Australia and New Zealand Horizon Scanning Network

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The production of this *Horizon scanning report* was overseen by the Health Policy Advisory Committee on Technology (HealthPACT), a sub-committee of the Medical Services Advisory Committee (MSAC). HealthPACT comprises representatives from health departments in all states and territories, the Australia and New Zealand governments; MSAC and ASERNIP-S. The Australian Health Ministers' Advisory Council (AHMAC) supports HealthPACT through funding.

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Introduction

The National Horizon Scanning Unit, Department of Public Health, University of Adelaide, on behalf of the Medical Services Advisory Committee (MSAC), has undertaken an Horizon Scanning Report to provide advice to the Health Policy Advisory Committee on Technology (Health PACT) on the state of play of the introduction and use of the combined positron emission tomography (PET) and computerised axial tomography (CT) scanner (Horizon Scanning Register number: 0000013).

Siemens Limited currently manufacture the Siemens ECAT PET scanner and have TGA approval for marketing this combined positron emission tomography (PET) and computerised axial tomography (CT) scanner in Australia for both *diagnostic* oncological imaging and management or staging of carcinoma through CT attenuation correction of PET scans.

This Horizon Scanning Report is intended for the use of health planners and policy makers. It provides an assessment of the current state of development of combined positron emission tomography and computed tomography (PET-CT), its present use, the potential future application of the technology, and its likely impact on the Australian health care system.

This Horizon Scanning Report provides a preliminary assessment of the safety, effectiveness, cost-effectiveness and ethical considerations associated with the use of combined PET-CT when utilised for the *diagnosis* of carcinomas of the thorax (including lung), abdomen, head and neck. Therefore this Horizon Scanning Report does not address the established practice, in the Australian health system, of managing or staging carcinoma utilising the CT component of combined PET-CT scanners for PET attenuation correction.

Background

Description of the Technology

PET is a minimally invasive procedure, which utilises the radionucleotide 2-[^{18}F] fluoro-2-deoxy-D-glucose (^{18}F-FDG) tracer, a radio-analogue of glucose with a half-life of approximately two hours, to produce diagnostic images. The radiation emitted during a PET procedure passes from inside the body and is registered by a ring of detectors surrounding the patient. This is called an ‘emission scan’ (Figure 1a). As the radiation passes through the body some of it is absorbed in the tissues of the body, a phenomenon called ‘attenuation’. The degree of attenuation will vary according to the density of the surrounding organs eg liver and bone will attenuate more than the lungs. If correction is not made for attenuation the resulting PET scan will be distorted. In the past, attenuation correction was achieved by shining a beam of radiation (using a radiation rod) through the body,

from many angles and measuring how much radiation is absorbed. A 'map' of attenuation is built up and used to correct the emission scan (Figure 1b).

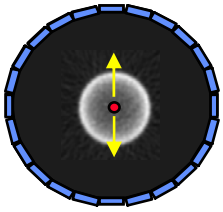

Figure 1a Emission scan scan

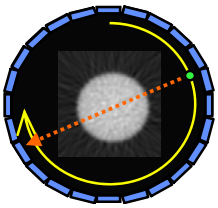

Figure 1b Corrected emission

The main clinical application of PET is oncological imaging due to the tendency of tumours to have an increased utilisation of glucose compared to surrounding normal tissue or to benign neoplasms (Phelps 2000; Bristow et al 2003). With other types of tracers PET can be used to assess blood flow, metabolism and protein synthesis (Schoder et al 2003).

CT scans use a computer to assimilate multiple X-ray images into a 2-dimensional cross-sectional image, which may reveal many soft tissue structures not shown by conventional radiography. CT is used extensively for cancer diagnosis and management and is used to monitor therapy by assessing changes in lymph node size (Townsend & Beyer 2002). CT technology has also replaced the use of a radiation rod and is currently used to build attenuation maps for PET scans. CT has several advantages over the use of a radiation rod including a faster acquisition time (scanning time reduced by 25%) and images with better anatomical detail, which has the effect of improving specificity and reducing the number of 'false positives', thus reducing potentially invasive and expensive investigation (personal communication, Dr Jane Jacobs[1]).

The Procedure

The first prototype PET-CT was developed in 1998 and installed at the University of Pittsburgh. Commercial PET-CT scanners were available from 2001 onwards. Prior to the development of the combined PET-CT, fusion images were achieved *post hoc* by overlapping images from separate CT and PET scans using specialised software. Image overlapping was successful for fixed organs such as the brain but not for internal abdominal organs, which could move independently between scans. Fusion imaging has been described as time consuming and errors may occur due to patient movement or discrepancies in patient position between scans. To overcome these technical difficulties, a scanner that combines both technologies was developed to accurately acquire aligned anatomical and functional images in the same scanning session (Townsend & Beyer 2002; Beyer et al 2000).

[1] Dr Jane Jacobs, Health Technology Assessment Team, Office of the Chief Health Officer, Queensland Health

The CT component of the PET-CT consists of a spiral or helical CT, which acquires multiple axial slice images by the continuous movement of the patient bed. The CT scanner has a metal ring that produces X-rays in the spectra 110kV_p and 130 kV_p. The X-ray tube, cooling system, detectors and readout electronics are mounted on the rotating support of the CT scanner. The PET components are mounted to the rear of the CT support and include the detectors, coincidence processor and the optically coupled data transmitters. The device is housed in a single gantry. All commercial PET/CT scanners are currently available with multi-slice CT technology, allowing reduced imaging time from 100 seconds for a 100 axial field-of–view to 40 seconds or less (Figure 2).

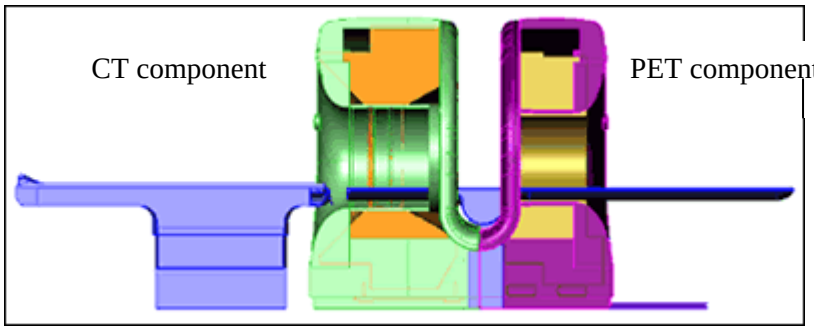

Figure 2 Open PET-CT design (University of Maryland 2003)

In combined PET-CT systems, the CT data reveals anatomical information about the patient, whereas PET provides predominantly functional and metabolic information. In addition, CT data is used to calculate the attenuation correction for the PET scan (Schoder et al 2003).

