

**OctreoScan®
scintigraphy for gastro-
entero-pancreatic
neuroendocrine tumours**

August 1999

MSAC application 1003

Final assessment report

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

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

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Executive summary

The procedure

OctreoScan® scintigraphy (OctreoScan) is a diagnostic test for gastro-entero-pancreatic (GEP) neuroendocrine tumours. It is a nuclear medicine scan that is capable of imaging the entire body.

The Medicare Services Advisory Committee — its role and approach to assessments

The Medicare 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 Minister for Health and Aged Care on the evidence relating to the safety, effectiveness and cost-effectiveness of new 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. The medical literature on the new technology is searched and evidence is assessed. A team from the Australasian Cochrane Centre was engaged to conduct a systematic review of literature on OctreoScan. A supporting committee with expertise in this area then evaluated the evidence and provided advice to MSAC.

Assessment of OctreoScan® scintigraphy for gastro-entero-pancreatic neuroendocrine tumours

The clinical studies undertaken to date on the sensitivity and specificity of OctreoScan all have methodological limitations, including the failure to compare OctreoScan in a blinded trial with an acceptable ‘gold standard’, thus leaving open the possibility of bias.

There is some evidence that OctreoScan results in a change in management in a proportion of patients, but there are no randomised controlled trials available to support the improved outcomes for patients who receive OctreoScan.

Clinical need

GEP neuroendocrine tumours are relatively rare. Estimates of the incidence of carcinoid tumours vary between 7 and 13 cases per million population per year. The incidence of clinically significant pancreatic endocrine tumours (PETs) is even rarer, with an estimated incidence of 3.6 to 4 per million population per year. The prevalence in series of random autopsies is surprisingly high (1%), indicating that the vast majority of tumours do not present clinically.

In tumours that present clinically, the majority have metastatic disease at the time of presentation. The presence of hepatic and extrahepatic metastases is a major determinant of the management of disease. This is particularly so for gastrinomas, where the development of medication which is able to control the hypersecretion of gastric acid has meant that the growth and metastatic spread of disease is an important determinant of long-term survival.

Insulinomas should be removed because there is a high rate of cure following removal. Surgery for carcinoid tumours is potentially curative but there is wide variation in the studies of cure rates following surgery. Prognosis appears to be related to tumour size, although this is less so in midgut carcinoids.

The treatment of metastatic disease has become more important as the ability to effectively treat the functional syndromes has increased. Previously, patients were more likely to die as a result of the hormonal excess than from the tumour per se. Options for the treatment of metastatic disease include chemotherapy, hormonal therapy with octreotide, alpha-interferon, hepatic artery embolisation, and surgical debulking. The treatment of choice for carcinoid syndrome is octreotide therapy. Liver transplantation has been attempted in a small number of cases, but hepatic recurrence is common and it is unclear whether transplantation prolongs survival.

Safety

OctreoScan appears to be safe at the currently recommended dosages.

Effectiveness

OctreoScan appears to have some theoretical advantages over other forms of imaging (for example it is able to image the entire body). However, it is difficult to assess the true sensitivity and specificity of OctreoScan because of the lack of data of sufficient methodological quality. In comparison with existing methods of imaging, the test appears more sensitive, but the test has not been compared in a blinded fashion with an acceptable gold standard, and the types of tests with which it has been compared have varied, even within the same study. Although the possibility of false positive results (and therefore a specificity of less than 100%) has been discussed, none of the trials reported data that would allow us to calculate an estimate of specificity.

The major advantages of the technique are its ability to detect extrapancreatic tumours and metastatic lesions outside of the abdomen and chest. Because OctreoScan images the whole body, it may also detect an unsuspected multiple endocrine neoplasia type 1 (MEN-1) tumour.

OctreoScan appears to be less sensitive in the detection of insulinomas, because of the lack of receptor sites on such tumours. Insulinomas also tend to be solitary tumours, not requiring whole body imaging.

Because the imaging of a tumour may not result in a change in clinical management, a test of greater sensitivity and specificity may not result in better outcomes for patients. There is some evidence that OctreoScan results in a change in management in a

proportion of patients. However, there is no evidence that this results in increased cure rates or survival time.

Cost-effectiveness

It is not possible to accurately estimate the cost-effectiveness of OctreoScan, because of the lack of validated data on the accuracy of the test and its influence on clinical outcomes.

Recommendations

MSAC recommended that on the strength of evidence relating to OctreoScan, public funding should be supported for this diagnostic test:

- where there is a suspected GEP neuroendocrine tumour, based on biochemical evidence, with negative or equivocal structural imaging from conventional radiology (computed tomography or magnetic resonance imaging); or
- where surgically amenable disease has been identified, based on biochemical evidence and conventional imaging, in order to rule out further metastatic disease.

Since there is currently insufficient evidence relating to the use of OctreoScan for the purposes of determining whether octreotide therapy is a viable therapeutic option, public funding should not be supported at this time for this use.

Introduction

The Medicare Services Advisory Committee (MSAC) has assessed OctreoScan® scintigraphy (OctreoScan)[†], which is a diagnostic test for the detection and localisation of gastro-entero-pancreatic neuroendocrine tumours.

MSAC evaluates new 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 shown 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 and health administration.

This report summarises the current evidence of the effectiveness of OctreoScan for the detection and localisation of gastro-entero-pancreatic neuroendocrine tumours.

[†] OctreoScan® is a registered tradename of Mallinckrodt Medical, Petten, Netherlands

Background

OctreoScan® scintigraphy for gastro-entero-pancreatic neuroendocrine tumours

Neuroendocrine tumours are derived from neural crest cells, which develop in the embryo and migrate throughout the body. Neuroendocrine tumours include the carcinoids tumours, pancreatic endocrine tumours, melanomas, phaeochromocytomas and medullary thyroid carcinomas. Such tumours are histologically similar and also share cytochemical features. Gastro-entero-pancreatic (GEP) neuroendocrine tumours include the carcinoid tumours and the pancreatic endocrine islet cell tumours. Both types of tumour are relatively rare. The majority of such tumours are malignant but are frequently slow growing.

Carcinoid tumours

Carcinoid tumours commonly originate in one of four sites: bronchus, appendix, rectum and jejunum-ileum.¹ For the purposes of this review, carcinoid tumours that originate in the gastrointestinal system have been included as GEP tumours.

Carcinoid tumours that originate in the midgut (jejunum, ileum, appendix, Meckel's diverticulum and ascending colon) often produce high levels of hormones, which cause a characteristic clinical syndrome known as carcinoid syndrome, the main feature of which is attacks of flushing. This may be accompanied by diarrhoea, pain, wheezing, lacrimation, itching, palpitations, or facial or conjunctival oedema. The attacks may occur spontaneously or be triggered by stress, alcohol, exercise, or food intake. Cardiac manifestations have been reported in 11–56% of patients, primarily due to fibrous deposits which cause constriction of the heart valves.^{2,3} For patients without systemic features, the most common clinical presentation is that of periodic abdominal pain. A summary of some of the features of carcinoid tumours is shown in Table 1.

Pancreatic endocrine tumours

The classification of pancreatic endocrine tumours (PETs) is shown in Table 2. PETs are defined as functional when they secrete hormones that produce a clinical syndrome. For example, a functional gastrinoma causes Zollinger–Ellison syndrome (ZES), which is a severe form of stomach and duodenal ulceration. Some of the clinical features of the more common PETs are described below.

Gastrinomas

The most common presenting symptom of a gastrinoma is abdominal pain due to acid secretion. The disease is suspected for patients with peptic ulcer plus diarrhoea, familial peptic ulcer, peptic ulcer in unusual locations and recurrent or resistant peptic ulcer. Many patients with gastrinomas have diarrhoea and in 15 to 18% of patients it is the only presenting symptom.⁴ Gastrinomas frequently have occult metastases and may have multifocal primary lesions.

