioimmunoscintigraphy in the differential diagnosis of hepatic mass lesion', *European Journal of Nuclear Medicine,* 22(4)**,** 385-388.

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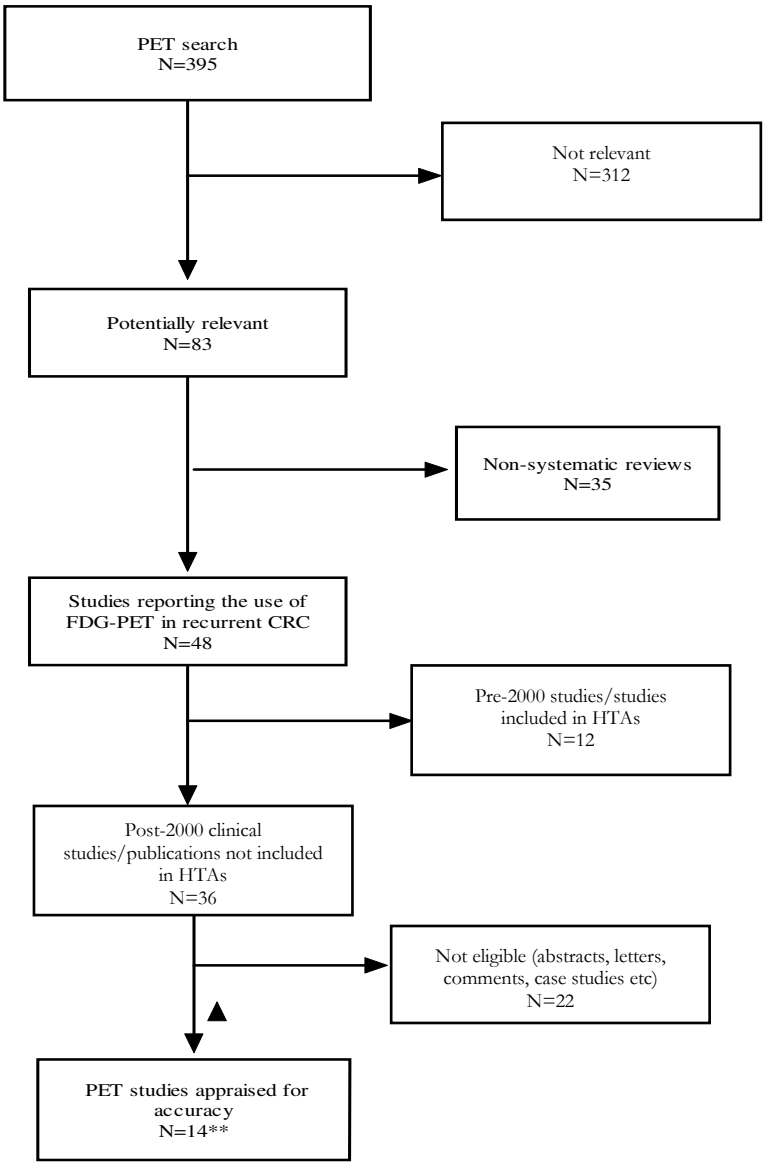
Appendix I Selection process for FDG-PET papers

Flow chart of post-2000 clinical studies/studies not included in HTA selection process for papers reporting on the accuracy of PET for the detection of recurrent colorectal cancer.



** N=12 studies appraised for FDG-PET alone, N=2 studies appraised for CEA-Scan and FDG-PET

Appendix J CEA-Scan® evidence tables

Evidence tables for studies included in the review of CEA-Scan® for recurrent or metastatic cancer.

Study	Study type	n	Indication	Patient population	Patient characteristics	Interpretation of imaging	Reported operating *characteristics	Gold standard	Potential bias	Quality grading[25]
Baulieu et al., (2001)	Case series Consecutive Prospective Comparative study of CEA-Scan® and CT-scan	40	Suspected recurrent CRC Confirmed recurrent CRC	Surgical patients presenting June 1997-Dec 2000 Suspected liver mets (n=32) Suspected local recurrence or peritoneal carcinosis (n=4) Rising CEA (normal CDM) (n=2) Parietal mets (n=1) Lumbo-aortic nodes (n=1)	Male=25 Female=15 Mean age=63yrs range=43-74yrs	•CEA-Scan® performed on all patients. • Surgery/histology not clear if all patients went to surgery (see summary and p1296) only lesions suspected of being malignant were biopsied. •CEA-Scan® blinding to surgical results not reported but likely (IS performed up to 2 weeks prior to surgery). •Surgery carried out with knowledge of CEA-Scan® results. •CEA-Scan® measured with knowledge of CT/other imaging results •Surgery/histology blinding to previous history not reported	**Patients with liver mets (n=40):** Sensitivity = 0.53 (0.36-0.70) Specificity = 1.00 (0.72-1.00) PPV = 100% NPV = 42% LR+ = ∝ LR- = 0.47 (0.32-0.68) Accuracy = 65%(50-78) **Patients with extra- hepatic abdominal mets (n=40):** Sensitivity = 1.00 (0.76-1.00) Specificity = 0.82 (0.64-0.92) PPV = 71% NPV = 100% LR+ = 5.6 (2.53-12.9) LR- = 0.00 Accuracy = 88% (74-95) *(95 % CI)	Findings at surgery - histology Only lesions suspected to be disease on CT/CEA-Scan® biopsied	Verification bias - surgery Review bias - only CEA-Scan® positive cases? Chemo prior to test	•ConsecutiveΥ •ProspectiveΥ •CEA-Scan® assessed against a valid gold standardΥ •CEA-Scan® blinded (likely) Υ •Surgery blindedς •Relevant popΥ **COMMENT** •Single CEA-Scan® n=51 •Two CEA-Scans n=8 •Pre-op chemo n-=4 •CEA-Scan® extra-hepatic abdominal FPs due to intestinal artefacts **STUDY CONCLUSIONS** CEA-Scan® inferior to CT scan for liver mets but superior for the detection of extra-hepatic abdominal disease