A standard PET/CT protocol begins with an injection of ^{18}F-FDG followed by a 60-minute uptake period. The patient is positioned inside the scanner and the first transaxial section to be imaged is aligned within the field-of-view of the CT (Townsend & Beyer 2002). Patients are asked to hold their breath for periods of up to 30 seconds during the acquisition of CT images to reduce scanning artifacts. The CT scan takes approximately 5-10 minutes, then the patient is moved into position for the acquisition of PET images. Total scanning time can range from 10-30 minutes (Beyer et al 2000; Townsend et al 2003). Data from the two images are combined into one image (Figure 3). Artifacts or mis-registration of the combined images during PET-CT scanning may occur due to the presence of dental implants, metallic objects in the body and patient respiration (Beyer et al 2003; Goerres et al 2002a; Goerres et al 2002b). A PET-CT hybrid unit may be used as a stand alone PET or CT-only scanner, depending on the clinical circumstances (Ell & von Schulthess 2002).

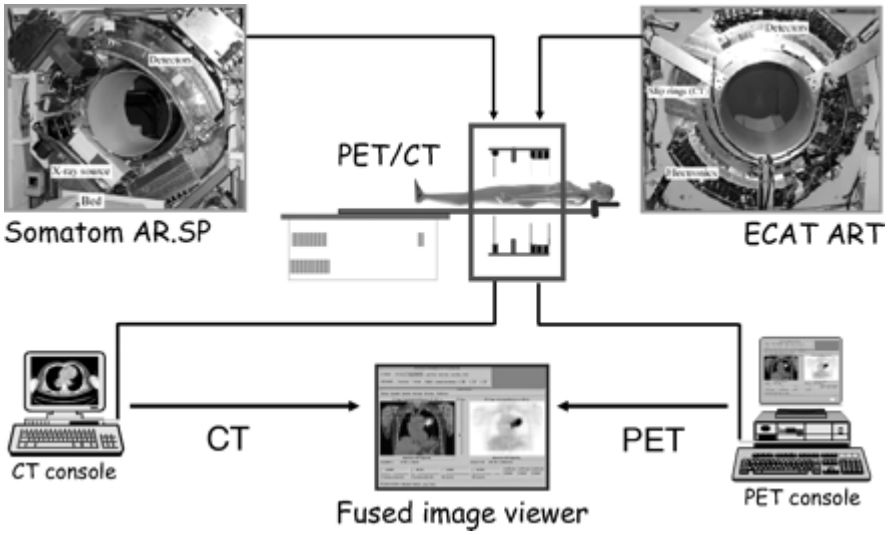

Figure 3 Combined PET-CT scanning process (Townsend & Beyer 2002)

Intended Purpose

PET-CT is primarily used in clinical oncology for the diagnosis and management of carcinomas of the thorax (including lung), abdomen, head and neck. Whole body scans may be performed to stage primary disease, to investigate metastatic spread and assess lymph node involvement (Beyer et al 2000; Schoder et al 2003).

In addition to clinical oncology applications, there is the potential for PET-CT technology to be utilised in the diagnosis and management of other clinical indications, including cardiovascular disease and neurology, e.g. Alzheimer's disease and epilepsy (Cohade & Wahl 2003; Hany et al 2002b).

Clinical Need and Burden of Disease

PET-CT has been proposed for use in the identification and management of oncology patients, including patients with carcinoma of the thorax, abdomen, head and neck. Table 1 summarises the number of newly diagnosed cancer cases and the age-standardised incidence and mortality rates for these types of cancer. In Australia for the year 2000 the total number of newly diagnosed cases for these cancers combined was 13,200 (AIHW & AACR 2003).

Table 1 Cancer in Australia in the year 2000

Carcinoma	Number of newly diagnosed cases	Age-standardised incidence rate per 100,000	Age-standardised mortality rate per 100,000
Thorax (trachea, bronchus and lung)	8,060 5,278 male 2,782 female	43 62 male 27 female	37 55 male 23 female
Brain	1,354 778 male 576 female	7 9 male 6 female	6 7 male 5 female
Stomach	1,980 1,267 male 713 female	11 15 male 7 female	6 9 male 4 female
Head and neck	1,806		
All cancers	85,213 45,935 male 39,296 female	451 536 male 390 female	188 245 male 148 female

(AIHW & AACR 2003)

During the year 2000, the Australian Institute of Health and Welfare reported a total of 85,231 newly diagnosed cases of cancer (all types) in the Australian population. Not all of these cancers may be currently diagnosed or staged utilising PET-CT; however, it may be possible in the future to adapt this technology for use in the diagnosis of colorectal, ovarian, endometrial, melanoma, uterine and breast carcinoma (Tatsumi et al 2003b; Tatsumi et al 2003a; Francis et al 2003; Cohade et al 2003a; Cohade et al 2003b). Crude numbers of cases have increased for most cancers since 1990 because, with the exception of cancer of the brain, the majority of these cancers occur in individuals over 45 years of age and Australia has an ageing population. Age-standardised incidence rates have decreased over the same period of time (AIHW).

The number of newly diagnosed cancers may not, however, give a clear indication as to the number of PET-CT procedures that may be required in Australia, as more than one scan may be performed on a single patient during the course of treatment. The number of CT scans conducted in Australia may give a better indication of the clinical need of PET-CT. The Health Insurance Commission does not report the number of CT scans conducted on oncology patients alone, however, they do report the number of CT scans conducted on the brain, chest and upper abdomen for all conditions as 770,255, during the period July 2002 to June 2003 (Health Insurance Commission 2002). In addition, numbers from the PET Data Collection reports the number of PET scans conducted in Australia, that were eligible for MBS funding, from eight participating sites during the period 1st March to 15th December 2003. During this 10.5-month period 8,131 patients received a PET scan with 97.6 per cent of these scans for oncology purposes. Of these oncology patients the indications were for re-staging (48.7%), staging (34.7%), diagnosis (13.9%) and therapeutic monitoring (2.6%). The main cancers assessed were lung

(22%), non-Hodgkin's Lymphoma (14%) and colorectal (14%) (ANZAPNM April 2004 newsletter[2]).