Table 1 Carcinoid tumours

Tumour location	% of total	Incidence of metastases (%)	Incidence of carcinoid syndrome (%)
Foregut			
Oesophagus	<1	–	–
Stomach	2	22	9.5
Duodenum	2.6	20	3.4
Pancreas	<1	20	20
Gall bladder	<1	33	5
Bile duct	<1	–	–
Ampulla	<1	14	–
Larynx	<1	50	–
Bronchus	11.5	20	13
Thymus	2	25	–
Midgut			
Jejunum	1.3	35	9
Ileum	23	35	9
Meckel's diverticulum	1	18	13
Appendix	38	2	<1
Colon	2	60	5
Liver	<1	–	–
Ovary	<1	6	50
Testis	<1	–	50
Cervix	<1	24	3
Hindgut			
Rectum	13	3	–

Source: De Vita VT, Hellman S and Rosenberg SA (eds.)⁹

Insulinomas

Insulinomas were first recognised by Whipple who described a triad of symptoms consisting of hypoglycaemia associated with blood sugar levels less than 50 mg/dL, with relief of symptoms following ingestion of glucose.⁶ Insulinomas are frequently solitary benign tumours.

Nonfunctional pancreatic endocrine tumours

Nonfunctional PETs do not secrete a peptide hormone causing any specific clinical symptoms. Many of the nonfunctional PETs present late, principally with symptoms due to obstructive or mass effects. They are usually quite large and locally invasive at the time of presentation.⁵

Multiple endocrine neoplasia type 1

Pancreatic endocrine tumours can form part of the syndrome of multiple endocrine neoplasia type 1 (MEN-1). This is an autosomal dominant disease with tumours involving the pituitary gland, parathyroid glands and pancreatic islets. Ppomas are the most common pancreatic endocrine tumours in MEN-1 patients, but 82% also develop a functional PET.⁷

Table 2 Types of gastropancreatic endocrine tumours

Tumour name	Syndrome name	Hormone producing symptoms	Malignant (%)	Location
Ppoma	Ppoma	None	>60	Pancreas
Non functioning	Nonfunctioning pancreatic endocrine tumour	None	>60	Pancreas
Symptoms due to released hormones				
Gastrinoma	Zollinger–Ellison syndrome	Gastrin	60–90	Pancreas (30–60%) Duodenum (30–43%) Other (10–20%)
Insulinoma	Insulinoma	Insulin	10–15	Pancreas (>99%)
VIPoma	Pancreatic cholera Verner-Morrison (WDHA – watery diarrhoea hypkalemia achlorhydria)	Vasoactive intestinal peptide (VIP)	80	Pancreas (90%) Adrenal (10%)
Glucagonoma	Glucagonoma	Glucagon	60	Pancreas (>99%)
Somatostatinoma	Somatostatinoma	Somatostatin		Pancreas (56%) Upper small intestine (44%)
GRFoma	GRFoma	Growth hormone-releasing peptide (GRF)	30	Pancreas (33%) Lung (53%) Small intestine(10%) Other (7%)
ACTHoma	Ectopic Cushing's syndrome	Adrenocorticotrophic hormone (ACTH)	>95 (pancreatic)	Pancreas (4–16%)

Source: De Vita VT, Hellman S and Rosenberg SA (eds.)⁵

How it works

OctreoScan is a diagnostic test for GEP neuroendocrine tumours. It is a nuclear medicine scan that is capable of imaging the entire body.

The technique, which was first described by Krenning et al in 1989⁸, is based on the presence of high affinity binding sites for somatostatin receptors on the surface of most GEP tumours^{9,10}. A radionuclide is attached to a somatostatin analogue called octreotide. The radiolabelled octreotide is injected into the patient, and radioactivity concentrates at tumours with somatostatin receptors and in organs that excrete the radionuclide. Scintigraphic imaging with a gamma camera is used to locate concentrations of radioactive activity, and thus localise tumour sites.

Initially, [¹²³I-Tyr³] was used to label octreotide, but this radionuclide had the following shortcomings:

- the labelling of [Tyr³]-octreotide with ¹²³I is a difficult process requiring advanced skills;
- high specific activity radiolabelled sodium iodide (Na¹²³I) is needed for the procedure, which is expensive and difficult to obtain;
- the timing of the labelling and scanning must coincide with the production and delivery schedule for Na¹²³I because of its short half life (13.2 hours); and

- because [Tyr³]-octreotide is largely excreted by the liver, biliary system and intestines, these organs have high levels of radioactivity, which makes interpretation of images difficult.¹¹

In OctreoScan, the octreotide is radiolabelled with the indium (In) derivative [¹¹¹In-DTPA-D-Phe¹]. This radionuclide has advantages over [¹²³I-Tyr³]-labelled octreotide in that it is comparatively easy to prepare and more generally available. In addition, it has a longer half life (2.8 days), which means scanning does not have to immediately follow production. Also, as it is rapidly excreted by the kidneys, there is much less interference from radioactivity in the intestines¹².

OctreoScan imaging is typically preceded by administration of laxatives to reduce the chance of radioactivity in the intestinal system. Planar antero–posterior whole body images are usually obtained 4 and 24 hours after injection of In-labelled octreotide. Single photon emission computerised tomography (SPECT) is often performed as well, usually at 24 and occasionally at 48 hours after the injection. SPECT is able to differentiate more easily between areas of pathological uptake and physiological uptake in the abdomen. It can also help to discriminate between mesenteric and bone lesions. Extra planar images may be obtained from areas of specific interest, using longer exposure time for more easily interpreted imaging.

Intended purpose

OctreoScan was approved by the Therapeutic Goods Administration (TGA) on 30 May 1996 for the localisation of GEP neuroendocrine tumours.

The information gained from scintigraphy of GEP tumours can be used for the following purposes:

- to determine the stage and extent of the disease;
- to localise a solitary tumour which may then be evaluated for resection;
- to plan palliative resection; and
- to evaluate the potential value of medical treatment with somatostatin analogues.

Clinical need/burden of disease

Incidence/prevalence of GEP neuroendocrine tumours

GEP neuroendocrine tumours are relatively rare. Estimates of the incidence of carcinoid tumours vary between 7 and 13 cases per million population per year.^{13,14} The incidence of clinically significant PETs is even rarer, with an estimated incidence of 3.6 to 4 per million population per year.^{15,16,17} The prevalence of the tumours in series of random autopsies is surprisingly high (1%), indicating that the vast majority of tumours do not present clinically.

In tumours that do present clinically, the majority have metastatic disease at the time of presentation. The presence of hepatic and extrahepatic metastases is a major determinant of the management of disease. This is particularly so for gastrinomas, where the development of medication that is able to control the hypersecretion of gastric acid has meant that the growth and metastatic spread of disease is an important determinant of long-term survival.¹⁸

Surgical removal of GEP neuroendocrine tumours

There is a lack of controlled studies that investigate whether surgical resection of a GEP tumour alters the natural history of the disease. A nonrandomised controlled trial at the National Institutes of Health (NIH) in the United States followed 98 patients with ZES who had the tumour resected and 26 patients who were treated medically.¹⁹ Three in the surgical group developed liver metastases and six in the medical group ($P < 0.003$). Two deaths occurred in the medical group due to metastatic disease and no disease-specific deaths occurred in the surgical group. This was not a randomised controlled trial, but there was no significant difference between the two groups on clinical or laboratory characteristics, or the duration of disease at baseline.