[25] Not reported scored as X unless any reason to suspect otherwise

Study	Study type	n	Indication	Patient population	Patient characteristics	Interpretation of imaging	Reported operating characteristics*	Gold standard	Potential bias	Quality grading
Fuster et al., 2003	Case series Consecutive Prospective Comparative study of CEA-Scan® and CT-scan	51	Suspected recurrence based on rising serum CEA and clinical suspicion of disease	Surgically resected with curative intent Dukes B (n=23) Dukes C (n=28) Raised serum CEA in 3 consecutive tests and clinically suspected recurrence **Exclusion:** 2nd primary or known residual disease	Male=24 Female=27 Mean age 68.9 +/-10.2yrs	• CEA-Scan® performed on all patients • Reference standard carried out for all scans - histopathology for CEA-Scan® + and or CT + scans/ clinical follow-up (minimum of six months) for image negative scans •CEA-Scan® blinding to surgery not reported but CEA-Scan® performed prior to surgery in a prospective study •Surgery performed with knowledge of the scan results, follow-up is unlikely to be blinded •Histolopathology assessment not reported to be blind to clinical and other imaging information • CEA-Scan® blinding to clinical and other imaging information not reported	**Liver mets (n=59 scans):** Sensitivity = 0.27(0.10-0.57) Specificity = 1.00 (0.93-1.00) PPV = 100.00% NPV = 85.71% LR+ = ∝ LR- = 0.72 (0.51-1.04) Accuracy = 86% (75-93) **Extra-hepatic abdominal and pelvic mets (n=59 scans):** Sensitivity = 0.78 (0.55-0.91) Specificity = 0.90(0.77-0.96) PPV = 78% NPV = 90% LR+ = 7.97 (3.04-20.89) LR- = 0.25 (0.10-0.59) Accuracy = 86% (75-93) **Thorax (n=59 scans):** Sensitivity = 0.22(0.06-0.55) Specificity = 1.00(0.93-1.00) PPV = 100.00% NPV = 87.72% LR+ = ∝ LR- = 0.78 (0.55-1.10) Accuracy = 88% (77-94) **All sites (n=186scans):** Sensitivity = 0.48 (0.33-0.63) Specificity = 0.97(0.93-0.99) PPV = 82.61% NPV = 87.12% LR+ = 17.34 (6.25-48.08) LR- = 0.54 (0.40-0.73) Accuracy = 86% (75-93) * (95% CI)	Histopathology (n=28 scans) or Clinical FU of at least 6 months (n=31 scans)	Some verification bias possible as only imaging + patients verified by histology test compared to a potentially invalid reference standard (FU<1yr) for image negative patients Review bias: in the reference standard, surgery and FU carried out with knowledge of results of all tests.	•Consecutive Y •Prospective Y •CEA-Scan® assessed against a valid gold standard Y •CEA-Scan® blinded (likely) Y •Surgery blinded ç •Relevant pop Y **COMMENTS** •Analyses by scans not patients: 8 patients had two scans ∴ 59 scans performed. •Most cases of FP due to radiotracer accumulation in urine or physiological bowel uptake. **STUDY CONCLUSIONS** CEA-Scan® superior to CT-scan for the detection of pelvic/extra-hepatic abdominal disease, inferior for the detection of liver and lung mets and limited usefulness in detection of distant mets. May be helpful when CT scans are inconclusive and FDG-PET not available.

Study	Study type	n	Indication	Patient population	Patient characteristics	Interpretation of imaging	Reported operating characteristics*	Gold standard	Potential bias	Quality grading
Hughes et al., 1997	Case series Prospective Multi-centre Open-label trial Comparative study of CEA-Scan® and CT-scan	209	**Group one:** Known recurrent CRC **Group two:** Suspected recurrent CRC	**All groups:** Pre-surgical evaluation **Group one:** At least one known lesion, (n=122) **Group two:** Occult disease, abnormal LFT, raised serum CEA or LDH or equivocal CDM (n=87) **Exclusion**: chemo/ radiotherapy within one month of CEA-Scan®, exposure to murine monoclonal antibodies	Male = 129 Female = 80 Age = 30-80yrs	•All patients had CEA-Scan® and surgical confirmation. •CEA-Scan® reading blinded to histology results • Histology assessment retrospective but blinded to CEA-Scan® results? (p623) •CEA-Scan® reading blinded to other tests, only basic clinical info known •Histology assessment not reported to be blind to clinical information	**Overall disease (Y/N, n=209)** Sensitivity = 0.52 (0.45-0.60) Specificity = 0.72 (0.58-0.83) PPV = 84% NPV = 33% LR+ = 1.90 (1.17-3.08) LR- = 0.66 (0.52-0.84) Accuracy = 57% (50-64) **Overall resectability (negative and non-resctable vs resectable pts, n=209)** Sensitivity = 0.64 (0.53-0.73) Specificity = 0.52 (0.43-0.61) PPV = 49% NPV = 67% LR+ = 1.33 (1.04-1.69) LR- = 0.70 (0.51-0.97) Accuracy = 57% (50-64) **Liver mets (Y/N n=100);** Sensitivity = 0.43 (0.33-0.53) Specificity = 0.43 (0.16-0.75) PPV = not calculated NPV = not calculated LR+ = 0.75 (0.38-1.49) LR- = 1.33 (0.55-3.12) Accuracy = 43% (34-53) **Liver mets resectability (negative and non-resectable vs resectable pts, n=100)** Sensitivity = 0.47 (0.32-0.63) Specificity = 0.41 (0.30-0.53) PPV = 29% NPV = 61% LR+ = 0.80 (0.53-1.19) LR- = 1.30 (0.85-2.00) Accuracy= 43% (33-53) ***(95% CI)**	Histopathology-exploration complete in 177 cases; partial in 32 cases	**Selection bias**: Trial patients only recruited, prognostic group of patients not reported **Verification bias:** 32 patients only had partial surgical exploration (recalculation omitting this group did not change overall results) Four patients with liver mets could not be verified Conflict of interest	•Consecutiveς •ProspectiveΥ •CEA-Scan® assessed against a valid gold standardΥ •CEA-Scan® blindedΥ •Surgery blindedς •Relevant popΥ