The number of procedures using PET-CT would increase if this technology were also utilised for cardiovascular and neurological disease diagnosis.

Stage of Development

Currently three models of combined PET-CT scanners are in operation in Australia. The Therapeutic Goods Administration lists the Siemens Limited *Biograph* (ARTG #72680), the *Discovery LS* by GE Medical Systems Australia (ARTG #82415) and the *Gemini* by Philips Medical Systems Australasia Pty Limited (ARTG #22982) on the Australian Register of Therapeutic Goods.

Combined PET-CT scanners are currently in limited use in public and private hospitals in Australia. There are approximately seven units in operation Australia wide, capable of scanning 12-15 oncology patients per day. Combined PET/CT scanners are currently used in Australian hospitals primarily as PET scanners, which use CT technology for attenuation correction of PET images (personal communication, Dr Jane Jacobs[3]). The current MBS funding arrangements allow the combined PET-CT to be reimbursed for PET scans only. The CT component of the PET-CT can be utilised only for the attenuation of PET scans, not for diagnosis (Medicare Benefits Schedule, 1 November 2003).

International utilisation of PET-CT is at a similar stage as in Australia, with gradual clinical acceptance of the benefits of a combined scanner. The use of PET imaging for oncology patients is increasing, with approximately 400,000 procedures conducted in the United States annually. It is estimated that the potential patient pool in the United States for PET would be 4 million patients (Missouri Department of Health and Senior Services).

PET-CT scanners can be used as PET or CT stand-alone scanners so it is feasible that the combined scanners would eventually replace existing stand-alone CT and PET scanners in major tertiary and teaching hospitals in Australia, through natural attrition. However, not all radiology practices would benefit from the acquisition of this technology (Schoder et al 2003).

[2] ANZAPNM is the Australian and New Zealand Association of Physicians in Nuclear Medicine

[3] Dr Jane Jacobs, Health Technology Assessment Team, Office of the Chief Health Officer, Queensland Health

Existing Comparators

Current diagnostic tools for the initial staging and management of various cancers include physical examination, CT, MRI and PET scans, fine needle biopsy, ultrasonography and X-rays (MSAC 2001). The most frequently used diagnostic imaging tool for cancers are CT scans, which provide anatomical information in respect to abnormal pathologic changes. CT scans may be limited in the detection of lesions that do not have good contrast with the surrounding tissue (Hany et al 2002b). These may be better detected using a PET scanner. Fusion images of PET and CT scans may be achieved *post hoc* by overlapping images from separate CT and PET scans using specialised software. Fusion imaging has been described as time consuming and errors may occur due to patient movement or discrepancies in patient position between scans. Fusion imaging is a developing field, however, and is not at present, a recognised gold standard for diagnostic oncology. Fusion imaging should not be considered as a suitable comparator for combined PET-CT.

A summary of outcomes comparing PET with CT for the staging of lung cancer is presented in Tables 2 and 3. Similar results have been reported for other cancers such as head and neck carcinomas (Health Technology Advisory Committee - Minnesota).

Table 2 Staging of lung cancer with regional ^{18}F-FDG PET and CT

Study	Wahl et al (1994)		Chin et al (1995)		Sasaki et al (1996)		Scot et al (1996)		Bury et al (1996)	
	PET	CT	PET	CT	PET	CT	PET	CT	PET	CT
Sensitivity	82%	64%	78%	56%	76%	65%	100%	67%	90%	72%
Specificity	81%	44%	81%	86%	98%	87%	100%	83%	86%	81%
Accuracy	81%	52%	80%	77%	93%	82%	100%	78%	-	
Positive predictive value	75%	44%	64%	63%	93%	61%	100%	67%	-	
Negative predictive value	87%	64%	89%	82%	93%	89%	100%	83%	-	

(Health Technology Advisory Committee - Minnesota)

Table 3 Staging of lung cancer with whole body ^{18}F-FDG PET and CT

Study	Walk et al (1995)		Sazon et al (1996)		Steinert et al (1997)	
	PET	CT	PET	CT	PET	CT
Sensitivity	83%	63%	100%	81%	89%	57%
Specificity	94%	73%	100%	56%	99%	94%
Accuracy	91%	70%			96%	85%
Positive predictive value	88%	54%			96%	76%
Negative predictive value	92%	79%			97%	87%

(Health Technology Advisory Committee - Minnesota)

Clinical Outcomes

Effectiveness

PET-CT vs PET

Three full text studies and five abstract studies were identified as assessing the effectiveness of PET/CT compared to PET alone (Table 4). The good quality, full text study by Lardinois et al (2003) reported PET-CT was significantly better, in terms of diagnostic accuracy, in determining both tumour and nodal stages ($p<0.001$ and $p=0.013$ respectively) for patients with non-small cell lung carcinoma, than PET alone. The two remaining lower quality full text studies by Charron et al (2000) and D'Amico et al (2002) reported that PET-CT was as good as, or better, at identifying cancerous lesions than PET alone. All five abstract studies reported on the sensitivity of PET-CT in detecting cancer in known cancer patients (cases). The sensitivity results are therefore likely to be affected by spectrum bias and the lack of a control group or disease-free patients means that specificity cannot be calculated meaningfully. The abstract study by Francis et al (2003) reported that clinical management of patients changed in 5/21 (25%) of patients. Three patients were correctly down staged negating the need for further treatment or imaging, one patient was upstaged to inoperable and in the remaining patient the improved localisation by PET-CT led to an altered surgical approach resulting in reduced morbidity.