Other case-series data have indicated improvements in survival rates after resection of a gastrinoma (see Table 3). Case-series data have also indicated that there has been an improvement in the cure rate following surgical resection of gastrinomas in recent years. This can be attributed to improvements in antisecretory treatment, and improvements in preoperative and intraoperative localisation.

Insulinomas should be removed because there is a high rate of cure following removal. Surgery for carcinoid tumours is potentially curative but there is wide variation in the studies of cure rates following surgery. Prognosis appears to be related to tumour size, although this is less so in midgut carcinoids²⁰.

The treatment of metastatic disease has become more important as the ability to effectively treat the functional syndromes has increased. Previously, patients were more likely to die as a result of the hormonal excess than from the tumour per se. Options for the treatment of metastatic disease include chemotherapy, hormonal therapy with octreotide, alpha-interferon, hepatic artery embolisation, and surgical debulking. The treatment of choice for carcinoid syndrome is octreotide. Liver transplantation has been attempted in a small number of cases, but hepatic recurrence is common and it is unclear whether transplantation prolongs survival.

Existing procedures

The diagnosis of a GEP tumour is usually made by detection of high levels of secreted hormone in serum. This may also require a stimulation test, such as the calcium test for insulinoma tumours or secretin test for gastrinoma tumours. Primary lesions may also be confirmed by biopsy and histological examination. After confirmation of the diagnosis, the patient is evaluated for management of the tumour. A combination of imaging modalities is used. Investigations that are used routinely are computed tomography (CT) scan, endoscopic and upper abdominal ultrasound and magnetic resonance imaging (MRI). Angiography and bone scans may also be used. In the past it has often been difficult to detect and localise GEP tumours.

Table 3 Prognosis in patients with Zollinger–Ellison syndrome related to tumour resectability

Tumour status	Patients	Survival rate (%)		Study
		5-year	10-year	
No tumour found	13	100	100	Malagelada et al 1983 ²¹
	6	100	–	Zollinger et al 1984 ²²
	10	90	90	Stabile and Passaro 1985 ²³
	8	ND	63	Zollinger 1985 ²⁴
	16	90	ND	Norton et al 1991 ²⁵
	15	93 (70–99)	84 (56–96)	Weber et al 1995b ¹⁸
Tumour resected	7	100	100	Malagelada et al 1983 ²¹
	22	76	–	Zollinger et al 1984 ²²
	10	90	90	Stabile and Passaro 1985 ²³
	33	69	62	Ellison et al 1987 ²⁶
	42	95	ND	Norton et al 1991 ²⁵
	53	100 (87–100)	96 (87–100)	Weber et al 1995b ¹⁸
Tumour incompletely resected or recurrence	10	75	20	Malagelada et al 1983 ²¹
	7	14	–	Zollinger et al 1984 ²²
	15	95	ND	Norton et al 1991 ²⁵
	34	100 (84–100)	93 (68–99)	Weber et al 1995b ¹⁸
Unresectable	13	80	–	Malagelada et al 1983 ²¹
	7	30	–	Zollinger et al 1984 ²²
	14	40	30	Stabile 1985 ²³
	15	20	–	Norton et al 1986 ²⁷
	18	18	ND	Norton et al 1991 ²⁵
	36	53 (35–69)	30 (14–52)	Weber et al 1995b ¹⁸

ND = no data obtained at 10 years; – = no data as yet
Numbers in brackets are 95% confidence intervals

Comparator

The main purpose of imaging in patients with GEP pancreatic neuroendocrine tumours is to localise the disease and to determine whether hepatic and extrahepatic metastases are present. In the major studies assessing the clinical effectiveness of OctreoScan, the technology has been compared with ‘conventional imaging modalities’ (CIM). However, these modalities have varied between sites and the types of tumours being investigated. The imaging techniques used in the diagnosis of GEP tumours are described briefly below.

Ultrasound

Abdominal ultrasound is frequently used as a first-line investigation in the diagnosis of GEP tumours but is relatively insensitive in the detection of GEP tumours. In one series, abdominal ultrasound detected only 15% of gastrinomas from 1 to 3 cm in size²⁸.

Endoscopic ultrasound

This form of ultrasonography is a more sensitive means of locating tumours in the duodenum and pancreas. In one series it detected more than 60% of gastrinomas and pancreatic tumours. The sensitivity of the technique, however, is extremely operator

dependent²⁹. Routine endoscopy is a relatively insensitive means of localising GEP tumours. Even gastrinomas are often not seen on routine endoscopy because they are often submucosal.

Computed tomography

The ability of CT scans to detect GEP tumours varies depending on the location of the tumour, the type of tumour and the size of the tumour. It is relatively more sensitive for detecting insulinomas and less sensitive for detecting gastrinomas. Contrast injections and helical scanning may improve the sensitivity of CT scans. In several of the studies, the intravenous contrast agent iopamidol 30% was used.

Magnetic resonance imaging

Improvements in MRI technology has resulted in better results compared to other routine imaging techniques for the detection of GEP tumours.³⁰ Delayed T1 images at least 5 minutes after contrast enhancement are able to distinguish malignant from benign hepatic lesions. However, artifacts caused by any movement of the patient reduce the sensitivity of MRI, especially for small pancreatic tumours.

Angiography

Angiography is frequently used if surgery is planned or if the results of other forms of imaging are equivocal. Imaging is achieved by injection of the splenic, superior mesenteric, gastroduodenal and hepatic arteries with contrast material. Digital subtraction angiography improves sensitivity and specificity.

Bone scan

This is a nuclear medicine scan for the detection of bone metastases.

Other methods

Other methods that are also used to localise GEP tumours include intraoperative ultrasound, intraoperative transillumination, portal venous sampling, intra-arterial stimulation with calcium (for insulinomas) and intra-arterial stimulation with secretin (for gastrinomas). These techniques can be useful for detecting occult tumours. For ethical reasons relating to their invasive nature, however, these methods have not been used in large studies of unselected patients with GEP tumours.

Marketing status of the technology

OctreoScan was approved by the TGA on 30 May 1996 for the localisation of GEP neuroendocrine tumours.

Current reimbursement arrangement

Currently there is no specific Medicare Benefits Schedule (MBS) item number for OctreoScan.

Approach to assessment

Review of literature

MSAC reviewed the literature available on OctreoScan and provided expert advice. The methodology used in this review of the evidence of literature on the effectiveness and safety of OctreoScan has followed the methods outlined in the Cochrane Collaboration Handbook and Irwig et al (guidelines for meta-analyses evaluating diagnostic tests) as closely as possible.^{31,32}

Literature search

The medical literature was searched to identify relevant studies and reviews, details follow:

- Medline (1989 to November 1998)
 - MeSH (keyword system): octreotide — diagnostic use
 - Text: octreotide, OctreoScan, scintigraphy (filtered by neuroendocrine)
- Cochrane Library (issue 4, 1998)
 - Text: octreo*
- EMBASE (1989 to December 1998)
 - Text: octreotide or OctreoScan (filtered by diagnosis and neuroendocrine)
- Healthstar (1989 to December 1998)
- National Health Service (NHS) Database of Economic Evaluations (searched December 1998)
- Best Evidence (1998 issue)
 - Text: octreo*

(where: * = wildcard)

Internet sources including Oncolink, International Society for Technology Assessment in Health Care (ISHTAC) and other health technology assessment sites were examined.

Searches were restricted to the period after 1989, since the relevant OctreoScan technology was not available before this time.

Reference lists of reviews and other articles were searched.

In addition, data was available from unpublished trials that formed part of the European Multicentre Trial (EMT) conducted by Mallinckrodt Medical Petten, a manufacturer of OctreoScan technology (OctreoScan®).