Study	Study type	n	Indication	Patient population	Patient characteristics	Interpretation of imaging	Reported operating characteristics*	Gold standard	Potential bias	Quality grading
Lechner et al., 2000	Case series Consecutive Prospective Single institution One arm Open label Surveillance trial Historical control group (n=69) for outcome.	40	Rectal cancer monitored for recurrence	Rectal ca resected with curative intent Dukes B (n= 11) Dukes C (n= 29) Extra-peritoneal rectal cancer, 63% middle rectum, 37% lower rectum **Exclusion**: Dukes A	Male=23 Female=17 Age 42-87yrs	• Only CEA-Scan® positive or discordant results were verified by surgery rest by FU •CEA-Scan® interpreted blind to surgery results •Surgery not reported to be blind to imaging results. •CEA-Scan® interpreted blinded to clinical info except site of primary •Biopsy interpretation not reported to be blind to clinical information	**Patients (N=40):** Sensitivity = 1.00 (81-100) Specificity = 0.79 (0.60-0.91) PPV = 76.2% NPV = 100% LR+ = 4.80 (2.20-10.47) Accuracy = 88% (74-95) **Lesions (N=219):** Sensitivity = 0.94(0.73-0.99) Specificity = 0.98(0.94-0.99) PPV = 76.2% NPV = 99.5% LR+ = 38.02(15.87-91.10) LR- = 0.06(0.01-0.40) Accuracy = 97% (94-99) * (95% CI)	Biopsy or aspiration cytology or clinical follow-up >=5years or until recurrence	Verification bias Review bias surgery Imperfect gold standard when aspiration cytology used? Conflict of interest	•ConsecutiveΥ •ProspectiveΥ •CEA-Scan® assessed against valid gold standardΥ •CEA-Scan® blindedΥ •Surgery blindedς •Relevant popΥ **COMMENTS** •Some patients had repeat CEA-Scan® **STUDY CONCLUSIONS** CEA-Scan® included in intensive surveillance disclosed rectal ca recurrence at a stage that allowed salvage therapy in 37.5% of patients

Study	Study type	n	Indication	Patient population	Patient characteristics	Interpretation of imaging	Reported operating characteristics *	Gold standard	Potential bias	Quality grading
Lechner et al., 1993	Case series Prospective	15 (47)	Recurrent CRC Primary CRC	Pre-surgical Recurrent CRC (n=15) Primary CRC (n=32)	Sex ratio not reported **Whole group (N=47):** Mean age = 67.2yrs Range 39-89yrs	•All patients had CEA-Scan® and a biopsy/surgical procedure •Blinding not reported for CEA-Scan® or reference standard •Blinding to previous clinical information not reported.	**Recurrent patients reported by scans (n=36)** Sensitivity = 1.00 (0.76-1.00) Specificity = 0.88 (0.69-0.96) PPV = 80% NPV = 100% LR^+ = 8.00 (2.78-23.06) LR^- = 0.0 Accuracy = 92% (78-97) * (95% CI)	Biopsy/surgical procedure	Selection bias Reference bias Small sample size	•Consecutiveς •ProspectiveΥ •CEA-Scan® assessed against valid gold standardΥ •CEA-Scan® blindedς •Surgery blindedς •Relevant popς **COMMENTS** •Some patients had repeat scans • CEA-Scan® FP due to antibody accumulation in hepatic flexure and bladder **STUDY CONCLUSIONS** No objections to repeat CEA-Scan® which provides important information in the primary diagnosis and follow-up of VCRC patients.

Study	Study type	n	Indication	Patient population	Patient characteristics	Interpretation of imaging	Reported operating characteristics*	Gold standard	Potential bias	Quality Grading
Moffat et al., 1996	Case series Prospective Multi-center Open label Phase III trial Comparative study CEA-Scan® with CDM/CT	210	Known recurrent /metatstic CRC n=122 (25 primary disease 11 with mets) Suspected recurrent CRC n=88	**Group one:** Surgical patients with at least one known lesion<=0.5cm **Group two:** Abnormal and increasing liver enzymes, serum CEA, or lactic dehydrogenase or with abnormal clinical symptoms or signs. No or equivocal CDM	Male=130 Female=80 Age 30-84yrs	•CEA-Scan® and histology performed on all patients •Blinding of CEA-Scan® to biopsy results not reported but probably – look for protocol and see Hughes •Blinding of biopsy to CEA-Scan® results not reported. •CEA-Scan® interpreted without knowledge of other tests but with basic clinical information	**All patients, all sites (n=210)** Sensitivity = 0.71 (0.64-0.78) Specificity = 0.63 (0.44-0.79) PPV = 91.4% (85.4-95.5) NPV = 28.2 (18.1-40.1) LR+ = 1.901 LR- = 0.459 Accuracy = 70% (63-76) **Liver (n=81)** Sensitivity = 0.63 (0.52-0.73) **Extra-hepatic abdomen (n=69)** Sensitivity = 0.55 (0.43-0.67) **Pelvis (n=81)** Sensitivity = 0.69 (0.58-0.79) **Known disease (inc 25 primary CRC11 with dilatant mets)** **All sites (n=122)** Sensitivity = 0.78 (0.70-0.85) Specificity = 0.86 (0.49-0.97) PPV = 97% NPV = 36% LR+ = 5.48 (0.89-33.71) LR- = 0.25 (0.16-0.40) Accuracy = 79% (71-85) **Liver** Sensitivity = 0.75 PPV = 95.5% Accuracy = 82.6% **Extra-hepatic abdomen** Accuracy = 0.78 **Pelvis** Accuracy = 73.4% * (95% CI) *Note: occult disease not reported separately for CEA-Scan®*	Biopsy	Selection bias: trial patients Review bias: surgery Conflict of interest	•Consecutiveς •ProspectiveΥ •CEA-Scan® assessed against a valid gold standardΥ •CEA-Scan® blindedΥ •Surgery blindedς •Relevant popΥ **COMMENT** •Repeat CEA-Scan® in 22 patients •25 patients not recurrent disease •CEA-Scan-FP either inflammation or fibrotic tissue **STUDY CONCLUSIONS** CEA-Scan® superior to CDM in the extra-hepatic abdomen and complementary in the liver. CEA-Scan® only rarely induces a HAMA response