Table 4 Effectiveness of PET-CT vs PET alone

Study	Level of evidence	Study Design	Population	Outcomes
Lardinois et al (2003), Switzerland	1b	Cross-classification of patients on PET-CT and PET and CT Scans interpreted independently by two review boards	49 consecutive patients with known or suspected NSCLC [a]	Diagnostic Accuracy Tumour stage (n=40) [b] PET-CT vs PET p< 0.001 Node Stage (n=37)[b] PET-CT vs PET p= 0.013
Charron et al (2000), USA	3b	Cross-classification of patients on PET-CT and PET	32 patients with various known or suspected cancers	Improved localisation of 13/55 (24%) lesions in 9/32 (28%) of patients
D'Amico et al (2002), USA	3b	Cross-classification of patients on PET-CT and PET Scans interpreted independently by two assessors	21 patients with known or suspected thoracic malignancies	PET and PET-CT identified 23 lesions in 18/21 (86%) of patients PET-CT was concordant with PET in 16/21 (76%) of patients
Bar-Shalom et al (2002) , Israel Abstract	4	Cross-classification of patients on PET-CT and PET	134 patients with 315 lung (43), lymphoma (23), gastrointestinal (21), breast (10), genito-urinary (9), melanoma (7) and other (14) cancerous lesions	PET-CT improved diagnosis in 64/134 (48%) patients or 112/315 (36%) equivocal lesions
Francis et al (2003), United Kingdom Abstract	4	Cross-classification of patients on PET-CT and PET Scans interpreted independently by two assessors	21 consecutive patients with colorectal cancer	Total lesions identified by PET = 77–84% PET-CT = 74-81% Definite anatomical localisation PET = 78–96% PET-CT = 95-99% Certainty of diagnosis PET = 72-86% PET-CT = 94-99% Clinical management changed in 5/21 (24%) of patients

Goerres et al (2003), Switzerland Abstract	4	Cross-classification of patients on PET-CT and PET and CT	87 patients with head and neck cancer	Diagnostic confidence [c] Mean ranking PET 4.0 ± 1.4 PET-CT 4.0 ± 1.5 Wilcoxon Difference between PET and PET-CT p = 0.0047 No difference between PET and CT p = 0.035 Freidman test Significant difference between methods p=0.0042 Kendalls Tau beta for the agreement of PET vs PET-CT 0.60 for restaging 0.45 for staging
Osman et al (2002), USA Abstract	4	Cross-classification of patients on PET-CT and PET Scans interpreted independently by two assessors	34 patients with lung cancer	Sensitivity of PET-CT = 75-78% Equivocal and probable lesions reduced with PET-CT vs PET alone = -32– -30% Definite diagnostic lesion detection increased with PET-CT vs PET alone = 5-8% Number of definite localisations increased with PET-CT vs PET alone = 34-41%
Yeung et al (2002), USA Abstract	4	Cross-classification of patients on PET-CT and PET Scans interpreted independently by two assessors	100 consecutive patients with 150 lesions of head and neck (21), abdominal (40) and chest (39) malignancies	PET-CT better defined localisation of abnormality in 76/150 (51%) of all lesions 21/32 (66%) head and neck cancer, p<0.01 34/56 (61%) abdominal cancer, p<0.01 12/62 (19%) chest malignancy, ns PET-CT improved diagnosis in 28/49 (57%) equivocal lesions 7/100 (7%) cases were undetected by CT alone.

[a] NSCLC = non-small cell lung carcinoma, [b] Author's statistical analysis: paired sign test, [c] Author's statistical analysis: Wilcoxon signed rank test and Freidman test used to compare ranking and Kendalls Tau beta was used to assess agreement between methods

PET-CT vs CT

One full text study and five abstract studies assessed PET-CT compared to CT alone (Table 5). The good quality study by Lardinois et al (2003) reported PET-CT was significantly better, in terms of diagnostic accuracy, in determining tumour stage (p=0.001) but not nodal stage (p=0.12) for patients with non-small cell lung carcinoma, than CT alone. Four of the poor quality abstract studies described an improvement in the number of additional lesions identified by PET-CT compared to CT alone ranging from 45-80 per cent. These studies also reported a change in the clinical management in 35-73 per cent of patients. The abstract study by Bhatnagar et al (2002) reported 15/20 (65%) of patients experienced a change in their clinical management after PET-CT scanning. Three of these patients received chemotherapy instead of surgery, eleven patients received salvage chemotherapy instead of observation, one patient received increased radiation therapy and one patient's management

was altered to observation rather than chemotherapy after returning a negative PET-CT result. Similar results were reported in the two studies by Blodgett et al (2002) and Heron et al (2002).

One of the abstract studies indicated improved diagnostic confidence in the results of a PET-CT compared to CT alone.

Table 5 Effectiveness of PET-CT vs CT alone

Study	Level of evidence	Study Design	Population	Outcomes
Lardinois et al (2003), Switzerland	1b	Cross-classification of patients on PET-CT and CT, compared to full diagnostic work-up Scans interpreted independently by two review boards	49 consecutive patients with known or suspected NSCLC[a]	Diagnostic Accuracy Tumour stage (n=40) [b] PET-CT vs CT alone p= 0.001 Node Stage (n=37) [b] PET-CT vs CT alone p= 0.12
Bhatnagar et al (2002), USA Abstract	4	Cross-classification of patients on PET-CT and CT	20 patients with ovarian carcinoma	PET-CT identified additional lesions in 16/20 (80%) patients than with CT alone Clinical management changed in 15/20 (65%) of patients
Blodgett et al (2002), USA Abstract	4	Cross-classification of patients on PET-CT and CT	15 patients with ovarian carcinoma	PET-CT identified additional lesions in 12/15 (80%) patients than with CT alone Clinical management changed in 11/15 (73%) of patients
Blodgett et al (2002), USA Abstract	4	Cross-classification of patients on PET-CT and CT	11 patients with cervical carcinoma	PET-CT identified additional lesions in 5/11 (45%) patients than with CT alone Clinical management changed in 5/11 (45%) of patients
Goerres et al (2003), Switzerland Abstract	4	Cross-classification of patients on PET-CT and CT	87 patients with head and neck cancer	Diagnostic confidence [c] Mean ranking CT 3.8 ± 1.7 PET-CT 4.0 ± 1.5 Wilcoxon Difference between PET-CT and CT p = 0.0001 No difference between PET and CT p = 0.035 Freidman test Significant difference between methods p=0.0042 Kendalls Tau beta for the agreement of PET vs CT 0.18 for restaging 0.15 for staging CT vs PET-CT 0.52 for restaging 0.35 for staging
Heron et al (2002), USA Abstract	4	Cross-classification of patients on PET-CT and CT	17 patients with cervical carcinoma	PET-CT identified additional lesions in 9/17 (53%) patients than with CT alone Clinical management changed in 6/17 (35%) of patients

[a] NSCLC = non-small cell lung carcinoma, [b] Author's statistical analysis: paired sign test, [c] Author's statistical analysis: Wilcoxon signed rank test and Freidman test used to compare ranking and Kendalls Tau beta was used to assess agreement between methods