Inclusion/exclusion criteria

Citations that discussed the use of OctreoScan in tumours other than GEP tumours were first excluded. The abstracts of the remaining 211 studies were assessed and a list of 97 primary studies was compiled for possible inclusion in this review (see Bibliography).

To qualify for inclusion, studies had to be primary studies comparing OctreoScan with any other form of detection and/or localisation of GEP neuroendocrine tumours.

Out of these 97 studies, those with fewer than 25 patients (53 studies), or for which an English language version of the study was not available (7 studies) were not considered further.

The majority of the studies reported on the ability of OctreoScan to detect lesions compared to other forms of imaging. The results from these studies were commonly in the form of the number of sites detected by OctreoScan versus the number of sites detected by conventional imaging modalities. Most studies reported the number lesions but some studies reported the number of patients. The number of patients in whom additional sites were detected was also reported.

Most of the potentially eligible studies fell into three main categories, either as part of the University Hospital Rotterdam study (UHR), the United States National Institutes of Health (NIH) prospective study of patients with ZES, or the European Multicentre Trial (EMT). The European Multicentre Trial was sponsored by Mallinckrodt Medical Petten, a manufacturer of OctreoScan technology (OctreoScan[®]) at 15 centres between August 1991 and May 1993.

Multiple publication of data derived from the same patient pool or cumulatively, without cross-reference, is common practice among the investigators active in this field. Some investigators were contacted and clarification was obtained in some cases, but not all. This made it very difficult to summarise the data and precluded meta-analysis. The EMT database was particularly impenetrable. Several investigators separately published the findings obtained from patients studied at their institutions. These reports duplicate or overlap patients included in the overall EMT summary report by Krenning et al 1996³³. Mallinckrodt files document the studies undertaken at 11 of the 15 centres involved in the EMT. Two studies documented in the Mallinckrodt files have also been reported in five publications, as far as we can determine^{34,35,36,37,38,39}. Four studies have been reported in seven publications that, as far as we can determine, were originally part of the EMT but are not documented in the Mallinckrodt file^{40,41,42,43,44,45,46}.

Table 4 shows the location and source of the studies we identified as potentially eligible for inclusion in this review and illustrates the problem of multiple publication from the same study and partial and possible overlap of studies.

Taking into consideration duplicate publication, adequacy of test protocol and availability of useful data, four studies were selected for inclusion in this review. These studies are indicated in Table 4 and further details are given in Appendix C. Overview summaries of the European studies (EMT and UHR) by Krenning et al^{33,52} were also considered.

Table 4 Location and source of studies

Location	Source
University Hospital Dijkzigt, Rotterdam (UHR)	Kwekkeboom et al 1993 ⁴⁷ (n=30)* Kwekkeboom and Krenning 1996 ⁴⁸ (n=30)* Kwekkeboom et al 1996 ⁴⁹ (n=30)* <i>Known overlap (same study)</i> Krenning et al 1993 ¹¹ (n=128) <i>Possible overlap</i>
National Institutes of Health, Bethesda, USA (NIH)	Gibril et al 1996 ³⁰ (n=80) Termanini et al 1997 ⁵⁰ (n=122)* <i>Known overlap</i> Jensen et al 1997 ⁵¹ (n=122) <i>Probable overlap</i> Alexander et al 1998 ⁵² (n=35) <i>Probable overlap</i>
European Multicentre Trial (EMT)	Krenning et al ³³ (n= 350) <i>Overview of other EMT studies</i>
EMT/UHR	Krenning et al 1994a,b ³ <i>Overview of EMT and UHR studies</i>
EMT Study centre 1: Georg-August Universität, Göttingen	Nauck et al 1994 ³⁹ (n=34)
EMT Study centre 2: University of Louvain Medical School, Louvain	Pauwels et al 1994 ⁴⁰ (n=30)* Jamar et al 1995 ⁴¹ (n=38) Jamar et al 1995 ⁴¹ (n=47) <i>Possible overlap</i>
EMT Study centre 3: Universitäts Klinikum, Berlin	Scherubl et al 1993 ⁴² (n=40) Wiedenmann et al 1994 ⁴³ (n=74) <i>Probable overlap</i>
EMT Study centre 4: Philipps Universität, Marburg	Joseph et al 1993 ⁴⁴ (n=85) Kisker et al 1997 ⁴⁵ (n=55) <i>Possible overlap</i>
EMT Study centre 7: Groupe Hospitalier Bichat, Paris	Cadiot et al 1997 ³⁴ Lebtahi et al 1998 ³⁵ <i>Probable overlap</i>
EMT Study centre 13: University of Uppsala, Uppsala	Westlin et al 1992 ³⁶ (n=40) Westlin et al 1993a,b ³⁷ (n=40) <i>Known overlap (same study)</i> Kalkner et al 1995 ³⁸ (n=100) <i>Possible overlap</i>
EMT Study centre 5: Hôpital Neuro-Cardiologique, Lyon Study centre 6: Universitätsspital Zürich, Zurich Study centre 7: Groupe Hospitalier Bichat, Paris Study centre 8: St Bartholomew's Hospital, London Study centre 9: Nuklearmedizinische Klinik der Technischen Universität München, Munich Study centre 10: Hammersmith Hospital, London Study centre 11: Westfälische Wilhelm Universität Münster, Münster Study centre 12: Hadassah University, Jerusalem Study centre 13: University of Uppsala, Uppsala Study centre 14: Academisch ziekenhuis Leiden, Leiden Study centre 15: Sahlgrenska Sjukhuset, Gothenberg	Unpublished: Mallinckrodt Medical Pettenn (n=247).
Groupe Hospitalier Bichat, Paris	Lebtahi et al 1996 ³⁴ (n=160) Lebtahi et al 1997 ³⁵ (n=160)* <i>Probable overlap with each other, no overlap with EMT</i>

* Studies included in the review (see Appendix C for further details)

Extraction of data

Data were extracted independently from the four included studies by two reviewers. Any differences found in the data extracted were discussed or referred to a third reviewer.

Assessment of quality

Each of the studies included in this review was assessed for quality using the following three criteria based on recommendations for assessing the scientific validity of estimates of diagnostic accuracy:³²

- the study examined a consecutive series or a random selection of a consecutive series of patients;
- all participants in the study received both OctreoScan and a comparator test; and
- the results for each test were interpreted without knowledge of the results of the other test.

Expert advice

A supporting committee, including members with expertise in relation to management of GEP neuroendocrine tumours, was convened to assess the evidence on this procedure. In selecting members for supporting committees, MSAC's approaches appropriate medical colleges, associations or specialist societies for nominees. Membership of the supporting committee is shown at Appendix B.

Results of assessment

Is it safe?

OctreoScan should only be used by qualified personnel with the appropriate government authorisation for the use and manipulation of radionuclides. OctreoScan may be received, used and administered only by authorised persons in designated clinical settings.

The diagnostic imaging dose of octreotide for OctreoScan is ten-times lower than the therapeutic dose. It is therefore not expected that imaging will result in significant somatostatin effects.

The most extensive data on adverse effects were reported in the European Multicentre Trials (EMT). In these 15 trials, all patients were monitored for heart rate, blood pressure and respiratory frequency, 15 minutes and 10 minutes before injection and at five and 30 minutes after injection. Clinical signs and symptoms were also recorded. Laboratory analyses of haematology, serum biochemistry and urinalysis before and four hours after injection were also performed.

There were 12 adverse effects reported from the total of 482 patients. This represented 2.3% of all administered doses. Of these 12 patients, nine were evaluated in the trials. Two patients were excluded in retrospect due to protocol violations and one excluded after it was confirmed the patient did not have a GEP neuroendocrine tumour. There were two fatal incidences, which separate expert opinions agreed were not related to the infusions.