Study	Study type	n	Indication	Patient population	Patient characteristics	Interpretation of imaging	Reported operating characteristics *	Gold standard	Potential bias	Quality Grading
Libutti et al., 2001	Case series Prospective Comparative study of CEA-Scan®, FDG-PET and blind second-look surgery	30	**Arm one:** Known recurrence **Arm two:** Asymptomatic, rising serum CEA	**All patients:** Confirmed CRC 18yrs or more ECOG 0 or 1 No contraindications for surgery **Arm one (n=15):** No evidence of abdominal disease CEA>6µg on two successive tests **Arm two (n=15)** Surgical patients Single known site deemed resectable **Exclusion** Extra-abdominal disease, evidence of unresectable disease, visible disease in abdomen **Note:** 2 patients excluded after discovered to have extra-abdominal disease (FDH-PET) after the start of the study	**Arm one** M: F 10:5 Age mean=61.9 (41-74yrs) **Arm two** M: F 10:5 Age Mean=57.9 (38-75yrs)	•All study patients had CEA-Scan® and PET •All study patients without evidence of extra-hepatic abdominal disease had the reference test (abdominal exploration) •Blinded surgeon model 1st surgeon = 3rd "test" •CEA-Scan® interpreted blind to all surgical results •PET interpreted blind to all surgical results • 1st surgeon blinded to CEA-Scan® and PET results • 2nd surgeon not blinded to CEA-Scan® or PET results •PET and CEA-Scan® interpretation was independent (blinded) •2nd surgeon not blinded to clinical information •CEA-Scan® blinding to clinical information not reported? Not blinded to CT •PET blind to clinical and radiographic info	**CEA-Scan: Patients n=28** Sensitivity = 0.18 (0.07-0.39) Specificity = 0.33 (0.10-0.70) LR+ = 0.27 (0.10-0.78) LR- = 2.45 (0.78-7.74) PPV = 50% NPV = 10% Accuracy = 21% (10-40) **CEA-Scan: Lesions=119** Sensitivity = 0.05 (0.02-0.12) Specificity = 0.86 (0.72-0.94) LR+ = 0.36 (0.10-1.27) LR- = 1.10 (0.96-1.26) PPV = 44% NPV = 29% Accuracy = 30% (23-39) **FDG-PET: Patients n=28** Sensitivity = 0.88(0.71-0.96) Specificity = 0.50(0.09-0.91) LR+ = 1.77 (0.44-7.12) LR- = 0.23 (0.04-1.33) PPV = 96% NPV = 25% Accuracy = 86% (69-94) **FDG-PET: Lesions=119** Sensitivity = 0.57 (0.47-0.67) Specificity = 0.65 (0.49-0.78) LR+ = 1.63 (1.01-2.63) LR- = 0.66 (0.47-0.93) PPV = 78% NPV = 41% Accuracy = 60% (51-68) * (95% CI)	Histopathology close FU AND Imaging (p785)	Selection bias Invalid gold standard Imaging, definitive pathology and close FU of patients served as the gold standard (p785) Review bias: final diagnosis used in the calculation of accuracy?	•Consecutiveς •ProspectiveΥ •CEA-Scan® assessed against valid gold standardς •CEA-Scan® blindedΥ •Surgery blindedς •Relevant popς **COMMENT** •Most patients had prior chemotherapy /radiotherapy **STUDY CONCLUSIONS** FDG-PET can predict patients who would benefit from a laparotomy. CEA-Scan® failed to predict unresectable disease and predicted resectable or treatable disease in 13% of study patients

Study	Study type	n	Indication	Patient population	Patient characteristics	Interpretation of imaging	Reported operating characteristics *	Gold standard	Potential bias	Quality Grading
Patt et al., 1994	Case series Prospective	16	Suspected recurrence based on rising serum CEA	Resected CRC, Disease free Fit enough for surgery **Exclusion** Patients not candidates for surgical exploration	Male=7 Female=9 Age=median 56yrs(37-77yrs)	• All patients had CEA-Scan® and laparotomy •CEA-Scan® interpreted without knowledge of histopathology results •Surgery not blinded to CEA-Scan® •CEA-Scan® interpreted without knowledge of clinical information (blinded) •Surgery blinding to other clinical information not reported •Decision to perform laparotomy was independent of CEA-Scan® results	**Patients (n=15)** Sensitivity = 1.00 (0.76-1.00) Specificity = 0.67 (0.21-0.94) LR+ = 3.00 (0.61-14.86) LR- = 0 PPV = 92% NPV = 100% Accuracy = 93% (70-99) **All sites (n=56)** Sensitivity = 0.81 (0.62-0.91) Specificity = 0.83 (0.66-0.93) LR+ = 4.85 (2.13-11.02) LR- = 0.23 (0.10-0.52) PPV = 81%, NPV = 83% Accuracy = 82% (70-90) **Liver (sites, n=18)** Sensitivity = 0.67 (0.30-0.90) Specificity = 1.00 (0.75-1.00) LR+ = ∝ LR- = 0.33 (0.11-1.03) PPV = 100%, NPV = 86% Accuracy = 89% (67-97) **Extra-hepatic abdomen (sites,n=19)** Sensitivity = 0.90 (0.60-0.98) Specificity = 0.67 (0.35-0.88) LR+ = 2.70 (1.05-6.96) LR- = 0.15 (0.02-1.02) PPV = 75%, NPV = 86% Accuracy = 79% (57-91) **Pelvis (sites,n=19)** Sensitivity = 0.80 (0.49-0.94) Specificity = 0.78 (0.45-0.94) LR+ = 3.60 (1.02-12.70) LR- = 0.26 (0.07-0.93) PPV = 80%, NPV = 78% Accuracy = 79% (57-91) *(95% CI)	Laparotomy (n=15)	**Selection bias:** Small sample Conflict of interest One patient did not go to laparotomy	•Consecutiveς •ProspectiveϒCEA assessed against valid gold standardϒ •CEA blindedϒ •Surgery blindedς •Relevant popς? **COMMENT** CEA-Scan® FP due to inflammatory process **STUDY CONCLUSIONS** CEA-Scan® may help to detect occult metastatic cancer missed by CT-scan