PET-CT vs Diagnostic Work-up

Four full text studies and nine abstract studies compared PET-CT to the gold standard of diagnostic work-up, which included histological, surgical and clinical follow-up (Table 6). The good quality full text study by Cohade et al (2002) reported PET-CT had a sensitivity and specificity of 86 and 67 per cent, respectively, for the detection of lesions in patients with known or suspected colorectal cancer. The slightly poorer quality study (non-consecutive patients) by Bristow et al (2003) determined that PET-CT correctly predicted epithelial ovarian cancer lesions in 96 per cent of cases identified as positive. Overall the sensitivity of PET-CT for the full text studies ranged from 62 to 98 per cent, and the specificity ranged from 67 to 99 per cent, depending on the type of cancer, the stage of cancer and whether the results were analysed lesion-by-lesion or on a patient basis. The sensitivity of PET-CT reported in the predominantly poor quality abstract studies ranged from 56 per cent in the study by Moe et al (2002) for patients with increased tumour markers, to 100 per cent in the study by Buck et al (2003) for the detection of a primary lung carcinoma. The specificity of PET-CT reported in these abstract studies ranged from 68 per cent in the study by Mor et al (2002) to 93 per cent in the studies by Freundenberg et al (2002) and Israel et al (2003).

Three poorer quality abstract studies reported changes in the clinical management in 22-30 per cent of patients after PET-CT imaging when compared to diagnostic work-up. Israel et al (2003) reported a change in clinical management for 17/57 (30%) of patients, which included radio and/or chemotherapy instead of surgery for ten patients, two patients underwent an altered surgical approach, radiation fields were modified in three patients and two patients had their treatment regime altered from curative to a palliative approach. Similar results were reported by Mor et al (2002) and Steinert et al (2002).

Table 6 Effectiveness of PET-CT vs diagnostic work-up

Study	Level of evidence	Study Design	Population	Outcomes
Cohade et al (2003), USA	1b	Cross-classification of patients on PET-CT and full diagnostic work-up Scans interpreted independently	45 consecutive patients with known or suspected history of colorectal cancer	Lesion analysis PET-CT Sensitivity[d] 86% (89/104) 95% CI [77-91%], p=0.8 Specificity[d] 67% (12/18) 95% CI [44-84%], p=0.6 PET-CT vs PET alone Equivocal lesions reduced by 50% Definite lesion characterisation increased by 30% Number of definite localisations increased by 25% Overall correct staging increased from 78% to 89% with PET-CT on a patient-by-patient analysis
Bristow et al (2003), USA	3b	Cross-classification of patients on PET-CT and surgical reassessment	22 patients with suspected recurrent epithelial ovarian cancer	PET-CT – patient based accuracy for recurrent tumour prediction Specificity 75% Sensitivity 83% PPV [a] 94% NPV [b] 50% PET-CT – lesion based accuracy Specificity 95% PPV [a] 96% NPV [b] 56%

Antoch et al, (2003b), Germany	4	Cross-classification of patients on PET-CT and histology and radiological follow-up	98 consecutive patients with known malignant disease: bronchial carcinomas (29), unknown primary site (12), head and neck (13), melanomas (13), genitourinary (8), gastrointestinal (6), thyroid (6), pleural mesotheliomas (6), liver (3) and bone (2) carcinomas	Staging of tumours PET-CT Overall TNM staging Sensitivity = 86% T-stage (n=46) Sensitivity = 88% N-Stage (n=98) Sensitivity = 98% N-Stage (n=98) All cancers PET-CT sensitivity 95% specificity 92% PPV [a] 88% NPV [b] 96% M-stage (n=98) PET-CT Sensitivity = 97% M-stage (n=98) All cancers PET-CTI sensitivity 93% specificity 95% PPV [a] 93% NPV [b] 95% Lung PET-CT sensitivity 89% specificity 94% PPV [a] 86% NPV [b] 96% Liver PET-CT sensitivity 86% specificity 96% PPV [a] 80% NPV [b] 98% Bone PET-CT sensitivity 62% specificity 96% PPV [a] 73% NPV [b] 94% Other organs PET-CT sensitivity 73% specificity 99% PPV [a] 92% NPV [b] 95%
Antoch et al, (2003a), Germany	4	Cross-classification of patients on PET-CT and histological follow-up Scans interpreted independently by three teams	27 patients with NSCLC[c]	Tumour stage correctly defined PET-CT 26/27 (96%) PET-CT led to clinical management change in 4/27 (15%) of patients when compared to PET N-staging with PET-CT sensitivity 89% specificity 94% PPV[a] 89% NPV[b] 94%

Burger et al (2002), Switzerland Abstract	3b	Cross-classification of patients on PET-CT and histological work-up Scans interpreted independently by two assessors	65 patients with known or suspected colorectal carcinoma	Over- or under-staging PET-CT 10% Inter-observer variability between PET-CT kappa = 0.744
Hany et al (2002), Switzerland Abstract	3b	Cross-classification of patients on PET-CT (10,40,80, 120mA) and PET, compared to histological work-up	53 patients with diagnosed or highly suspected malignancy	Accuracy ratios PET 91% PET-CT 10 97% PET-CT 40 97% PET-CT 80 98% PET-CT 120 98% Significant difference in diagnostic accuracy between PET and PET-CT ($p<0.01$)[e]
Cohade et al (2003), USA Abstract	4	Cross-classification of patients on PET-CT and clinical and diagnostic work-up Scans interpreted independently	46 patients with recurrent ovarian cancer	Equivocal reduced with PET vs PET-CT from 17 to 9 (–47%) Detection of macroscopic disease PET-CT sensitivity 80% specificity 88% Agreement between PET and PET-CT Kappa =0.87, 95%CI [0.72-1.01]
Cohade et al (2003), USA Abstract	4	Cross-classification of patients on PET-CT and PET, compared to clinical and diagnostic work-up	15 patients with endometrial carcinoma	PET and PET-CT congruent in detection of cancer for 11/15 patients (9 true positive, 2 true negative, 1 false positive) PET demonstrated 40 grade 3/4 lesions and 5 equivocal lesions PET-CT demonstrated 45 grade 3/4 lesions and 0 equivocal lesions
Buck et al (2003), Germany Abstract	4	Cross-classification of patients on PET-CT and histological work-up	63 patients with carcinoma of the lung	Detection of primary tumour sensitivity 100% specificity 80% Differentiation between nodal positive and negative sensitivity 75% specificity 88%
Freundenberg et al (2002), USA Abstract	4	Cross-classification of patients on PET-CT and clinical and diagnostic work-up, using ^{124}I	12 patients with thyroid carcinoma	PET-CT sensitivity 97% specificity 93%