The adverse reactions included sweating, hypotension, headache, pain in limbs, fever, flushes, nausea, stomach spasms, weakness and dizziness. Of these 12 adverse reactions, none required treatment and all were of a relatively short duration.

No clinically significant changes in vital signs or urine composition were observed. It was reported that some statistically significant changes in haematology and serum biochemistry were observed, but none of these were clinically significant and there were no overall trends.

Is it effective?

For diagnostic tests, 'effectiveness' has two components: the accuracy of the test and the effectiveness of patient management options if a positive test result is obtained.

Accuracy of the test

The accuracy of a diagnostic test is measured primarily by its sensitivity and specificity, which are measured as follows:

$$\text{Sensitivity} = \frac{\text{true positive results}}{\text{true positive} + \text{false negative results}}$$

$$\text{Specificity} = \frac{\text{true negative results}}{\text{true negative} + \text{false positive results}}$$

Ideally, the sensitivity and specificity are calculated by comparison with a 'gold standard' test (that is, one with a sensitivity and a specificity as close to 100% as possible). In the case of GEP tumours, the gold standard is histological diagnosis of surgical specimens.

In the conventional terminology regarding diagnostic test evaluation, sensitivity and specificity refer to the ability of the test to differentiate between those who have the disease in question and those who do not. However, in all the studies located the data reported does not include whether the patients who were studied have the disease or not. Instead, the studies report data on whether OctreoScan is able to detect the primary or metastatic lesions of the disease compared with the ability of CIM to detect such lesions. The use of the terms 'false positive' and 'false negative' is therefore problematic as the presence or absence of lesions from either OctreoScan or CIM does not exclude or confirm the presence of disease.

In some of the studies, the possibility of OctreoScan resulting in false positive and false negative results was discussed. False positive results can occur in the presence of inflamed tissues (such as sarcoidosis, inflammatory bowel disease and rheumatoid arthritis), meningiomas, metastatic breast cancer, neuroblastomas, oat cell carcinoma of the lung and ovarian tumours. False negative results occur because of the lack of somatostatin receptor sites on the tumour, in lesions less than 1 cm, lesions which are closely adjacent and in lesions hidden by physiological enhancement of the liver and kidneys during excretion of the drug. While these issues were discussed, none of the studies reported numbers of cases and it was therefore impossible to calculate the sensitivity and the specificity of the test in the conventional meanings of those terms.

In all of the eight studies that have been included in the review, the ability of OctreoScan to detect the presence and location of lesions has been compared with a combination of CIM. Even within the trials, the combination of imaging modalities was not standard and various combinations of the modalities were used in different patients. Estimates of sensitivity and specificity based on comparison with a test that is not an independent gold standard can be misleading⁵⁶.

Patient outcomes

Even though all of the studies reported data on the ability of OctreoScan to detect and localise lesions, this is not a good indicator of the usefulness of the test. If surgery is not an option, localisation of a lesion may have no effect on management. For example, if a patient has known metastatic disease, the ability to detect additional lesions will have no effect on clinical management. Therefore an increase in 'sensitivity' as reported in the studies may not translate into improved outcomes for the patient. Where it was possible from the data reported, we attempted to determine the ability of OctreoScan to differentiate patients with a primary lesion only, hepatic metastases and extrahepatic metastases, and compared this with the data reported in the same studies on the ability of CIM to make the same differentiation.

The ideal method for assessing patient outcomes after using a diagnostic test, is a randomised controlled trial examining outcomes of importance to patients, such as survival times and quality of life, in those who have had the test compared with those who have not had the test. No trial of this sort was available.

Another potential use of OctreoScan is to predict whether a patient with metastatic disease may benefit from treatment with the somatostatin analogue, octreotide.

Quality assessment

Study quality was poor, or at least poorly reported, in most cases. Only two studies were assessed to be adequate on all three of the quality criteria applied.^{50,54} In the others, it was unclear whether a consecutive series of patients was examined, or if there was blinded interpretation of the results from OctreoScan and CIM.

None of the studies provided data that could be used to determine sensitivity and specificity of OctreoScan. Most trials reported what they referred to as 'sensitivity', but this was a misnomer. What they in fact reported was the percentage detection rate in terms of patients or lesions.

Several aspects of the design and conduct of the studies impact on the reliability of the data that they provide. One of these is the test protocol, which was highlighted by Krenning et al³³ in a comparison of the UHR study and the EMT study.

The question about the adequacy of the test protocol was raised because the OctreoScan detection rate of 80% on a patient basis in the EMT study was lower than expected. A previous study of 130 patients with GEP neuroendocrine tumours at the Erasmus University Hospital, Rotterdam (UHR), showed an 88% detection rate¹¹. The authors suggested that the differences may have occurred because the scanning procedures used at some centres in the EMT study were inadequate (EP Krenning, personal communication). Some patients in the EMT study may have received an inadequate dose of radionuclide compared with a minimal dose of 200 megabecquerels (MBq) in the UHR study. Furthermore, abdominal SPECT was not performed in all patients in the EMT study and lateral planar abdominal scanning is not an adequate substitute for SPECT (EP Krenning, personal communication). This may explain why only 73% of gastrinoma patients had a positive scan compared with 12/12 patients in the UHR study.

The Mallinckrodt files also point out that some investigators in the EMT study deviated from the sponsor's protocol in terms of dose and timing of the test and scanning procedure. It is not possible without individual patient data to determine which patients at which study centres were examined by a protocol for which there is empirical evidence that it was inadequate. Professor Krenning advises that the EMT study not be used as a basis for assessing the appropriateness of OctreoScan for detecting GEP tumours (EP Krenning, personal communication).

Results

An overall summary of the results from the EMT was published by Krenning et al 1996³³ that compared the findings of the study with those from the UHR study.^{46,47} According to the summary report, 399 patients were enrolled in the EMT, 350 met the inclusion criteria and were retained for the analysis of efficacy. Patient follow-up data was updated in April 1994 and re-analysed in May 1994. Conventional imaging modalities included ultrasound, CT, MRI, angiography, and biopsy or surgery. It is not clear from the reports, however, which patients did and did not have surgical investigation.

In the EMT study by Pauwels et al,⁴⁰ 42 patients had no previously known tumour detected by CIM, OctreoScan was positive in 11/42 patients and 12/16 of the lesions detected were confirmed as true positive findings. Of 178 patients in the EMT study with a single known lesion, OctreoScan demonstrated multiple tumour sites in 62 of these patients and 60% of the lesions detected were confirmed.⁴⁰ The impact on clinical management was assessed by questionnaires completed by investigators on 235 patients from 13 of the centres participating in the EMT study. Overall, OctreoScan findings led to changes in the clinical management of 94/235 patients (40%). Scintigraphy findings had an impact on the surgical decision in 29 cases; surgery was performed in 21 cases and cancelled in eight. Octreotide therapy was started in 47 patients and 18 patients had their dose modified.⁴⁰

Studies including patients with insulinoma report lower scintigraphy detection rates for this type of tumour than with other GEP tumour types. Comparing the EMT results⁴⁰ with the UHR results,^{46,47} detection of GEP tumours expressing a high concentration of octreotide receptors, such as carcinoids, glucagonoma and nonsecreting pancreatic endocrine tumours, was high in both studies. According to the authors, the differences in scanning procedures are apparently not that significant for these types of tumours. The results from the two studies, however, show large differences in the detection rate of gastrinomas and insulinomas on a patient basis.^{40,46,47}

In the EMT study, eight patients strongly suspected of having a gastrinoma had a positive CIM and negative scintigrams. CIM tumour localisation was pancreas (3), duodenum (3), liver (1) and liver hilus (1). In 6/8 of these patients the dose was between 100 and 129 MBq and/or no abdominal SPECT had been performed. In 17 CIM negative patients strongly suspected of having a gastrinoma, octreotide scintigraphy found lesions in six patients. CIM and scintigraphy combined localised lesions in 56/67 patients suspected of having a gastrinoma.⁴⁰

In the EMT study, 17/24 patients suspected of having an insulinoma had a lesion found by CIM, whereas 9/17 had a positive scintigram.⁴⁰ In 3/8 patients with a negative scintigram, the dose was between 103 and 123 MBq and no abdominal SPECT had been performed. OctreoScan found a lesion in 3/7 CIM-negative patients. CIM and scintigraphy combined localised lesions in 19/24 patients suspected of having a gastrinoma. The authors suggest that this could be due to differences in scanning procedures used in the two studies. In the EMT, false negative scintigrams were especially obtained in patients who received a lower dose and who were not investigated with SPECT. If SPECT was used, the counting time per view was shorter than used in the Rotterdam study.³³

A summary of the results is in Table 5.