Study	Study type	n	Indication	Patient population	Patient characteristics	Interpretation of imaging	Reported operating characteristics	Gold standard	Potential bias	Quality Grading
Sirisriro et al., 1996	Case series Consecutive Prospective?	24	Known recurrent disease Suspected recurrent disease	**All patients:** Histologically proven CRC Normal renal function Good performance status (Karnofsky >60%) Raised serum CEA **Groups:** Recurrent lesions (n=10) Occult disease (n=12) Equivocal lesions (n=2)	Male =13 Female=11 Mean age=59.8years (37-81)	•CEA-Scan® performed on all patients, reference test not performed on all patients? •CEA-Scan® interpreted without knowledge of surgery results (blinded) •Surgery not blinded to CEA-Scan® results •CEA-Scan® blind to basic clinical information but not blind to previous imaging results •Surgery not blind to clinical information	**Patients (n=24)** Sensitivity = 0.95 (0.75-0.99) Specificity = 0.60 (0.23-0.88) PPV = 90%, NPV = 75% LR+ = 2.37 (0.81-6.97) LR- = 0.09 (0.01-0.67) Accuracy = 88% (69-96) **Liver (n=24)** Sensitivity = 0.71 (0.36-0.92) Specificity = 1.00 (0.81-1.00) PPV = 100%, NPV = 89% LR+ = ∝ LR- = 0.29 (0.09-0.92) Accuracy = 92% (74-98) **Abdomen (n=23)** Sensitivity = 0.93 (0.69-0.99) Specificity = 0.89 (0.57-0.98) PPV = 93%, NPV = 89% LR+ = 8.36 (1.31-53.34) LR- = 0.08 (0.01-0.54) Accuracy = 91% (73-98) **Pelvis (n=24)** Sensitivity = 0.70 (0.40-0.89) Specificity = 0.79 (0.52-0.92) PPV = 70%, NPV = 79% LR+ = 3.27 (1.11-9.64) LR- = 0.38 (0.14-1.02) Accuracy = 75% (55-88) **All Sites (n=71)** Sensitivity = 0.81 (0.64-0.91) Specificity = 0.90 (0.77-0.96) PPV = 86%, NPV = 86% LR+ = 8.06 (3.13-20.76) LR- = 0.22 (0.10-0.44) Accuracy = 86% (76-92) *(95% CI)	Histopathology from second-look laparotomy Different standards for pts and lesions, e.g. TP/TN/FP lesions reference = histopathology FN lesions reference = consensus /CDM or histology "True" diagnosis = consensus which included CEA-Scan® results (p570)	**Review bias:** Surgery **Selection bias**: Small sample, good performance status, normal renal function **Verification bias:** some patients (FN 6/71) verification included CDM (p570) Gold standard for positive disease may have included CEA-Scan® results	•ConsecutiveΥ •ProspectiveΥ •CEA –Scan assessed against a valid gold standardς •CEA-Scan® blindedΥ •Surgery blindedς •Relevant popς **COMMENT** Invalid gold standard **STUDY CONCLUSIONS** CEA-Scan® is potentially useful in detecting recurrent CRC in patients with rising serum CEA particularly when CDM is negative or equivocal

Study	Study type	n	Indication	Patient population	Patient characteristics	Interpretation of imaging	Reported operating characteristics*	Gold standard	Potential bias	Quality Grading
Willkomm et al., 2000	Case series Prospective Comparative study of CEA-Scan®, PET and CDM	28	Suspicion of recurrence based on clinical symptoms or rising serum CEA Known recurrence based on conventional imaging	Previously resected CRC (rectal cancer 79%, colon cancer 21%) Documented lesions (n=13) Symtomatic (n=2) Asymptomatic, rising serum CEA (n=13)	Male=15 Female=13 Age=63yrs	•All patients had CEA-Scan® - not all patients had SPECT of the liver •All patients had the reference standard (surgery or FU) •All patients had FDG-PET **CEA-Scan®** •CEA-Scan® was not reported to be blind to surgery •Surgery/FU was not reported to be blind to CEA-Scan® results •CEA-Scan® was interpreted without the knowledge of other imaging studies including FDG-PET **FDG-PET** •FDG-PET not reported to be blind to surgery •FDG-PET was interpreted without the knowledge of other imaging studies including CEA-Scan®. •Surgery/FU was not reported to be blind to FDG-PET imaging results	**CEA-Scan® local recurrence (n=28)** Sensitivity = 0.89 (0.56-0.98) Specificity = 1.00 (0.83-1.00) PPV = 100%, NPV = 95% LR+ = ∝ LR- = 0.11 (0.02-0.70) Accuracy = 96%(82-99) **CEA-Scan® liver mets (n=28)** Sensitivity = 0.11 (0.02-0.44) Specificity = 1.00 (0.83-1.00) PPV = 100%, NPV = 70% LR+ = ∝ LR- = 0.89 (0.71-1.12) Accuracy = 71%(53-85) **CEA-Scan® distant mets (n=28)** Sensitivity = 0.25 (0.05-0.70) Specificity = 1.00 (0.86-1.00) PPV = 100%, NPV = 89% LR+ = ∝ LR- = 0. 75 (0.43-1.32) Accuracy = 89% (73-96) **FDG-PET local recurrence (n=28)** Sensitivity = 1.00 (0.70-1.00) Specificity = 0.95 (0.75-0.99) PPV = 90%, NPV = 100% LR+ = 19.00 (2.82-128.0) LR- = ∝ Accuracy = 96% (82-99) **FDG-PET liver mets (n=28)** Sensitivity = 1.00 (0.70-1.00) Specificity = 1.00 (0.83-1.00) PPV = 100% NPV = 100% LR+ = ∝ LR- = ∝ Accuracy = 100% (88-100) **FDG-PET distant mets (n=28)** Sensitivity = 1.00 (0.51-1.00) Specificity = 1.00 (0.86-1.00) PPV = 100%, NPV = 89% LR+ = ∝ LR- = ∝ Accuracy = 100% (88-100)	Histology from surgery (n-=14) for patients eligible for surgery or clinical FU 6-19 months (n=14) and radiology in patients who were not eligible for surgery. **Note** • It was not always clear which scan results were confirmed by follow-up. •The abstract suggests that confirmation of findings included CDM and table 4 indicated that patients not going to surgery were verified by radiology	**Selection bias** **Review bias:** surgery?	•Consecutiveς •ProspectiveϒY •CEA-Scan® assessed against a valid gold standardς •CEA-Scan® blindedς •Surgery blindedς •Relevant popς **COMMENT** Liver and distant mets confirmed by clinical FU or CT/radiology (invalid standard) in patients not eligible for surgery