Israel et al (2003), Israel Abstract	4	Cross-classification of patients on PET-CT and histological, radiological and clinical follow-up Scans interpreted independently	57 patients with cervical (38), ovarian (13) and endometrial (6) cancer	PET-CT Sensitivity = 93% Specificity = 93% PET-CT improved image interpretation in 48/86 (56%) lesions in 29/57 (51%) patients than PET and/or CT Clinical management changed in 17/57 (30%) of patients
Mor et al (2002), Israel Abstract	4	Cross-classification of patients on PET-CT and clinical and diagnostic work-up Scans interpreted independently	54 patients with increased tumour markers	PET-CT sensitivity 56% specificity 68% PPV [a] 87% NPV [b] 78% PET-CT altered clinical management in 15/54 (28%) of patients
Steinert et al (2002), Switzerland Abstract	4	Cross-classification of patients on PET-CT and PET, compared to surgical staging	46 patients with NSCLC [c]	T classification 15/46 (33%) inconclusive PET results PET-CT correctly defined 12/15 (80%) of these (p=0.0002) N classification 13/46 (28%) inconclusive PET results PET-CT correctly defined 11/13 (85%) of these (p=0.002) Clinical management changed in 10/46 (22%) of patients

[a] PPV = positive predictive value, [b] NPV = negative predictive value, [c] NSCLC = non-small cell lung carcinoma, [d] Author's statistical analysis: McNemar test, [g] Author's statistical analysis: paired sign test, [e] Authors statistical analysis using chi –squared

Safety

None of the full text or abstract studies reported on the safety of PET-CT. The obvious safety outcome of concern is the number of false positives and negatives reported. False positive results may occur due to the intense FDG uptake in brown adipose tissue, especially in the neck and supraclavicular region (Steinert & von Schulthess 2002). These false positive findings may result in patients undergoing unnecessary surgery, chemotherapy or radiotherapy. In addition, expert opinion suggests that the consequences of a false positive PET-CT scan in patients with non-small cell lung carcinoma may result in these patients being deemed incurable leading to inappropriate under treatment. False negative results may also occur if the intense FDG uptake in adipose tissue obscures true abnormalities (Schoder et al 2003). False negatives give false reassurance to patients that they are disease free and therefore may have serious consequences in terms of their future treatment.

Only those studies that compared PET-CT results to a full diagnostic work-up could accurately report on the rate of false positives and negatives (Table 6). The full text study by Cohade et al (2002), the highest available level of evidence (1b), reported false positive and false negative rates of 33 and 14 per cent, respectively.

Another safety issue that should be considered is the radiation dose that patients receive when undergoing a combined PET-CT scan. The dose of radiation may be decreased if the patient is undergoing a combination PET-CT scan, however the dose would be markedly increased if patients underwent both a CT and PET scan separately.

Potential Cost Impact

Cost Analysis

The capital cost of a single PET/CT machine is approximately $2-5 million AUD. This would limit its introduction to all but major medical centres.

Existing Cost-effectiveness Evidence

To date, no economic analyses of combined positron emission tomography/ computerised tomography (PET/CT) scanning have been identified from the literature. Quality of life studies using the combined technology are also absent. Existing cost-effectiveness studies have evaluated the scanning of cancer patients first with CT and followed, if indicated, by PET (Scott et al 1998; Comber et al 2003).

Management of Cancer

At present, Medicare benefits are not payable for any CT scan rendered using a hybrid PET-CT scanner (Medicare Benefits Schedule, 1 November 2003). The Medical Services Advisory Committee has approved a 3C determination for the interim funding, in Australia, of FDG-PET for the diagnosis and staging of certain cancers, listed under the Medicare Benefits Schedule (MBS) item numbers 61523-61649 (Health Insurance Determination, HS/6/01). Indications covered by these item numbers include; lymphoma, squamous cell carcinoma of the head and neck, sarcoma and whole body studies for primary carcinoma of the uterine cervix, staging of oesophageal or gastric carcinoma and suspected recurrent epithelial ovarian carcinoma (MSAC 2001).

In Australia, the most numerous patient type receiving an FDG-PET scan are patients suffering from cancer of the thorax, brain carcinoma, cancer of the stomach, head and neck. This number combined for an eligible population of 13,200 in 2000 (AIHW). Therefore, with an average fee per FDG PET scan of $950 the expected baseline cost per year would be $12.5 million for scanning these newly diagnosed cancer patients (Miles 2001).

However, approximately 85,231 patients were diagnosed with cancer in Australia in the year 2000 (AIHW). If it is assumed that every newly diagnosed cancer patient is eligible for at least one FDG PET scan per year the additional cost (this estimate does not include the cost of performing a CT scan) could balloon out to over $81 million per year.

While this assumption overestimates the number of cancer patients that would receive this test in the first year of their treatment (as not all patients would

require a FDG PET scan), the derived cost does not include the number of patients with suspected cancer that would undergo FDG PET and CT for diagnostic purposes. In addition, expert opinion has suggested some cancer patients, particularly those with melanomas and cancer affecting the brain, could receive a second scan in the same year due to the potential for rapid growth of these types of cancers. This would add to the cost in rebates from Medicare for FDG PET/CT scanning of newly diagnosed cancer patients.

Management of Neurological and Cardiovascular Disorders

More recently, FDG PET/CT is being used for the evaluation of refractory epilepsy (MBS#61559) with a fee of $918 per scan, and for the evaluation of ischaemic heart disease (MBS#61562) with a fee of $899 per scan. In Australia between 2000 and 2001 patients admitted to hospital for management of dementia or complex epilepsy amounted to 12,000 separations from public hospitals. Assuming that all of these patients are eligible for FDG PET/CT scans Medicare rebates would amount to another $11 million AUD per year.