Table 5 Comparison of the ability of conventional imaging and OctreoScan to detect lesions in patients with GEP tumours

Study	<i>n</i>	CIM positive	OctreoScan positive	CIM and OctreoScan both positive	CIM and OctreoScan both negative
Pauwels et al 1994 ⁴⁰ (EMT)	30	24 (80%)	26 (87%)	23 (77%)	3 (10%)
Lebtahi et al 1997 ⁵⁴	160	114 (71%)	125 (78%)	97 (61%)	18 (11%)
Termanini et al 1997 ⁴⁹ (NIH)	122	76 (62%) All gastrinoma	75 (61%)	122 (100%)	29 (24%)
Kwekkeboom et al 1993, 1996 ^{46,47} (UHR)	30	21 (70%) All carcinoids	24 (80%)	21 (70%)	6 (20%)

CIM = conventional imaging modality; OctreoScan = indium-labelled octreotide scintigraphy; *n* = number of patients

In two of the included studies, the effect of OctreoScan on the clinical management of patients with GEP tumours was studied. Termanini et al (NIH)⁴⁹ prospectively enrolled 122 consecutive patients with Zollinger–Ellison syndrome. The treatment plan was determined after the results of CIM were performed (CT scan, MRI, ultrasound, selective angiography and bone scan). OctreoScan was then performed (without knowledge of the CIM results) and then the plan of treatment again determined. It would appear from the results that the second treatment plan was decided with knowledge of both sets of results, rather than knowledge of the OctreoScan results alone. The results of the study are shown in Table 6.

Table 6 Change in management after OctreoScan

Scintigraphy result which changed management	Clinical category at time of scan					Total (<i>n</i> =122)
	Initial evaluation (<i>n</i> =17)	Cured after surgery (<i>n</i> =18)	Not cured after surgery (<i>n</i> =50)	No surgery (<i>n</i> =12)	Metastatic liver disease (<i>n</i> =25)	
Only test positive for:						
– primary lesion	1	–	11	3	–	15
– liver metastases	–	–	2	–	–	2
– bilateral liver metastases	–	–	–	–	3	3
– bone metastases	–	–	–	–	2	2
Clarified lesion seen on CIM	7	4	11	3	8	33
Identified additional metastases	–	–	–	–	2	2
Total with changed management	8	4	24	6	15	57

n = number of patients

Source: Termanini et al 1997 (NIH study)⁴⁹

The second study by Lebtahi et al (Paris)⁵⁴ reported on the impact of OctreoScan to differentiate between patients with primary lesions, hepatic metastases and extrahepatic metastases. The study analysed data from 160 consecutive patients who presented between 1992 and 1995. The breakdown of patients by tumour was 78 patients with Zollinger–Ellison syndrome, 38 patients with a carcinoid tumour and 44 patients with other types of neuroendocrine tumours. Histological confirmation of the tumour was obtained in 142 of the 160 patients. 108 of the patients were investigated as part of primary staging of the tumour and 52 patients were investigated for recurrence after surgery. Because the data are presented in a way that the categories could be overlapping, it is difficult to give clear results but the results of staging appeared to be as shown in Table 7.

Table 7 Clinical category after imaging

Category	After CIM	After both CIM and OctreoScan
No known lesion	46	4?
Primary lesion	44	61?
Liver metastases	59	53
Extrahepatic metastases	11	42
Total	160	160

CIM = conventional imaging modality; OctreoScan = indium-labelled octreotide scintigraphy; ? = not clear from original study
Source: Lebtahi et al 1997⁵⁴

The authors of this study reported that the patient classification changed in 24% of cases and that the surgical strategy changed in 25% of cases. This was primarily because a large proportion of patients thought not to have hepatic or extrahepatic metastases by CIM did have such lesions. It was impossible to extract from the data reported in the study the number of patients who would have been in each category if scintigraphy alone had been performed.

In another report of the same study, which emphasised the cost effectiveness aspects of somatostatin receptor scintigraphy, Kwekkeboom et al also reported on sensitivity of OctreoScan.⁴⁸ In 30 carcinoid patients, scintigraphy was more sensitive than CT scan, ultrasound and radiography. The results are shown in Table 8.

Table 8 Lesions detected by applied imaging techniques for 30 carcinoid patients

Region	No of lesions	Imaging technique			
		CT (%)	Ultrasound (%)	Radiography (%)	OctreoScan (%)
Head/neck	2	100	–	–	100
Supraclavicular	2	–	–	–	100
Chest	15	67	–	20	100
Upper abdomen	17	46	20	–	100
Liver	12	86	82	–	58
Lower abdomen	21	20	–	–	100

CT = computed tomography; OctreoScan = indium-labelled octreotide scintigraphy
Note: Percentages reflect the numbers of patients studied.
Source: Kwekkeboom et al 1996⁴⁸

Treatment with somatostatin analogues is a therapeutic option for patients with metastatic disease. Several of the studies referred to the fact that OctreoScan may be predictive of response to treatment with octreotide. One study appeared to support this hypothesis⁵⁷. This study compared the uptake of OctreoScan by carcinoid tumour lesions with response to octreotide therapy. Of the 30 patients, 12 patients were assessed retrospectively and 18 patients assessed prospectively. Of the 27 patients who had a positive scintigraphy scan, 22 responded to somatostatin analogue treatment. None of the three patients who had a negative scan responded to treatment.

None of the studies reported on the acceptability of the test to patients.

Discussion

From review of the literature, an unbiased estimate of the sensitivity and specificity of the test could not be determined.

The most sensitive method for localisation of GEP tumours appeared to be intraoperative ultrasound plus palpation. No studies were available which directly compared OctreoScan with this method.

In the study on the value of OctreoScan on management of gastrinomas, the addition of the test resulted in a change in management in 57 of 122 patients (47%).⁵¹ In this study, there was a high proportion of patients presenting for reassessment after failure of surgical cure (50 patients compared with 17 for initial evaluation). It is difficult to assess how typical this would be of patients presenting in other clinics. It was noted in this study that OctreoScan was useful for differentiating between haemangiomas and metastases in the liver. CIM frequently cannot distinguish between the two types of lesions. OctreoScan on the other hand is only positive for metastatic lesions and not benign haemangiomas. Even though the authors concluded that the test should be the initial imaging study of choice in patients with gastrinomas, they were aware that 'it still remains unclear whether the routine use of SRS will either increase cure rate or extend survival in patients with Zollinger–Ellison syndrome'.