Study	Study type	n	Indication	Patient population	Patient characteristics	Interpretation of imaging	Reported operating characteristics*	Gold standard	Potential bias	Quality Grading
Willkomm et al., 2000 (Cont.)							**CEA-Scan® asymptomatic local recurrence (n=13,3TP)** Sensitivity = 1.0 (0.44-1.00) Specificity = 1.00 (0.73-1.00) PPV = 100%, NPV = 100% LR+ = ∝ LR- = ∝ Accuracy = 100%(77-100) **CEA-Scan® asyptomatic liver mets (n=13,6TP)** Sensitivity = 0.00 (0.00-0.39) Specificity = 1.00 (0.65-1.00) PPV = ?, NPV = 54% LR+ = ∝ LR- = 1.00(1.00-1.00) Accuracy = 54% (29-77) **CEA-Scan® asymptomatic distant mets (n=13,3TP)** Sensitivity = 0.33 (0.06-0.79) Specificity = 1.00 (0.73-1.00) PPV = 100%, NPV = 78% LR+ = ∝ LR- = 0.67 (0.30-1.48) Accuracy = 85% (58-96) **FDG-PET asymtomatic local recurrence (n=13,3TP)** Sensitivity = 1.00 (0.44-1.00) Specificity = 1.00 (0.73-1.00) PPV = 100%, NPV = 100% LR+ = ∝LR- = 0.00 Accuracy = 100% (77-100) **FDG-PET asymptomatic liver mets (n=13,6TP)** Sensitivity = 1.00 (0.61-1.00) Specificity = 1.00 (0.65-1.00) PPV = 100%, NPV = 100% LR+ = ∝ LR- = 0.00 Accuracy = 100% (77-100) **FDG-PET asymptomatic distant mets (n=13,3TP)** Sensitivity = 1.00 (0.44-1.00) Specificity = 1.00 (0.73-1.00) PPV = 100%, NPV = 100% LR+ = ∝ LR- = 0.0 Accuracy = 100% (77-100)			

Study	Study type	n	Indication	Patient population	Patient characteristics	Interpretation of imaging	Reported operating characteristics*	Gold standard	Potential bias	Quality Grading
Willkomm et al., 2000 (Cont.)							**CEA-Scan® symptomatic local recurrence (n=15, 6+)** Sensitivity = 0.83 (0.44-0.97) Specificity = 1.00 (0.71-1.00) PPV = 100, NPV = 90% LR+ = ∝ LR- = 0.17 (0.03-1.00) Accuracy = 93% (70-99) **CEA-Scan® symptomatic liver mets (n=15,3+)** Sensitivity = 0.33 (0.06-0.79) Specificity = 1.00 (0.76-1.00) PPV = 100%, NPV = 86% LR+ = ∝ LR- = 0.67 (0.30-1.48) Accuracy = 87% (62-96) **CEA-Scan® symptomatic distant mets (n=15, 1+*)** Sensitivity = 0.00 (0.00-0.79) Specificity =1.00 (0.78-1.00) PPV = ?, NPV = 93% LR+ = ∝ LR- = 1.00 (1.00-1.00) Accuracy = 93% (70-99) **FDG-PET symptomatic local recurrence (n=15, 6+)** Sensitivity = 1.00 (0.57-1.00) Specificity = 0.89 (0.57-0.98) PPV = 83%, NPV = 100% LR+ = 9.00(1.42-57.12) LR- = ∝ Accuracy = 93% (70-99) **FDG-PET symptomatic liver mets (n=15,3+)** Sensitivity = 1.00 (0.44-1.00) Specificity = 1.00 (0.76-1.00) PPV = 100%, NPV = 100% LR+ = ∝ LR- = ∝ Accuracy = 100% (80-100) **FDG-PET symptomatic distant mets (n=15,1+*)** Sensitivity = 1.00 (0.21-1.00) Specificity = 1.00 (0.78-1.00) PPV = 100%, NPV = 100% LR+ = ∝ LR- = ∝ Accuracy = 100% (80-100) * (95% CI)			*Only 1 event i.e. only 1 pt with distant mets

Study	Study type	n	Indication	Patient population	Patient characteristics	Interpretation of imaging	Reported operating characteristics*	Gold standard	Potential bias	Quality Grading
Willkomm et al., 2000 (Cont.)							**CEA-Scan® all sites (n=140 lesions)** Sensitivity = 0.42 (0.24-0.61) Specificity = 1.00 (0.97-1.00) PPV =100%, NPV = 89% LR+ = LR- = 0.58 (0.42-0.82) Accuracy = 90% (84-94) **FDG-PET all sites (n=140 lesions)** Sensitivity = 1.00 (0.86-1.00) Specificity = 0.99 (0.95-1.00) PPV = 96%, NPV = 100% LR+ = 116 (16-817) LR- = 0 Accuracy = 99% (96-100) * (95% CI)			

Appendix K Is there effective treatment for recurrent colorectal cancer?

More than 50 per cent of colorectal cancer patients suffer recurrence, with the risk of recurrence increasing with the stage of disease (Dukes A 0-13 per cent, Dukes B 11-61 per cent, Dukes C 32-88 per cent) and the location of the primary tumour (right colon 24 per cent, transverse colon 10 per cent, left colon 11.5 per cent, sigmoid colon 34 per cent, low rectum 3-50 per cent (Frizelle et al., 1998).