It should be emphasised that these approximations are all dependent upon several major variables. Firstly, the numbers of patients determined to be eligible for combined PET/CT will have a significant impact on the overall cost to Medicare and the state health budgets. Clinical practice may limit the number of patients that would require scans. For example, a cost-effectiveness analysis of PET after CT in identifying metastases found that PET was a more cost-effective procedure when used only after a negative result from the CT scan (Scott et al 1998). Secondly, survival of patients into their second year and beyond may necessitate additional scans to monitor the condition. These scans would add to the yearly costs of providing this technology.
Finally, without direct evidence it is difficult to estimate what the extent of any cost savings and quality of life changes could be expected from potential earlier or more accurate detection and management of the above conditions.

Ethical Considerations

Informed Consent

Patients offered combined PET-CT must be informed of both the potential increased diagnostic benefits and potential harms of conducting a PET-CT scan. Potential harms include, particularly, the considerable differences in invasiveness and time taken to conduct the procedure, between undergoing a CT or PET scan alone, compared to a combined PET-CT scan.
Oncology patients undergoing this procedure as participants in a clinical trial fall into the category of persons in dependent or unequal relationships. As such, the possibility that their relationship with researchers/clinicians may impair their consent means that Human Research Ethics Committees will need to be satisfied that consent is both informed and voluntary (NHMRC 1999). Researchers must give patients an assurance that their care will not be compromised in any way if they refuse to participate in, or withdraw from, a clinical trial.

Risks and Benefits for Patients

Due to the newness of the technology, there may be a period of time where the technical ability to read and interpret PET-CT scans by clinicians and radiologists may not be as rigourous and skilful as their ability to read and interpret CT or PET scans alone. Clinicians and radiologists should ensure that patient diagnosis and treatments are not disadvantaged by this factor. One possibility is to ensure that clinicians produce reports on patients with independently assessed PET, CT and PET-CT scans for comparison for a specified period of time.

Access Issues

This technology is currently available in approximately seven centres in the eastern states of Australia. Due to the expense of acquisition of PET-CT scanners it is likely that they will only be purchased by large tertiary hospitals and would not be made available in rural areas of Australia.

Training and Accreditation

Training

The development of combined PET/CT scanning technology has introduced the consideration of what technologists and specialists have the appropriate skills and accreditation to interpret PET/ CT images and results.

Specialists

In Australia, the Joint Specialist Advisory Committee in Nuclear Medicine (JSAC) provides an accreditation system for PET available to recognised nuclear medicine specialists only. This process requires the specialist to attend an accredited PET training site (of which there are 10 around Australia, covering every State) for a minimum of 20 weeks, and report on a minimum of 300 PET oncology scans. At present, the majority of trained nuclear medicine specialists are physicians, not trained radiologists and therefore a single specialist trained in the interpretation of both CT and PET scans would be rare. Present practice is for a radiologist and a nuclear medicine specialist to interpret the results of CT and PET conjointly. Currently in Australia, the CT component of a PET-CT scanner is used for attenuation correction of PET scans. As no diagnostic CT study is produced when CT is used for attenuation purposes, additional radiologists would not be required.

Technicians

While regulations may vary, radiographers in NSW are not permitted to perform PET and nuclear medicine technicians are not certified to perform CT. However, the University of Sydney is presently providing a course stream that endeavors to train nuclear medicine technicians to operate hybrid PET/CT systems. These students must undergo a three-year undergraduate course in nuclear medicine technology for certification as a nuclear medicine technologist. For further certification to operate the combined PET/CT

systems only, a 16-week post-graduate course in medical radiation is offered (University of Sydney 2003).

Clinical Guidelines

In Australia, there are no clinical practice guidelines available for the use of the hybrid system of FDG PET/CT. However, as present policy prohibits the use of the hybrid system for both scans, CT must be performed separately. Recommendations for the use of PET or CT are generally found within the clinical practice guidelines of the specific disease condition. For example, countries other than Australia have produced recommendations for PET use specifically for the management of cancer (Bourguet et al 2003).

Limitations of the Assessment

Methodological issues and the relevance or currency of information provided over time are paramount in any assessment carried out in the early life of a technology.

Horizon Scanning forms an integral component of Health Technology Assessment. However, it is a specialised and quite distinct activity conducted for an entirely different purpose. The rapid evolution of technological advances can in some cases overtake the speed at which trials or other reviews are conducted. In many cases, by the time a study or review has been completed, the technology may have evolved to a higher level leaving the technology under investigation obsolete and replaced.

An Horizon Scanning Report maintains a predictive or speculative focus, often based on low level evidence, and is aimed at informing policy and decision makers. It is not a definitive assessment of the safety, effectiveness, ethical considerations and cost effectiveness of a technology.

In the context of a rapidly evolving technology, an Horizon Scanning Report is a ‘state of play’ assessment that presents a trade-off between the value of early, uncertain information, versus the value of certain, but late information that may be of limited relevance to policy and decision makers.

Search strategy used for the Report

The medical literature (Table 7) was searched utilising the search terms outlined in Table 8 to identify relevant studies and reviews, until February 2004. In addition, major international health assessment databases were searched.

Table 7 Literature sources utilised in assessment

Source	Location
Electronic databases	
AustHealth	University library
Australian Medical Index	University library
Australian Public Affairs Information Service (APAIS) - Health	University library
Cinahl	University library
Cochrane Library – including, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials (CENTRAL), the Health Technology Assessment Database, the NHS Economic Evaluation Database	University library
Current Contents	University library
Embase	Personal subscription
Pre-Medline and Medline	University library
ProceedingsFirst	University library
PsycInfo	University library
Web of Science – Science Citation Index Expanded	University library
Internet	
Current Controlled Trials metaRegister	http://controlled-trials.com/
EuroScan database (members only)	http://www.publichealth.bham.ac.uk/euroscan/members/
Health Technology Assessment international	http://www.htai.org
International Network for Agencies for Health Technology Assessment	http://www.inahta.org/
Medicines and Healthcare products Regulatory Agency (UK). • Medical Device Alert Safety warnings • Device evaluations • Diagnostic imaging review • Disability equipment assessments	http://www.medical-devices.gov.uk/