Because the use of octreotide therapy requires binding of the somatostatin analogue to receptors on the tumour, a logical hypothesis would be that the response to octreotide therapy may be predicted by the density of receptors on the tumours as indicated by OctreoScan. A small study, which was conducted both retrospectively and prospectively, appeared to support this hypothesis.⁵⁷ However, a prospective study on an adequate number of patients could not be found. Octreotide is currently subsidised under the Pharmaceutical Benefits Scheme for the treatment of carcinoid syndrome and preliminary scanning with OctreoScan is not a condition for benefit.

What are the economic considerations?

The main focus of this report has been a systematic review of the effectiveness of OctreoScan as a diagnostic test. It was not possible within the scope of this review to do a full economic evaluation of the technology. However, some comments can be made on the costs and consequences of the use of this technology.

Costs

The following costs have been supplied by the Australasian and New Zealand Association of Physicians in Nuclear Medicine (Inc) in their position statement on OctreoScan directed to the Health Insurance Commission on 30 July 1996:

Recommended descriptors

- (A) neuroendocrine imaging with OctreoScan — including planar imaging on one or more occasions and SPECT.
- (B) neuroendocrine imaging with OctreoScan — including planar imaging on one or more occasions.

Costing for (A) ie whole body and SPECT

OctreoScan — 6.6 mCi (244 MBq)	\$1850.00
Delivery fee	\$17.00
Whole body imaging	\$300.00
SPECT	\$110.00
TOTAL	\$2277.00

Costing for (B) ie whole body planar

OctreoScan — 3.3 mCi (122 MBq)	\$1500.00
Delivery fee	\$ 17.00
Whole body imaging	\$300.00
Radiopharmaceutical discount ^a	-\$60.00
TOTAL	\$1757.00

^a This test will be done infrequently, but in a small percent of cases (5–10%) two planar studies could be done at the same time with a single 6.6 mCi dose. Thus an equivalent discount has been applied.

OctreoScan is considerably more expensive than CIM for the investigation of GEP tumours. This additional expenditure may be considered ‘value for money’ if the information gained from the investigation is of greater value than the additional cost.

If the data were available, the costs and consequences of the following diagnostic strategies should be compared:

- CIM only;
- OctreoScan only;
- CIM followed by OctreoScan if metastatic lesions not detected by CIM;
- OctreoScan followed by CIM if metastatic lesions not detected by scintigraphy; and
- CIM and OctreoScan.

Based on an estimated incidence of 11 to 17 cases of GEP tumour per million population per year, there will be approximately 200 to 500 new cases per year in Australia. There is a high level of uncertainty regarding the potential financial impact of introducing OctreoScan onto the MBS. It is unknown what proportion of these cases will receive a scan or a repeat scan and the proportion of patients who would be treated in the private sector. In several of the studies included above, a high proportion of the patients being scanned were receiving a second or further follow-up scan.

As an indication of the financial implications of providing testing on the MBS, if we assume 350 cases per year, that 30% are treated in the private sector that each patient receives an average of one scan and that the scan costs \$2277, the total cost would be \$239,085. This is on the assumption that the test is only used in patients with biochemically proven disease.

Two studies have examined the cost-effectiveness of OctreoScan. The first study attempted the complex task of estimating the incremental cost-effectiveness of OctreoScan versus CIM.⁴⁸ This paper evaluated the effects of adding OctreoScan to a diagnostic workup for a number of neuroendocrine tumours, including carcinoid ($n = 20$), gastrinomas ($n = 12$) and insulinomas ($n = 24$). The data are based on patients who

were included in the University Hospital Rotterdam (UHR) trials and all of the above qualifications concerning the selection of patients and the methodology of the trials apply to the cost-effectiveness data just as they do to the studies of effectiveness.

This study found that the scan was able to detect lesions that could not be identified by other forms of imaging in 15% of carcinoid patients and there was a 100% increase in the total number of lesions. This was achieved at a cost of approximately an additional \$900 per patient (the cost data having been collected in 1993). For gastrinoma patients, the addition of OctreoScan resulted in a doubling of primary and total tumours detected at an additional cost of approximately \$1000 and for insulinoma there was an increase in the detection of tumours of 15% at a cost of approximately \$500 per patient. The paper does not attempt to quantify how many of these lesions were clinically significant and the effect of scanning on improvements in treatment planning or patient outcomes. Because of the lack of clinically meaningful outcomes data, it is difficult to assess whether the additional expenditure is of value or not.

The second paper, Woodward et al, attempted to model the impact of scintigraphy in patients with carcinoid tumour who were patients judged eligible for resection on the basis of CIM⁵⁸. The model predicted a net saving per patient scanned but the estimates are highly sensitive to the relative costs of surgery and imaging. Because medical costs are considerably less expensive in Australia than in the United States, it is difficult to extrapolate from this data whether there would be net savings or costs in the Australian context. The study also suggests an average increase of only 0.02 'health status adjusted life years' (equivalent to 7.3 additional days in perfect health) achievable through the use of OctreoScan.

The model used in this paper is based on highly uncertain data. For example, the model used an estimate of sensitivity of 90% based on Krenning's reports and then assumed specificity to be equal to sensitivity. The values for adjusting quantity of life for health status were based on the opinion of one treating physician.

In the real world of medicine, cost-effectiveness will also be affected by the care with which patients are selected for OctreoScan, whether it is used in cost-effective sequencing of a diagnostic strategy, or simply as an add-on to existing protocols, the rate at which the technology replaces exploratory surgery, and the frequency of palliative or 'heroic' surgery undertaken in the presence of disseminated disease.

Implications for current resources

The number of persons diagnosed with GEP tumours each year in Australia is quite small (probably between 200 and 500 per year). Even if there was a major change in the method of testing for the disease, this is unlikely to have a major impact on the overall usage of medical imaging facilities in Australia.

Other considerations

Consequences of testing

The possible consequences of testing are the detection of primary and metastatic lesions. The localisation of primary tumours may assist in allowing surgical resection of the lesion. Identification of metastatic lesions may result in patients avoiding surgery where there is no chance of surgical cure.

Although the evidence for the effectiveness of OctreoScan is very limited, the patients who are most likely to benefit from scanning are those with a suspected tumour who have negative or equivocal results on the basis of conventional imaging modalities, and those with an apparently solitary lesion as shown by CIM and where the tumour is being considered for resection.

Another group of patients who may potentially benefit from OctreoScan are those in whom octreotide therapy is being considered. It appears that clinical response is related to the density of somatostatin receptors in the tumour and scanning may help to predict those patients who could benefit from such therapy. This information is only useful if a change in patient management may result in patients receiving octreotide therapy and reducing the cost of therapy and adverse effects.

Access to technology

The test can be performed at any nuclear medicine facility. There does not appear to be any difficulty in having access to the technology.

Further research and development

None of the studies that were identified allowed for an unbiased estimate of the sensitivity or specificity of OctreoScan. The impact of scintigraphy on the outcome of disease could also not be assessed. These areas and also studies on the cost effectiveness of OctreoScan require further research to enable an informed decision on the value of OctreoScan to be made.

Conclusions

Safety

OctreoScan appears to be safe at the currently recommended dosages.

Effectiveness

OctreoScan appears to have some theoretical advantages over other forms of imaging (for example it is able to image the entire body). However, there is a lack of data of sufficient methodological quality to assess the true sensitivity and specificity of OctreoScan.

Compared with existing methods of imaging, the test appears more sensitive, but the test has not been compared in a blinded fashion with an acceptable gold standard and the types of tests with which it has been compared has varied, even within the same study. Although the possibility of false positive results (and therefore a specificity of less than 100%) has been discussed, none of the trials reported data that would allow us to calculate an estimate of specificity.