Recurring disease may present with rising serum CEA (asymptomatic or occult disease) or with a number of symptoms (symptomatic or known disease) including change in bowel habit, rectal bleeding and abdominal pain. The most common sites of metastases and relapse are the liver, the peritoneal cavity, the pelvis, the retroperitoneum and the lungs. The majority of recurrences are multifocal and are usually treated palliatively with systemic chemotherapy. However, patients with isolated liver or lung metastases, or limited volume local recurrence are candidates for potentially curative surgery. The primary purpose of determining disease extent in relapsed patients is to identify the small proportion of patients who could benefit from surgery and determine appropriate management and therapy for the remainder (Guillem et al., 1997).

There are a number of problems associated with the diagnosis of recurrent CRC and the determination of the extent of disease, particularly when the recurrence is local, or it occurs in the region of anastomosis or the lymph nodes, or has spread diffusely to distant sites. The main problems are:

- detection of small-volume disease;
- distinguishing post-therapy scar tissue and inflammation from recurrent disease;
- ruling out extra-hepatic spread or distant metastases in patients with limited lung or liver lesions;
- long asymptomatic lead time for distant metastases;
- treatment efficacy for recurrent or metastatic colorectal cancer.

Survival rates in treated patients

Primary colorectal cancer is curable by surgery and up to 70 per cent of newly presenting colorectal patients undergo potentially curable resection (Headrick et al., 2001). However, a significant proportion of these patients relapse and die of their disease (up to 50 per cent) and nearly a quarter will recur within two years of their "curative" surgery (Renehan et al., 2002, Lonneux et al., 2002). Untreated recurrent colorectal cancer has a generally poor prognosis and less than 5 per cent of patients will survive five years (Penna and Nordlinger, 2002, Frizelle et al., 1998). For treated patients a median survival of 31-40 months has been reported (Cunningham et al., 1997). Five-year survival rates are closely correlated with stage of disease, ranging from 90 per cent for patients with Stage I disease

to less than 10 per cent for patients presenting with late stage, i.e. extensive metastatic disease (Lonneux et al., 2002). For carefully selected patients with recurrent local disease or limited liver and lung metastases further treatment offers the possibility of cure, see Table 20.

Table 20 Recurrence rates and five-year survival rates for treated relapsed colorectal patients

Site of recurrence	Recurrence	5yr survival*	Publication
Locoregional and anastomosis	3-25%	8-28%	(Huguier et al., 1998)
Liver	26-50%	25-48%	(Nordingler et al., 1996)
Lung	10%	20-44%	(Mcafee et al., 1992)
Distant sites (ovary,bone,brain)	2-7%	Unlikely	(Goldberg et al., 2004)

*selected population

The differentiation of scar tissue and inflammation arising from primary treatment of malignant lesions is a particular problem in these patients, together with the identification of occult and small volume disease. Asymptomatic patients presenting with rising serum CEA and no other evidence of recurrence also represent a challenge. Careful determination of the extent of disease in these patients is important if unnecessary or inappropriate treatment is to be avoided.

Treatment of recurrent disease

Resection is the mainstay of treatment for colorectal cancer and is the only therapy that offers the possibility of cure. Although patients may relapse again, it is believed that the natural history of colorectal cancer is altered by surgery with curative intent (Steele and Ravikumar, 1989, Steele, 1991). Regional or systemic chemotherapy has an important role to play in patients who are not eligible for surgery. Radiotherapy used in combination with chemotherapy may be useful in the treatment of disease in the pelvis, and radical radiotherapy may be effective in patients with non-resectable pelvic recurrence (Hatfield and Sebag-Montefiore, 2003).

Locoregional recurrence

Local recurrence is common in patients with rectal cancer and locoregional control is a major issue in the treatment of these patients (Michel et al., 1999, Santiago et al., 2002).

Limited local recurrence, i.e. recurrence without disseminated disease, occurs in up to one third of rectal cancer patients and may be successfully treated by surgery. Without surgical intervention, the five-year survival rate is less than five per cent. However, for selected patients, surgery may increase the five-year survival rate significantly (Frizelle et al., 1998, Huguier and Houry, 1998). Locoregional recurrence accompanied by generalised abdominal spread of the disease is usually incurable (Bleeker et al., 2001).

Liver and lung metastases

There have been no randomised controlled trials of surgery in this patient group and the highest level of evidence available (mostly well-designed case series) has been used to establish the effectiveness of surgery. After surgery for primary CRC, 30-40 per cent of patients who recur with metastatic disease have the liver as the only distant site of disease. For isolated liver metastases, patients who do not have further surgery have a median survival of 6-12 months. Systematic chemotherapy may extend this to between 12-18 months, with surgery achieving an estimated five-year survival of 25-40 months (Fong, 1999). Thus, for patients who relapse with isolated liver lesions, surgery is the standard of care (Dangelica et al., 2002).

For patients with liver metastases, the cure rate with surgery alone is 25-35 per cent (Hugh et al., 1997) with a reported five-year survival of more than 40 per cent in selected patients (Tilsed, 1999). Only 5-7 per cent of all patients with liver metastases are eligible for surgery. For patients with extensive liver or lung metastases who are not eligible for surgery, chemotherapy may be administered to reduce disease bulk (Sobrero et al., 2000). Patients with further relapse in the liver may be considered for a second liver resection (Muratore et al., 2001).

The resection of pulmonary metastases may also be curative and five-year survival rates of 24-43 per cent have been reported (Rena et al., 2002, van Halteren et al., 1999). This compares with no survivors at five years reported for patients with untreated but potentially resectable lung metastases (Wanebo et al., 1978, Wilson and Adson, 1976). Patients with solitary metastases have a better prognosis than those with multiple metastases, with five-year survival rates of 43.6 per cent and 34 per cent respectively (Rena et al., 2002).

Local recurrence after the excision of pulmonary metastases is a problem. Re-operation is a viable option for a small group of patients and five-year survival rates of 30-50 per cent have been reported in patients in whom disseminated disease can be ruled out (Rena et al., 2002, Mcafee, 1992, Kandioler et al., 1998). Surgery in patients undergoing liver or lung resection is not without its risks and mortality rates of 2 per cent have been associated with the resection of pulmonary metastases (Rena et al., 2002) and 0-5 per cent for liver resections (Penna and Nordlinger, 2002). Postoperative complications have been reported in approximately 25 per cent of patients (Nordlinger et al., 1996, Scheele et al., 1995) and postoperative morbidity after lung and liver resection in 2-12 per cent of patients (Penna and Nordlinger, 2002). The risks associated with surgery are important considerations and because the long-term survival benefits of liver resection are small, they must be comparatively low.