National Library of Medicine Health Services/Technology Assessment Text	http://text.nlm.nih.gov/
National Library of Medicine Locator Plus database	http://locatorplus.gov
New York Academy of Medicine Grey Literature Report	http://www.nyam.org/library/greylit/index.shtml
Scirus – for Scientific Information Only	http://www.scirus.com
Trip database	http://www.tripdatabase.com
U.K. National Research Register	http://www.update-software.com/National/
US Food and Drug Administration, Center for Devices and Radiological Health. • Manufacturer and User facility Device Experience (MAUDE). MAUDE data represents reports of adverse events involving medical devices. • PreMarket Approvals database	http://www.fda.gov/cdrh/databases.html
Websites of Health Technology Agencies	See Appendix D
Websites of Specialty Organisations	Dependent on technology topic area
Hand Searching	
Recent (previous year) issues of seminal journals in the specialty area	Library or electronic access
Expert Clinicians	
Studies and information not found in regular searches	Horizon Scanning Network consultants
Pearling	
All included articles have their reference lists searched for additional relevant source material	

Table 8 Search terms utilised

Search terms
MeSH
tomography, emission-computed; tomography, x-ray computed; neoplasms
Text words
PET scan*, CT scan* , PET, CT, neoplas*, cancer*, carcinoma*
Limits
Human, English

Availability and Level of Evidence

Twenty-five papers were included for assessment in this report, seven of which were full text studies and the remaining 18 were abstract studies. All studies included for assessment in this report were classified according to the levels of evidence for assessing diagnostic accuracy (Table 9). There were two level 1b, five level 3b and eighteen level 4 evidence studies included for assessment.

Table 9 Levels of evidence for assessing diagnosis[a]

Level of evidence	Study design
1a	SR (with homogeneity*) of Level 1 diagnostic studies; CDR with 1b studies from different clinical centres
1b	Validating** cohort study with good† reference standards; or CDR tested within one clinical centre
1c	Absolute SpPins and SnNouts††
2a	SR (with homogeneity*) of Level ≥2 diagnostic studies
2b	Exploratory** cohort study with good† reference standards; CDR after derivation, or validated only on split-sample§ or databases
2c	n/a
3a	SR (with homogeneity*) of 3b and better studies
3b	Non-consecutive study; or without consistently applied reference standards
4	Case-control study, poor or non-independent reference standard
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

[a] (Phillips et al 2001). SR = systematic review; CDR = clinical decision rule - these are algorithms or scoring systems which lead to a prognostic estimation or a diagnostic category; RCT = randomised controlled trial; n/a = not applicable. * Homogeneity means a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. Studies displaying worrisome heterogeneity should be tagged with a "-" at the end of their designated level. ** Validating studies test the quality of a specific diagnostic test, based on prior evidence. An exploratory study collects information and trawls the data (e.g. using a regression analysis) to find which factors are 'significant'. † Good reference standards are independent of the test, and applied blindly or objectively to all patients. Poor reference standards are haphazardly applied, but still independent of the test. Use of a non-independent reference standard (where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference') implies a level 4 study. †† An "Absolute SpPin" is a diagnostic finding whose Specificity is so high that a Positive result rules-in the diagnosis. An "Absolute SnNout" is a diagnostic finding whose Sensitivity is so high that a Negative result rules-out the diagnosis. § Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into "derivation" and "validation" samples.

Sources of Further Information

No other sources of information have been identified.

Conclusions

PET scanners are utilised in oncology imaging to provide diagnostic images of tumour growth and spread. CT images give greater anatomical detail in respect to lymph node metastasis, and may indicate tumour spread. By combining these two imaging techniques into one scanner, PET-CT, it is hoped that diagnostic capability will increase, be more accurate, expose patients to a reduced radiation load, increase patient throughput and improve the treatment and management of patients. There is also a potential for PET-CT to be used in the diagnosis and management of cardiovascular and neurological disease.

Current indications for the use of PET-CT are carcinomas arising in the head and neck, thorax and abdomen. In the year 2000 there were approximately 13,000 newly diagnosed cases of these cancers. However, this figure does not include individuals previously diagnosed with the cancer or those suspected (but subsequently unconfirmed) of having cancer. During the course of treatment patients may undergo more than one PET-CT scan. In addition, it is likely that the ability to diagnose other types of cancer with this technology will increase. These factors are likely to increase the utilisation of PET-CT scanners in the Australian health system.

PET-CT appears to provide improved diagnostic capabilities when compared to PET or CT alone, depending on the type of tumour, the stage of tumour and whether analysed on a lesion-by-lesion basis or by patient. The highest level of available evidence (1b) suggests that PET-CT is significantly more accurate at determining non-small cell lung carcinoma tumour and node staging than PET alone. Further low level evidence indicates that PET-CT improves the localisation of lesions by 19 to 66 per cent and decreases the number of equivocal lesions by approximately 30 per cent, when compared to PET alone.

Low quality abstract studies reported that PET-CT changed the clinical management of patients in one study when compared PET alone, in four studies when compared to CT alone and in three studies when compared to the gold standard of diagnostic work-up. Changes in clinical management include patients receiving chemotherapy instead of surgery, receiving salvage chemotherapy instead of observation, receiving increased radiation therapy and receiving observation rather than chemotherapy or surgery after returning negative PET-CT results. However, there is currently no available evidence to indicate the effect on patient health resulting from these changes in clinical management.

Level 1b evidence also indicates significant improvements in non-small cell lung carcinoma tumour staging with PET-CT, although not in nodal staging, compared to CT alone. Lower level evidence reports improvements in the identification of the number of lesions with PET-CT, ranging from 45-80 per cent, and changes in clinical management in 35-73 per cent of patients, compared to CT alone.

The specificity for PET-CT when compared to the gold standard of diagnostic and histological work-up, in level 1b evidence, is 67 per cent. In addition, the sensitivity in this study was reported as 86 per cent with an associated false positive rate of 14 per cent, which indicates a substantial proportion of false positive diagnoses of colorectal cancer lesions. A slightly poorer quality study (level 3b) suggests PET-CT can positively predict 96 per cent of epithelial ovarian cancer lesions. Diagnostic accuracy, therefore appears to vary according to the tumour type and staging of the disease.

Data on the safety of PET-CT is very limited. It is likely that radiation doses delivered to patients are reduced if patients undergo a combined PET-CT scan, compared to undergoing separate PET and CT scans.

Currently, access to PET-CT is limited to a few hospitals in capital cities in Australia. The capital cost of purchasing a PET-CT scanner is estimated to be $2-5 million AUD, which would limit its introduction to all but major hospitals. If PET-CT was utilised for all patients with newly diagnosed cancers of all types for at least one scan, the estimated costs to the health system would be $81 million per year.

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