The major advantages of the technique are its ability to detect primary pancreatic tumours not in the pancreas and metastatic lesions outside of the abdomen and chest. Because OctreoScan images the whole body, it may also detect an unsuspected MEN-1 tumour.

OctreoScan appears to be less sensitive in the detection of insulinomas, because of the lack of receptor sites on such tumours. Insulinomas also tend to be solitary tumours, not requiring a whole body technique.

Because the imaging of a tumour may not result in a change in clinical management, a test of greater sensitivity and specificity may not result in better outcomes for patients. There is some evidence that OctreoScan results in a change in management in a proportion of patients. However, there is no evidence that this results in increased cure rates or survival time.

Cost-effectiveness

It is not possible to accurately estimate the cost-effectiveness of OctreoScan, because of the lack of validated data on the accuracy of the test and its influence on clinical outcomes.

Other considerations

None of the studies identified allowed for an unbiased estimate of the sensitivity or specificity of OctreoScan. The impact of scintigraphy on the outcome of disease could also not be assessed. These areas and also studies on the cost-effectiveness of

OctreoScan require further research to enable an informed decision on the value of OctreoScan to be made.

Recommendations

MSAC recommended that on the strength of evidence relating to OctreoScan, public funding should be supported for this diagnostic test:

- where there is a suspected gastro-entero-pancreatic neuroendocrine tumour, based on biochemical evidence, with negative or equivocal structural imaging from conventional radiology (CT or MRI); or
- where surgically amenable disease has been identified, based on biochemical evidence and conventional imaging, in order to rule out further metastatic disease.

Since there is currently insufficient evidence pertaining to the use of OctreoScan for the purposes of determining whether octreotide therapy is a viable therapeutic option, public funding should not supported at this time for this use.

Appendix A MSAC terms of reference and membership

The terms of reference of MSAC are to advise the Commonwealth Minister for Health and Aged Care 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;
- 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; and
- references related either to new and/or existing medical technologies and procedures.

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

Member	Expertise
Professor David Weedon (Chair)	pathology
Ms Hilda Bastian	consumer health issues
Dr Ross Blair	vascular surgery (New Zealand)
Mr Stephen Blamey	general surgery
Dr Paul Hemming	general practice
Dr Terri Jackson	health economics
Professor Brendon Kearney	health administration and planning
Mr Alan Keith	Assistant Secretary, Diagnostics and Technology Branch, Commonwealth Department of Health and Aged Care (from 3 May 1999)
Dr Richard King	gastroenterology
Dr Michael Kitchener	nuclear medicine
Professor Peter Phelan	paediatrics
Dr David Robinson	plastic surgery
Ms Penny Rogers	Assistant Secretary, Diagnostics and Technology Branch, Commonwealth Department of Health and Aged Care (until 3 May 1999)
Associate Professor John Simes	clinical epidemiology and clinical trials
Dr Bryant Stokes	neurological surgery, representing the Australian Health Ministers' Advisory Council (from 1 January 1999)
Dr Doris Zonta	population health, representing the Australian Health Ministers' Advisory Council (until 31 December 1998)

Appendix B Supporting committee

Supporting committee for MSAC application 1003

OctreoScan® scintigraphy for gastro-entero-pancreatic endocrine tumours

Dr Richard King (Chair) member of MSAC
MBBS, FRACP
Director, General Medical and Emergency
Medicine, Southern Health Care Network,
Victoria

Dr Terri Jackson member of MSAC
MA, PhD
Senior Research Fellow,
Health Economics Unit, Monash University
and Manager of the Hospital Services
Research Group (HSRG).

Dr Michael Kitchener member of MSAC
MBBS, FRACP
Senior Visiting Medical Specialist,
Queen Elizabeth Hospital, Adelaide;
Director, Nuclear Medicine,
Dr Jones and Partners,
St Andrews Hospital, Adelaide

Dr Rodney Hicks co-opted member
MBBS, FRACP
Director of Diagnostic Imaging, and
Director of Nuclear Medicine and Positron
Emission Tomography,
Peter MacCallum Cancer Institute, Melbourne

Appendix C Studies included in the review

Study	Location/date	Population	QS	Age (years)/gender (M/F)	Study focus	Protocol	Reference test
Krenning et al 1996 ^{33†}	European Multicentre Trial (EMT) in 15 institutes August 1991 to May 1993; follow-up updated April 1994	350 patients: 67 ZES 24 Insulinoma 184 Carcinoid 5 Glucagonoma 8 VIPoma 2 Somatostatinoma 60 NFICT	1: U 2: A 3: U	Varied	Localisation of tumour and detection of metastases	Varied	CT, MRI, ultrasound, angiography, biopsy
Pauwels et al 1994 ⁴⁰	EMT (Louvain Belgium) study date not reported	30 patients: 7 Gastrinoma 2 Insulinoma 14 Carcinoid 4 non-functioning pancreatic tumor 2 MEN-1 1 motilin secreting tumor	1:U 2:A 3:U	Not reported	Localisation of tumour and detection of metastases	198 (161–235) MBq octreotide Planar at 4 and 24 h SPECT at 24 h	CT, MRI, abdominal ultrasound, endoscopic ultrasound, angiography
Kwekkeboom et al 1993, 1996 ^{46,47,48}	UHR (Rotterdam, Netherlands) June 1988 – September 1990	30 patients with gut carcinoid tumors	1: U 2: A 3: U	Mean age 61 (16–81) 17 M;3 F	Localisation of tumour and detection of metastases Detection of recurrence	248 to 360 MBq octreotide Planar at 24 and 48 h after injection SPECT? not reported	CT, ultrasonography, chest X-ray, bone scan
Termanini et al 1997 ⁴⁹	National Institutes of Health (NIH) (Bethesda, USA) June 94 to April 96	122 patients with ZES (includes 80 patients also in Gibril 1996 ³⁰)	1:A 2:A 3:A	Mean age 53 (17–78) 69 M;53 F	To assess the effect of SRS use in clinical management	222 MBq octreotide SPECT 35 min at 4 and 24 h Planar: 30 min whole body scan at 4 h; 10 min spot views as needed	CT, MRI, ultrasound, angiography, bone scan
Lebtahi et al 1997 ⁵⁴	Paris, France November 1992 to September 1995	160 adults: 38 Carcinoid 44 other GEP	1: A 2: A 3: A	Mean age 52 (49–55) 88 M;72 F	Localisation of tumour and detection of metastases Detection of recurrence	135 MBq octreotide SPECT abdominal in 64 patients (timing not reported) Planar at 4 h: anterior and posterior abdominal images; 24 h: anterior, posterior, lateral and oblique views of abdomen; anterior and posterior head, chest, pelvis	CT, abdominal ultrasound, endoscopic ultrasound, MRI, chest X-ray, abdominal angiography

† Overview summary of EMT study

QS — quality score viz:

1 = consecutive studies of patients or random sample; 2 = all patients had both tests ; 3 = OctreoScan results and reference test results each interpreted blind to each other

A = adequate; I = inadequate; U = unclear

Abbreviations

CIM	conventional imaging modalities
CT	computed tomography
EMT	European Multicentre Trial
GEP	gastro-entero-pancreatic
OctreoScan	OctreoScan scintigraphy
MBq	megabequerel
MBS	Medicare Benefits Schedule
MEN-1	multiple endocrine neoplasia type 1
MRI	magnetic resonance imaging
MSAC	Medicare Services Advisory Committee
NHMRC	National Health and Medical Research Council
NIH	National Institutes of Health (United States)
PET	pancreatic endocrine tumour
SPECT	single photon emission computerised tomography
TGA	Therapeutic Goods Administration
UHR	University Hospital, Rotterdam
ZES	Zollinger–Ellison syndrome

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