In selected cases, combined resection of liver and lung metastases may be considered (Penna and Nordlinger, 2002) and five-year survival rates of 31 per cent have been reported for patients undergoing both hepatic and pulmonary metastases resection (Kobayashi et al., 1999). Patients undergoing both hepatic and pulmonary metastases resection have a morbidity of 12 per cent and a five-year survival of 305 months with a median follow-up of 62 months (Headrick et al., 2001).

Advanced disease

After potentially curative resection approximately 50 per cent of patients will go on to develop advanced disease (Dangelica et al., 2002). Surgery for locally advanced recurrent disease does not result in significant cure rates (Tilsed et al., 1999) and until recently, survival beyond one year has been uncommon. Diffuse extra-hepatic disease is generally considered to contraindicate surgery and imparts a very poor prognosis (Rodgers and McCall, 2000).

Chemotherapy is the mainstay of treatment for advanced disease. It has been shown to significantly improve survival over supportive care, at 8.0 versus 11.7 months median survival (Simmonds, 2000) and significantly lower the risk of mortality at one year, risk ratio 0.69;95 per cent CI 0.60-0.81 (Jonker et al., 2000). The number of metastatic sites may be used to identify a sub-set of patients for whom conventional treatments should be avoided and aggressive therapy or supportive care only considered (Massacesi et al., 2002).

The most widely used chemotherapy agent is intravenous 5-fluorouracil (5-FU), which is usually combined with folinic acid or oral capecicitine (National Institute for Clinical Excellence, 2003). Patients who progress on this treatment may be treated with irinotecan in combination with 5-FU and folinic acid (Saltz et al., 2001) or with oxaliplatin combined with 5-FU and folinic acid in the FOLFOX regimen (Goldberg et al., 2004).

A review of the evidence for the clinical effectiveness of irinotecan and oxaliplatin by the National Institute for Clinical Excellence (NICE) in the UK (Jones et al., 2001) concluded that there was good evidence to suggest that irinotecan, used in combination with 5-FU and folinic acid as first- or second-line therapy, may increase survival. The evidence for a survival benefit for oxaliplatin combinations was less clear. However, in a recent report of a RCT comparing three different two-drug combinations of 5-FU, irinotecan and oxaliplatin (Goldberg et al., 2004) reported a significant advantage in survival for the FOLFOX regimen compared to the control combination of irinotecan, 5-FU and folinic acid. Patients treated with FOLFOX chemotherapy were reported to have a median survival of 19.5 months. Oxaliplatin is now listed on the PBS for use in Australia as a first-line agent in advanced colorectal cancer and will be administered in conjunction with 5-FU and folinic acid.

Pre-treatment with combination chemotherapy (neo-adjuvant chemotherapy) in patients with initially unresectable disease has been shown to reduce the volume of disease to resectable levels and improve survival. This is comparable to the survival of patents undergoing resection alone (Bismuth et al., 1996, Sobrero et al., 2000). Bismuth et al., (1996) reported surgical resection in 16 per cent of patients not previously considered for surgery after chemotherapy with 5-FU and oxaliplatin or CPT-11 and five-year survival rates comparable to those for patients with resectable lesions.

Follow-up for recurrence

Intensive follow-up has been advocated in the international literature to enable the early detection of recurrent disease and improve survival after curative surgery. However, controversy has remained despite a number of randomised controlled trials and two meta-analyses examining the value of intensive follow-up.

In 2002, Reneham et al., reported the results of a further meta-analysis that included only randomised controlled trials (previous meta-analyses have included a wide mixture of study types) and modern follow-up regimens, i.e. computed tomography or frequent measurements of CEA, or both. The authors concluded that intensive follow-up after curative surgery reduces mortality at five years by 9-13 per cent. Intensive follow-up was also significantly associated with earlier detection of all recurrences (8.5 months difference in means, 95 per cent CI 7.6-9.4, P<0.001) and an increased rate for isolated recurrences (RR 1.61, 95 per cent CI 1.12-2.32, P=<0.011). There have been no randomised controlled trials of early treatment versus symptomatic treatment of advanced colorectal cancer patients who are ineligible for surgery. Glimelius et al., (1992) reported a median survival of 14 months for patients treated with chemotherapy before they became symptomatic, versus nine months for patients with delayed treatment.

There is currently no consensus in Australia on the best follow-up procedure for colorectal cancer and practice varies considerably. New guidelines for the management of colorectal cancer are currently being developed by the NHMRC.

Summary of the effectiveness of treatment for recurrent colorectal cancer

- Many patients present with occult disease that is below the resolution limits of conventional anatomical imaging techniques.
- Patients with isolated lesions to the liver or lungs can benefit from surgery and may be cured.
- Patients with liver metastases and unresectable extra-hepatic disease need to be spared the added trauma of unnecessary surgery.
- The survival of patients with advanced disease may be improved with systematic chemotherapy.
- In early studies, untreated liver metastases had a 0.9 per cent survival at four years (Penna and Nordlinger, 2002).
- Current anatomical imaging techniques fail to detect occult disease and micro metastases which are probably there at presentation, causing the extent of recurrent disease to be underestimated and sub-optimal and/or costly management strategies adopted unnecessarily (Lechner et al., 2000a).

Abbreviations

AIHW	Australian Institute of Health and Welfare
CEA	carcinoembryonic antibody
CI	confidence interval
CRC	colorectal cancer
CT	computed tomography
DRG	diagnosis related group
FDG	fluorine-18-labelled 2-fluoro-2-deoxy-glucose
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
MBS	Medicare Benefits Schedule
MSAC	Medical Services Advisory Committee
NHMRC	National Health and Medical Research Council
PBS	Pharmaceutical Benefits Scheme
PET	positron emission tomography
PYLL	Person years of life lost
RCT	randomised controlled trial
TGA	Therapeutic Goods Administration

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